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

Running title: Sieira et al.; Programmed electrical stimulation in Brugada

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Abstract

**Background** - The prognostic value of electrophysiological investigations in individuals with Brugada syndrome remains controversial. Different groups have published contradictory data. Long-term follow up is needed to clarify this issue.

**Methods and Results** - Patients presenting with spontaneous or drug-induced Brugada type I electrocardiogram (ECG) and in whom PES was performed at our institution were considered eligible for this study. A total of 403 consecutive patients (235 males, 58.2%; mean age: 43.2±16.2 years) were included. VA during PES were induced in 73 (18.1%) patients. After a mean follow-up time of 74.3±57.3 months, (median 57.3), 25 arrhythmic events occurred (16 in the inducible group and 9 in the non inducible). VA inducibility presented a hazard ratio for events of 8.3 (95% CI 3.6 – 19.4), p<0.01.

**Conclusions** - Programmed ventricular stimulation of the heart is a good predictor of outcome in individuals with Brugada syndrome. 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 non inducible asymptomatic individuals.

**Key words**: Brugada syndrome, prognosis, arrhythmia
Introduction

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

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. Therefore, identifying patients at higher risk for ventricular arrhythmias (VA) is of utmost importance. Symptoms or spontaneous type I pattern have been consistently identified as high-risk categories by different investigators. Nevertheless arrhythmic events in patients not included in these groups are not insignificant.

The value of the inducibility of ventricular arrhythmias (VA) by programmed electrical stimulation (PES) remains controversial. Our group was the first to suggest its prognostic significance and it was reaffirmed by our subsequent data. 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 Conference to a IIb in the 2013 Expert Consensus Statement:

Data on long-term follow-up (longer than 5 years) of BS patients are sparse, especially when focused in PES. Furthermore, none of the major PES registries have a mean follow-up longer than 40 months. As the risk of SD in BS persists lifelong, longer follow up is necessary to clarify this issue.

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 registry was initiated at OLV Ziekenhuis (Aalst, Belgium) and continued at Universitair Ziekenhuis Brussel (Brussels, Belgium). The ethics committee of the Universitair 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 been already included in previous registries. Study inclusion criteria consisted of (1) spontaneous or drug-induced Brugada type I electrocardiogram (ECG), (2) PES VT induction protocol performed and (3) follow up longer than one year achieved. 404 patients fulfilled all of them. Medical history, physical examination and baseline ECG were obtained. Underlying structural cardiac abnormalities were excluded in all patients with non invasive methods (echocardiogram, stress test, 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 one 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 symptomatic if they had presented with syncope (excluding vasovagal or due to a
non arrhythmic cause) and/or aborted SD. Patients not fulfilling this definition were considered asymptomatic.

**Electrophysiological study (EPS)**

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 0.2 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 ventricular tachycardia (VT), or monomorphic VT lasting more than 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 minutes period to unmask the diagnostic ECG pattern of BS in case of non-diagnostic 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 to baseline interval, when frequent premature ventricular beats (PVCs) or type 1 Brugada ECG occurred or in the case of development of high-degree AV-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 (SND). ICD programming at the time of implantation changed over the time. VF detection rate was increased from 180 to more than 200 bpm 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 two investigators independently. Appropriate therapies were defined as shocks or anti-tachycardia pacing (ATP) delivered for VT or VF and inappropriate therapies were defined as those delivered in the absence of VA. Electrical storm was defined by 3 or more sustained episodes of VT, VF, or ICD appropriate shocks within 24 hours.

Statistical analysis

Data are presented as mean ± standard deviation or as absolute values and percentages where appropriate. Comparison between continuous variables was performed using the unpaired Student’s t-test or U Mann-Whitney test as appropriate. The X2 test or the Fisher’s exact test were 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 less than 0.05 was considered statistically significant.
Statistical analyses were conducted using the SPSS software (SPSS v22, Chicago, IL, USA).

Results

Study population

A total of 404 consecutive BS patients (235 males, 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 one 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 non-spontaneous 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 AV block was induced and more than 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 mutation in the 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, but this trend was non significant (32.0% vs. 23.6%, p=0.08). Patients undergoing PES before 2005 presented more frequently spontaneous type I pattern (30.2% vs. 9.0% p<0.01) and had a broader QRS (101.3±15 ms vs. 91±21.5 ms, p<0.01). These BS patients were less
frequently probands (17% vs. 44.1%, p<0.01) and had more history of AF (13.2% vs. 5.4%, p<0.01) and SND (3.3% vs. 0%, p<0.01). Of note, the rate of ICD implantations was similar in both groups (41.8% and 41.4%, p=0.95).

