Management of Brugada Syndrome
Thirty-Three-Year Experience Using Electrophysiologically Guided Therapy With Class 1A Antiarrhythmic Drugs
Bernard Belhassen, MD; Michael Rahkovich, MD; Yoav Michowitz, MD; Aharon Glick, MD; Sami Viskin, MD

Background—Information on long-term clinical outcome of patients with Brugada syndrome treated with electrophysiologically guided class 1A antiarrhythmic drugs (AAD) is limited.

Methods and Results—An aggressive protocol of programmed ventricular stimulation was performed in 96 patients with Brugada syndrome (88% males; mean age, 39.8±15.9 years). Ten patients were cardiac arrest survivors, 27 had presented with syncope, and 59 were asymptomatic. Ventricular fibrillation was induced in 66 patients, including 100%, 74%, and 61% of patients with cardiac arrest, syncope, and no symptoms, respectively. All but 6 of the 66 patients with inducible ventricular fibrillation underwent electrophysiological testing on quinidine (n=54), disopyramide (n=2), or both (n=4). Fifty-four (90%) patients were electrophysiological responders to >1 AAD with similar efficacy rates (≈90%) in all patients groups. Patients with no inducible ventricular fibrillation at baseline were left on no therapy. After a mean follow-up of 113.3±71.5 months, 92 patients were alive, whereas 4 died from noncardiac causes. No arrhythmic event occurred during class 1A AAD therapy in any of electrophysiological drug responders and in patients with no baseline inducible ventricular fibrillation. Arrhythmic events occurred in only 2 cardiac arrest survivors treated with implantable cardioverter–defibrillator alone but did not recur on quinidine. All cases of recurrent syncope (n=12) were attributed to a vasovagal (n=10) or nonarrhythmic mechanism (n=2). Class 1A AAD therapy resulted in 38% incidence of side effects that resolved after drug discontinuation.

Conclusions—Our data suggest that electrophysiologically guided class 1A AAD treatment has a place in our therapeutic armamentarium for all types of patients with Brugada syndrome. (Circ Arrhythm Electrophysiol. 2015;8:1393-1402. DOI: 10.1161/CIRCEP.115.003109.)

Key Words: Brugada syndrome ■ cardiac arrest survivor ■ disopyramide ■ quinidine ■ syncope

Implantation of an automatic cardioverter–defibrillator (ICD) has been universally recommended for patients with Brugada syndrome (BrS) who survived a cardiac arrest (CA; class I indication) and is considered useful in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular tachyarrhythmias (class IIa indication).1 In asymptomatic BrS individuals who have inducible sustained ventricular fibrillation (VF) at electrophysiological study (EPS), ICD implantation is controversial and has a class IIb indication.1 1992,7 we realized that some of our patients with idiopathic VF had, in fact, this newly described entity and that their long-term course on quinidine therapy was as good as that of patients with idiopathic VF. Consequently, we extended our experience using electrophysiologically guided class 1A AAD therapy in all BrS patients with inducible VF. In this study, we report our long-term experience in a large cohort of BrS patients with various clinical presentations who underwent electrophysiologically guided class 1A AAD therapy.

Methods

Study Group
Our study cohort consisted of 96 consecutive patients with BrS who underwent baseline EPS between November 1981 and December 2014. Of these 96 patients, 10 (10.5%) presented with CA and 27 (28%) with syncope, whereas 59 (61.5%) were asymptomatic. Three (30%) of the CA survivors were presented with arrhythmic storm. Also, 3 patients with CA were studied before the Brugada et al’s6 publication (Figure 1) and were initially reported as having idiopathic VF.2 The syncope group included 10 patients with syncope of...
WHAT IS KNOWN

- In patients with Brugada syndrome, a negative electrophysiologic study using standard protocols of programmed ventricular stimulation does not rule out the small but definite risk of future arrhythmic event.
- ICD is considered by most cardiac electrophysiologists as the only effective therapy for preventing sudden cardiac death in high risk patients with BrS.

WHAT THE STUDY ADDS

- Using an aggressive protocol of programmed ventricular stimulation achieved a negative predictive value of 100% during long-term follow up.
- Class 1A antiarrhythmic drugs (mainly quinidine) were effective in preventing re-induction of ventricular fibrillation in ~90% of patients.
- No arrhythmic events occurred during class 1A antiarrhythmic therapy in any of electrophysiologic-drug responders treated with these medications during a mean follow-up period of close to ten years.

