Asymptomatic Brugada Syndrome  
Clinical Characterization and Long-Term Prognosis

Juan Sieira, MD; Giuseppe Ciconte, MD; Giulio Conte, MD; Gian-Battista Chierchia, MD; Carlo de Asmundis, MD; Giannis Baltogiannis, MD; Giacomo Di Giovanni, MD; Yukio Saitoh, MD; Ghazala Irfan, MD; Rubén Casado-Arroyo, MD; Justo Julià, MD; Mark La Meir, MD; Francis Wellens, MD; Kristel Wauters, MD; Gudrun Pappaert, RN; Pedro Brugada, MD

Background—Among Brugada syndrome patients, asymptomatic individuals are considered to be at the lowest risk. Nevertheless, arrhythmic events and sudden cardiac death are not negligible. Literature focused on this specific group of patients is sparse. The purpose of this study is to investigate the clinical characteristics, management, and long-term prognosis of asymptomatic Brugada syndrome patients.

Methods and Results—Patients presenting with spontaneous or drug-induced Brugada type I ECG and no symptoms at our institution were considered eligible. A total of 363 consecutive patients (200 men, 55.1%; mean age, 40.9±17.2 years; 41 [11.3%] with spontaneous type I ECG) were included. Electrophysiological study was performed in 321 (88.4%) patients, and ventricular arrhythmias were induced in 32 (10%) patients. An implantable cardioverter defibrillator was implanted in 61 (16.8%) patients. After a mean follow-up time of 73.2±58.9 months, 9 arrhythmic events occurred, accounting for an annual incidence rate of 0.5%. Event-free survival was 99.0% at 1 year, 96.2% at 5 years, and 95.4% at 10 and 15 years. Univariate analysis identified as risk factors: electrophysiological study inducibility (hazard ratio, 11.4; P<0.01), spontaneous type I (hazard ratio, 4.0; P=0.04), and previous sinus node dysfunction (hazard ratio, 8.0; 95% confidence interval, 1.0–63.9; P=0.05). At the multivariate analysis, only inducibility remained significant (hazard ratio, 9.1; P<0.01).

Conclusions—Arrhythmic events in asymptomatic Brugada syndrome patients are not insignificant. Ventricular arrhythmia inducibility, spontaneous type I ECG, and presence of sinus node dysfunction might be considered as risk factors and used to drive long-term management.

Key Words: arrhythmias, cardiac ■ Brugada syndrome ■ death, sudden, cardiac ■ defibrillators, implantable ■ prognosis

Brugada syndrome (BS) is an inherited syndrome characterized by coved-type ST-segment–elevation in the right precordial leads (V1–V3) and increased risk of sudden cardiac death (SCD) in the absence of structural heart disease.

The placement of an implantable cardioverter defibrillator (ICD) remains the therapy with most proven efficacy to prevent SCD in patients with BS.2,3 Therefore, identifying patients at higher risk for ventricular arrhythmias (VAs) is of utmost importance.

Presentation as SCD or syncope has been consistently identified as risk factors for events by different investigators.4,5 Nevertheless, arrhythmic events in asymptomatic patients are not insignificant.4,6,7 Risk stratification of asymptomatic BS patients remains challenging and controversial. Literature focused in this group is sparse and usually mixes asymptomatic patients and those with previous syncope.5,6 Furthermore, data on long-term follow-up (>5 years) of patients with BS are infrequent; none of the major BS registries have a mean follow-up >40 months.8,9 As the risk of sudden death in patients with BS is a lifelong issue, longer follow-up is necessary to help clarify this question.

The purpose of this study was to analyze our single-center 20 years’ experience in asymptomatic BS patients, with focus on the search of predictors of arrhythmic events.

Study Population
Since 1992, all consecutive patients diagnosed with BS have been included in a registry and followed in a prospective fashion. The ethics committee of the Universitair Ziekenhuis Brussel-Vrije Universiteit Brussel approved the study protocol. A total of 549 patients with BS have been included in the registry from 1992 to 2013. Among them,

Received December 22, 2014; accepted July 8, 2015.
Correspondence to Juan Sieira, MD, Heart Rhythm Management Centre, UZ Brussel-VUB, Laarbeeklaan 101, 1090 Brussels, Belgium. E-mail jasieira@gmail.com

© 2015 American Heart Association, Inc.

doi:10.1161/CIRCEP.114.003044

Circ Arrhythm Electrophysiol is available at http://circep.ahajournals.org

1144
WHAT IS KNOWN

- Asymptomatic Brugada syndrome patients are considered to have a low arrhythmic risk.
- Arrhythmic events and sudden cardiac death are not negligible.
- Risk stratification in this patients is controversial

WHAT THE STUDY ADDS

- Arrhythmic events in asymptomatic BS patients are not insignificant, with an annual incidence rate of 0.5%.
- Inducibility of ventricular arrhythmias during programmed stimulation of the heart identifies a subgroup of patients at higher risk (HR: 9.1).

