Arrhythmic Events in Brugada Syndrome: A Nationwide Israeli Survey of the Clinical Characteristics, Treatment, and Long-Term Follow-up (ISRABRU-VF)

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ABSTRACT: **Background:** Limited information exists about detailed clinical characteristics and management of the small subset of Brugada syndrome (BrS) patients who had an arrhythmic event (AE).

Objectives: To conduct the first nationwide survey focused on BrS patients with documented AE.

Methods: Israeli electrophysiology units participated if they had treated BrS patients who had cardiac arrest (CA) (lethal/aborted; group 1) or experienced appropriate therapy for tachyarrhythmias after prophylactic implantable cardioverter defibrillator (ICD) implantation (group 2).

Results: The cohort comprised 31 patients: 25 in group 1, 6 in group 2. Group 1: 96% male, mean CA age 38 years (range 13–84). Nine patients (36%) presented with arrhythmic storm and three had a lethal outcome; 17 (68%) had spontaneous type 1 Brugada electrocardiography (ECG). An electrophysiology study (EPS) was performed on 11 patients with inducible ventricular fibrillation (VF) in 10, which was prevented by quinidine in 9/10 patients. During follow-up (143 ± 119 months) eight patients experienced appropriate shocks, none while on quinidine. Group 2: all male, age 30–53 years; 4/6 patients had familial history of sudden death age < 50 years. Five patients had spontaneous type 1 Brugada ECG and four were asymptomatic at ICD implantation. EPS was performed in four patients with inducible VF in three. During long-term follow-up, five patients received ≥ 1 appropriate shocks, one had ATP for sustained VT (none taking quinidine). No AE recurred in patients subsequently treated with quinidine.

Conclusions: CA from BrS is apparently a rare occurrence on a national scale and no AE occurred in any patient treated with quinidine.

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KEY WORDS: Brugada syndrome (BrS), cardiac arrest (CA), arrhythmic events (AE), quinidine, appropriate shocks

More than 20 years ago, the Brugada brothers reported on eight patients with recurrent episodes of aborted sudden death and no demonstrable heart disease that showed a peculiar electrocardiography (ECG) pattern of ST elevation in the right precordial leads [1]. Such patients represent only 6–32% of the Brugada syndrome (BrS) patients included in the largest series [2,3], and most studies on the topic have mainly dealt with patients without previous aborted cardiac arrest. To the best of our knowledge, no study has focused on the detailed clinical, ECG, electrophysiological characteristics, diagnostic workup, and long-term management of this relatively small group of patients with a ventricular arrhythmic event (AE).

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The original ISRABRU trial [4] was designed to assess the efficacy and complications of implantable cardioverter defibrillator (ICD) therapy in 59 Israeli patients with BrS who received an ICD for various clinical indications, including 11 patients with aborted cardiac arrest [4]. Appropriate device therapy was found to be limited to cardiac arrest survivors while none of the other BrS patients, including those with syncope and/or inducible ventricular fibrillation (VF), suffered an AE [4].

In the present study, we report the results of a nationwide Israeli survey including all patients with BrS who had experienced an AE (ISRABRU-VF):

- Group 1: Cardiac arrest aborted or resulting in death
- Group 2: Arrhythmic event documented after prophylactic ICD implantation.

Table 1. Clinical characteristics, diagnostics, treatment, and long-term follow-up of patients