During long-term quinidine therapy, 9 drug electrophysiological responders consented to undergo 1 (n=8) or 2 (n=1) additional EPS for the following reasons: (1) to confirm the long-term efficacy of the same dose (n=4) or of a lower dose (n=1) of medication; (2) to attest that replacement of QBS with HQC did not affect drug response (n=2); and (3) to assess the mechanism of syncope that occurred during quinidine therapy (n=3). Serum blood levels of quinidine were determined at each electrophysiologic study.

**PVS Protocol**

In the first study patient, our protocol included only the right ventricular apex (RVA), a maximum of 2 extrasustimuli and 2 basic cycle lengths (protocol 1). In 1983, we added pacing from the RV outflow tract (protocol 2; 2 patients). From 1988, the protocol included 3 extrasustimuli delivered from the RVA and the RV outflow tract (protocols 3A and 3B). The entire double or triple extrastimulation protocol at the RVA was always performed before moving to the RV outflow tract. A stimulus current of 5 diastolic threshold (but never >3 mA) was initially used (protocols 1, 2, and 3A), whereas 2-diastolic threshold stimulus current was used during the past 7 years (protocol 3B). From the beginning, our protocol included the repetition (n=10) of double extrastimulation at the shortest coupling intervals that resulted in ventricular capture while in 1988 we added the repetition (n=5) of triple extrastimulation at the shortest coupling intervals (protocols 3A and 3B).

**Definitions**

VF is a polymorphic ventricular tachyarrhythmia (cycle length <200 ms) that required cardioversion for termination or resulted in clinical CA before spontaneous termination. A patient was considered inducible if VF was induced. Spontaneous arrhythmic event (AE) was defined as sudden death, an episode of documented VF requiring resuscitation or an appropriate ICD shock for VF.

**Follow-Up**

Patients were discharged with the medication regimen that prevented induction of VF and were followed as out-patients every 6 to 12 months. Holter monitoring was yearly performed. Special attention
was given to gastrointestinal disorders, platelet count number, liver function tests, serum potassium levels, and QTc values. Quinidine serum levels were checked every 6 months, and the drug dose was modified if necessary to achieve serum levels similar to those found during the last EPS. Patients with inducible VF who did not respond to drugs or were drug intolerant were advised to undergo ICD implantation. In addition, the potential risks and benefits of drug discontinuation with ICD implantation were discussed with each patient at least once yearly. Patient compliance with medications was estimated during each follow-up visit and defined as excellent, moderate, or poor as detailed elsewhere."3

Patients with ICD were followed up at 3 to 6 months intervals. At each visit, they were questioned about the presence of syncope or device discharges and their ICD interrogated. Patients with no inducible VF were followed on no therapy on yearly basis. In patients in whom different modes of management were applied during follow-up, all therapy periods were accounted separately. All patients who were alive were also contacted by telephone in November and December 2014. No patients were lost to follow-up.

**Results**

**Patient Clinical Characteristics**

Our population study included 96 patients (88.5% males; mean age, 39.8±15.9 [19–80] years) who underwent a total of 184 EPS (Table 1). The first 7 patients studied were from the CA group, whereas syncopal and asymptomatic patients were studied beginning in April 1999. Both age and sex were similar in all 3 patient groups. A spontaneous Brugada ECG type 1 was observed in 50%, 26%, and 36% in patients presenting with CA, syncope, or no symptoms, respectively. The proportion of patients with a familial history of BrS or sudden death at the age of <60 years was similar in all 3 patient groups (26%–31%).

**Baseline EPS**

Baseline EPS were performed in the absence of antiarrhythmic medications in all but 2 patients, who were receiving amiodarone after their index spontaneous VF (Table 2). Protocol 3A (n=65) and protocol 3B (n=31) were the most used. VF was induced in 66 (68.8%) of the 96 study patients (100%, 74%, and 61% in the CA, syncope, and asymptomatic groups, respectively; Figure 2). The inducibility rates were not significantly affected by the PVS protocol used (3A versus 3B). They were higher in the CA group (100%) than in the non-CA group (65%). The inducibility rate was higher in men than in women (76% versus 62%).