363 patients (66.1%) had no prior SCD or syncope. Study inclusion criteria consisted of (1) spontaneous or drug-induced Brugada type I ECG and (2) no previous syncope or SCD. Medical history, physical examination, and baseline ECG were obtained, and underlying structural cardiac abnormalities were excluded in all patients by means of echocardiography. Other noninvasive methods (such as stress test or nuclear magnetic resonance) or invasive methods (coronary angiography, left and right ventriculography, and myocardial biopsies) were used at the discretion of the treating physician. ECGs were classified as Brugada coved-type (type I), saddleback (type II), or normal. An ECG was considered diagnostic of BS if a coved-type ST elevation ≥2 mm was documented in ≥1 lead from V1 to V3 in the presence or absence of a sodium-channel blocker agent. All baseline and drug-induced 12-lead ECGs were recorded at a paper speed of 25 mm/s and an amplitude of 10 mm/mV with the right precordial leads positioned at the sternal margin of the third and fourth intercostal space. Two independent experienced electrophysiologists analyzed all ECGs; in case of disagreement, a third physician was consulted. Genetic testing with sequence analysis of SCN5A was recommended for all patients with diagnosis of BS.

Ajmaline Challenge

Ajmaline (1 mg/kg) was administered intravenously over a 5-minute period to unmask the diagnostic ECG pattern of BS in case of nondiagnostic baseline ECG. The test was considered positive for BS only if coved-type I ECG was documented in ≥1 right precordial leads (V1–V3). Ajmaline infusion was discontinued before reaching the target dose if QRS prolongation exceeded 30% compared with baseline interval, when frequent premature ventricular beats or type I Brugada ECG occurred or in the case of development of high-degree atrioventricular-block. Ajmaline-induced sustained VA was defined as the occurrence of ventricular fibrillation (VF) or sustained ventricular tachycardia (VT).

Electrophysiological Study

Electrophysiological study (EPS) included basal measurements of conduction intervals and programmed ventricular stimulation. As reported elsewhere, the protocol used a single site of stimulation (right ventricular apex), 3 basic pacing cycles (600, 500, and 430 ms), and introduction of 1, 2, and 3 ventricular premature beats down to a minimum of 200 ms. A patient was considered inducible if a sustained VA (VF, polymorphic VT, or monomorphic VT lasting >30 s or requiring emergency intervention) was induced.

ICD Implantation

Beginning from 2005, the indication for ICD therapy was determined using the recommendations of the Second Brugada Consensus Conference. Patients with inducible VAs during EPS were considered at high risk of future arrhythmic events, and the implantation of an ICD was considered. The choice between single- and dual-chamber devices was driven by the presence of previous episodes of supraventricular arrhythmias or the evidence of sinus node dysfunction (SND). The device was usually programmed to treat ventricular rates >200 beats per minute, and occasionally a VT monitoring zone was added. However, these settings were adjusted on the basis of the individual clinical history and to avoid recurrences of inappropriate interventions during the follow-up.

Follow-Up

Clinical follow-up of patients consisted of physical examination and ECG performed at least every 6 months in case of patients with an ICD implanted and every 2 years elsewhere. Clinical data were regularly collected. Follow-up of ICDs was performed at 1 and 3 months after implantation and thereafter every 6 months. All available electrograms of appropriate and inappropriate shocks were analyzed by at least 2 investigators independently. Appropriate therapies were defined as shocks or antitachycardia pacing delivered for VT or VF, and inappropriate therapies were defined as those delivered in the absence of VAs. Electrical storm was defined by ≥2 sustained episodes of VT, VF, or ICD appropriate shocks within 24 hours.