Variable	Group 1 (n=25)	Group 2 (n=6)
Age range, years (mean ± SD)	13–84 (38 ± 16)	41–53 (46 ± 5)
Male, n (%)	24 (96)	6 (100)
Jewish ethnicity, n (%)	22 (88)	6 (100)
Family history of BrS or SCD, n (%)	8 (32)	4 (67)
Presenting symptom at initial assessment	Aborted CA (n=25)	Syncope (n=2), Asymptomatic (n=4)
Arrhythmic event / ICD discharge during sleep, n (%)	4 (16)	1 (17)
Apparent arrhythmic event trigger, n (%)	7 (28)	2 (33)
Initial arrhythmia as storm, n (%)	9 (36)	0
Exitus as a result of CA, n (%)	3 (12)	0
Spontaneous type 1 ECG during follow-up, n (%)	18 (72)	4 (67)
Drug provoked type 1 ECG, n (%)	6 (24)	2 (33)
Initial misdiagnosis of BrS, n (%)	8 (36)*	0
Coronary evaluation, n (%)	14 (56)	3 (50)
Diagnostic EPS at initial assessment, n (%)	11 (44)	4 (67)
Inducible VF at baseline EPS, n (%)	10/11 (91)	3/4 (75)
Repeat EPS on QND, n (%)	10/10	1/6 (17)
QND proved effective at EPS, n (%)	9/10 (90)	1/1
Treatment at hospital discharge	ICD (n=13), quinidine (n=8), ICD + quinidine (n=1)	ICD (n=6)
Late ICD complications, n (%)	4/19 (21)	2/6 (33)
Patients with appropriate ICD discharges, n (%)	8/19 (42)	6/6
Suppression of recurrent arrhythmic events with standard dose quinidine, n (%)	6/7 (86)	6/6
Follow-up duration, months, range (mean + SD)**	0-402 (149 ± 118)	20-169 (107 ± 45)
Treatment at last follow-up	ICD (n=7), quinidine (n=2), ICD + quinidine (n=10), No treatment (n=2)***	ICD (n=2), ICD + quinidine (n=4)

*Not including three patients from group 1 diagnosed prior to 1992

**Group 1: since initial CA; group 2: since ICD implantation

***Additional three died, and one lost to follow-up

BrS = Brugada syndrome, CA = cardiac arrest, ECG = electrocardiography, EPS = electrophysiological study, ICD = implantable cardioverter defibrillator, SCD = sudden cardiac death, SD = standard deviation

We provide a detailed description of the patients' clinical characteristics, diagnostics, treatment, and longterm follow-up.

PATIENTS AND METHODS

DATA COLLECTION

All 21 Israeli electrophysiology units participated in a survey of patients (past and present) with BrS who had suffered an AE. Twelve out of 21 centers had appropriate patients for inclusion in the study. After approval by the local institutional review boards, the physicians in each institution retrieved all the relevant data from patient medical charts and completed a specific questionnaire regarding each BrS patient who suffered cardiac arrest (group 1) or BrS patients with an appropriate therapy (ICD shock or anti-tachycardia pacing [ATP]) following a prophylactic ICD implantation (group 2). The study's primary investigator (E.L.) reviewed all data with the local cardiac electrophysiologists between June and November 2015.

DATA PARAMETERS

Collection of data for each eligible patient included the following: demographics, medical history, familial history, cardiac arrest characteristics including possible triggers and pre-monitory symptoms, data regarding other arrhythmias, ECG-type of Brugada pattern, workup for diagnosis of BrS including pharmacologic challenge with sodium blockers, results of an electrophysiologic study (EPS) and genetic studies if available, ECG characteristics of documented arrhythmias (spontaneous or ICD-recorded), patient management including medications and ICD data, and long-term follow-up.

DATA ANALYSIS

Data are presented as mean or median of absolute values and percentages where appropriate. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

STUDY PATIENTS

A total of 31 BrS patients from 12 medical centers met the study inclusion criteria, several of them were included in previous publications [5,6] [Table 1]. Group 1 comprised 25 patients and group 2 included 6 patients. Participating EP units had at least one eligible patient, and Tel Aviv Medical Center had the largest number of patients, with 13.

GROUP 1: ABORTED CARDIAC ARREST

Demographics

A cardiac arrest event, as the initial presentation of BrS, occurred in 25 patients with 1.5–34 years of follow-up and only one patient was lost to follow-up. The vast majority of patients (96%) were

male, with a single 24 year old female who also was the only case of in-hospital cardiac arrest [7]. There were 22 Jewish patients and 3 Muslim Arab patients. Age at the time of cardiac arrest ranged from 13 to 84 years (mean 38, median 34 years). Only two patients were adolescents (age 13 and 14 years). Three patients died as a result of the cardiac arrest event: one after 5 days and one after 3 months, neither regaining consciousness, and one after 10 years due to complications of severe anoxic brain damage.

