Long-term follow-up of primary prophylactic implantable cardioverter-defibrillator therapy in Brugada syndrome

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Aims To analyse the follow-up data of implantable cardioverter-defibrillator (ICD) therapy in Brugada syndrome (BS).

Methods and results We conducted a retrospective, single centre study of 47 patients (mean age: 44.5 ± 15 years) with BS, who underwent primary prophylactic ICD implantation. All patients had baseline spontaneous (23 patients) or drug-induced (24 patients) coved type I ECG pattern. All patients were judged to be at high risk because of syncope (26 patients) and/or a positive family history of sudden death (26 patients). During a median follow-up of 47.5 months, seven patients had appropriate shocks. The presence of spontaneous type I ECG and non-sustained ventricular tachyarrhythmia in the ICD datalog suggested a trend towards shorter appropriate shock-free survival by Kaplan–Meier analysis (P = 0.037 and P = 0.012, respectively). Seventeen patients received inappropriate shocks (IS); eight patients for sinus tachycardia; six patients for new onset atrial arrhythmias; and five patients for noise oversensing. In multivariable Cox-regression analysis, new onset atrial fibrillation (AF) and less than 50 years of age were independent predictors of significantly shorter IS-free survival (P = 0.04 and P = 0.036, respectively).

Conclusion In high-risk patients with BS, primary prophylactic ICD therapy is an effective treatment. In this, young and otherwise healthy patient population, the IS rate is high.
undergoing an ICD implantation with the diagnosis of BS. All patients included until November 2004 in the general database were entered retrospectively and after November 2004 prospectively in the ICD database. The ICD database for the purpose of this study was last assessed in October 2005. Patients were included in the current study if they met all of the following inclusion criteria: (i) documentation of spontaneous or drug-induced ≥2 mm coved (type I) Brugada ECG pattern; (ii) no history of aborted sudden cardiac death; (iii) ICD implantation and/or follow-up (longer than 3 months) in our centre; (iv) positive family history of sudden death (at an age ≤65 years) and/or history of syncope (at any age) and/or sustained ventricular arrhythmia induced during the EP study. Sixty consecutive patients were screened for inclusion in the analysis. Thirteen patients were excluded: three patients had only saddle back type ST-elevation documented; two patients had shorter than 3 months follow-up, and eight patients had aborted sudden cardiac death prior to the ICD implantation. The remaining 47 patients were included. The clinical data on 29 of these patients has been published in previous studies.1,4

ECG definitions

BS was diagnosed, if a coved type ≥2 mm ST-elevation was documented in ≥1 lead from V1 to V3 either spontaneously or after class I anti-arrhythmic drug (AAD) administration. Based on our previous experience, if the ST-elevation was of the coved type, patients with negative/isoelectric or positive T waves were included (Figure 1) and were classified as having type I ECG pattern. An ECG was classified as type II, if in the presence of ≥2 mm J point elevation, >1 mm saddle back type ST-elevation with positive T wave was documented. An ECG was classified as type III, if ≤1 mm saddle back or coved type ST-elevation was observed in the right precordial leads. The ECG was classified as normal, if the above-mentioned ST abnormalities were absent. In the case of each patient, attempts were made to collect and analyse the largest number of 12-lead ECGs possible. The collected ECGs were classified as baseline and follow-up ECGs depending on whether they were documented prior to or after the ICD implantation, respectively. The baseline ECG was classified as type I if prior to the ICD implantation at least one ECG with coved type I ST-elevation was documented. A patient was classified as having spontaneous type I ECG, if either at baseline or during follow-up he has had at least one documented coved type I ECG.

Class I anti-arrhythmic drug test

Class I anti-arrhythmic drug test was performed to unmask the diagnostic ECG pattern at the investigators preference for diagnostic purposes. Most frequently, intravenous ajmaline 0.7 mg/kg administered in 5 min, and less often flecainide 2 mg/kg or procainamide 10 mg/kg given over a 10 min-period were used for this purpose. The test was considered positive only if coved type I ECG was documented (Figure 1).