Statistical Analysis

Data are presented as mean±SD or as absolute values and percentages where appropriate. Comparison between continuous variables was performed using the unpaired Student t test or Mann–Whitney U test as appropriate. The χ² test or the Fisher exact test was used to compare categorical variables. Sensitivity, specificity, and area under the curve were created by means of a receiver operating characteristic curve analysis. Event-free survival was estimated by Kaplan–Meier method and compared by log-rank test. Hazard ratios were calculated using Cox proportional hazards regression models. Cox regression analysis was used to create a predictive model. The variables included were those that showed statistical significance at the univariate analysis. A P value <0.05 was considered statistically significant. Statistical analyses were conducted using the SPSS software (SPSS v22, Chicago, IL).

Results

Study Population

A total of 363 consecutive BS patients (200 men, 55.1%; mean age: 40.9±17.2, ranging from 0.5 to 80.9 years) fulfilled inclusion criteria. Baseline clinical characteristics of study population are shown in Table 1.

At the time of diagnosis, 42 patients (11.6%) were <18 years and 23 (6.3%) >65 years. Eighty-seven (23.9%) patients were probands, and the remaining 276 (76.0%) patients were diagnosed during family member screening. They belonged to 199 different families. One hundred eighty-two (50.1%) patients had familial history of SCD, 33 (37.9%) among 87 probands and 149 (54.0%) of 276 familial screening patients.

Spontaneous type 1 ECG was present in 41 (11.3%) patients with a mean ST-elevation of 2.7±1.2 mm. The remaining 322 (88.7%) patients were diagnosed after a pharmacological challenge test. It was performed in 301 (93.5%) patients with ajmaline, in 6 (1.9%) with procainamide, and in 15 (4.7%) patients with flecainide.

Three hundred twenty-one (88.4%) patients underwent an EPS. Among whom, in 32 (10.0%) patients, a sustained VA was induced. In 27 (84.4%) of these latter, VF was the induced rhythm, and in 5 (15.6%) patients, it was VT. Inducible
subjects were more frequently men (84.4% versus 52.6%; \( P < 0.01 \)), presented more spontaneous type I pattern (50.0% versus 8.7%; \( P < 0.01 \)) and had a wider QRS (107.7±14.8 versus 93.8±19.4; \( P < 0.01 \)) when compared with noninducible subjects with EPS (n=289).

A total of 224 genetic tests (61.7%) were obtained and 49 of them (21.9%) resulted positive for mutation in the SCN5A gene.

**Time Evolution**

The clinical profile of the patients evolved over the time (Table 2). Patients before 2005 presented more frequently spontaneous type I pattern (16.4% versus 7.8%; \( P = 0.02 \)) and had a broader QRS (99.9±16.1 versus 82.4±24.1 ms; \( P < 0.01 \)). These BS patients were less frequently probands (14.4% versus 30.4%; \( P < 0.01 \)) and had more history of atrial fibrillation (13.0% versus 2.3%; \( P < 0.01 \)). Of note, inducibility rates dropped from 15.9% before 2005 to 5.8% from 2005 and the rate of ICD implantation was also lower after this year, although not statistically significant (23.3% and 12.2%; \( P = 0.16 \)).

**Management**

An ICD was implanted in 61 (16.8%) patients. Reasons for implantation were spontaneous Brugada type I ECG and sustained VAs induced during EP study in 11 patients (18.0%), spontaneous Brugada type I ECG and family history of SD in 7 patients (11.5%), and sustained VAs during ajmaline challenge in 5 patients (8.2%). The remaining patients received an ICD because of ajmaline-induced Brugada type I ECG with sustained VAs induced during EPS in 20 (32.8%) patients or family history of SD in 13 (21.3%) patients, 1 (1.6%) had a spontaneous nonsustained polymorphic VT registered, 1 (1.6%) had nocturnal palpitations, and 2 (3.3%) for personal preference. One patient (1.6%), initially asymptomatic, received an ICD after an aborted SCD.

**Follow-Up**

Among the entire population, a follow-up >6 months was available for 303 (83.5%) patients. Among these, during a mean follow-up of 73.2±58.9 months, 9 patients presented arrhythmic events. These consisted in 6 appropriate shocks delivered by the ICD, 2 SCD, and 1 aborted SCD. Table 3 summarizes clinical characteristics of patients with events.

Event rate was 0.5% per year. Kaplan–Meier event-free survival was 99.0% at 1 year, 96.2% at 5 years, and 95.4% at 10 and 15 years. Figure 1 shows cumulative event-free survival according to Kaplan–Meier method.