Initial arrhythmic events

Of the 25 initial cardiac arrest events, only 4 (16%) occurred during sleep, while the remaining 21 occurred either during the day or night while the patients were awake. The cardiac arrest episode occurred during active exercise in one patient and while driving in another. Arrhythmic storm (AE requiring ≥ 3 direct current [DC] defibrillation within 24 hours) was the initial presentation in 9 (36%) of the 25 patients in this group, with 2 of these patients dying as a result.

Patient history

Prior cardiac conditions were identified in seven cardiac arrest patients: three patients had suffered from recurrent syncope prior to cardiac arrest including two erroneously treated as epilepsy, which were later attributed to an AE [Figure 1]. One patient had undergone prior slow pathway ablation for recurrent atrioventricular nodal reentry tachycardia (AVNRT), and one patient had corrected congenital heart disease with atrial fibrillation. Three patients had recurrent atypical chest pain and one patient had a history of undocumented recurrent palpitations. Prior diagnosis of BrS (type 1) was made in a single patient 1 year before the cardiac arrest, following ECG performed after a syncopal episode that was suspected to be neurally mediated. This patient initially refused to undergo EPS and ICD implantation.

A recognized trigger of the cardiac arrest event was found in seven patients (28%) in this group: concurrent febrile illness (n=2), ethanol consumption (n=2), stress condition (n=2), and post-prandial vagal malaise (n=1).

BrS workup

Of the 25 patients in group 1, cardiac arrest was documented in 3 patients between 1981 and 1986; that is, before the Brugada brothers' publication [1]. These three patients were initially classified as idiopathic VF [8].

In 14 of the remaining 22 patients, the initial diagnosis was BrS or suspected BrS. In the remaining 8 patients, either idiopathic VF (n=5), arrhythmogenic right ventricular cardiomyopathy (n=1), hypertrophic cardiomyopathy (n=1), or acute coronary syndrome (n=1) was the initial diagnosis, and these diagnoses were later excluded. During the workup following aborted cardiac arrest, eight patients underwent flecainide testing that showed a type 1-Brugada-ECG. In one patient, the test was stopped early with no specific response. This patient had spontaneous type 1 ECG documented several years later.

EPS was performed in 11 (44%) of the 25 patients, 10 of them at the Tel Aviv Medical Center as routine evaluation. These 10 patients all had inducible VF with programmed ventricular stimulation [6]. In six of the ten patients, VF was induced with ≤ 2 ventricular extrastimuli [8] [Figure 2A]. However, in the single patient studied at another center as part of cardiac arrest evaluation with type 2 Brugada-ECG, no ventricular arrhythmias were induced; only AVNRT was induced during isoproterenol infusion. Coronary angiography was performed in 14 patients, showing normal results in 13 and a 50% lesion in the left circumflex coronary artery in one patient. In two other patients, the probability of coronary artery disease was ruled out by non-invasive testing. Genetic testing was performed in 7 (28%) of the 25 patients, and a *SCN5A* gene mutation was found in only one [9].

Late sequelae

In addition to the three lethal consequences of the cardiac arrest (as described previously), transient post-resuscitation

Figure 1. Electrocardiography tracings of a 21 year old male (same patient as Figure 2, Figure 3) admitted following a third episode of suspected epilepsy within the prior 9 months occurring during phenylhydantoin therapy (20 July 1994).
[A] Several premature ventricular complexes (PVC) with a left bundle branch block configuration and normal QRS axis are present in electrocardiography lead I. In lead II, rapid polymorphic ventricular fibrillation and ventricular tachycardia events were triggered by a very short coupled PVC with similar QRS morphology. The arrhythmia was successfully converted by direct current shock.
[B] Electrocardiography performed later showed a typical type 1 Brugada-electrocardiography pattern in V1, V2, and aVL.

