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Clinical differences between drug-induced type 1 Brugada pattern and syndrome

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Abstract

Background: Diagnosis of Brugada syndrome (BrS) may be established by exposing a Type 1 Brugada pattern using a sodium channel blocker. Data on the outcomes of different patient populations with drug-induced Type 1 Brugada pattern are limited. The present study reports on the characteristics and outcome of subjects with ajmaline induced Type 1 Brugada pattern.

Methods: A multicenter retrospective study including all consecutive cases of ajmaline-induced Type 1 Brugada pattern from seven centers.

Results: A total of 260 patients (69.9% males, mean age 43.4 ± 13.5) were included. Additional characteristics included history of syncope ($n = 56$, 21.5%), family history of BrS ($n = 58$, 22.3%) or sudden cardiac death ($n = 47$, 18.1%) and ventricular fibrillation ($n = 3$, 1.2%). Patients were divided into those meeting current diagnostic criteria for drug-induced BrS (DIBrS) and compared to the drug-induced Brugada pattern (DIBrECG). Females were significantly overrepresented in the DIBrS group ($n = 50$, 40% vs. $n = 29$, 21.5%, $p = .001$). A significantly higher prevalence of type 2/3 Brugada ECG at baseline was found in the DIBrECG group ($n = 108$, 80.8% vs. $n = 75$, 60% in the DIBrS, $p = .026$). During a median follow up of three (IQR 1.50–5.32) years, a single event of significant arrhythmia occurred in the DIBrS group.

Conclusion: Less than half of subjects with ajmaline-induced Brugada pattern met current criteria for BrS. These individuals had very low rate of adverse outcomes during a follow up of 3 years, irrespective of the indication for the test or eligibility for the BrS diagnosis.

KEYWORDS
ajmaline, Brugada ECG pattern, Brugada syndrome, sodium channel blocker challenge test

1 | INTRODUCTION

Brugada syndrome (BrS) is a genetic and electrical heart disease that can result in sudden cardiac death (SCD) of young, otherwise healthy individuals with an ostensibly normal heart.[1] The diagnostic criteria of the syndrome have evolved over the past three decades[2–4] but the identification of a type 1 Brugada ECG remains its essential component.[1]

Type 1 Brugada ECG might not present spontaneously, and sometimes unmasking by a sodium channel blocker (SCB) is needed.[5] However, the clinical relevance of a positive SCB test, in asymptomatic patients, remains uncertain.[6] It is well established that patients who exhibit a spontaneous type 1 Brugada pattern have a notably greater risk of SCD compared to those with a drug induced Brugada pattern.[7] Moreover, it becomes increasingly clear that a positive sodium channel blocker test is insufficient to establish a diagnosis of Brugada syndrome.[5,8] Furthermore, there is no universally accepted indication for performing the test, resulting in a heterogeneous tested population limiting any analysis of the specificity of the test. Despite all that, subjects with a positive SCB test are at increased risk for SCD and may receive a defibrillator in case of syncope.[6,9]

As with any screening test, it is reasonable to assume that pre-test probability plays a crucial role in the positive predictive value of the result. Currently, there are limited data on the common clinical scenarios that prompt the use of a sodium channel blocker challenge, as well as the long-term outcome of patients with positive results.[6] The latest European Cardiology Society (ESC) guidelines present a new set of diagnostic criteria that narrow the definition of BrS to include only selected patients with drug induced Type 1 Brugada pattern. The differences between these newly defined populations as well as their outcomes have never been studied.

The present study, set out to investigate a large international population of subjects with a positive SCB challenge, and compare those who met the contemporary criteria of Brugada syndrome to individuals who merely had a drug induced Brugada type 1 ECG, assess their clinical characteristics, response to sodium channel blocker test, management, and outcome.

2 | METHODS

2.1 | Study design

This is a multicenter international retrospective analysis including all subjects with a positive ajmaline challenge test. Centers with experience in treating BrS were invited to participate by collecting all eligible patients. All cases were reviewed and, if considered eligible, divided into 2 groups based on the current diagnostic criteria for BrS[1]:

1. *Drug induced Brugada syndrome* (DIBrS)—induced type 1 ECG pattern with documented PVT/VF, arrhythmic syncope, or family history of BrS or SCD.
2. *Drug induced Brugada ECG* (DIBrECG)—induced type 1 ECG pattern in the absence of any of the aforementioned features.

2.2 | Inclusion and exclusion criteria (Figure 1)

Adult patients (aged ≥18 years) with an ajmaline challenge test resulting in a type 1 Brugada pattern. All tracings recorded during ajmaline were carefully reviewed by an experienced electrophysiologist (AS and AM).