Arrhythmic event-free survival in patients in whom an ICD was implanted was 94.8% at 1 year, 89.5% at 5 years, and 86.7% at 10 and 15 years. Event-free survival in patients without an ICD was 100% at 1 year and 97.9% at 5 years and beyond. This difference was statistically significant (\( P < 0.01 \); Figure 2).

**ICD Patients Follow-Up**

Among 61 patients with ICD, after a mean follow-up of 96.8±72.3 months (no patient was lost), 6 appropriate therapies were documented. All of them were because of VF, with a cycle length lower than 300 ms. Sixteen (26.2%) were men with mean age at diagnosis of 45.8±15.9, and spontaneous type I was present in 21 (34.4%) patients. EPS was performed in 56 (91.8%) individuals, and inducible VAs during EPS were observed in 31 patients (50.8% of patients who underwent EPS).

Incidence of events in this group was 1.4% per year (SE, 0.6). Significantly higher to non-ICD patients, who presented 3 events (among 242 patients with a mean follow-up of 67.8±54.3 months). Incidence rate in this latter group was 0.22% per year (SE, 0.12; Cox regression: hazard ratio [HR], 7.7; 95% confidence interval [CI], 1.9–30.6; \( P < 0.01 \)). Five

### Table 1. Baseline Clinical Characteristics of Study Population

<table>
<thead>
<tr>
<th>Study Population, n=363</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (±SD, range)</td>
<td>40.9±17.2, 0.5–80.9</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>200 (55.1)</td>
</tr>
<tr>
<td>Spontaneous type I ECG, n (%)</td>
<td>41 (11.3)</td>
</tr>
<tr>
<td>Proband, n (%)</td>
<td>87 (24.0)</td>
</tr>
<tr>
<td>Family history of SCD, n (%)</td>
<td>182 (50.1)</td>
</tr>
<tr>
<td>Previous atrial fibrillation, n (%)</td>
<td>24 (6.6)</td>
</tr>
<tr>
<td>Previous SND, n (%)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>PR, ms (±SD)</td>
<td>167.5±32.3</td>
</tr>
<tr>
<td>QRS, ms (±SD)</td>
<td>95.3±20.0</td>
</tr>
<tr>
<td>HV, ms (±SD)</td>
<td>45.6±9.2</td>
</tr>
<tr>
<td>PES inducible, n (%)</td>
<td>32 (10.0)</td>
</tr>
<tr>
<td>SCN5A mutation, n (%)</td>
<td>49 (21.9)</td>
</tr>
<tr>
<td>ICD implantation, n (%)</td>
<td>61 (16.8)</td>
</tr>
</tbody>
</table>

*HV indicates HV interval; ICD, implantable cardioverter defibrillator; PES, programmed electric stimulation; PR, PR interval; SCD, sudden cardiac death; and SND, sinus node dysfunction.

*Percentages are calculated only among patients who underwent the test (321 patients underwent PES and 224 patients underwent genetic test).
(83.3%) patients with events were men, 4 (66.6%) presented spontaneous type I, and 5 (83.3%) patients presented inducible VAs during EPS.

Mean number of appropriate shocks delivered per patient was 3.8±5.5. Mean time until first shock was 15.7±28.3 months with a range from 0.1 to 48.2 months. A nonsustained VT was documented in 1 patient.

Nine patients (14.8%) had inappropriate shocks after a mean of 34.2±36.8 months. Mean number of inappropriate shocks delivered per patient was 2.0±1.4. Inappropriate shocks were because of sinus tachycardia in 1 patient, noise on the ventricular channel after lead fracture in 1 patient, T-wave oversensing in 1 patient, and atrial fibrillation with high ventricular rate in 6 patients.

During follow-up, 6 patients (9.8%) experienced device-related complications. Complications consisted in fracture of ventricular electrode and subsequent extraction and replacement in 5 patients and infection in 1 other.

### Mortality
Six patients (1.7%) died during follow-up. Causes of death were SCD in 2 patients, acute myocardial infarction with myocardial rupture and cardiogenic shock in 1, and noncardiac causes in the remaining 3 patients.

### Discussion
More than 20 years after the first description of the BS, management of asymptomatic patients remains challenging and controversial. When considering the whole spectrum of BS patients, several risk factors, such as spontaneous type I or presence of symptoms, have been consistently identified and therefore are universally accepted.10,11,14 As the risk of SCD in BS patients persists lifelong, long-term follow-up is of utmost importance.