### Table 1. Main Study Results

<table>
<thead>
<tr>
<th>Patient Presentation</th>
<th>Aborted CA (n=10)</th>
<th>All (n=27)</th>
<th>SUO (n=10)</th>
<th>WS (n=17)</th>
<th>Asymptomatic (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>9 (90%)</td>
<td>25 (93%)</td>
<td>10 (100%)</td>
<td>15 (88%)</td>
<td>51 (86%)</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>21–57 (34±13)</td>
<td>19–80 (42±16)</td>
<td>19–80 (45±22)</td>
<td>23–61 (38±10)</td>
<td>18–79 (40±14)</td>
</tr>
<tr>
<td>ECG BrS type 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>5 (50%)</td>
<td>7 (26%)</td>
<td>2 (20%)</td>
<td>5 (29%)</td>
<td>21 (36%)</td>
</tr>
<tr>
<td>During pharmacological testing</td>
<td>5 (50%)</td>
<td>20 (74%)</td>
<td>8 (80%)</td>
<td>12 (71%)</td>
<td>38 (64%)</td>
</tr>
<tr>
<td>Familial history of BrS/SCD</td>
<td>3 (30%)</td>
<td>7 (26%)</td>
<td>3 (30%)</td>
<td>4 (24%)</td>
<td>18 (31%)</td>
</tr>
<tr>
<td>Inducible VF at EPS</td>
<td>10 (100%)</td>
<td>20 (74%)</td>
<td>8 (80%)</td>
<td>12 (70.5%)</td>
<td>36 (61%)</td>
</tr>
<tr>
<td>EP-guided class 1A AAD</td>
<td>10 (100%)</td>
<td>19 (95%)</td>
<td>8 (100%)</td>
<td>11 (92%)</td>
<td>31 (86%)</td>
</tr>
<tr>
<td>Responders</td>
<td>9 (90%)</td>
<td>17 (89.5)</td>
<td>8 (100%)</td>
<td>9 (82%)</td>
<td>28 (90%)</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>1 (10%)</td>
<td>2 (10.5%)</td>
<td>0</td>
<td>2 (18%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Initial treatment assigned in inducible patients (n=66)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only class 1A AAD</td>
<td>8</td>
<td>18</td>
<td>8</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Only ICD</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Both class 1A AAD+ICD</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No treatment</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Treatment at last follow-up (n=62) or at death (n=4) in inducible patients*</td>
<td>2</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Only class 1A AAD</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Only ICD</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Class 1A AAD+ICD</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No treatment</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Mean follow-up duration (mo) in inducible patients (n=66)</td>
<td>219.6±123.2</td>
<td>112.7±45</td>
<td>117.4±44.4</td>
<td>109.6±45.2</td>
<td>97.8±50.5</td>
</tr>
<tr>
<td>Of all patients</td>
<td>146.4±90.9</td>
<td>60.3±69.2</td>
<td>78.4±70.9</td>
<td>47.2±64.8</td>
<td>65.6±52.5</td>
</tr>
<tr>
<td>On class 1A AAD (with or without ICD)</td>
<td>88.8±34.4</td>
<td>64.8±37.1</td>
<td>95±0</td>
<td>54.7±37.7</td>
<td>90.1±56</td>
</tr>
<tr>
<td>On no treatment</td>
<td>185.5±116.5</td>
<td>92.8±28.4</td>
<td>72.3±34.6</td>
<td>103.1±17.2</td>
<td>92±1.36</td>
</tr>
<tr>
<td>Mean follow-up duration (mo) in noninducible patients</td>
<td>129.9±27</td>
<td>142±5</td>
<td>125±30.5</td>
<td>86.8±52</td>
<td></td>
</tr>
</tbody>
</table>

AAD indicates antiarrhythmic drug, BrS, Brugada syndrome; CA, cardiac arrest; EPS, electrophysiological study; ICD, implantable cardioverter–defibrillator; SCD, sudden cardiac death; SUO, syncope of unknown origin; VF, ventricular fibrillation; and VVS, vasovagal syncope.

*ICD was not accounted if the device has been extracted or reached end-of-life (n=4).
women (76.5% versus 9.1%) and in the presence (88%) versus in the absence (59%) of spontaneous Brugada ECG type 1.

VF induction was achieved with 1, 2, or 3 ventricular extra-stimuli in 3, 38, and 25 patients, respectively. Induction of VF with <2 extrastimuli was achieved in 60%, 50%, and 69.5% of patients presenting with CA, syncope, or no symptoms, respectively. In the 3 patient groups, VF was induced during repetition of double or triple extrastimulation in 30%, 45%, and 50% of patients, respectively. The RV A was the site of VF induction in 90%, 45%, and 50% in the 3 patient groups, respectively.

In patients with inducible VF, the mean coupling intervals of extrastimuli S3 and S4 that induced VF were usually <200 ms.

