Brugada syndrome (BS) is an inheritable syndrome characterized by coved-type ST-segment–elevation in the right precordial leads (V1 through V3) and increased risk of sudden death (SD) in the absence of structural heart disease.1 Editorial see p 757

For most investigators, the placement of an implantable cardioverter defibrillator (ICD) remains the only therapy with proven efficacy to prevent SD in patients with BS.2 Therefore, identifying patients at higher risk of ventricular arrhythmias (VA) is of utmost importance. Symptoms or spontaneous type I pattern have been consistently identified as high-risk categories by different investigators.3,4 Nevertheless, arrhythmic events in patients not included in these groups are not insignificant.

The value of the inducibility of VA by programmed electric stimulation (PES) remains controversial. Our group was the first to suggest its prognostic significance and it was reaffirmed by our subsequent data.5,6 Nevertheless, other groups failed to confirm its utility. Several consensus documents have addressed this issue and the recommendation of PES for risk stratification has dropped from a IIa indication in the Second Brugada Syndrome Consensus Conference4 to a IIb in the 2013 Expert Consensus Statement.7

The purpose of this study was to analyze our single-center experience of PES VA inducibility in patients with BS gathered in the last 20 years, since the first description of the syndrome.

Methods

Study Population

Since 1992 all consecutive patients diagnosed with BS have been included in a registry and followed in a prospective fashion, this
WHAT IS KNOWN

- Risk stratification in Brugada syndrome is important to guide implantable cardioverter defibrillator implantation and prevent sudden cardiac deaths.
- Recognized risk factors include symptoms, male sex, and spontaneous type I ECG pattern, but the role of programmed electric stimulation remains controversial.

WHAT THE STUDY ADDS

- In this relatively large patient cohort induced ventricular arrhythmias were associated with increased risk of arrhythmic events during long-term follow-up.
- The findings support the use of programmed ventricular stimulation to help risk stratify patients with a type I Brugada ECG that is present spontaneously or after pharmacological challenge.

registry was initiated at OLV Ziekenhuis (Aalst, Belgium) and continued at Universiteit Ziekenhuis Brussel-Vrije Universiteit Brussel has approved the study protocol. A total of 524 patients with BS have been included in the registry from 1992 to 2012. Among them, 459 patients (87.6%) underwent PES. Some 137 have already been included in previous registries. Study inclusion criteria consisted of (1) spontaneous or drug-induced Brugada type I ECG, (2) PES ventricular tachycardia (VT) induction protocol performed, and (3) follow-up longer than 1 year achieved. A total of 404 patients fulfilled all of them. Medical history, physical examination, and baseline ECGs were obtained. Underlying structural cardiac abnormalities were excluded in all patients with noninvasive methods (echocardiogram, stress test, and nuclear magnetic resonance) or invasive methods (coronary angiography, left and right ventriculography, and myocardial biopsies) used at the discretion of the treating physician. ECGs were classified as Brugada coved-type (type I) or 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 standard location and 1 intercostal space higher, 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 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. Patients were considered as asymptomatic if they had presented with syncope (excluding vasovagal or because of a nonarrhythmic cause) or aborted SD. Patients not fulfilling this definition were considered symptomatic.

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. The stimulation current was 4 mA and 2.0 ms width, and no repetition of extrastimulation was performed. This protocol differs from the ones used in other BS registries. A patient was considered inducible if a sustained ventricular arrhythmia (ventricular fibrillation [VF], polymorphic VT, or monomorphic VT lasting >30 seconds or requiring emergency intervention) was induced. 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 through 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 VF or sustained VT.

ICD Implantation

Beginning from 2005, the indication to ICD therapy was determined using the recommendations of the Second Brugada Consensus Conference. 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. ICD programming at the time of implantation changed over the time. VF detection rate was increased from 180 to >200 beats per minute, and a monitor zone was added. Moreover, long-detection intervals (30 of 40 intervals) were adopted. 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 symptomatic and device therapy patients and every 2 years elsewise. 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 VA. Electrical storm was defined by ≥3 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. 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. 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 404 consecutive BS patients (235 men, 58.2%; mean age, 43.2±16.2; ranging from 4.0 to 80.9 years) underwent a PES from 1992 to 2012 and had a follow-up longer than 1 year. Seventeen patients (4.2%) presented with aborted SD, 114 (28.6%) had at least 1 episode of syncope, and 273 (67.6%) were asymptomatic. Seventeen of this latter presented a previous typical vasovagal syncope. Baseline clinical characteristics of study population are shown in Table 1. At the time of diagnosis, 37 patients (9.2%) were younger than 18 years and 32 (7.9%) older than 65. Seventy-five patients (18.6%) had a spontaneous type I ECG pattern. Among nonsymptomatic type I pattern, ajmaline challenge
was used in 367 (90.8%), procainamide in 11 (2.7%), and flecainide in 26 (6.4%). During ajmaline challenge, 2 patients presented a VA, no high degree atrioventricular block was induced and >30% QRS prolongation was observed in 52.8% of patients (mean prolongation 34.9%). Patients belonged to 200 different families. A total of 242 genetic tests (59.9%) were obtained and 53 of them (21.9%) resulted positive for the \( \text{SCN5A} \) gene.