Electrophysiological study

The EP study was performed at the investigators preference for risk stratification purposes. Our routine minimum ventricular arrhythmia induction protocol included two basic cycle lengths and two extra systoles, with a minimum coupling interval of 200 ms from one site in the right ventricle. In <10% of the patients, the EP study was performed in other centres with three basic cycle lengths and/or three extrasystoles and/or two different sites, with coupling intervals down to ventricular refractoriness. The result of the EP study was only considered positive if sustained ventricular arrhythmia (lasting >30 s, accompanied with syncope or requiring intervention for termination) was induced.

ICD implantation and follow-up

Single- or dual-chamber ICDs were implanted depending on the investigators preference. The decision was based on the presence of a history of supraventricular arrhythmias and/or of concomitant pacing indication. The defibrillators were implanted between November 1991 and January 2005, with 46 of the 47 implants (96%) being performed after February 1996. Implantation was performed with a non-thoracotomy transvenous lead system in all patients. Of the 47 patients, 44 (94%) underwent the implantation procedure in our centre, performed by four cardiovascular surgeons. Of the 47 first implants, 36 (77%) were performed by one operator having more than 10 years experience in arrhythmia surgery. With the exception of the first implant, from 1996, in each patient an attempt was made to introduce the shock lead through the cephalic

Figure 1 Examples of positive ajmaline test results. (A) The baseline 12-lead ECG shows right bundle branch block without significant ST-elevation. Following intravenous ajmaline administration, coved type ST-elevation with negative T waves in lead V1-V2 appears. (B) The baseline ECG in lead V2 shows saddle back type II ST-elevation, which converts to coved type I ST-elevation following ajmaline administration. (C) Baseline type III ST-elevation in lead V1. Note the coved type I ST-elevation after ajmaline administration in lead V1 with a positive T wave.
vein. With the exception of the first patient, all patients received third generation defibrillators capable of recording and storing electrocardiographic data at the time of episodes with shock. The programming was left to the investigators preference. According to our routine protocol used since 1991, at the time of the implantation, in 41 of the 47 patients (87%), a single VF zone was programmed with a lower detection rate of 180 b.p.m. (19 patients) or between 190 and 222 b.p.m. (22 patients). The pacing was programmed to a back-up rate of 35–50 b.p.m. in 45 of the 47 patients (96%).

**Follow-up**

The patients were followed in the outpatient clinic 1, 3, and 6 months after implant, then every 6 months regularly, or in case of symptomatic shock therapy. At each visit, a 12-lead ECG was also recorded and analysed. The clinical data were collected and analysed for all events with shocks. All available electrograms (EGM) of appropriate and inappropriate shocks were analysed by at least two investigators independently. In case of disagreement, the tracings were reanalysed until consensus was reached. The shock was classified as appropriate, if corresponding to the clinical symptoms (presyncope, syncope) the analysis of the onset, stability, QRS morphology, and termination of the tachycardia with shock suggested a ventricular origin. In the absence of electrocardiographic storage capacities of the defibrillator (one patient), the shock was called appropriate if it was preceded by syncope.

**Statistical analysis**

Continuous variables are expressed as mean ± SD or median (interquartile ranges). The Fisher’s exact tests were used to compare categorical values. The two-sided unpaired Student’s t-test was used to compare continuous variables. For each variable, univariate Kaplan–Meier survival analysis was used to investigate for significant differences between groups in the time to the first event (appropriate or inappropriate shock or lead failure). Subsequently, the variables which showed a P-value < 0.05 in Kaplan–Meier analysis were entered in the multivariable Cox-regression analysis. To test the proportional hazard assumption for each variable, an interaction variable with time was created and included in the Cox-regression analysis. Testing the significance of this variable indicated whether the proportional hazard assumption was reasonable. To test the linearity assumption, quadratic terms of continuous variables were entered in the Cox regression. A P-value < 0.05 was considered significant for the Student’s t-test and for the Cox-regression analysis. In case Fisher’s exact or Kaplan–Meier analysis tests were performed, a P-value ≤ 0.01 was considered significant to account for the inflation of the experiment-wise type 1 error due to multiple testing.