Initial EPS on Class 1A AAD
Six patients with inducible VF at baseline did not undergo electrophysiological drug testing on class 1A AAD because of patients’ refusal (n=3), severe conduction disturbances (n=2), or clinical intolerance to QBS (n=1). The remaining 60 patients underwent drug testing on quinidine (n=54; QBS [n=41], HCQ [n=13]), disopyramide (n=2), or both medications (n=4). Overall, 54 (90%) of the 60 patients were electrophysiological responders to at least 1 AAD. These 54 patients included a similar proportion of patients with spontaneous Brugada ECG type 1 (48.5%) than of patients with drug-induced Brugada ECG type 1 (52.3%).

Quinidine prevented reinduction of sustained VF in 52 (89.6%) of the 58 patients tested (Figure 2). The efficacy rates were similar regardless of symptoms at presentation. QBS at a mean dose of 1406±242 mg was effective in 40 (89%) of 45 patients, whereas HCQ at a mean dose of 900 mg was effective in 12 (92.3%) of 13 patients. The mean effective quinidine serum levels were 2.49±0.8 mg/L (1.29–5.2) and 1.18±0.44 mg/L (0.8–1.9) for QBS and HCQ, respectively. In 2 of 3 patients who responded to 1250 to 1500 mg QBS, a lower dose (1000 mg) was similarly effective in preventing VF induction.

Late Electrophysiological Testing on Class 1A AAD
Of the 9 patients who underwent repeat EPS on quinidine to 17 (mean, 6.8±4.4) years after the initial EPS for

<table>
<thead>
<tr>
<th>Table 2. Results of Baseline Programmed Ventricular Stimulation in the Study Patients</th>
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<tbody>
<tr>
<td>Patient Presentation</td>
</tr>
<tr>
<td>Induction of VF</td>
</tr>
<tr>
<td>Inducible group (n=66)</td>
</tr>
<tr>
<td>PVS protocol</td>
</tr>
<tr>
<td>No. 1</td>
</tr>
<tr>
<td>No. 2</td>
</tr>
<tr>
<td>No. 3A/3B</td>
</tr>
<tr>
<td>Number extrastimuli at VF induction</td>
</tr>
<tr>
<td>1 ES</td>
</tr>
<tr>
<td>2 ES</td>
</tr>
<tr>
<td>3 ES</td>
</tr>
<tr>
<td>Site of VF induction</td>
</tr>
<tr>
<td>RVA</td>
</tr>
<tr>
<td>RVOT</td>
</tr>
<tr>
<td>VF induction with repetition</td>
</tr>
<tr>
<td>Mean S2/S3/S4 CI at VF induction (CL 600)</td>
</tr>
<tr>
<td>Mean S2/S3/S4 CI at VF induction (CL 400)</td>
</tr>
<tr>
<td>Noninducible group (n=30)</td>
</tr>
<tr>
<td>PVS protocol</td>
</tr>
<tr>
<td>No. 1</td>
</tr>
<tr>
<td>No. 2</td>
</tr>
<tr>
<td>No. 3A/3B</td>
</tr>
<tr>
<td>Mean shortest S2/S3/S4 CI at CL 400 ms from RVOT</td>
</tr>
</tbody>
</table>

CA indicates cardiac arrest; CI, coupling intervals; CL, basic cycle length; ES, extrastimulus/extrastimuli; NA, not applicable; PVS, programmed ventricular stimulation; RVA, right ventricular apex; RVOT, right ventricular outflow tract; SUO, syncope of unknown origin; VF, ventricular fibrillation; and VVS, vasovagal syncope.
reasons listed above, noninducibility of VF was confirmed in 8 patients despite the use of more aggressive PVS protocols at repeat EPS in 2 patients (Figures 3 and 4). VF was inducible in 1 patient studied on a lower dose of QBS. In 1 patient who developed late (7 years) intolerance to HCQ, repeat EPS on disopyramide showed inducible VF.

