Oral flecainide is not sensitive enough to rule out Brugada-Syndrome

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Abstract

Objectives-The Brugada syndrome is a heterogeneous genetic disease that predisposes one to life-threatening ventricular tachyarrhythmia and sudden cardiac death (SCD). In this study, we sought to compare the efficacy of intravenous Procainamide versus oral Flecainide to unmask the typical electrocardiographic changes of this syndrome.

Methods-From October 2001 to December 2010, we evaluated patients with the Brugada Type Electrocardiographic (ECG) pattern. In these patients, 104 patients (83%) were male. The mean age of the participants was 39.16±7 years (16 to 75), and the mean follow-up was 48±3 months. All of the subjects underwent IV Procainamide and oral Flecainide challenge test. Among these patients 19 patients had positive results.

Results- Nineteen patients had positive responses (15%); 18 of them were male (94.7%) and one of them was female. These 19 patients all had a positive Procainamide challenge test. Only 9 of these patients had a positive Flecainide test. In the diagnosed Brugada Syndrome patients, IV Procainamide had a 100% positive response rate in comparison to a 47.4% positive rate in oral Flecainide.

Conclusions-Different Brugada challenge tests have different sensitivities in the diagnosis of BS. IV procainamide is more sensitive than oral Flecainide and the latter cannot be used solely to rule out BS (Iranian Heart Journal 2012; 13 (1):34-39).

Keywords: Brugada syndrome ■ Flecainide challenge test ■ IV procainamide challenge test
The only proven way to prolong the survival of patients with the Brugada syndrome is to implant an Implantable Cardioverter-Defibrillator (ICD). It is obvious that implanting an ICD is necessary in patients who have experienced aborted SCD, but a great percentage of these patients present with SCD as their initial presentation, which signifies the importance of proper risk stratification to find those patients who may benefit from ICD implantation. Thus far, the only indications of ICD implantation are Type 1 Brugada ECG pattern (spontaneous or induced) associated with aborted SCD or unexplained syncope.

Material and Method

Patient Selection
From October 2001 to December 2010, we evaluated patients with Brugada Type Electrocardiographic (ECG) pattern. The three Brugada ECG patterns of the Brugada syndrome are as follows:
Type 1 is characterized by a prominent coved ST-segment elevation, accompanied by a J-wave amplitude or elevated ST-segment elevation ≥ 2 mm at its peak followed by a negative T-wave; type 2 has a J-wave amplitude ≥ 2 mm, which gives rise to a gradual descending ST-segment elevation (remaining ≥1 mm above the baseline) followed by a positive or biphasic T-wave, resulting in a saddle-back configuration; Type 3 pattern shows either a coved or saddleback appearance associated with a right precordial ST-segment elevation up to 1 mm. Patients with type 2 or type 3 ECG pattern were selected to be enrolled in the study.

Inclusion Criteria
The patients with type 2 or 3 Brugada ECG pattern had to have the following criteria in order to be selected for the study:
2. Normal exercise tolerance test and/or coronary angiography as indicated in patients with coronary artery risk factor or history compatible with coronary artery disease.
3. Filling of informed consent.
4. The patients had to have an indication for Brugada challenge test with drugs. These indications included unexplained syncope (N=41), unexplained aborted SCD (N=7), palpitation, dizziness, typical or atypical chest pain associated with Brugada type 2 or 3 ECG pattern in the absence of any other explainable cause (N=68), and family history of documented Brugada syndrome (N=10). Patients with acute electrolyte imbalance such as hyperkalemia that could interfere with the ECG results were excluded from the study.

Brugada Challenge Test
After obtaining informed written consent, a standard twelve-lead ECG (paper speed 25mm/sec and amplitude of 1mv/mm) was taken from every enrolled patient. Two sets of Brugada challenge test was performed in each patient. The first test was performed using an infusion 10mg/Kg of intravenous Procainamide in 10 minutes. Continuous heart monitoring was performed during the test with a standard two-lead bedside monitor. The infusion of Procainamide was terminated when a major adverse event occurred, defined as ventricular arrhythmias or important conduction slowing (prolongation of the QRS ≥ 30% of the basal value). A standard twelve-lead ECG with pericordial leads at their standard place was obtained in minutes 5 and 10 of infusion and then 5 and 15 minutes after that. All of the patients were monitored for 1-6 hours after drug administration with the bedside monitor. Then, another provocative test was performed at least 24 hours later (with the ECG returned to the baseline feature) with 400 mg of oral Flecainide. After the ingestion of the drug, the patients were monitored for at least 6 hours.
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with the standard bedside monitor. At 15-minute intervals up to 1 hour, a standard twelve-lead ECG was taken with the pericordial leads in the standard position.