Despite that asymptomatic status represents the biggest subgroup in patients with BS,15 a lack of robust evidence-based recommendations exists. The relatively low event rate in this group and the limited follow-up time of published studies might be responsible for this situation.11,16 Furthermore, heretofore no study has focused only in this subgroup of patients to address these questions.

We present the long-term follow-up of one of the biggest cohorts of asymptomatic patients with BS. To the best of our knowledge, the follow-up in our study is the longest reported up to date. Nine arrhythmic events occurred (2 SCD, 1 aborted SCD, and 6 ICD appropriate shocks), accounting for an annual incidence of 0.5%.

### Event Rate
When assessing the risk of SCD in patients with BS, special attention should be paid to the annual event rate. In our study, the annual incidence of arrhythmic events was 0.5%. This rate is lower than that initially reported by our group, but similar to more recent registries, such as the France, Italy,
Netherlands, Germany (FINGER) registry (0.5%).

This striking difference may be because of a selection bias, as initial reports included patients at higher risk. BS patients’ characteristics and risk profile have changed over the years. After 2005, fewer patients presented with spontaneous type 1 and inducibility rate has also dropped after 2005. Female sex has been related to better outcome.

One interesting finding of this study is that women constitute the 45% of the entire population. Male predominance has been universally reported in major BS studies: 80% in the Programmed Electrical Stimulation Predictive Value (PRELUDE) registry and 70% in the FINGER registry. The reason that may explain this finding could be the proactive search of BS and an exhaustive familial screening program established at our institution. The population characteristics of this study might fit better with the actual BS profile and it is similar to recent series.

An annual event rate of 0.5% in these asymptomatic BS patients might appear low. We must not forget that our population is formed by healthy individuals with a mean age of 40.9 years and therefore a long life expectancy. Although evolution of arrhythmic risk over years is uncertain, taking into consideration the previous facts, this figure becomes significant.

**Risk Factors**

With only 9 events in the entire population, the search of predictors of arrhythmic events is challenging (see Limitations section). Nevertheless, we identified inducible VAs during EPS strongly associated with events (HR, 9.1). Spontaneous type 1 ECG pattern and previous history of SND presented a univariate significant association (HR, 4.0 and 8.0, respectively), which was lost in the multivariate model. Male sex presented a borderline association (HR, 6.7; P=0.07).
The balance between benefits and complications after ICD implantation is particularly important when dealing with asymptomatic patients. Nine (14.8%) patients experienced inappropriate shocks and 6 (9.8%) had device-related complications. These figures might seem high but we have to consider that 3 of the arrhythmic events were SCD and 2 of these patients actually died. Taking into account these considerations, the benefit outweighs the risks.

**Limitations**

The fact of being a single-center experience spanning for a 20-year period makes the population to present heterogeneous clinical characteristics. However, period of diagnosis did not behave as a confounding factor. Despite it is one of the studies in asymptomatic BS with a longer follow-up, patients with BS present a lifelong risk of arrhythmias, therefore, a mean follow-up of 6 years might be considered short. Screening of structural heart disease is in line with other major BS registries, involving echocardiography in all patients and other advanced imaging techniques in selected patients at the discretion of the responsible clinician. The main limitation is

---

**Table 4. Univariable Analysis and Multivariable Model**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS inducibility</td>
<td>11.4</td>
<td>2.7–41.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Spontaneous type I</td>
<td>4.0</td>
<td>1.1–14.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Previous SND</td>
<td>8.0</td>
<td>1.0–63.9</td>
<td>0.049</td>
</tr>
<tr>
<td>Male sex</td>
<td>6.7</td>
<td>0.8–53.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.0</td>
<td>0.9–1.1</td>
<td>0.21</td>
</tr>
<tr>
<td>Previous AF</td>
<td>1.1</td>
<td>0.1–9.0</td>
<td>0.91</td>
</tr>
<tr>
<td>Proband status</td>
<td>2.5</td>
<td>0.6–10.1</td>
<td>0.20</td>
</tr>
<tr>
<td>SCD family history</td>
<td>1.1</td>
<td>0.3–4.3</td>
<td>0.84</td>
</tr>
<tr>
<td>Diagnosis before 2005</td>
<td>0.9</td>
<td>0.2–4.0</td>
<td>0.93</td>
</tr>
</tbody>
</table>

**Multivariable model**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS inducibility</td>
<td>9.1</td>
<td>1.8–46.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Spontaneous type I</td>
<td>1.3</td>
<td>0.2–7.1</td>
<td>0.75</td>
</tr>
<tr>
<td>Previous SND</td>
<td>5.1</td>
<td>0.5–48.6</td>
<td>0.16</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CI, confidence interval; EPS, electrophysiological study; HR, hazard ratio; ICD, implantable cardioverter defibrillator; SND, sinus node dysfunction; and SCD, sudden cardiac death.