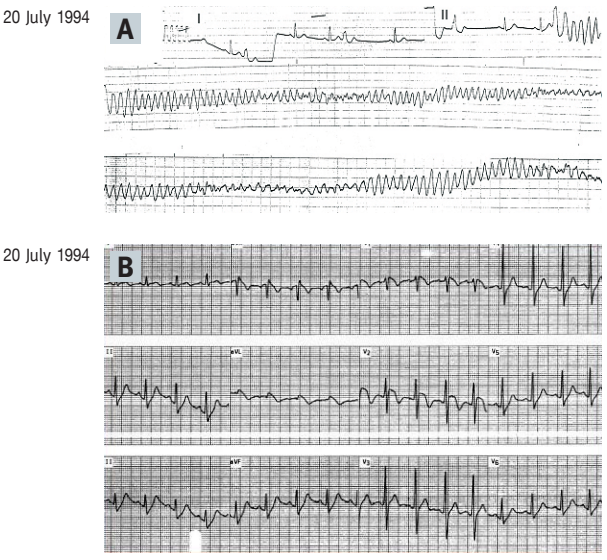
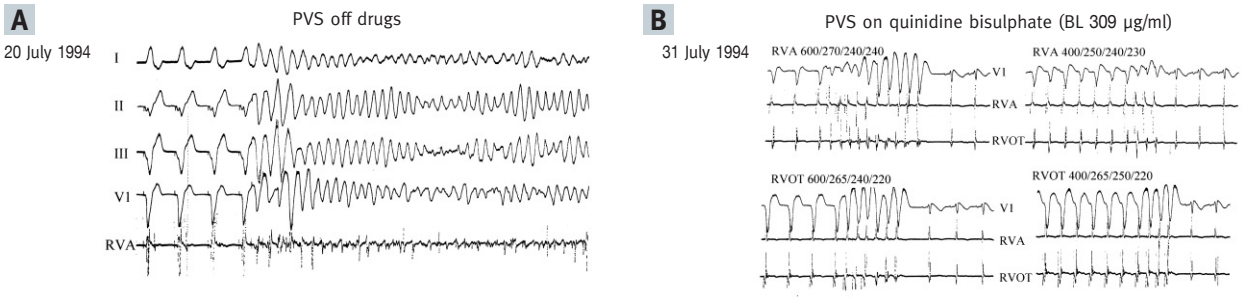


Figure 2. Results of an electrophysiologic study performed at the Tel Aviv Medical Center on a 21 year old male (same patient as Figure 1, Figure 3). **[A]** During an off-medication study (27 July 1994), a sustained polymorphic ventricular fibrillation and ventricular tachycardia event is induced with double extra-stimulation delivered from the right ventricular apex **[B]** After 4 days of treatment with quinidine bisulfate, only a few ventricular responses are induced during repetition (n=5) of triple extra-stimuli delivered at the shortest coupling interval from the right ventricular apex and the right ventricular outflow tract



PVS = pulmonary valve stenosis

infectious disease requiring treatment occurred in three cardiac arrest survivors, while two other patients had persistent mild memory disturbances.

Follow-up

Quinidine was given at hospital discharge to 9 (36%) of the 25 patients in group 1 following non-inducibility of VF at repeat EPS [Figure 2B]. ICD was implanted (initially and during follow-up) in all but six patients. ICD implantation was not performed on the three patients who had a subsequent lethal outcome and not on the first three study patients treated at the Tel Aviv Medical Center who were discharged on quinidine therapy based on EPS results.

During follow-up 8 (42%) of the 19 patients with an ICD received at least one appropriate DC shock (including the two adolescent patients). None of them were concurrently treated with quinidine. Recurrent AE presented as an arrhythmic storm in four out of nine recurrences. At the time of appropriate ICD therapy, mean and median age were 42 and 37 years, respectively, with a range of 13–84 years. Time from initial cardiac arrest event to first appropriate ICD shock ranged from 2 weeks to 89 months, with a mean and median of 33 and 18 months, respectively. Of the nine patients who presented initially with an arrhythmic storm, five (55.5%) had a recurrent AE, including four who exhibited a recurrent arrhythmic storm. Recurrence of AE resulted in initiation of quinidine treatment in 7/8 patients, leading to complete suppression of the arrhythmias using standard doses of quinidine (600 mg of hydroquinidine hydrochloride daily) in six patients and higher doses (2000 mg of quinidine bisulfate daily) in one.

Inappropriate ICD shocks occurred in five additional patients in this group: as a result of supraventricular tachycardia (n=2), following exercise induced sinus tachycardia (n=1), due to T wave oversensing (n=1), and of an unknown cause (n=1) in a patient who also received an appropriate shock. Device-related complications were encountered in four cases, two of them requiring re-intervention (*Staphylococcal* infection requiring extraction and re-implant, noise on atrial electrode), while two other patients with a late thrombus on the ventricular electrode were treated conservatively with no apparent clinical consequence.