**Results**

**Patient characteristics**

The baseline characteristics of the 47 patients are shown in Table 1. At the time of the implantation, the mean age was 44.5 ± 15 years (range from 6 to 67 years). At the time of implant, 29 patients (62%) were ≤ 50 years. The class I antiarrhythmic drug test was performed in 41 patients (87%). In the remaining six patients, the baseline ECG showed obvious type I coved ECG pattern, thus the test was felt to have no added diagnostic value and was not performed. According to our protocol, an EP study was performed in all patients with the exception of a 6-year old child, who developed recurrent VF during the ajmaline test, requiring resuscitation. During the EP study, 38 of the 46 patients (83%) had inducible sustained ventricular arrhythmia. Eight patients (17%) were not inducible, but were judged to be at high risk on the basis of other risk factors. Four of them had both a positive family history of sudden death and syncope. Two patients had strongly positive family history of sudden death and one patient had syncope.

**ICD implantation**

A dual-chamber ICD was implanted in 11 patients (23%) and a single-chamber in the remaining 36 patients (77%). At first implant, only one patient (2%) had perioperative complication in the form of pocket infection. One patient (2%), who underwent an abdominal pulse generator implantation in 1991, required a subcutaneous patch implantation owing to high defibrillator threshold (DFT).

**Follow-up**

The median follow-up was 47.5 months (4 years) with a range from 4.5 months to 13 years. Twenty-five percentage of the patients had < 28 months and 25% ≥ 70 months follow-up. Only one patient was lost to our follow-up after 4.5 months, whereas all other patients presented for all the regular scheduled follow-up visits. None of the patients died during follow-up. Twenty patients underwent altogether 50 repeat surgical procedures. During these procedures, only one patient had pneumothorax as perioperative complication. Interestingly, one patient, who had at the initial implant normal DFT’s, had at the time of the battery replacement high DFT’s, requiring subcutaneous patch implantation.

Four patients had recurrent syncope without any episode in the ICD datalog during follow-up. Given the clinical circumstances, all four events were considered to be of vasovagal in origin. Three of the four patients had syncopal episodes prior to the ICD implant and none of them had appropriate therapy. The patient, who had no previous syncope, also had appropriate therapy for ventricular arrhythmia. However, the episode of syncope without therapy was preceded by vagal symptoms.

**ECG findings**

The analysis of a large number of 12-lead ECGs during follow-up showed that all 23 patients with baseline type I

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**Table 1** Baseline clinical characteristics of the 47 study patients

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>44.5 ± 15</td>
</tr>
<tr>
<td>Male sex</td>
<td>35 (75%)</td>
</tr>
<tr>
<td>Resting ECG</td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>23 (49%)</td>
</tr>
<tr>
<td>Type II</td>
<td>9 (19%)</td>
</tr>
<tr>
<td>Type III</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Normal</td>
<td>9 (19%)</td>
</tr>
<tr>
<td>Positive family history of sudden death</td>
<td>26 (55%)</td>
</tr>
<tr>
<td>Syncope prior to ICD</td>
<td>26 (55%)</td>
</tr>
<tr>
<td>Positive family history and syncope</td>
<td>14 (30%)</td>
</tr>
<tr>
<td>EP study performed</td>
<td>46</td>
</tr>
<tr>
<td>Inducible (%)</td>
<td>38 (83%)</td>
</tr>
<tr>
<td>AF prior to ICD</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Cephalic/subclavian shock lead insertion</td>
<td>21/24</td>
</tr>
</tbody>
</table>

*aData available in 45 patients.*
coved ECG had intermittent type I pattern and had at least one non-coved ECG documented during follow-up. Meanwhile, five of the nine patients (56%) with baseline type II ECG, and one of the six patients (17%) with baseline type III ECG, had at least one documented type I coved ECG during follow-up. However, in spite of the frequent ECG examinations, none of the nine patients with baseline normal ECG had type I coved ECG during follow-up.

Altogether 29 patients (62%) had spontaneous coved type I ECG documented at least on one occasion, either prior or after the ICD implantation.