No study, focused only in asymptomatic patients, with enough power is found in the literature. The FINGER registry performs an analysis in the asymptomatic subgroup. This group consisted of 654 individuals who presented 10 events over a mean follow-up of 31.9 months. Our present study doubles this follow-up. They report a univariate statistical significant association between inducible VAs during EPS and events with a HR of 5.2. No other variables were associated with the outcomes. These investigators constructed a multivariate predictive model introducing age, sex, spontaneous type I, and inducibility, where this latter lost the statistical signification. Considering the number of events, such analysis might be underpowered and extracting conclusions of it should be done with caution.

The PRELUDE registry offers valuable and unique information about the role of EPS in BS patients without prior SCD. Of note, this registry includes patients with prior syncope, and no analysis is performed in the asymptomatic subgroup patients. Syncope, spontaneous type I ECG, ventricular refractory period <200 ms, and fragmented QRS showed a statistical association with arrhythmic events during follow-up. Inducibility was not associated with a higher risk of SCD. A lower event rate and inducibility are found in our study (0.5% and 10%, respectively) when compared with the PRELUDE registry (1.5% and 40%, respectively). This point might be of importance. Our stimulation protocol involves only 1 site (right ventricular [RV] apex), whereas the PRELUDE registry uses a 2-site protocol (RV apex and RV outflow tract). If the PRELUDE protocol stimulation was only performed at the RV apex, the inducibility rate would be significantly reduced (55% of VAs induced were achieved at the RV apex). Summarizing, the population characteristics and protocol of PRELUDE and our study differ significantly and therefore are not completely comparable.

The relation between SND and arrhythmic events is of special interest and has never been described before. Although when introduced in the adjusted model, SND loses its significance, the limited number of patients exhibiting SND might be responsible, making the model underpowered to demonstrate this relation. Conduction disturbances in BS have been associated with a worst outcome, and relation between SND, sodium channelopathies, and BS is well known. The mechanism responsible for this is not clear; a more expressive form of the disease might be involved. Specific studies with biggest population and follow-up should be performed to clarify this issue.

It is universally accepted that cardiogenic syncope in patients with BS confers a highest risk of events because it is attributed to VAs. In this scenario, SND may lead to a misdiagnosis of the subjacent mechanism, attributing the event to a VA when bradycardia is the real cause. Interestingly, if SND confers a worst prognosis, syncope due to this cause should be managed more aggressively.

We think that EPS in patients with BS has a high performance. It might identify subjects at higher risk, confirm the presence of SND, clarify the cause of syncope, or treat supraventricular arrhythmias that eventually might lead to inappropriate ICD therapies.

**ICD Population**

ICD asymptomatic BS patients constitute a subgroup of special interest as they are considered at special high risk of SCD. Among 61 patients with ICD, 6 appropriate therapies were documented. Annual event rate in this subgroup is 1.4%. This incidence is significantly higher than the non-ICD patients. Sacher et al report a slightly lower event rate (12% at 10 years) in asymptomatic patients with an ICD. In our study, all of them but one were men, 66.6% had spontaneous type I and 66.6% presented inducible VAs during EPS. Few information has been published about this specific subgroup. Sacher et al report that among the 12 asymptomatic patients, who received a shock, all had spontaneous type I ECG and all but one were inducible. Similar findings were reported by our group.

The PRELUDE registry offers valuable and unique information about the role of EPS in BS patients without prior SCD. Of note, this registry includes patients with prior syncope, and no analysis is performed in the asymptomatic subgroup patients. Syncope, spontaneous type I ECG, ventricular refractory period <200 ms, and fragmented QRS showed a statistical association with arrhythmic events during follow-up. Inducibility was not associated with a higher risk of SCD. A lower event rate and inducibility are found in our study (0.5% and 10%, respectively) when compared with the PRELUDE registry (1.5% and 40%, respectively). This point might be of importance. Our stimulation protocol involves only 1 site (right ventricular [RV] apex), whereas the PRELUDE registry uses a 2-site protocol (RV apex and RV outflow tract). If the PRELUDE protocol stimulation was only performed at the RV apex, the inducibility rate would be significantly reduced (55% of VAs induced were achieved at the RV apex). Summarizing, the population characteristics and protocol of PRELUDE and our study differ significantly and therefore are not completely comparable.