Patients who underwent an ajmaline challenge with protocols involving other doses than 1 mg/kg or another class I antiarrhythmic agent were excluded. Patients with pre-existing spontaneous type 1 pattern on baseline ECG (including high precordial lead positions), or with incomplete follow up, or cases where the ECG tracings were not available for review were excluded. We further excluded patients with any other structural heart disease.

2.3 | Data collection

The study was approved by the Sheba medical center Institutional Review Board (IRB) committee as well as by the local IRBs in all participating centers. Demographic and clinical data were collected using a computerized structured data collection sheath. Data was extracted from the patient's medical records, national mortality registrar (where applicable), and a structured phone interview. All the collected data including ECG recordings were manually reviewed and reaffirmed by the contributing co-authors. Brugada ECG patterns were classified according to current guidelines[1] (Table S1).

2.4 | Ajmaline challenge test

The test was performed using local protocols at the discretion of the preforming physician. Briefly, the precordial leads were placed on 2nd, 3rd, and 4th intercostal spaces on both sides of the sternum (high lead positions).The ECG was reviewed for spontaneous type 1 Brugada ECG prior to ajmaline administration. A 12-lead ECG was continuously recorded starting prior to drug administration and subsequently at regular interval throughout the ajmaline infusion and for 5–10 min thereafter. The ECG was monitored for the development of the type 1 Brugada pattern. The maximal ST elevation in any lead was measured as was the ST elevation at 40 and 80 ms after the peak.[10] The occurrence of ventricular arrhythmia or conduction abnormalities was also recorded. The decision to terminate the ajmaline infusion before the full dose was reached, was at the physician's discretion.

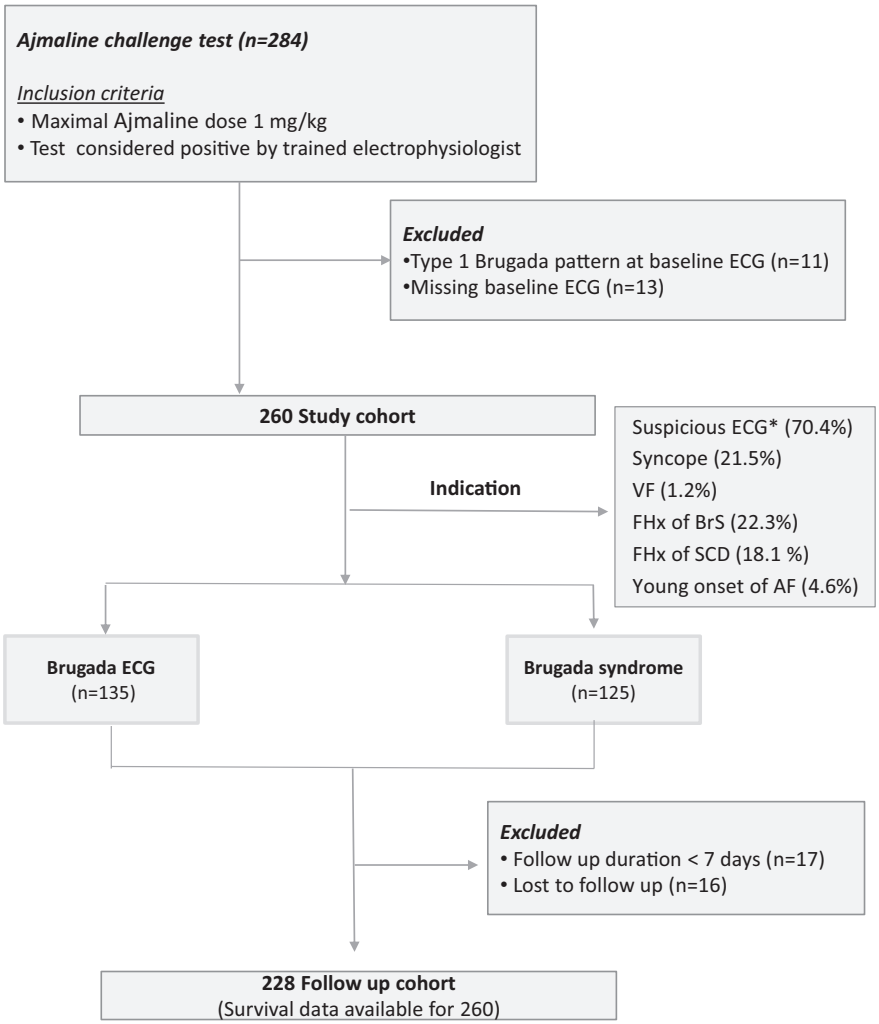

FIGURE 1 Study flowchart. AF, atrial fibrillation; BrS, Brugada syndrome; FHx, family history; SCD, sudden cardiac death; VF, ventricular fibrillation.