**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 ventricular fibrillation was the induced rhythm and in 13 (17.8%) it was VT (polymorphic in 11 patients and monomorphic in 2, with a CL 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% vs 52.3%, p<0.01), presented more spontaneous type I pattern (42.5% vs 13.3%, p<0.01) and had a wider QRS (106.8±15.0 vs 96.0±18.0, p<0.01). Symptomatic patients had a higher rate of inducibility (56.2% vs 27.2%, p<0.01). No difference in inducibility rate was found between patients with vasovagal syncope and non vasovagal syncope (p=0.20).

**ICD implantation**

One hundred sixty eight patients (41.6%) received an ICD. Ninety-six (29.0%) belonged to the non-inducible group and 72 (98.6%) of the inducible group. Among non inducible patients, reasons for ICD implantation were: presentation as SD in 13 (13.5%) patients, as syncope in 77 (80.2%), spontaneous type I and/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 SCD.

**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 SCD that was resuscitated. Sixteen (64.0%) were in the inducible group and 9 (36%) in the non-inducible patients. All inducible group events consisted in appropriate ICD shocks whilst in the non-inducible group there were 8 appropriate ICD shocks and one resuscitated SCD (in a patient without ICD). Table 3 summarizes clinical characteristics of non-inducible patients with events.

Figure 1 shows cumulative event free survival according to Kaplan Meir method in the overall population. Event free survival for the non-inducible 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 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 one 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 one of the patients. They did not receive a previous appropriate shock. Both were treated with quinidine with no further arrhythmic recurrences.

Among patients with syncope, 14 (12.3%) experienced a recurrent syncope during follow up: 9 (11.7%) in the non-inducible 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 and ICD 30 patients (17.9%) had inappropriate shocks after a median of 32.8 months (IQR 9.1-76.6 months from ICD implantation). Median number of inappropriate shocks delivered per patient was 1.0 (25% percentile: 1.0 and 75% percentile: 3.0). Inappropriate shocks were due to sinus tachycardia in 5 patients, noise on the ventricular channel after lead fracture in 7 patients and T-wave over-sensing in 4 patients. The remaining 14 subjects experienced inappropriate shocks due to AF episodes with fast ventricular rate.

During follow-up, 28 patients (16.7%) experienced device-related complications. Complication consisted in 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%) males). Causes of death were: urinary septic shock after a device revision in 1 patient, one cardiogenic shock after an acute myocardial infarction with myocardial rupture in 1 patient and the remaining
10 died from non cardiac 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% CI 3.6 – 19.4), p<0.01. Other variables showed relationship with occurrence of arrhythmic events. 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 SCD 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 AF (HR 0.84 95% CI 0.920 – 3.56, p= 0.81), previous SND (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 I ECG pattern or previous symptoms, have been consistently identified by different groups and therefore are universally accepted. This is not the case of induced VA by PES. Our group proposed almost 15 years ago its value in predicting arrhythmic events. Heretofore, 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 exits around this topic. Furthermore, as the risk of SD in BS patients persists lifelong, very long-term follow-up is of great importance.
In this study we examined the value of PES as predictor of SD in one 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 PRELUDE \(^8\), 1.6% in the FINGER registry \(^9\)). 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 due to a selection bias, as initial reports included patients at higher risk. BS patients characteristics and risk profile have changed along the years. After 2005, fewer patients presented with SCD 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 around 30% more patients.

In the PRELUDE registry VA inducibility was not associated with a higher risk of
presenting SCD. This study enrolled 308 with a mean follow up of 34 months. Survival curves of inducible and non-inducible patients were almost identical. Compared to our study, event rate is similar (0.9% vs 1.5%) but inducibility is higher (16% vs 40%). This point might be of importance. Our stimulation protocol involves only one site (right ventricular (RV) apex) whilst the PRELUDE registry uses a two-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, as 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 centres, 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 two site stimulation). PES inducibility was a significant non-adjusted 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 done 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, non-inducible 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. Though 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 least 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 in order to rule out the presence of SND or supraventricular arrhythmias as potential cause of the event. Currently, ICD therapy is considered in order 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, as 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. Similarly, prolonged sinus node recovery time and sino-atrial conduction time as well as slowed atrial conduction have been reported in association with the syndrome and can lead to syncope.

We believe that EPS in BS patients 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 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\textsuperscript{21}. Therefore EPS in BS patients is of utility in different fields: prognostic, diagnostic and even therapeutic.