The clinical profile of the patients changed over the time (Table 2). Of note, inducibility rates dropped from 28.6% before 2005 to 9.5% from 2005. Clinical presentation of patients undergoing PES was similar in both groups. Nevertheless, more patients presented with syncope since 2005 (mean proportion 34.9%). Patients belonged to 200 different families. A total of 242 genetic tests (59.9%) were obtained and 53 of them (21.9%) resulted positive for mutation in the \( \text{SCN5A} \) gene.

Table 1. Baseline Clinical Characteristics of Study Population According to VA Inducibility

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=404)</th>
<th>PES Noninducible (n=331)</th>
<th>PES Inducible (n=73)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43.2±16.2</td>
<td>43.0±16.9</td>
<td>44.3±13.5</td>
<td>0.48</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>235 (58.2)</td>
<td>173 (52.3)</td>
<td>62 (84.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Spontaneous type I ECG, n (%)</td>
<td>75 (18.6)</td>
<td>44 (13.3)</td>
<td>31 (42.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Proband, n (%)</td>
<td>129 (31.9)</td>
<td>111 (33.5)</td>
<td>18 (24.7)</td>
<td>0.14</td>
</tr>
<tr>
<td>Aborted SD, n (%)</td>
<td>17 (4.2)</td>
<td>13 (3.9)</td>
<td>4 (5.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>Syncope, n (%)</td>
<td>114 (28.6)</td>
<td>77 (23.3)</td>
<td>37 (50.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Asymptomatic, n (%)</td>
<td>273 (67.6)</td>
<td>241 (72.8)</td>
<td>32 (43.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Family history of SD, n (%)</td>
<td>187 (46.3)</td>
<td>150 (45.3)</td>
<td>37 (50.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>Previous atrial fibrillation, n (%)</td>
<td>36 (8.9)</td>
<td>28 (8.5)</td>
<td>8 (11.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Previous SNO, n (%)</td>
<td>6 (1.5)</td>
<td>4 (1.2)</td>
<td>2 (2.7)</td>
<td>0.33</td>
</tr>
<tr>
<td>PR, ms</td>
<td>173.4±31.0</td>
<td>171.7±33.0</td>
<td>177.9±24.8</td>
<td>0.18</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>98.9±17.9</td>
<td>96.0±18.0</td>
<td>106.8±15.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HV, ms</td>
<td>46.1±10.0</td>
<td>45.7±9.7</td>
<td>47.4±10.9</td>
<td>0.31</td>
</tr>
<tr>
<td>( \text{SCN5A} ) mutation, n (%)*</td>
<td>53 (21.9)</td>
<td>43 (21.3)</td>
<td>10 (22.2)</td>
<td>0.84</td>
</tr>
<tr>
<td>ICD implantation, n (%)</td>
<td>168 (41.6)</td>
<td>96 (29.0)</td>
<td>72 (98.6)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Percentages are calculated only among patients with genetic test.

ICD indicates implantable cardioverter defibrillator; PES, programmed electric stimulation; SD, sudden death; SNO sinus node dysfunction; and VA, ventricular arrhythmias.

Symptomatic patients had a higher rate of inducibility (56.2% versus 27.2%; \( P<0.01 \)). No difference in inducibility rate was found between patients with vasovagal syncope and nonvasovagal syncope (\( P=0.20 \)).