Drug Tolerance
Quinidine therapy was initially given to 61 patients and resulted in side effects in 23 (38%) patients. During follow-up, no patient treated with either quinidine or disopyramide developed any arrhythmia associated with QT prolongation. Side effects occurred within a few days in 4 patients, within 4 months in 14 patients, and after 1 to 10 years of treatment in 5 patients. In all patients but 4 this resulted in drug discontinuation. Quinidine-related side effects included >1 of the following: diarrhea (n=11), thrombocytopenia (n=4), fever (n=2), allergic reaction (n=1), esophagitis (n=1), sinus node dysfunction (n=1), lupus erythematosus-like syndrome (n=1), hepatitis (n=1), hyperpigmentation (n=1), and marked weakness (n=1). In all patients, side effects resolved without sequelae on discontinuation of the medication. One patient continued having diarrhea on 750 mg QBS and was given oral cholestyramine (4 g BID). This medication suppressed diarrhea without impairing the electrophysiological response to the drug. Treatment with disopyramide was well tolerated in 4 of 6 patients. Of the remaining 2 patients, 1 agreed to renew QBS (+cholestyramine).

Drug Compliance
Of the 57 patients initially assigned to AAD, only 34 (60%) patients were actually receiving these medications at the completion of follow-up mainly because of drug-induced side effects. At last follow-up, 6 of 9 (67%) CA survivors, 8 of 18 (44%) patients with syncope, and 20 of 30 (67%) asymptomatic patients were still treated with class 1A AAD (with or without ICD). However, among the patients still treated an excellent compliance to medications was observed in 89%, 75%, and 83% patients presenting with CA, syncope, or no symptoms, respectively.

ICD Therapy
An ICD was implanted in 20 study patients (ie, in 30% of patients with inducible VF): shortly after the initial electrophysiological work-up in 8 patients and at a later stage in the remaining 12 patients. Indications for ICD implantation were (1) intolerance to AAD (n=9) associated with good electrophysiological response to medication (n=8), (2) patient’s preference despite good electrophysiological response to drug (n=4), (3) failure of class 1A AAD to prevent VF induction (n=3), (4) severe cardiac conduction disorders (n=2), (5) failure of disopyramide at EPS after late intolerance to quinidine (n=1), (6) intolerance to AAD precluding electrophysiological drug testing (n=1), and (7) patient’s refusal to undergo electrophysiological drug testing (n=1).

Complications (1–3 per patient) related to ICD implantation occurred in 11 (55%) patients: inappropriate shocks (n=5) that resulted in severe psychological disturbances in 1 patient, infections (n=2) requiring device extraction in both patients, lead thrombosis (n=2), lead fracture (n=2), iatrogenic pneumothorax during surgical revision because of oversensing of electric noise (n=1) and severe brachial plexus injury (n=1). In the latter patient, the brachial plexus injury resolved after months of physiotherapy and the device was removed years thereafter because of patient preference. ICD was not reimplanted in the 3 patients in whom it was removed. In 1 CA survivor, the device was not replaced when it reached end-of-life.
Long-Term Follow-Up

Mode of Management

Table 1 shows the treatment initiated after the initial electrophysiological work-up and the 1 received at completion of follow-up (up to death in 4 patients) in the study patients who had inducible VF at baseline EPS. The 30 patients with no inducible arrhythmias at baseline EPS were followed on no AAD and none received an ICD.

Follow-Up Duration

Mean follow-up duration was longer in the CA group (219.6±123.2 months) than in the syncope group (112.7±45 months) or the asymptomatic group (97.8±50.5 months). The follow-up duration in noninducible patients and in all subgroups of inducible patients according of their treatment is presented in Table 1.

Medical Events

After a mean follow-up of 113.3±71.5 months, all but 4 of the study patients were alive. Four patients died from noncardiac causes 1 to 10 years after initial work-up. Of the remaining alive patients, only 1 developed significant heart disease during follow-up. This patient who survived with CA in 1981 had no significant coronary artery disease at that time but required coronary bypass surgery 18 years later because of severe 3-vessel disease. Of note, our CA survivor of female sex had 2 uneventful pregnancies and normal childbirth during 17 years of quinidine therapy.

Arrhythmic Events

Of the 96 study patients, only 2 had documented AE during follow-up. These 2 patients initially presented with CA and arrhythmic storm and were advised to continue QBS that was effective at EPS in one of them. In both patients, arrhythmic storms recurred 30 and 67 months after they discontinued quinidine. The arrhythmias were successfully managed by their ICD although the clinical outcome in 1 patient was near fatal because of shock-refractory VF. Renewal of quinidine in both cases prevented recurrence of AE during the following 18 years and 13 months, respectively.