All 21 patients were examined between 2014 and 2015. Eleven of them were taking quinidine regularly, while a single patient who was intolerant to quinidine was receiving sotalol. Two patients who initially did not receive an ICD and were treated with quinidine had voluntarily stopped treatment after 18 and 22 years, respectively, without AE recurrence (16 and 7 years of follow-up, respectively, after treatment discontinuation). Another patient who presented with arrhythmic storm has been treated long-term with quinidine after reverting to a non-inducible state during EPS, without any AE recurrence during 22 years [Figure 3].

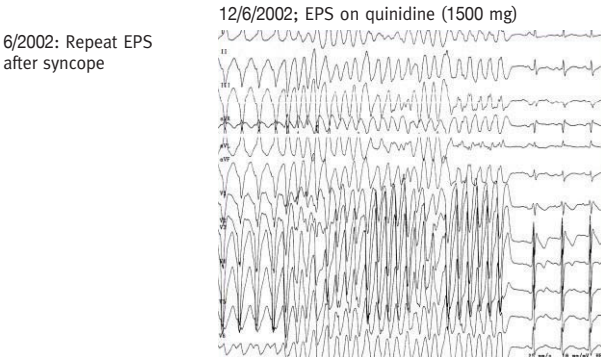
GROUP 2: APPROPRIATE ICD THERAPY AFTER PROPHYLACTIC IMPLANTATION

All six patients in group 2 were male, aged 41–53 (mean 46 ± 5) years old and all were of Jewish ethnicity. Their past medical history included recurrent chest pain (n=1) and syncope (n=1). Spontaneous type 1 Brugada-ECG was observed in five of the group 2 patients. In four patients, a family history of BrS and sudden cardiac arrest at a young age (< 55 years old) was noted (two were included in our group 1) as the indication for ICD implantation. In the latter two patients in group 2, ICD was implanted due to highly suspected arrhythmia-related syncope with an intermittent type 2 Brugada-ECG pattern, positive flecainide test in one, and a positive EPS (with type 1 ECG) in the other.

BrS workup

Coronary artery disease was ruled out in the four patients in this group. A flecainide test was performed in three cases, all yield-

Figure 3. About 8 years later, while taking quinidine, the patient (same patient as Figure 1, Figure 2) experienced a syncopal episode of unclear origin. At repeat electrophysiologic study (EPS) on quinidine, nonsustained polymorphic ventricular tachycardia (4 seconds) could be induced. An implantable cardioverter defibrillator (ICD) was implanted and quinidine continued. Three months later and 9 months later, the patient had recurrent syncope without arrhythmia documentation at ICD interrogation suggesting the non-arrhythmic origin of his syncopal events. In 2010 at ICD battery depletion and following a repeat negative EPS on quinidine, the patient agreed with our recommendation not to replace his ICD and to continue quinidine (300 mg three times a day). During a total of 22 years follow-up; this patient with BrS and initial recurrent aborted cardiac arrest remained arrhythmia-free on quinidine only.



ing a positive result. An EPS was performed in 4/6 patients and a sustained ventricular arrhythmia inducible in three of these four patients. In one patient AVNRT was also induced. Genetic testing for *SCN5A* mutations was performed in a single patient with a negative result.

Device therapies and follow-up

Five patients received at least one appropriate ICD therapy and one patient received only anti-tachycardia pacing for non-sustained irregular ventricular tachycardia (cycle length 223–289 msec). A possible trigger for arrhythmic events was found in three patients: alcohol consumption (n=1), urinary micturition (n=1), and excessive emotional stress (n=1). All initial events occurred when patients were not being treated with quinidine. Recurrent appropriate ICD shocks occurred in four patients in which quinidine was voluntarily stopped prior to the recurrence due to intolerance. Re-initiation of quinidine after the recurrence led to complete eradication of future AE. A repeat EPS following quinidine initiation was performed only in one patient and showed no inducible arrhythmias.

Inappropriate therapy occurred in three patients in group 2 and resulted from rapid supraventricular tachycardia (n=2) and a lead fracture with subsequent DC shocks (n=1).

