Brugada syndrome: clinical and pathophysiological aspects
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5.2 Are Women with Severely Symptomatic Brugada Syndrome Different from Men?


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Abstract

Introduction: Spontaneous type I ECG has been recognized as a risk factor for sudden cardiac death (SCD) in Brugada syndrome, but studied populations predominantly consisted of men. We sought to investigate whether a spontaneous type I ECG pattern was also associated with SCD in women with symptomatic Brugada syndrome. Other known risk factors were also examined for gender-specificity.

Methods: Patients with severely symptomatic Brugada syndrome, defined as resuscitated SCD and/or appropriate implantable cardioverter-defibrillator (ICD) shock were included from 11 European centers. Clinical data, investigation of family history, twelve-lead ECG and results of electrophysiological study (EPS) were collected. The average follow-up was 4±3 years.

Results: Fifty-eight patients fulfilled the inclusion criteria (mean age 47±11 years, 8 women). Thirty-six men (72%) but only two women (25%) had a spontaneous type I ECG at baseline (p=0.02). Maximal ST elevation before or after drug challenge was 3.7±1.3 in men vs 2.4±0.7 mm in women (p=0.007). The proportion of patients with a family history of SCD or a SCN5A mutation was not significantly different between men and women. Of those patients with high-risk Brugada syndrome who underwent EPS, 76% (12/25) of men and 50% (2/4) of women had a positive study.

Conclusion: In contrast to men, most women with Brugada syndrome and resuscitated SCD or appropriate ICD shock do not have a spontaneous type I ECG pattern. In addition, the degree of ST elevation is less pronounced in women than in men. While women represent a lower risk group overall, risk factors established from a predominantly male population may not be helpful in identifying high risk females.
Manifestation of Brugada Syndrome in Women

Introduction

Mutations in the SCN5A gene, which encodes the α subunit of the sodium channel protein, are responsible for a subset of patients with Brugada syndrome. This gene displays an autosomal dominant mode of transmission. While men and women are expected to inherit the defective gene equally, disease manifestation is clearly predominant in males. Up to now, Brugada syndrome population studies that evaluated risk factors for sudden cardiac death (SCD) were mainly composed of men. Whether women with severely symptomatic Brugada syndrome share the same characteristics and risk factors, such as a spontaneous type I ECG pattern is not known. We sought to investigate whether a spontaneous type I ECG pattern was also prevalent in women with severely symptomatic Brugada syndrome. Other known risk factors were also examined for gender-specificity.

Methods

Study Population

Consecutive patients with Brugada syndrome were enrolled in a multicenter registry from 11 participating centers in Europe. Patients were included in the present study only if they had a type I ECG pattern on at least one baseline ECG spontaneously, or after provocation with a class I anti-arrhythmic drug. A type I ECG was defined as a prominent coved ST-segment elevation displaying J-point amplitude or ST-segment elevation ≥2 mm at its peak in lead V1 through V3. The choice of class I drug was determined by its availability in the participating hospitals: intravenous ajmaline (1 mg/kg body weight at a rate of 10 mg/min) or flecainide (2 mg/kg body weight over 10 minutes with a maximum of 150 mg). In addition, treadmill exercise testing, biochemical analysis, and, in some cases, coronary angiography excluded acute ischemia and metabolic or electrolyte disturbances. The total Brugada syndrome population followed in these centres numbered 739, with 211 women (29%). These centers were the “reference arrhythmic department” for their geographical area and included all patients with Brugada syndrome whether or not they were symptomatic. The following clinical data were collected in all 11
participating centers: gender, age and circumstances at diagnosis, indication for implantable cardioverter-defibrillator (ICD) implantation (when appropriate), family history of SCD (< 45 years of age). Patients with resuscitated SCD and/or appropriate ICD shock in the context of Brugada syndrome were considered as “severely symptomatic” Brugada syndrome and included in the current analysis. All patients included in this study had at least three baseline ECGs and/or 24 hours continuous 12-lead ECG reviewed. When invasive electrophysiological testing (EPS) was performed, the protocol consisted of ventricular stimulation from 2 sites at 2 drive cycle lengths with up to 3 extrastimuli until 200 ms. All these severely symptomatic patients were prospectively followed for 4 ± 3 years.

**Statistical Methods**

Values are expressed as mean ± standard deviation. Comparison of categorical values was performed using a Fisher’s exact test. Continuous parameters were compared using the non-parametric Mann-Whitney test. A p-value < 0.05 was considered significant.