Four (40%) of our CA survivors (all with inducible VF) did not exhibit recurrent AE during long-term follow-up ranging from 7 to 20 years while on no AAD:

1. Our first study patient (11/1981) had inducible VF and received electrophysiologically guided QBS therapy regularly for 5 years (Figures 1 and 2); he then decided to discontinue the medication and remained well for the next 6 years. At this point, he underwent repeat EPS that showed persistent off-drug inducible VF that was prevented by quinidine therapy (Figures 3 and 4). The patient renewed QBS but developed thrombocytopenia

Figure 3. Data from the electrophysiological study performed 11 years later (July 7, 1992) while on no antiarrhythmic medication. A. Single ventricular complexes were induced during repetition (n=5) of double right ventricular apex (RVA) extrastimulation at the same coupling intervals (600/250/200). B. Ventricular fibrillation was induced at the sixth trial of double extrastimulation using the same coupling interval. RVO indicates right ventricular outflow. Reprinted from Belhassen et al.

Figure 4. A few days after administration of quinidine (1500 mg/d), ventricular fibrillation could no longer be induced using repetition (n=10) of double extrastimulation and repetition (n=5) of triple extrastimulation at the shortest coupling intervals delivered from the right ventricular apex (RVA) and the RV outflow (RVO) tract. Note a persistent Brugada sign in lead V1. Reprinted from Belhassen et al.
after 3 years of treatment. For the past 20 years, he has remained arrhythmia free on no medications and repeatedly refused ICD implantation.

2. Our CA survivor of female sex was 24 years old at the time of her CA. She was uneventfully treated for 17 years (1985–2002) with electrophysiologically guided QBS before she decided to get an ICD; no AE has occurred during the following 13 years on no AAD.

3. One patient was uneventfully treated with QBS alone for 22 years (1986–2008) when he was recommended by his doctor to discontinue the medication; no AE has occurred during the subsequent 7 years.

4. One patient had CA 10 years before EPS showed inducible VF; he has remained arrhythmia free on ICD without medication for the subsequent 7 years, enjoying an arrhythmia-free period of 17 years after his index CA.

**Syncopal Events**

Syncope occurred during follow-up in 12 patients from all groups: CA (n=2), SUO (n=2), SVV (n=5), and asymptomatic (n=3). Nine of these 12 patients had inducible VF at baseline EPS. One CA survivor with arrhythmic storms (7/1994) in whom the electrophysiological quinidine response was confirmed after 5 years, remained asymptomatic for 8 years on 1500 mg QBS. Then he had SUO that prompted a third EPS on QBS. Although only nonsustained polymorphic ventricular tachycardia (4 s) could be induced, an ICD was implanted and QBS continued. Three months and 9 months later, the patient had recurrent syncope without arrhythmia documentation at ICD interrogation in both instances. After comprehensive discussion with the patient, it was decided to continue quinidine only and not to replace the ICD on battery depletion; no further syncope occurred during follow-up in this patient. In 10 of the remaining 11 patients with recurrent syncope (on quinidine, n=6; on ICD+quinidine, n=2; and on no therapy, n=3), the clinical story strongly suggested vasovagal syncope; in 1 patient wearing an implantable ECG recorder the loss of consciousness episodes was clearly attributed to epilepsy.

**Patients With No Baseline Inducible Arrhythmias**

All these patients remained asymptomatic during follow-up.

**Discussion**

Quinidine has been extraordinarily effective in the treatment of VF storms in patients with BrS, even at low doses. In small patient series, the drug also has shown an apparent excellent long-term efficacy when given to inducible patients with BrS who were drug responders at electrophysiological testing. The experience with disopyramide, another class 1A AAD, is much more limited but its efficacy seems to be acceptable.

**Baseline VF Inducibility**

In our study, the inducibility rates of VF were 100%, 74%, and 61% for patients who presented with CA, syncope, and the asymptomatic ones, respectively. These figures are higher than those reported in a meta-analysis (72%, 59%, and 40%) or from those recently reported by Sieira et al (23.5%, 32.5%, and 11.7%) in similar patient cohorts. In the PRogrammed ELectrical stimUlation preDictive valuE (PRELUDE) registry of patients without previous CA, VF inducibility rate was 41%

The higher VF inducibility rate in our study mainly resulted from the aggressiveness of our EPS protocol that is probably the most aggressive ever used in the electrophysiological assessment of patients with BrS. The rationale behind the use of this aggressive protocol was 2-fold: (1) to maximize the negative predictive value of EPS and (2) to assess the effects of class 1A AAD in a great number of inducible patients, especially in CA survivors for whom we have been looking for an alternative option to ICD therapy.