**ICD Implantation**

One hundred sixty-eight patients (41.6%) received an ICD. Ninety-six (29.0%) patients belonged to the noninducible group and 72 (98.6%) of the inducible group. Among noninducible patients, reasons for ICD implantation were presentation as SD in 13 (13.5%) patients, as syncope in 77 (80.2%), spontaneous type I or family history of SD in 5 (5.2%) patients, and sustained VA during ajmaline challenge in 1 (1.1%). Interestingly, 4 asymptomatic patients with no VA inducibility presented syncope during follow-up and an ICD was implanted. In the PES inducible group, 4 (5.5%) patients had a SD and 37 (50.7%) syncope. The remaining 32 (43.8%) patients in this group received an ICD for induced VA during PES. Among these latter, 15 (46.9%) had a spontaneous type I ECG, 29 (90.6%) were males, and 15 (46.9%) had a family history of SD.

**Follow-Up**

During a mean follow-up of 74.3±57.3, median 57.3 months (25% percentile: 25.9 months and 75% percentile: 57.3 months), 25 arrhythmic events were reported in the entire population. These consisted in 24 appropriate shocks delivered by ICD and 1 aborted SD that was resuscitated. Sixteen (64.0%) were in the inducible group and 9 (36%) in the noninducible patients. All inducible group events consisted of appropriate ICD shocks, whereas in the noninducible group there were 8 appropriate ICD shocks and 1 resuscitated SD (in a patient without ICD). Table 3 summarizes clinical characteristics of noninducible patients with events.

**PES Inducibility**

Among the 404 patients that constituted the entire study population, 73 (18.1%) had a sustained VA induced by PES. In 60 (81.2%) of them, VF was the induced rhythm and in 13 (17.8%) it was VT (polymorphic in 11 patients and monomorphic in 2, with a cycle length of 375 and 355 ms).

Clinical characteristics of patients according to inducibility are reported in Table 1. Inducible subjects were more frequently males (84.9% versus 52.3%; \( P<0.01 \)), presented more spontaneous type I pattern (42.5% versus 13.3%; \( P<0.01 \)) and had a wider QRS (106.8±15.0 versus 96.0±18.0; \( P<0.01 \)).
Figure 1 shows cumulative event-free survival according to Kaplan–Meier method in the overall population. Event-free survival for the noninducible group was 99.0% at 1 year and 96.8% at 5, 10, and 15 years. Among the inducible patients, it was 89.0% at 1 year, 78.4% at 5 years, and 75.0% at 10 and 15 years. This difference was statistically significant (P < 0.01).

Among asymptomatic patients, those without PES inducibility had an event-free survival of 100.0% at 1 year and 99.2% at 5, 10 and 15 years. Inducible subjects event-free survival was 90.6% at 1 year and 79.5% at 5, 10, and 15 years. PES inducibility remained significative (P < 0.01; Figure 2).

Sensitivity of PES for predicting arrhythmic events was 64.0% and specificity was 86.6%. Positive predictive value was 21.6% and negative predictive value 97.7%. If restricted to asymptomatic patients, these values increased to a sensitivity

### Table 2. Baseline Clinical Characteristics of Study Population According to Diagnosis Year

<table>
<thead>
<tr>
<th></th>
<th>Group I &lt;2005</th>
<th>Group II ≥2005</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>428±15.5</td>
<td>43.5±16.9</td>
<td>0.66</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>113 (62.1)</td>
<td>122 (55.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Spontaneous type I ECG, n (%)</td>
<td>55 (30.2)</td>
<td>20 (8.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Proband, n (%)</td>
<td>31 (17.0)</td>
<td>98 (44.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aborted SD, n (%)</td>
<td>10 (5.5)</td>
<td>7 (3.2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Syncope, n (%)</td>
<td>43 (23.6)</td>
<td>71 (32.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Asymptomatic, n (%)</td>
<td>129 (70.9)</td>
<td>144 (64.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Family history of SD, n (%)</td>
<td>93 (51.1)</td>
<td>94 (42.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous atrial fibrillation, n (%)</td>
<td>24 (13.2)</td>
<td>12 (5.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Previous SND, n (%)</td>
<td>6 (3.3)</td>
<td>0 (0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PR, ms</td>
<td>173.0±30.7</td>
<td>174.8±32.2</td>
<td>0.71</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>101.3±15.9</td>
<td>91.0±21.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HV, ms</td>
<td>46.5±10.0</td>
<td>44.7±10.1</td>
<td>0.32</td>
</tr>
<tr>
<td>Inducibility, n (%)</td>
<td>52 (28.6)</td>
<td>21 (9.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SCN5A mutation, n (%)*</td>
<td>16 (21.9)</td>
<td>37 (22.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>ICD implantation, n (%)</td>
<td>76 (41.8)</td>
<td>92 (41.4)</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmic event, n (%)</td>
<td>16 (8.8)</td>
<td>9 (4.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>Median time to arrhythmic event (percentile 25% and 75%)</td>
<td>72.2 (13.3, 89.2)</td>
<td>13.7 (8.4, 32.8)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Group I refers to patients with diagnosis made before 2005 and Group II refers to patients with a diagnosis during or after 2005. P value of arrhythmic event is calculated by means of Cox regression method. ICD indicates implantable cardioverter defibrillator; SD, sudden death; and SND, sinus node dysfunction.