During the 2–14 year follow-up period after ICD implantation, two patients required re-intervention due to lead fracture and the need for lead repositioning. The ICD generator was replaced once in four patients, and a single patient underwent a total of two ICD replacements.

At the last follow-up, all group 2 patients were alive and doing well. Four of the patients were being treated with quinidine, one with beta-blocker medication and one was taking no anti-arrhythmic medication.

DISCUSSION

We report on the first comprehensive national survey selectively on the subset of patients with BrS who suffered from an AE. To the best of our knowledge, the current nationwide survey reports the longest follow-up of BrS AE among the previous cohorts in the field [2,10,11].

COMPARISON WITH PRIOR STUDIES

The prevalence of BrS among patients with apparently normal hearts who exhibit SCD is low, which explains why most studies reporting patients with cardiac arrest have generally gathered the experience of several centers from either one [12] or from multiple countries [2]. The Brugada group in Belgium collected 25 patients with aborted cardiac arrest during a 20 year period [3]. Kim et al. [13] reported the first Asian nationwide registry of ICD recipients due to BrS (similar to the initial ISRABRU registry [4]). We report, to the best of our knowledge, the first European nationwide series focusing solely on BrS patients who had an AE. In addition, our cohort included a long follow-up of BrS cardiac arrest survivors as well as an alternative mode of management (quinidine) not used by others. Publication of nationwide BrS registries enable insight into possible characteristic differences between cardiac arrest survivors from various countries.

EPIDEMIOLOGIC CONSIDERATIONS

Our nationwide survey comprised a total of 31 BrS patients exhibiting a potentially lethal event over a period of up to 35 years, including three patients with aborted cardiac arrest treated several years prior to the Brugada brothers' publication [1]. There were 25 cardiac arrest survivors (alive at hospital admission) and 6 BrS patients who received appropriate therapy from an implanted ICD. The latter group of patients was not represented in the ISRABRU study [4] in which only cardiac arrest BrS survivors were found to receive appropriate therapy from their ICD device. Despite the fact that this number of patients might be an underestimation due to recall bias of older cases by current EP physicians and other cases of sudden cardiac death that did not reach the hospital, it enables additional insight into the profiling of the minority of BrS patients with malignant arrhythmias. Although our data do not allow accurate calculation of the incidence of survivors of a potentially lethal BrS event, we can infer that the current prevalence of these cases in Israel is extremely low (27 live

cases out of a population of 8.4 million people; Israeli Central Bureau of Statistics, report 355/2015, 31 December 2015). Even when considering the most conservative estimates of the incidence of BrS in the population being from 0.05% [14] up to 0.5% in the healthy population [8], the expected rate of all patients in Israel with BrS is ≥ 4200 and the presumed prevalence of a potentially lethal BrS event among those with the syndrome is only 0.6% or less.

Despite inherent flaws, this calculation raises a considerable challenge to current recommendations [15] for implanting ICD devices in a sizeable number of BrS patients [3], as well as that of the issue of treatment cost-effectiveness that is beyond the scope of the present study. Our results are discordant from those of Delise and colleagues [16], who showed that AE mainly occurred in patients implanted with an ICD, although that cumulative analysis excluded patients with a history of cardiac arrest.

DEMOGRAPHIC CONSIDERATIONS

In our study, 96% of cases in group 1 and all cases (100%) in group 2 were males. These findings are congruent with the results of most previous studies, which show a male predominance ranging from 89 and 94% among patients with aborted cardiac arrest [2,17], especially from South East Asia, which was almost entirely composed of males [18]. The Pedro Brugada group also reported a male predominance among their patients with AE but of a lesser degree (64%) than in all other studies [3]. Sieira and colleagues from the Brugada group [19] recently showed that males have double the rate of cardiac arrest at presentation (5.4% vs. 2.6%), and that following ICD implantation the annual event rate was threefold higher in males.

The mean ages at onset of AE in our study were 38 and 46 years for groups 1 and 2, respectively, and similar to those observed in prior studies [2,3,17]. However, one patient from group 1 was 84 years old at the time of his presenting cardiac arrest. After excluding other potential causes of cardiac arrest, he received an ICD. Two weeks later he had a recurrent AE appropriately treated with the ICD. He then started with quinidine treatment, which prevented further AE and recurrent syncope previously attributed to epilepsy. AE in elderly (> 70 years) patients with BrS is very rare [20] and to the best of our knowledge our patient is the oldest one with aborted cardiac arrest ever reported.