**Appropriate shocks**

Seven patients had 17 episodes of appropriate shocks during follow-up (Figure 2A). The mean time to first appropriate

![Figure 2](image-url)
therapy was 13 months (ranging from 3 days to 4 years). All seven patients were male, three of them had a positive family history and three of them had an episode of syncope prior to the ICD implantation (one patient had both positive family history and an episode of syncope) (Table 2). However, two patients had neither family history of sudden death nor syncope. All seven patients had during the follow-up documented spontaneous coved type I ECG. In three of them, the ajmaline test was not performed because of the obvious baseline type I ECG pattern. Spontaneous type I ECG, the absence of ajmaline test, and non-sustained ventricular tachyarrhythmia (NSVT) in the ICD datalog tended to occur more frequently among patients who had appropriate shock (P = 0.034, P = 0.035, and P = 0.018, respectively). In Kaplan–Meier analysis, the presence of spontaneous type I ECG (P = 0.037) and NSVT in the ICD datalog (P = 0.012) suggested a trend towards shorter appropriate shock survival, whereas the absence of class I AAD test (P = 0.002) predicted significantly shorter appropriate shock-free survival. Cox-regression analysis was performed with the presence of spontaneous type I ECG, NSVT in the ICD datalog, and the absence of class I AAD test as independent variables. However, in the Cox-regression analysis, none of these parameters was a significant predictor of appropriate shock-free survival.

EGM findings

In six patients, 14 intracardiac and/or shock electrograms were available for analysis. Five episodes were due to VF in four patients and nine episodes were due to monomorphic ventricular tachycardia/flutter in three patients (Figure 3). Six of the nine monomorphic ventricular arrhythmia occurred in two patients under quinidine treatment, either for recurrent ventricular arrhythmia or for atrial fibrillation (AF).

Inappropriate shocks

Seventeen patients had IS during follow-up (Table 3, Figure 4A). On an average, 2.8 (range 1–8) episodes occurred per patient. The time to the first IS was 13.8 ± 20 months (ranging from 1 day to 5.4 years). In three patients, the IS occurred in the VT zone, but in only one of the three patients had the VT zone lower detection rate under 180 b.p.m. The remaining 14 patients received IS in the VF zone, with lower detection rates ≥180 b.p.m.

The leading cause of IS was sinus tachycardia; eight patients received IS in 17 episodes of sinus tachycardia. The average rate of sinus tachycardia was 184 ± 11 b.p.m. The first IS occurred 4.5 ± 5.2 months after the implantation. The patients with IS due to sinus tachycardia tended to be younger than the rest of the population; mean age 36.4 ± 8 vs. 46.2 ± 15 years (P = 0.08), respectively.

The second most frequent reason was supraventricular tachycardia (SVT) in six patients; atrial tachycardia in one patient; atrial flutter in two patients; and AF in three patients. Two of the six patients in this group had a dual-chamber device. However, all the shocks occurred in the VF zone, with an average rate of 197 ± 28 b.p.m. (Figure 5). All six patients developed the atrial arrhythmia following the ICD implantation, and therefore were not on any medication at the time of the IS.

Five patients received IS for lead sensing malfunction (noise). One patient received IS for T wave oversensing and one patient for NSVT.

The corrective measures in the sinus tachycardia group were re-programming a single VF zone with a lower detection rate from 195 to 200 b.p.m. in seven patients, and in one patient the programming of a fast VT zone between 180 and 210 b.p.m. with onset criteria on and a VF zone >210 b.p.m. One patient received beta-blocker therapy in addition. In the last mean 44.8 months of follow-up, none of these patients had repeat shock for sinus tachycardia. In three patients of the SVT group, we initiated sotalol and in one patient bisoprolol therapy; two patients underwent isthmus ablation; one patient received an atrial lead. The lower VF zone detection rate was reprogrammed to 200 b.p.m. in three patients and in one patient a second fast VT zone (182–222 b.p.m.) with SVT enhancement criteria on was also programmed. The mean shock-free follow-up in these six patients following the corrective measures was 37.7 months. Interestingly, none of the patients who have received sotalol or beta-blocker therapy had any worsening of ventricular arrhythmias.