*Percentages are calculated only among patients with genetic test.

### Table 3. Clinical Characteristics of Noninducible Patients Presenting Arrhythmic Events During the Follow-Up

<table>
<thead>
<tr>
<th>Patient</th>
<th>Event</th>
<th>Sex</th>
<th>Age, y*</th>
<th>Proband</th>
<th>Family History of SD</th>
<th>Spontaneous Type I</th>
<th>Symptoms at Presentation</th>
<th>f-QRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ICD shock</td>
<td>Male</td>
<td>52.8</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>SD</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Aborted SD</td>
<td>Male</td>
<td>53.8</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Asymptomatic</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>ICD shock</td>
<td>Male</td>
<td>8.3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Syncope</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>ICD shock</td>
<td>Male</td>
<td>15.1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>SD</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>ICD shock</td>
<td>Male</td>
<td>36.7</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Syncope</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>ICD shock</td>
<td>Female</td>
<td>43.0</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Syncope</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>ICD shock</td>
<td>Male</td>
<td>59.8</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Syncope</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>ICD shock</td>
<td>Female</td>
<td>60.3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>SD</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>ICD shock</td>
<td>Male</td>
<td>69.8</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Asymptomatic</td>
<td>No</td>
</tr>
</tbody>
</table>

f-QRS indicates fragmentation of QRS complex; ICD, implantable cardioverter defibrillator; and SD, sudden death.

*Age indicates age at arrhythmic event.
of 75.0% and a specificity of 91.3% and predictive values to 18.2% and 98.3%, respectively.

Two patients (0.5%) presented an electrical storm during the follow-up. One man and 1 woman with age at the time of electrical storm of 53.8 and 44.3 years, respectively. Both had a SD as initial presentation and did not showed spontaneous type I ECG pattern. Inducible VA was present in only 1 of the patients. They did not receive a previous appropriate shock. Both were treated with quinidine with no further arrhythmic recurrences.

![Figure 1. Event-free survival according to Kaplan–Meier method.](image1)

![Figure 2. Event-free survival in asymptomatic patients according to Kaplan–Meier method.](image2)
Among patients with syncope, 14 (12.3%) experienced a recurrent syncope during follow-up: 9 (11.7%) in the noninducible group and 5 (13.3%) in the inducible group \(P=0.74\). No VA was responsible of this event (no VA was recorded by the ICD). No patient with previous vasovagal syncope presented an arrhythmic event.

**ICD Complications**

Among the 168 patients that received an ICD, 30 patients (17.9%) had inappropriate shocks after a median of 32.8 months (interquartile range, 9.1–76.6 months from ICD implantaion). Median number of inappropriate shocks delivered per patient was 1.0 (25% percentile: 1.0 and 75% percentile: 3.0). Inappropriate shocks were because of sinus tachycardia in 5 patients, noise on the ventricular channel after lead fracture in 7 patients, and T-wave oversensing in 4 patients. The remaining 14 subjects experienced inappropriate shocks because of atrial fibrillation episodes with fast ventricular rate.

During follow-up, 28 patients (16.7%) experienced device-related complications. Complications were: fracture of ventricular electrode and subsequent extraction and replacement in 14 patients, lead dislocation in 7 patients, and pulse generator migration in 2 individuals leading to revision of the device in all of them. The other 5 patients had a device infection, which led to replacement of the device.

**Mortality**

Twelve patients (3.0%) died during the follow-up (mean age, 62.1±15.2; 11 [91.7%] men). Causes of death were urinary septic shock after a device revision in 1 patient, 1 cardiogenic shock after an acute myocardial infarction with myocardial rupture in 1 patient, and the remaining 10 died from noncardiac causes.