In agreement with previously reported data [3], the majority (76%) of our group 1 patients exhibited cardiac arrest as the presenting symptom without any previous warning symptoms. This finding is in agreement with data from the literature showing that only one-quarter of BrS patients with cardiac arrest had a history of syncope. Since most of these patients (12 out of 19) had spontaneous Brugada type 1 ECG, one may speculate that prior diagnosis of BrS followed by extensive cardiac workup could have led to therapeutic measures and hopefully prevented their AE.

The time of AE occurrence in our cohort deserves attention as only 16% of patients in group 1 exhibited cardiac arrest during sleep, and no recurrent AE in this group of patients occurred while sleeping. In addition, only one AE occurred while sleeping among the six group 2 patients (one patient had two separate AEs). These results are in sharp contrast with those observed in the Asian population where the vast majority of events occur predominantly at night and during sleep [21] suggesting that increased vagal tone may not be as influential in Caucasians. Furthermore, increased sympathetic tone might play a greater role in exacerbating BrS in Caucasians [22], although we observed only one AE during exercise in our cohort. Further studies are warranted to explore this issue.

BRS WORKUP FOLLOWING A CARDIAC ARREST EVENT

Our data show an important discrepancy in the diagnostic workup of BrS patients following a cardiac arrest event. Diagnosis of BrS may not always be a straightforward task following cardiac arrest, even for expert electrophysiologists. In fact, eight group 1 patients were initially incorrectly misdiagnosed. We observed no uniform evaluation approach to cardiac suspected arrest due to BrS, including inconsistencies in performing pharmacological testing and EPS to establish a diagnosis. Genetic testing in this high-risk population was rarely performed, with only eight patients in both groups tested for known mutations of BrS, yielding only one positive result (12.5%). Although prior reports from the last decade have advocated for a systemic assessment and uniform approach to patients with cardiac arrest in the absence of structural or coronary heart disease [23], future guidelines and consensus papers should re-emphasize this issue in the evaluation of suspected cardiac arrest from BrS. All of our cases of initial misdiagnoses occurred prior to the 2013 inherited primary arrhythmia syndromes consensus document [15], but it is likely that some of the earlier initially misdiagnosed patients would have been diagnosed more promptly due to updated knowledge and consideration of BrS.

QUINIDINE TREATMENT

Quinidine has been shown to be extremely effective in the treatment of BrS patients, specifically those with arrhythmic storms [7]. Currently, guidelines give a class IIa indication for treatment with quinidine for those with ≥ 2 VF episodes within a 24 hour period [15]. Quinidine was given during follow-up to 15 patients in group 1. The majority of these cases (n=10) were treated with quinidine following a satisfactory response at EP study [6,7], while the others began the medication only following a recurrent AE. Our current results provide additional insight into the extraordinary efficacy of quinidine in abolishing recurrent VF/VT events in this population of cardiac arrest survivors and receivers of appropriate ICD therapy for BrS. Recurrent arrhythmias in this population were only observed

in patients in whom quinidine was not given or discontinued (voluntarily or due to side effects) [5]. Re-initiation of quinidine in patients with recurrent AE prevented future events, although it required an increase of dosing in a single case. Similarly, all patients from group 2 exhibited their initial appropriate ICD therapy while not being treated with quinidine, and later recurrences in four patients only occurred when patients stopped the medication. In light of these findings, we suggest that all BrS patients with a recurrent AE (after aborted cardiac arrest or a primary indication for implantation), especially those presenting with arrhythmic storms, should be given quinidine indefinitely to avoid further AE.

ARRHYTHMIA RECURRENCE

Recurrent AE occurred in 8/21 (38%) cardiac arrest survivors up to 8 years after the initial event and presented as appropriate device therapy. Our observed rates of recurrent events are slightly lower than those observed in prior studies [2,3], possibly as a result of widespread usage of quinidine as a preventive measure in our cohort. In these eight patients, the AE recurrence occurred as arrhythmic storms in 50%, with variable timing between 2 weeks to 8 years following the primary event. This result is comparable to reported rates of VF storm among BrS patients with recurrence following ICD implantation.