**Results**

Fifty-eight patients (mean age 47±11 years; 8 women (14%); 8% of all Brugada syndrome patients followed in the 11 centers) met preset criteria for severely symptomatic Brugada syndrome in this international registry (n= 739). Clinical and electrocardiographic characteristics are summarized in the table (see below). The proportion of men with severely symptomatic Brugada syndrome was significantly higher than the proportion of women (9.5% vs. 3.8%, p=0.009). The 8 women were not significantly older than the men at the time of onset of symptoms (50 ±13 vs. 45 ±11, p=0.22). Diagnosis was made because of aborted-SCD (33 men and 3 women), syncope (11 men and 4 women), and a VT in 1 woman. Six men were asymptomatic, but experienced ICD shocks during follow-up. All patients underwent ICD implantation (the six asymptomatic men because of a positive EPS). A higher proportion of men had a spontaneous type I ECG at baseline (72% of men vs. 25% of women, p=0.02). In the remaining individuals, a type I ECG
pattern was present only after drug challenge (14 men and 6 women). Maximal ST segment elevation, measured either before or after drug challenge, was 3.7 ±1.3 mm in men vs. 2.4 ±0.7 mm in women (p= 0.007). In patients without spontaneous type I ECG pattern (n=20), 12 of 14 men and 4 of 6 women underwent flecainide challenge, the remaining patients had ajmaline. Figure 1 shows the ECGs of the eight women. The onset of ventricular tachyarrhythmia in a female patient was not preceded by ST segment elevation (Figure 2). There was no difference between men and women with regard to the duration of PR and QTc intervals. The proportion of patients with a family history of SCD was not significantly different between both groups, nor was the presence of a SCN5A mutation (Table).

Appropriate shocks occurred in 25 men (8 with prior aborted-SCD, 12 implanted for syncope and 5 previously asymptomatic patients) after a mean follow-up of 24 ± 35 months and in 6 women (1 with prior aborted-SCD, 4 implanted for syncope and 1 implanted for sustained monomorphic ventricular tachycardia (VT) after a mean follow-up of 25 ± 33 months.

Ventricular arrhythmias in women were polymorphic ventricular tachycardia or ventricular fibrillation (VF) in 7 cases and monomorphic VT in 1 (case reported by Boersma et al³). Arrhythmic storm was the clinical presentation in 2 women. Isolated ventricular arrhythmias at night or during periods of high vagal tone were observed in 2 female patients with ICD shocks. There was no identifiable arrhythmic trigger in 4 cases. None of the arrhythmic events was related to exertion. Concerning men, 23 had a polymorphic VT or VF and 2 monomorphic VT. Eight men experienced arrhythmic storms. Of the 17 remaining men, 10 experienced shocks at night, 6 during the daytime and 1 during both.

EPS was performed in 29 (50%) patients of our study (n=58). Of these severely symptomatic patients, 19/25 (76%) men and 2/4 (50%) women had inducible ventricular tachyarrhythmia (p=ns).
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Table: Clinical and electrocardiographic characteristics of patients with severely symptomatic Brugada syndrome according to gender.

<table>
<thead>
<tr>
<th></th>
<th>Males (n=50)</th>
<th>Females (n=8)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>45 ±11</td>
<td>50 ±13</td>
<td>p=0.22</td>
</tr>
<tr>
<td>Prior resuscitated SCD</td>
<td>33 (66%)</td>
<td>3 (38%)</td>
<td>p=0.03*</td>
</tr>
<tr>
<td>Appropriate shock</td>
<td>25 (50%)</td>
<td>6 (75%)</td>
<td>p=0.26</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>15 (30%)</td>
<td>2 (25%)</td>
<td>p=0.99</td>
</tr>
<tr>
<td>Spontaneous type I ECG</td>
<td>36 (72%)</td>
<td>2 (25%)</td>
<td>p=0.02*</td>
</tr>
<tr>
<td>PR, ms</td>
<td>185 ±31</td>
<td>192 ±50</td>
<td>p=0.63</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>408 ±40</td>
<td>440 ±63</td>
<td>p=0.08</td>
</tr>
<tr>
<td>Maximal ST elevation, mm</td>
<td>3.7 ± 1.3</td>
<td>2.4 ± 0.7</td>
<td>p=0.007*</td>
</tr>
<tr>
<td>Mean ST elevation in pts with spontaneous type I ECG, mm</td>
<td>2.8 ± 1 (36 pts)</td>
<td>2.3 ± 0.9 (2 pts)</td>
<td>p=0.54</td>
</tr>
<tr>
<td>Positive EPS</td>
<td>19/25 (76%)</td>
<td>2/4 (50%)</td>
<td>p=0.25</td>
</tr>
<tr>
<td>SCN5A mutation carriers</td>
<td>13/42 (31%)</td>
<td>3/7 (43%)</td>
<td>p=0.79</td>
</tr>
</tbody>
</table>

* indicates statistical significance
Figure 1: ECGs with maximal degree of ST elevation in the eight women with severe symptoms. The first three ECGs belong to women who received an ICD because of aborted-SCD.
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Discussion

Women with Brugada syndrome have a lower prevalence (3.8%) of life-threatening arrhythmias compared to men (9.5%) in this non-selected international Brigade population (739 pts). The subgroup of women with severely symptomatic Brugada syndrome displayed a spontaneous type 1 ECG pattern less frequently than men. Also, the amount of ST segment elevation in the right precordial ECG leads is less accentuated compared to the severely symptomatic men.