The patients with IS tended to be younger than the patients without; mean age: 39.2 ± 11 vs. 47.5 ± 16 years (P = 0.06), respectively. Among patients with IS, significantly more patients were less than 50 years, and significantly more of them had new onset AF during follow-up (P = 0.006 and P < 0.001, respectively). In the univariate Kaplan–Meier analysis, new onset AF and less than 50 years of age predicted significantly shorter IS-free survival (P = 0.005 and P = 0.01, respectively) (Figure 4B). Subsequently, new onset AF and less than 50 years of age were entered in Cox-regression analysis. In Cox-regression analysis, new onset AF and less than 50 years of age remained significant independent predictors of shorter IS-free survival (P = 0.005 and P = 0.036, respectively).

Lead-related complications

During the follow-up, six patients developed recurrent lead sensing malfunctions (noise/myopotential oversensing) requiring new lead implantation. Five of the six patients presented with IS, and one with high impedance and pacing threshold. The malfunctioning lead was implanted through the cephalic vein in three and through the subclavian vein in three patients. The new lead was implanted on an average of 38 months (range 15–88 months) after the first implant. The patients with lead malfunction were significantly younger at the time of first implantation than the patients without; mean age: 32 ± 6 vs. 46.4 ± 14 years (P = 0.02), respectively. Univariate Kaplan–Meier

| Table 2 Clinical characteristics of the seven patients who had appropriate shocks |
|-----------------|-----------------|
| Age at implant (years) | 50 ± 13 |
| Male sex | 7 patients |
| Baseline type I | 5 patients |
| Ajmaline test not performed | 3 patients |
| Spontaneous type I ECG | 7 patients |
| Syncope | 3 patients |
| Positive family history | 3 patients |
| Inducible at EP study | 7 patients |
| NSVT | 4 patients |
Figure 3  Example of initiation of monomorphic VT in a 64-year-old male patient taking quinidine therapy. The top tracings show the ventricular and the bottom the shock electrograms. (A) Notice the baseline AF with fast ventricular rates and the short run of NSVT. This VT was terminated with the first shock (not shown). (B) Two minutes later another VT episode with a different morphology was initiated. This VT was also successfully terminated by the first shock, which also converted the patient to sinus rhythm (not shown).
improve our risk stratification strategies to help us identify studies prove this hypothesis, it is desirable to try to death in BS.4–6 However, until further long-term follow-up it is reasonable to hypothesize a life-long risk of sudden in BS is to predict the timing of the transition from asympto-

during their lifetime. Although one of the main difficulties with BS (and other primary electrical diseases) and the there are major differences between the patient population with BS (and other primary electrical diseases) and the SCD-HeFT patient population. The two most important ones are the young age of our patients and the absence structural heart disease. As the mean age of our patient population is 44 years, and because there are no other competing risk factors, the life expectancy of our patients with effectively treated ventricular arrhythmias would be more than 30 years. If the annual event rate following the implan-

Table 3 Clinical characteristics of patients who had inappropriate shocks or other complications

<table>
<thead>
<tr>
<th>Inappropriate shocks</th>
<th>17 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at implant (years)</td>
<td>39.2 ± 11</td>
</tr>
<tr>
<td>Male sex</td>
<td>13 patients</td>
</tr>
<tr>
<td>Single-chamber ICD</td>
<td>14 patients</td>
</tr>
<tr>
<td>Dual-chamber ICD</td>
<td>3 patients</td>
</tr>
<tr>
<td>IS for sinus tachycardia</td>
<td>8 patients</td>
</tr>
<tr>
<td>IS for SVT</td>
<td>6 patients</td>
</tr>
<tr>
<td>IS for noise oversensing</td>
<td>5 patients</td>
</tr>
<tr>
<td>IS for NSVT</td>
<td>1 patient</td>
</tr>
<tr>
<td>IS for T wave oversensing</td>
<td>1 patient</td>
</tr>
<tr>
<td>Lead-related complications</td>
<td>6 patients</td>
</tr>
<tr>
<td>Age at implant (years)</td>
<td>31.7 ± 6</td>
</tr>
<tr>
<td>Male sex</td>
<td>6 patients</td>
</tr>
<tr>
<td>Other ICD complications</td>
<td>4 patients</td>
</tr>
<tr>
<td>Pulse generator migration</td>
<td>1 patient</td>
</tr>
<tr>
<td>High DFT</td>
<td>2 patients</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1 patient</td>
</tr>
</tbody>
</table>

analysis revealed a trend towards shorter lead failure-free survival in patients less than 50 years of age (P = 0.047).