Importantly, in a single study [17] focusing on BrS cardiac arrest survivors, the only associated factor with VF recurrence was early re-polarization in the inferolateral leads. Our results suggest that a presenting arrhythmic storm may be an additional predictor for arrhythmic recurrence. Five out of the eight patients with recurrent AE in our study actually presented with arrhythmic storms at the time of their initial cardiac arrest. This result is in agreement with prior reports regarding the implication and long-term management of arrhythmic storms in BrS [7]. Moreover, out of the nine patients who presented with arrhythmic storms, two patients died early in the course of the disease, and only two had no subsequent events. We also observed that "VF storm begets VF storm," as three recurrent AEs that occurred as an arrhythmic storm had an identical initial presentation. These findings infer that those patients with an electric storm at presentation should be treated aggressively as they are most likely to recur, and frequently in a malignant way [5].

LIMITATIONS

In addition to the inherent underestimation of events described in this article, there are other limitations that should be addressed. First, the observatory and retrospective nature of the study and the small number of affected individuals prohibit the possibility of providing a robust model regarding insight to the factors leading to arrhythmia recurrence, besides the initial presentation of cardiac arrest as an arrhythmic storm. Second, since the study was not aimed to assess the outcome of all ICDs implanted in BrS patients (contrary to the original ISRABRU trial [4]), the actual number of ICDs implanted for primary prevention was not available; therefore, we are unable to assess the prevalence of AE in the group 2 population. Third, the relatively small number of individuals and follow-up on quinidine precludes a definitive evaluation regarding its degree of protection. Finally, although being a nationwide survey including all eligible BrS patients with a potentially lethal arrhythmic event, the results of this relatively small group may not be applicable to other populations, including non-Caucasian patients.

CONCLUSIONS

In the present study, we described in detail the clinical characteristics, diagnostic workup, and long-term follow-up of a relatively small subset of BrS patients who have experienced a potentially lethal cardiac event. Future studies should focus on identifying additional features that are associated with AE prediction and population based incidence of AE in BrS to reveal the actual risk of this syndrome.

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Capsule

Emptying the reservoir

Antiretroviral therapy can halt HIV-1 replication but cannot clear the hidden reservoirs of latent virus. **Lim** et al. treated simian immunodeficiency virus (SIV)-infected rhesus macaques with antiretroviral therapy with up to 19 doses of the Toll-like receptor 7 agonists GS-986 or GS-9620. By the third dose, all macaques experienced transient SIV plasma viremia within 48 hours. Dosing was also associated with activation of lymphocytes and reductions in SIV DNA in cells from the peripheral blood, lymph nodes, and gastrointestinal tract. When antiretroviral therapy ceased, two of nine treated macaques did not suffer rebound of virus and remained apparently virus-free and disease-free for more than 2 years.

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Eitan Israeli

Capsule

PTEN prevents the cytokine storm

An uncontrolled infection leads to sepsis, in which excessive production of proinflammatory cytokines, or a "cytokine storm," can cause potentially fatal tissue damage and organ failure. **Sisti** and colleagues found that septic mice had increased expression of the mRNA encoding the lipid and protein phosphatase PTEN. Mice lacking PTEN in myeloid cells showed greater inflammation, tissue injury, and mortality from sepsis. PTEN activity in the nucleus of macrophages induced the production of microRNAs that targeted *Myd88* mRNA, which encodes an adaptor protein required for cytokine production.

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Eitan Israeli

Capsule

Complement is a CD8+ T cell metabolic rheostat

Systemic lupus erythematosus (SLE) is associated with deficiencies in the complement protein C1q. Although C1q plays a role in the clearance of apoptotic cells, there are several redundant clearance pathways. Disruption of one pathway does not lead to an autoimmune defect. In a chronic graft-versus-host disease model of SLE, **Ling** et al. showed that C1q dampens $CD8^+$ T cell responses to self-antigens. C1q modulates metabolism through the mitochondrial cell-surface protein p32/gC1qR. The lack of C1q during a viral infection also enhances $CD8^+$ T cell responses. Thus, C1q plays a role as a "metabolic rheostat" for effector $CD8^+$ T cells.

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