Despite equal genetic transmission of the affected gene, the clinical phenotype is much more severe in men than in women. The basis for this intriguing sex-related difference in disease penetrance is not completely understood. It seems that the presence of a more prominent $I_{to}$ in the right ventricular epicardium in males contributes to their predisposition to develop the Brugada syndrome phenotype. However hormonal, environmental or genetic factors other than $SCN5A$ mutations may alter the function of $I_{to}$ or of other yet unknown factors that explain the gender difference in disease penetrance. In families with a particular $SCN5A$ mutation, Kyndt et al. reported a classical Brugada syndrome phenotype in males but an isolated cardiac conduction defect in females. Hong et al., however, described another specific $SCN5A$ gene defect with predominantly female phenotypic expression (characterized by ST segment elevation). It is also well established that sex hormones impact on cardiac cellular electrophysiology, in particular on cardiac repolarization. Matsuo et al. reported two cases of asymptomatic Brugada syndrome in which typical coved type ST segment elevation disappeared following orchiectomy, as therapy for prostate cancer. More recently, Shimizu et al. found no correlation between testosterone level and clinical presentation, degree of ST elevation, the presence of a $SCN5A$ mutation or events during follow-up, but males with Brugada syndrome men have higher testosterone levels than males without Brugada syndrome.

Regarding the gender difference in relation to the risk of developing ventricular arrhythmia, a previous meta-analysis combining 788 patients from three studies found a 3.47-fold increase in risk of event (syncope, SCD or ICD shock) in men vs. women with Brugada syndrome. In our study, the relative risk of aborted-SCD
or appropriate ICD shock is increased by a factor 2.5 in men vs. women over a follow-up period exceeding 3 years.

Spontaneous type I ECG is a risk factor for arrhythmic events in several large studies²,³, which included mainly men. However, no studies focused on women. In our population, only 25% of the women had a spontaneous type I ECG pattern, despite the occurrence of ventricular arrhythmias. Figure 2 contains tracings from a 33 year old woman with arrhythmic storm not controlled with either β-blocker or intravenous amiodarone infusion. Despite VF episodes, there was no ST elevation on 12 lead ECG. Brugada syndrome diagnosis was made 2 weeks later with flecainide challenge (Figure 3).

Based on these data, the absence of a spontaneous type I ECG in women may not be reassuring as suggested in the literature¹,². Right ventricular transmural epicardial or endocardial voltage gradients leading to ST elevation in the right precordial leads is one of the proposed mechanisms leading to the development of phase 2 reentry¹³, followed by ventricular arrhythmia. It is intriguing, given the mechanism proposed, that patients may develop ventricular arrhythmia in the context of Brugada syndrome without concomitant ST elevation. Alternative explanations have, however, been proposed¹⁴, such as structural cardiac disorders or the presence of slow-conducting tissue in the right ventricular outflow tract.
Figure 2: ECG during arrhythmic storm in a 33 year-old woman (patient 1). She was unsuccessfully treated with beta-blocker and amiodarone infusion and was then referred for polymorphic VT ablation. Panel (a) shows VF during monitoring and panel (b) non-sustained VT on 12 lead ECG 3 days later. Note the absence of ST elevation in the acute period as well as the T wave inversion and QT interval prolongation due to the combination of amiodarone and multiple shocks.
Figure 3: This is the same patient presented in Figure 2. Intravenous flecainide unmasked the Brugada phenotype two weeks after the end of the arrhythmic storm. Note the normalization of the QT interval. Genetic testing did not find any mutation in SCN5A, HERG and KVLQT1 genes.

Limitations
Although this is a large international multicenter cohort, there is still a relatively small number of female patients with severely symptomatic Brugada syndrome, limiting the statistical power. However this is the largest study so far comparing the clinical characteristics of men and women with severely symptomatic Brugada syndrome.

Conclusions
Women with Brugada syndrome have a lower risk (3.8%) of life-threatening arrhythmias than men (9.5%). Risk stratification in Brugada syndrome remains limited, but the female sub-population may be a particularly challenging group to characterize.
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Neither the presence of a spontaneous type I ECG nor the total magnitude of ST elevation seemed to correlate with severe symptoms in female Brugada syndrome patients. The role of EP study remains unclear both in symptomatic female and male Brugada syndrome patients. Further investigations are needed to identify better methods for risk stratification.
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