Our protocol used: (1) high stimulus strength (≤5 diastolic threshold) in 71% of our patients, (2) no minimal coupling intervals for extrastimuli, and (3) the use of repetition of double and triple extrastimulation at the shortest coupling intervals. All these techniques are well known to increase VF inducibility rate and actually achieved excellent protocol sensitivity (100%) in our patients with CA. In contrast, much less aggressive PVS protocols were used in most studies included in Fauchier et al’s meta-analysis and in the PRELUDE registry, whereas Sieira et al used the least aggressive protocol (single RVA site, limitation of coupling intervals to >200 ms, no repetition).

**Effects of Class 1A AAD on VF Inducibility at EPS**

In our study, class 1A AAD therapy was highly and similarly effective in preventing VF induction in all 3 patient groups (≈90% efficacy). We previously found similar success rate in patients with idiopathic VF suggesting that these medications are effective in patients with inducible VF and no obvious heart disease, irrespectively of the pathophysiological mechanism of the arrhythmia. In a 2-center French study involving 44 asymptomatic BrS patients with inducible VF who were treated with HQC, the latter was found to effectively prevent VF inducibility in 34 (77.3%) patients. In our study, 10 (91%) of the 11 asymptomatic patients tested on HQC responded to the medication using a PVS protocol much more aggressive than the one used by Bouzeman et al. The higher success rate achieved in our patients is probably because of the higher dose of HQC used: in the French study, the patients received a fixed dose of 600 mg HCHE while we used a dose of 900 mg in 9 patients and a dose of 600 mg in 2 patients (including the only 1 nonelectrophysiological responder to HQC).

In our study, an excellent long-term reproducibility of electrophysiologically guided quinidine therapy was found in 8 of 9 patients while the lack of reproducibility in the remaining patient was attributed to the lower drug dose tested at the repeated study. Such results have a great importance for the long-term medical management of patients with BrS but require close follow-up to detect any change in cardiac status or other abnormalities (such as electrolyte disturbances) that could affect the long-term safety of drug therapy.

**Outcome in Patients With No Inducible Arrhythmias**

In Fauchier et al’s meta-analysis of patients with syncope and asymptomatic patients who had no inducible VF, an...
AE occurred during mean follow-up ranging from 20 to 44 months in 4.3% and 1.1% of patients, respectively. Sieira et al\textsuperscript{20} reported rates of 5.2% and 0.8% in the same patient population during mean follow-up of 74.3±57.3 months. In PRELUDE,\textsuperscript{21} an AE occurred in 4.9% of BrS patients with no history of CA and no inducible VF during a median follow-up of 34 months. Our results in 30 non-CA patients who had no inducible arrhythmias at baseline EPS and were followed without therapy favorably compare with these results by showing a nil event rate of AE during much longer mean follow-up (129.9±27 months and 86.8±52 months in the syncpe and the asymptomatic groups, respectively). This attests of the high negative predictive value of our PVS protocol likely related to its aggressiveness. However, our results should be interpreted with caution because they dealt with a relatively small number of patients having a relatively low arrhythmic risk. In addition, we are aware that BrS is a disease that may aggravate during the time thus requiring long periods of follow-up before the long-term prognosis of patients with negative EPS could be ascertained. Therefore, we are advising our patients with no inducible arrhythmias to undergo repeat EPS every 5 to 10 years.

**Arrhythmic Events**

BrS patients with a history of CA are at the highest risk for recurrent AE in the absence of drug therapy. In their meta-analysis, Fauchier et al\textsuperscript{19} reported a 13.5% annual rate of AE or sudden death in these patients. In the FINGER (France, Italy, Netherlands, Germany) study,\textsuperscript{23} an AE occurred at a yearly rate of 7.7% during follow-up periods of 26 to 68 (mean, 44) months. Sacher et al\textsuperscript{24} reported a 48% rate of appropriate therapy 10 years after ICD implantation in CA survivors. Sieira et al\textsuperscript{20} found that a history of CA had a hazard ratio of 15.45 ≤21.5 years follow-up. These results suggest that quinidine therapy played an important role of in the lack of AE during long-term follow-up in these patients. Furthermore, as 12% of patients with BrS presenting with CA are prone to develop arrhythmic storms\textsuperscript{12} quinidine therapy ought to be discussed in those patients undergoing ICD implantation.