**Limitations**

Some limitations can be found in our study. The fact of being a single centre experience spanning for a 20-year period, makes the population to present heterogeneous clinical characteristics. However, period of diagnosis, when introduced in the multivariate model, did not behave as a confounding factor. Despite being one 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. Therefor patients with ICD could appear as more likely to present events during follow-up. Though ICD shocks do not entirely correspond to VA that lead to SCD, 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 Brugada syndrome. It might be of special value to guide further management when performed in asymptomatic individuals. The over- all accuracy of the test makes it a suitable screening tool to reassure non-inducible asymptomatic individuals.

**Conflict of Interest Disclosures:** None

**References:**


Table 1: Baseline clinical characteristics of study population according to VA inducibility

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 404)</th>
<th>PES non inducible (n =331)</th>
<th>PES inducible (n = 73)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>43.2±16.2</td>
<td>43.0±16.9</td>
<td>44.3±13.5</td>
<td>0.48</td>
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<tr>
<td>Male gender, n (%)</td>
<td>235 (58.2)</td>
<td>173 (52.3)</td>
<td>62 (84.9)</td>
<td>&lt;0.01</td>
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<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>
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<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>
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<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>
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<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>
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<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>
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<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>
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<tr>
<td>Previous SND, n (%)</td>
<td>6 (1.5)</td>
<td>4 (1.2)</td>
<td>2 (2.7)</td>
<td>0.33</td>
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<td>PR, ms</td>
<td>173.4±31.0</td>
<td>171.7±33.0</td>
<td>177.9±24.8</td>
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<td>QRS, ms</td>
<td>98.9±17.9</td>
<td>96.0±18.0</td>
<td>106.8±15.0</td>
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<td>HV, ms</td>
<td>46.1±10.0</td>
<td>45.7±9.7</td>
<td>47.4±10.9</td>
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<td>SCN5A mutation, n (%)*</td>
<td>53(21.9)</td>
<td>43(21.3)</td>
<td>10(22.2)</td>
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<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>

Abbreviations: PES programmed electrical stimulation, SD sudden death, SND sinus node dysfunction, ICD: implantable cardioverter defibrillator. *Percentages are calculated only among patients with genetic test.
Table 2: Baseline clinical characteristics of study population according to diagnosis year

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Group I &lt; 2005 (n =182)</th>
<th>Group II ≥ 2005 (n = 222)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>428±15.5</td>
<td>43.5±16.9</td>
<td>0.66</td>
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<td>Male gender, n (%)</td>
<td>113 (62.1)</td>
<td>122 (55.0)</td>
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<td>Spontaneous type I ECG, n (%)</td>
<td>55 (30.2)</td>
<td>20 (9.0)</td>
<td>&lt;0.01</td>
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<td>Proband, n (%)</td>
<td>31 (17.0)</td>
<td>98 (44.1)</td>
<td>&lt;0.01</td>
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<tr>
<td>Aborted SD, n (%)</td>
<td>10 (5.5)</td>
<td>7 (3.2)</td>
<td>0.24</td>
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<tr>
<td>Syncope, n (%)</td>
<td>43 (23.6)</td>
<td>71 (32.0)</td>
<td>0.06</td>
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<tr>
<td>Asymptomatic, n (%)</td>
<td>129 (70.9)</td>
<td>144 (64.9)</td>
<td>0.20</td>
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<tr>
<td>Family history of SD, n (%)</td>
<td>93 (51.1)</td>
<td>94 (42.3)</td>
<td>0.08</td>
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<tr>
<td>Previous atrial fibrillation, n (%)</td>
<td>24 (13.2)</td>
<td>12 (5.4)</td>
<td>&lt;0.01</td>
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<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>
</tbody>
</table>

Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Group I &lt; 2005 (n =182)</th>
<th>Group II ≥ 2005 (n = 222)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmic event</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. Abbreviations: PES: programmed electrical stimulation, SD: sudden death, SND: sinus node dysfunction, ICD: implantable cardioverter defibrillator. P value of arrhythmic event is calculated by means of Cox regression method. *Percentages are calculated only among patients with genetic test.
Table 3: Clinical characteristics of non inducible patients presenting arrhythmic events during the followup

<table>
<thead>
<tr>
<th>Patient</th>
<th>Event</th>
<th>Gender</th>
<th>Age*</th>
<th>Proband</th>
<th>Family History of SCD</th>
<th>Spontaneous type</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>SCD</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Aborted SCD</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>SCD</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>SCD</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>

**Abbreviations:** SD sudden death; f-QRS: fragmentation of QRS complex. *Age indicates age at arrhythmic event
Figure Legends:

**Figure 1:** Event free survival according to Kaplan Meir method.

**Figure 2:** Event free survival in asymptomatic patients according to Kaplan Meir method.
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 Julià, Mark La Meir, Francis Wellens, Kristel Wauters, Sophie Van Malderen, Gudrun Pappaert and Pedro Brugada

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