The relation between SND and arrhythmic events is of special interest and has never been described before. Although when introduced in the adjusted model, SND loses its significance, the limited number of patients exhibiting SND might be responsible, making the model underpowered to demonstrate this relation. Conduction disturbances in BS have been associated with a worst outcome, and relation between SND, sodium channelopathies, and BS is well known. The mechanism responsible for this is not clear; a more expressive form of the disease might be involved. Specific studies with biggest population and follow-up should be performed to clarify this issue.

It is universally accepted that cardiogenic syncope in patients with BS confers a highest risk of events because it is attributed to VAs. In this scenario, SND may lead to a misdiagnosis of the subjacent mechanism, attributing the event to a VA when bradycardia is the real cause. Interestingly, if SND confers a worst prognosis, syncope due to this cause should be managed more aggressively.

We think that EPS in patients with BS has a high performance. It might identify subjects at higher risk, confirm the presence of SND, clarify the cause of syncope, or treat supraventricular arrhythmias that eventually might lead to inappropriate ICD therapies.

**ICD Population**

ICD asymptomatic BS patients constitute a subgroup of special interest as they are considered at special high risk of SCD. Among 61 patients with ICD, 6 appropriate therapies were documented. Annual event rate in this subgroup is 1.4%. This incidence is significantly higher than the non-ICD patients. Sacher et al report a slightly lower event rate (12% at 10 years) in asymptomatic patients with an ICD. In our study, all of them but one were men, 66.6% had spontaneous type I and 66.6% presented inducible VAs during EPS. Few information has been published about this specific subgroup. Sacher et al report that among the 12 asymptomatic patients, who received a shock, all had spontaneous type I ECG and all but one were inducible. Similar findings were reported by our group.

The balance between benefits and complications after ICD implantation is particularly important when dealing with asymptomatic patients. Nine (14.8%) patients experienced inappropriate shocks and 6 (9.8%) had device-related complications. These figures might seem high but we have to consider that 3 of the arrhythmic events were SCD and 2 of these patients actually died. Taking into account these considerations, the benefit outweighs the risks.

**Limitations**

The fact of being a single-center experience spanning for a 20-year period makes the population to present heterogeneous clinical characteristics. However, period of diagnosis did not behave as a confounding factor. Despite it is one of the studies in asymptomatic BS with a longer follow-up, patients with BS present a lifelong risk of arrhythmias, therefore, a mean follow-up of 6 years might be considered short. Screening of structural heart disease is in line with other major BS registries, involving echocardiography in all patients and other advanced imaging techniques in selected patients at the discretion of the responsible clinician. The main limitation is
clearly the low event rate which limits the power for searching variables associated with the outcomes. Furthermore, the lack of association of some characteristics might be because of this fact. It is important to consider that, secondary to this, all tests are performed at a nominal level of 0.05, without consideration for type I error inflation, and consequently false relationships could have been included. The multivariate analysis should be taken with precaution as its power is limited.

Conclusions

Arrhythmic events in asymptomatic BS patients are not negligible, with an annual incidence rate of 0.5%. Risk stratification is specially challenging in this specific group. VA inducibility at EPS, spontaneous type I ECG, and presence of SND might be considered as risk factors and used to drive long-term management.

Disclosures

None.

References

Asymptomatic Brugada Syndrome: Clinical Characterization and Long-Term Prognosis
Juan Sieira, Giuseppe Ciccone, Giulio Conte, Gian-Battista Chierchia, Carlo de Asmundis, Giannis Baltogiannis, Giacomo Di Giovanni, Yukio Saitoh, Ghazala Irfan, Rubén Casado-Arroyo, Justo Julià, Mark La Meir, Francis Wellens, Kristel Wauters, Gudrun Pappaert and Pedro Brugada

Circ Arrhythm Electrophysiol. 2015;8:1144-1150; originally published online July 27, 2015; doi: 10.1161/CIRCEP.114.003044

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/8/5/1144