In their meta-analysis of BrS patients with inducible VF who presented with syncope or were asymptomatic, Fauchier et al\textsuperscript{19} found that an AE occurred during follow-up in 13.4% and 5.9% of these patients, respectively. In PRELUDE,\textsuperscript{21} a 3.9% incidence of AE was reported in BrS patients without previous CA who had inducible VF and were treated with class 1A AAD found effective at EPS. However, comparison of our results with those previously reported should be made with caution because some studies (such PRELUDE\textsuperscript{21}) reported a higher proportion of patients with spontaneous type 1 Brugada ECG (56% versus 32.5% in our study) that is known to be a powerful predictor of AE.\textsuperscript{21,23}

**Syncope**

Patients with BrS presenting with syncope constitute an important diagnostic and therapeutic challenge for several reasons: (1) some cases of syncope may actually be related to VF that terminates spontaneously, thus increasing the risk of sudden death in these patients; (2) vagal syncope is the most frequent cause of syncope in the general population\textsuperscript{23} and probably also in the population with BrS;\textsuperscript{26} (3) vagal hypertony may facilitate the onset of spontaneous VF in some patients with BrS;\textsuperscript{27} and (4) clinical symptoms suggesting of vagal syncope may also be observed in syncope of cardiac origin.\textsuperscript{28} Despite the latter limitation and the relative small number of our patients presenting with syncope, we attempted to clinically classify syncope as SUO or vasovagal syncope. It was interesting to note, albeit the differences were not statistically significant, that VF inducibility rate was the highest in those patients with SUO (80%), the lowest in asymptomatic patients (61.5%), and intermediate in patients with vasovagal syncope (70.5%). Such findings might suggest a slightly different arrhythmic risk in these 3 groups of patients. More importantly and in agreement with others,\textsuperscript{23} we found that the mechanism of syncope in our 12 patients who exhibited recurrent syncope was likely vasovagal or nonarrhythmic.

**Drug Tolerance and Compliance**

The incidence of drug-related side effects was similar to that observed in our previous study\textsuperscript{4} and played a deleterious role on patient management especially when the medication had to be discontinued after several months or years of treatment. In such cases, we have found it difficult to convince the patients to proceed with ICD therapy so that a non-negligible number of patients have finally opted for no therapy at all. However, compliance to medications was satisfactory in patients who well tolerated drug therapy and might even be improved by increasing the frequency of the patients’ visits at our consultation.

**Comparison With ICD Therapy**

The initial objective of our study was not to compare the efficacy and complications of electrophysiologically guided AAD therapy versus ICD, already discussed elsewhere,\textsuperscript{30} which should deserve a randomized study. However, we observed 2 interesting findings: (1) the incidence and the severity of ICD-related complications were higher than those related to drug therapy and are expected to increase during the time because of multiple ICD replacements needed during patient’s life, especially in the younger and (2) our management policy using electrophysiologically guided class 1A AAD therapy enabled us to implant ICD in only 20 (21%) of our study patients, that is lower than the implantation rate in other studies involving similar patient populations.
Study Limitations
Assessing the electrophysiological efficacy of AAD therapy after a few days of treatment in our patients is reasonable; however, establishing its long-term clinical efficacy is a more difficult task because of: (1) the small number of control patients with inducible VF initially assigned to no drug therapy; (2) the low incidence rate of AE rate in these patients including 40% of our CA survivors who have remained arrhythmia-free during long follow-up periods; and (3) the fact that a substantial number of patients have discontinued their medications during the course of the study mainly because of drug-related side effects. Therefore, we have been careful in ascribing the long-term beneficial results observed with class 1A AAD as an excellent clinical outcome in drug-treated patients rather than as an excellent long-term efficacy of the medications used.

Conclusions
The results of our single-center study in a large cohort of BrS patients with various clinical presentations and who have inducible VF using an aggressive PVS protocol show an excellent protective effect of class 1 AAD (mainly quinidine) during electrophysiological testing and an excellent clinical outcome in drug-treated patients. This result was achieved despite the fact that a substantial number of inducible patients were found to be on no treatment at the completion of follow-up. We think that electrophysiological specialists should discuss the electrophysiological class 1A AAD-guided option with their patients before choosing ICD providing: (1) the patients are committed to a life-long drug therapy and (2) they exhibit a good tolerance to the medication. Patients who refuse the ICD option (including CA survivors) may be good candidates for such type of management. Finally, patients with noninducible VF may be confident about the AE risk although longer follow-up is necessary before we can be conclusive on this point.

Disclosures
None.

References


Management of Brugada Syndrome: Thirty-Three-Year Experience Using Electrophysiologically Guided Therapy With Class 1A Antiarrhythmic Drugs
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