Discussion

Appropriate shocks

Event rates

During a median 4 years follow-up, seven patients experienced appropriate shocks for potentially life-threatening ventricular arrhythmias after implantation of an ICD for primary prevention in BS. This discharge rate is comparable to the ones reported in other primary prophylactic ICD trials of patients with structural or primary electrical diseases. In hypertrophic cardiomyopathy, annual appropriate discharge rates between 3.3 and 5% have been reported in well-documented large studies.9,10 In the long QT syndrome, the data over primary prophylactic ICD implantation are less clear, as the largest group reported up to date included only 10 patients.11–13 Annual appropriate shock rates from 1.9 to 21.5% have been reported in these small studies.11–13 In the primary prophylactic SCD-HeFT trial, which included patients with structural heart disease, the annual appropriate discharge rate was 5.1%.14 However, there are major differences between the patient population with BS (and other primary electrical diseases) and the SCD-HeFT patient population. The two most important ones are the young age of our patients and the absence of structural heart disease. As the mean age of our patient population is 44 years, and because there are no other competing risk factors, the life expectancy of our patients with effectively treated ventricular arrhythmias would be more than 30 years. If the annual event rate following the implantation remains constant in time, this means that all patients would receive a potentially life-saving appropriate therapy during their lifetime. Although one of the main difficulties in BS is to predict the timing of the transition from asymptomatic to symptomatic disease, available data indicates that it is reasonable to hypothesize a life-long risk of sudden death in BS.4–6 However, until further long-term follow-up studies prove this hypothesis, it is desirable to try to improve our risk stratification strategies to help us identify the individuals at risk of sudden death, without decreasing the specificity and losing young patients due to sudden death.

Predictors of appropriate shocks

Our previous studies identified the presence of a baseline abnormal ECG, syncope, and inducibility during the EP study as predictors of future arrhythmic events.4 When interpreting the results of the present study, similar to previous studies, we should emphasize that given the low event rates in a relatively small study population, it is very difficult to draw any definitive conclusions regarding predictors of future events.

In this study, likely due to the small patient population and low event rates, we could not confirm the previously well-established role of syncope as a predictor of future arrhythmic events.3–6 Interestingly, four patients had recurrent, most likely vasovagal syncope during follow-up (although the under-detection of spontaneously terminating ventricular arrhythmias cannot be excluded). This finding indicates that some patients had vasovagal syncope prior to the ICD implantation. In these patients, the presence of syncope likely falsely suggests an increased risk of sudden death. However, unfortunately, in this young patient population, it is not always easy to differentiate if the origin of the syncope is benign vasovagal or a potentially fatal, spontaneously terminating ventricular arrhythmias. Similarly, inducibility, during the EP study, was also not a predictor of appropriate shocks. However, it should be remembered that from our general BS patient population, all patients who were inducible and has had no previous cardiac arrest were included in the present study, as they all received an ICD. In the meantime, some patients who were not inducible but had other high-risk factors such as syncope and/or strongly positive family history were also included and served as the non-inducible control group. Thus, in our data analysis we compared the inducible patients with a specific biased control group of non-inducible but otherwise high-risk patient population in the presence of low follow-up event rates.

The results of the present study suggest a possible role for the presence of the spontaneous coved type I ECG pattern in the prediction of malignant ventricular arrhythmias. However, likely due to our small sample size and low event rate, in multivariable analysis, neither the presence of spontaneous type I ECG nor the absence of a class AAD test remained an independent predictor of future arrhythmic events. Our ICD study population was unique, as the regular follow-up allowed the analysis of a large number of ECGs over a long time period in each patient. Based on these frequent ECG examinations, we describe for the first time, that all patients with spontaneous coved type I ECG have non-diagnostic ECGs during follow-up. In the meantime, patients who have baseline repeatedly normal ECGs do not show conversion to spontaneous type I ECG during follow-up. This group did not have appropriate shocks in the first 5 years after ICD implantation.