**Univariate Analysis**

Univariate Cox regression model demonstrated that inducible PES patients presented a hazard ratio (HR) for arrhythmic events during follow-up of 8.3 (95% confidence interval [CI], 3.6–19.4; \(P<0.01\)). Other variables showed relationship with occurrence of arrhythmic events. Male sex had a HR of 5.05 (95% CI, 1.51–16.92; \(P=0.01\)), clinical presentation as syncope of 3.60 (95% CI, 1.40–9.30; \(P=0.01\)), as SD of 15.45 (95% CI, 5.20–45.98; \(P<0.01\)), and spontaneous type I of 2.66 (95% CI, 1.15–5.79; \(P=0.02\))

Variables that did not show statistical relationship with VA occurrence were age at diagnosis (HR, 1.00; 95% CI, 0.97–1.02; \(P=0.78\)), proband status (HR, 1.22; 95% CI, 0.52–2.87; \(P=0.64\)), previous atrial fibrillation (HR, 0.84; 95% CI, 0.920–3.56; \(P=0.81\)), previous sinus node dysfunction (HR, 2.50; 95% CI, 0.24–18.55; \(P=0.37\)), PR duration (HR, 1.00; 95% CI, 0.99–1.01; \(P=0.91\)), QRS duration (HR, 1.01; 95% CI, 0.99–1.04; \(P=0.37\)), measured HV (HR, 1.01; 95% CI, 0.96–1.06; \(P=0.71\)), and diagnosis before 2005 (HR, 0.59; 95% CI, 0.25–1.39; \(P=0.23\)).

**Discussion**

One of the most challenging aspects in the management of BS patients is SD risk stratification. Several risk factors, such as spontaneous type 1 ECG pattern and previous symptoms, have been consistently identified by different groups and therefore are universally accepted.\(^{6,11}\) This is not the case of induced VA by PES. Our group proposed almost 15 years ago its value in predicting arrhythmic events.\(^{13}\) Therefore, other groups failed to find this association. A recent meta-analysis found a relation with events in asymptomatic and patients presenting with syncope but great controversy still exists around this topic.\(^{8,14,15}\) Furthermore, as the risk of SD in BS patients persists lifelong, extended long-term follow-up is of great importance.

In this study, we examined the value of PES as predictor of SD in 1 of the biggest BS cohort and with the longest follow-up published up to date. PES inducibility is strongly related to arrhythmic events with a HR of 8.3.

When assessing the risk of SD in BS patients, special attention should be paid to 2 specific elements: the annual event rate and inducibility rate. In our present study, the event rate is 0.9% every year. This rate is lower than the initially reported by our group (4.5%) and similar to more recent reports (1.5% in the Programmed Electrical Stimulation Predictive Value [PRELUDE]\(^{6}\) and 1.6% in the France, Italy, Netherlands, Germany Brugada syndrome [FINGER] registry). The inducibility rate has also followed a similar course. The initial 40% inducibility rate reported has been reduced to 16%. This striking difference may be because of a selection bias, as initial reports included patients at higher risk. BS patient characteristics and risk profile have changed along the years. After 2005, fewer patients presented with SD and spontaneous type 1 and inducibility rate has also dropped after 2005. Summarizing, the population characteristics of this study might fit better with the actual BS profile and it is similar to recent series.

**Value of PES**

Studies addressing the value of PES in predicting arrhythmic events in BS are sparse and usually underpowered in the literature.\(^{14,16}\) Studies with sufficient number of patients and long follow-up usually focus in searching predictors and not specifically in PES value. Reports coming from our group, even when not designed to evaluate the role of PES, have consistently found inducibility as a predictor of SD \(^{6,11}\) but these findings confront with the ones published by other groups. The PRELUDE registry is the only study with enough power and follow-up that could shed light on this matter. Our present study doubles the follow-up time of the PRELUDE registry and involves ≈30% more patients.

In the PRELUDE registry, VA inducibility was not associated with a higher risk of presenting SD. This study enrolled 308 with a mean follow-up of 34 months. Survival curves of inducible and noninducible patients were almost identical. Compared with our study, event rate is similar (0.9% versus 1.5%) but inducibility is higher (16% versus 40%). 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 only performed at the RV apex, PRELUDE investigators report that the inducibility...
rate would be significantly reduced because 55% of VA induced were achieved at the RV apex, a figure similar to our study. As a consequence, we could hypothesize that a less aggressive stimulation protocol that interestingly avoids the RV outflow tract stimulation, where spontaneous VA arrhythmias originate, might increase the specificity of the test.