Definition of positive response
During the Procainamide test or Flecainide test with standard left-side pericordial leads, the positive response for the Brugada syndrome was defined as conversion to Brugada type I ECG pattern in at least two right pericordial leads (Fig. 1).

Statistical Analysis
Parameter values are expressed as mean ± SD. For comparison between the positive and the negative responders groups with normal distribution, the chi-Square test, and for those without normal distribution the non-parametric Mann-Whitney U-test was used. Statistical analysis was performed using SPSS (version 17.0). All the tests were two-sided and statistical significance was defined as P ≤ 0.05.

Results
From October 2001 to December 2010, we evaluated 126 patients with Brugada type ECG patterns. In these patients, 104 (83%) individuals were male. The mean age of the participants was 39.16±7 years (16 to 75), and the mean follow-up was 48±3 months. All of the patients underwent IV Procainamide and oral Flecainide challenge test. Nineteen patients had a positive response. The basic characteristics of the patients with a positive response are shown in Table I.

Table I. Basic characteristics of the patients with a positive Brugada challenge test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (N)</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>18</td>
<td>94.7%</td>
</tr>
<tr>
<td>Aborted SCD</td>
<td>2</td>
<td>10.5%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>3</td>
<td>15.8%</td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>1</td>
<td>5.3%</td>
</tr>
<tr>
<td>Palpitation</td>
<td>7</td>
<td>36.9%</td>
</tr>
<tr>
<td>Atypical chest pain and palpitation</td>
<td>3</td>
<td>15.8%</td>
</tr>
<tr>
<td>Presyncope</td>
<td>2</td>
<td>10.5%</td>
</tr>
<tr>
<td>Syncope</td>
<td>1</td>
<td>5.3%</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>5</td>
<td>26.3%</td>
</tr>
<tr>
<td>Positive SCN 5A</td>
<td>4</td>
<td>21%</td>
</tr>
<tr>
<td>ICD</td>
<td>9</td>
<td>47.4%</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>100%</td>
</tr>
</tbody>
</table>

Nineteen patients had a positive response (15%). Eighteen of them were male (94.7%) and one of them was female. These 19 patients all had a positive Procainamide challenge test. Only 9 of these patients had a positive Flecainide test. This is shown in Table II.

Table II. Result of different tests with different drugs

<table>
<thead>
<tr>
<th>Test</th>
<th>Number (N)</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procainamide test</td>
<td>19</td>
<td>100%</td>
</tr>
<tr>
<td>Flecainide routine left side position</td>
<td>9</td>
<td>47.4%</td>
</tr>
</tbody>
</table>

In the diagnosed Brugada Syndrome patients, IV Procainamide had a 100% positive response rate in comparison to a 47.4% positive rate in oral Flecainide.
IV Procainamide was more sensitive than oral Flecainide (P<0.0001), and 53.6% of the patients diagnosed as the Brugada Syndrome with IV Procainamide were missed with oral Flecainide.

**Discussion**

Provocation tests using Na+ channel blockers are often required to unmask the Brugada syndrome\(^\text{16}\). Although these tests are generally considered helpful for the diagnosis and risk stratification in this syndrome\(^\text{11}\) and Ajmaline was shown to possess the highest diagnostic yield followed by intravenous Flecainide and Procainamide,\(^\text{12}\) several issues still need to be resolved and remain the object of international debate\(^\text{13,14}\).

The reproducibility of Flecainide administration to unmask the BS ECG has been systematically assessed only in one study, which reported a concordant positive response of two tests performed on different days in all patients\(^\text{15}\). The authors suggested that a negative response to Flecainide challenge was sufficient to rule out the Brugada syndrome. But in this study, we proved it otherwise.

A cellular mechanism for the Brugada syndrome has been proposed in which accentuation of the epicardial action potential notch and eventual loss of the epicardial action potential dome results in ST-segment elevation, phase II reentry, and polymorphic ventricular tachycardia and fibrillation (VT/VF)\(^\text{16,17}\). The proposed mechanism involves a rebalancing of the currents available at the end of phase I of the epicardial action potential. Diminution of inward currents (INa and ICa) or enhancement of outward currents (Ito, IK-ATP) can result in the slowing of the second upstroke of the epicardial action potential, eventually leading to the loss of the action potential dome as a consequence of all-or-none repolarization at the end of phase I. Different positive response rates in different challenge test methods may be due to different capabilities of drugs in blocking these channels.

It is possible that drug-induced Brugada syndrome may be due to an individual susceptibility that favors drug-induced ECG abnormalities, possibly as a result of an increase in a latent ion-channel dysfunction. However, further evidence is needed to confirm this postulation.

**Conclusion**

Different Brugada challenge tests have different sensitivities in the diagnosis of the Brugada syndrome. IV Procainamide is more sensitive than oral Flecainide and the latter cannot be used to rule out the Brugada syndrome.

**References**


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