In the present study, we also describe a potentially new risk factor, the presence of NSVT. However, it should be remembered that the NSVT episodes saved in the ICD datalog, are not identical to the traditional definition of NSVT. The NSVT episodes in our trial met the rate and initial detection criteria in the VF zone, but terminated
during the duration criteria or more frequently in the charging period. Thus, the non-sustained episodes were fast (≥180 b.p.m.) and either long lasting (usually more than eight consecutive beats) or repetitive (runs of minimum five beats in the VF zone in close proximity). Furthermore, in multivariable analysis, in the presence of low event rates, NSVT was no longer a significant predictor. Further studies are needed to clarify the role of NSVT episodes in the ICD datalog in predicting future arrhythmic events.

Trigger of events
Surprisingly, and in contrast to a previous secondary prophylactic ICD population of five patients,7 in the present study, three of the six patients with available electrograms had monomorphic ventricular arrhythmia. Two of these patients were taking quinidine, one of them for recurrent ventricular arrhythmias and the other patient for AF. The first patient had VF prior to and monomorphic arrhythmia after the initiation of quinidine therapy. These findings suggest, first, that patients might have recurrent arrhythmias on quinidine treatment; secondly, that the anti-arrhythmic medications might influence the arrhythmia presentation and convert polymorphic to monomorphic ventricular arrhythmias.

Inappropriate shocks
One of the main findings of the present study is the very high IS rate. Previously, no data has been published over IS rates in BS.
Figure 5  Examples of IS for atrial arrhythmias with fast ventricular rates. On both ICD tracings the top tracings show the atrial, the middle the ventricular, and the bottom tracing the shock electrograms. (A) Initiation of AF, with ventricular rate at 238 b.p.m. during jogging in a 49-year-old male. AF has not been documented in this patient prior to the ICD implantation. (B) Initiation of 1:1 atrial tachycardia with a ventricular rate of 240 b.p.m. in a 32-year-old male patient.
Given the young age and active lifestyle of our patients, many of them engaging in regular sport activities, it is not surprising that the leading cause of IS was sinus tachycardia at rates >180 b.p.m. In addition, patients with BS, in contrast with the long QT and hypertrophic cardiomyopathy ICD populations are less likely to receive beta-blockers due to the previously described worsening effect of these drugs on the ST-elevation pattern.  In most cases of IS for sinus tachycardia, the reprogramming of higher lower detection rates was safe and prevented recurrent shocks.

The second most frequent reason for IS was atrial arrhythmia with fast ventricular rates. It is well documented that patients with BS have a higher risk of atrial arrhythmias.  In our study population, 12 patients were diagnosed with atrial arrhythmia. Interestingly, seven patients developed new atrial arrhythmia during follow-up. Given the absence of rate control medications, six of these patients presented with IS. The combination of the reprogramming of higher lower detection rates, initiation of anti-arrhythmic treatment (medical or catheter ablative), and/or upgrade to a dual-chamber system prevented in most cases the recurrence of IS. Interestingly, sotalol or other beta-blocker therapy did not worsen ventricular arrhythmias in any patient in our study population.

Accordingly, based on the results of this study, we have changed our routine programming protocol. Currently, in patients younger than 50 years, we program a single VF zone with a lower detection rate ≥200 b.p.m. In the presence of increased risk of fast atrial arrhythmias, anti-arrhythmic drug therapy, or documented ventricular tachycardia, the programming of a fast VT zone between 180 and up to 220 b.p.m. with SVT enhancement criteria (in single-chamber devices the onset criteria) is a reasonable alternative.

Another important reason for IS was the oversensing of noise in five patients. During our follow-up, altogether six patients required a new lead implantation because of the sensing or pacing malfunction of the lead. Manifest fracture was diagnosed in two patients, the remaining patients had likely insulation break or undiagnosed lead fracture. The patients with lead-related problems were younger and were all males, suggesting that the age and the active lifestyle of the patients was an important aetiological factor.