The FINGER study pooled the data from 11 European centers, involving 1029 BS patients. Events rate in this study was similar to ours (1.6%) but inducibility was again achieved in 40% of patients (EPS protocol included 2-site stimulation). PES inducibility was a significant nonadjusted predictor of events in the whole cohort and also when restricted to asymptomatic patients. It lost significance when introduced in the predictive model. We must consider that this study was not designed to specifically study the value of EPS inducibility, and statistic adjustment was performed not to adjust confusion but to create a predictive model.

Test Performance
The overall accuracy of the test makes it suitable to be used as a screening tool. Special attention should be paid to the fact that, if no arrhythmias are induced, the patient remains in low-risk category. Negative predictive values are 97.7% in the entire population and 98.3% in the asymptomatic group. Nevertheless, noninducible patients are not risk-free patients. Among this specific group, other risk factors should be assessed. The inability of induce a VA during PES is a marker of good prognosis, especially in asymptomatic patients and becomes a reassuring condition for a watchful follow-up.

Selection of stimulation protocol might be important. Although there is no ideal protocol, a more aggressive stimulation might lead to an increase in sensitivity but a decrease in specificity therefore making the test useless. An adequate balance between them should be achieved. Our protocol is one of the less aggressive in literature; maybe this can explain the divergent results between our study and other major registries.

It is also important to highlight that PES in BS patients is not confined solely to VA inducibility. It might be valuable in the evaluation of patients with syncope to rule out the presence of sinus node dysfunction or supraventricular arrhythmias as potential cause of the event.17,18 Currently, ICD therapy is considered to prevent SD in patients presenting with a syncopal episode, if no cause is found. The decision to perform an ICD implantation in this setting has to be taken after a careful evaluation of the episode because in this category of patients it is not always easy to differentiate its origin. In our study, 12% of patients with syncope experienced further episodes during the follow-up, but no VA was detected. Approximately 20% of BS patients can develop supraventricular arrhythmias that can be a potential cause of the syncopal episodes or inappropriate shocks.16 Similarly, prolonged sinus node recovery time and sinoatrial conduction time, as well as slowed atrial conduction, have been reported in association with the syndrome and can lead to syncope.20

We think that EPS in BS patients has a high performance. It might identify subjects at higher risk, confirm the presence of sinus node dysfunction, clarify the cause of syncope, or treat supraventricular arrhythmias that can mislead the diagnosis or eventually lead to inappropriate ICD therapies. Some groups have even showed the value of EPS to evaluate the response to antiarrhythmic drugs.21 Therefore, EPS in BS patients is of use in different fields: prognostic, diagnostic, and even therapeutic.

Limitations
Some limitations can be found in our study. The fact of being a single-center experience spanning for a 20-year period, causes the population to present heterogeneous clinical characteristics. Despite being 1 of the studies in BS with longest follow-up, patients with BS present a lifelong risk of arrhythmias, therefore, a mean follow-up of 7 years might be considered short. Initial shorter detection intervals might have led to deliver shocks in self-terminating episodes. Therefore, patients with ICD could seem as more likely to present events during follow-up. Although ICD shocks do not entirely correspond to VA that lead to SD, they have been also considered as events in other major BS registries.

Conclusions
Programmed ventricular stimulation of the heart is a good predictor of outcome in individuals with BS. It might be of special value to guide further management when performed in asymptomatic individuals. The overall accuracy of the test makes it a suitable screening tool to reassure noninducible asymptomatic individuals.

Disclosures
None.

References


Prognostic Value of Programmed Electrical Stimulation in Brugada Syndrome: 20 Years Experience

Juan Sieira, Giulio Conte, Giuseppe Ciconte, Carlo de Asmundis, Gian-Battista Chierchia, Giannis Baltogiannis, Giacomo Di Giovanni, Yukio Saitoh, Ghazala Irfan, Ruben Casado-Arroyo, Justo Juliá, Mark La Meir, Francis Wellens, Kristel Wauters, Sophie Van Malderen, Gudrun Pappaert and Pedro Brugada

_Circ Arrhythm Electrophysiol._ 2015;8:777-784; originally published online April 22, 2015; doi: 10.1161/CIRCEP.114.002647

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2015 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-3149. Online ISSN: 1941-3084

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/8/4/777

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Arrhythmia and Electrophysiology_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Arrhythmia and Electrophysiology_ is online at:
http://circep.ahajournals.org/subscriptions/