Limitations

The major limitations of our study are the small number of patients, the low event rates, and its retrospective nature. Furthermore, the follow-up of 4.5 years, in patients with life-long risk of arrhythmias, should still be considered short. Accordingly, all of our results, especially regarding the predictors of appropriate events should be interpreted with great caution. In addition, the classification of appropriate and inappropriate therapies in single-chamber devices is sometimes difficult. This might have lead to the underestimation of appropriate shock rates. Finally, it can be argued that our initial routine lower VF zone detection rate programming of 180 b.p.m. was rather conservative and does not mirror the current clinical practice. However, it should be noted that many of the patients were implanted between 1992 and 2000, when little was known about the arrhythmia characteristics of patients with BS, especially in the presence of anti-arrhythmic drug therapy.

Conclusions

In high-risk patients with BS without previous cardiac arrest, ICD therapy is an effective (seven patients need to be implanted with an ICD to treat one potentially lethal arrhythmia) and safe treatment. In this young and otherwise healthy patient population, the IS rate is very high. The inappropriate shocks are frequently due to sinus tachycardia or new onset atrial arrhythmias with fast ventricular rates. Careful programming of the device is necessary to avoid these complications, especially in young (<50 years of age) patients. Lead-related problems are frequent in this patient population, likely also due to the young age and active lifestyle of the patients.

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References

Clinical vignette

Epicardial ablation of an arrhythmogenic left ventricular micro-aneurysm guided by fusion of electro-anatomical activation maps and computed tomography images

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A 32-year-old male patient presented with palpitations and near loss of consciousness during exercise because of a broad complex tachycardia of 230 bpm terminating spontaneously. A 12-lead ECG showed sinus rhythm, small Q-waves in the inferolateral leads, an incomplete right bundle branch block (RBBB), and VPBs with an RBBB morphology and a north-west axis. Echocardiogram and coronaryography were normal. The left ventriculography showed a small aneurysm (14 mm × 10 mm) in the inferolateral wall. This was confirmed by a 16-slice computed tomography (CT) study. No sustained arrhythmia could be induced during programmed electrical stimulation; isoprenaline initiated a VT with a cycle length of 220 ms and a morphology identical to the VPBs. An arrhythmogenic left ventricular micro-aneurysm was diagnosed and scheduled for ablation.

Dedicated software (CARTO Merge, Biosense Webster) segmented the three-dimensional CT data into the right ventricle, the left ventricle with the micro-aneurysm, and the aortic root. An epicardial activation map obtained via open subxyphoidal pericardial access showed a non-uniform propagation pattern with an ‘island’ of late, low-amplitude, and fragmented potentials at the inferolateral wall of the left ventricle. Pacing at this site resulted in a QRS morphology identical to the induced VT and the spontaneously occurring VPBs. Merging of CT images and the electro-anatomical activation map demonstrated that the anatomical position of the micro-aneurysm overlapped with the arrhythmogenic substrate identified during mapping. An ablation line encircling the arrhythmogenic substrate and the aneurysm resulted in the disappearance of VPBs and non-sustained VT. Isoprenaline failed to initiate the arrhythmia.

Panel A. The 12-lead ECG during sinus rhythm, the spontaneously occurring VPBs (RBBB morphology and north-west axis), and epicardial pace mapping from the epicardial aneurysm.

Panel B. Small aneurysm (yellow arrows) detected during ventriculography.

Panel C. Upper part: three-dimensional CT imaging of the single micro-aneurysm at the inferolateral free wall of the left ventricle (left anterior oblique view with four-chamber view cutplane). Lower part: segmented data set (CARTO Merge, left posterior oblique view). The micro-aneurysm is shown in blue (outpouching of the lumen on the endocardial delineation).

Panel D. ‘Merge’ between the three-dimensional CT and the epicardial activation map (blue and purple colours indicate the latest activation). The arrhythmogenic substrate was found to overlap the anatomical position of the micro-aneurysm.