The ajmaline challenge test was preformed according to the standard practice of the participating centers and was based on a clinical suspicion of BrS in an individual patient rather than as part of a population screening initiative. The indication for each test were collected as part of the study

2.5 | Follow up

The structure and intensity of follow up varied greatly between centers and between patient profiles and ranged from a single in-clinic visit to a well-structured biannual visit. All subjects were advised to avoid known triggers of arrhythmia in BrS, namely prompted treatment of fever, moderation of alcohol consumption, avoidance of large meals and drugs with a sodium blocking effect. To account for the differences in the follow up protocols all patients underwent a standard structured interview designed specifically for this study and included all-cause death, sustained arrhythmia, arrhythmic syncope and implantation of cardiac monitoring devices or defibrillators (ICDs).

2.5.1 | Observation of a spontaneous type 1 Brugada ECG on follow up

In order to avoid potential bias arising from variable follow up protocols and other factors associated with the capture of a spontaneous type 1 Brugada ECG over time, we performed an ECG follow-up analysis in a subgroup of patients managed by a single center (Savigliano, Italy). In this center, all patients were invited for biannual in-clinic visits that included a clinical evaluation, high lead ECG and a 12-lead Holter monitoring (with the precordial leads in

the high lead position). The observation of a type 1 Brugada ECG pattern on an ECG and/or Holter was independently adjudicated by two experienced electrophysiologists (AS, AM).

2.6 | Statistical analysis

The normal distribution of age and weight was assessed and reaffirmed by Kolmogorov–Smirnov test. Continues variables were presented with means and standard deviations when applicable and with median and inter-quartile ranges (IQR) when appropriate. Differences were assessed using *t*-test or Mann–Whitney *U* test as applicable. Nominal variables were presented as proportions and compared using Chi-squared test or a Fisher exact test as appropriate. Event rates during follow up were estimated using the Kaplan–Meier method and compared using the log-rank test. A probability value $<.05$ was considered statistically significant. Statistical analysis was performed using SPSS, version 24 (IBM, Armonk, NY).

3 | RESULTS

3.1 | Study population

Seven centers from five countries (France, Italy, Switzerland, the Netherlands and Israel) agreed to participate, collecting a total of 284 consecutive patients with a positive ajmaline challenge test. However, 11 (3.9%) had a spontaneous type 1 Brugada ECG at baseline, and 13 (4.6%) patients had missing baseline ECG information and were all excluded from further analysis (Figure 1). A total of 260 patients comprised the final study population.

Table 1 describes the baseline characteristics of the study cohort. Most patients were male ($n=181$, 69.9%), with an average age of 43.4 ± 13.5 years at time of drug challenge. All patients except one were Caucasians. The majority of patients ($n=183$, 70.4%) had a type 2 or 3 Brugada ECG at baseline (see Table S1 for criteria). Additional reasons for the ajmaline challenge test were a personal history of syncope (21.5%), family history of BrS (22.3%), family history of SCD (18.1%), or atrial fibrillation (AF) onset at a young age (4.6%). In 3 (1.2%) cases the test was done as part of an evaluation following a ventricular fibrillation (VF) event (1.1%).

Female patients had a higher proportion of family history of BrS (39.2% vs. 14.9% in males, $p<.001$) and a higher rate of syncope (29.1% vs. 18.2% in males, $p=.05$). No other difference could be observed between genders (Table S2).

3.2 | Drug-induced Brugada ECG versus drug-induced Brugada syndrome

Following a review of the patients' history, cases meeting the current ESC guideline diagnostic criteria for Brugada syndrome[1] were defined as drug-induced Brugada syndrome (DIBrS, $n=125$, 48.1%, Table 1). The remainder were labeled as drug-induced Brugada ECG (DIBrECG, $n=135$, 51.9%). Female patients were significantly over-represented in the DIBrS group (40% vs. 21.5%, $p=.001$) and had a 2.49 (interquartile range: 1.46–4.43) fold higher likelihood of meeting the diagnostic criteria for the syndrome. Age at diagnosis and ethnicity were not different between the groups. As was the proportion of patients with young onset of AF.

All patients presented in sinus rhythm at the time of the ajmaline test. T wave inversion in right precordial leads was present twice more often in the DIBrS group but did not reach significance ($n=16$, 13.6% vs. $n=10$, 7.9% in the DIBrECG, $p=.155$), with a similar J point elevation at baseline (Table 1). The QRS morphology differed significantly between two groups with a significantly higher prevalence of a type 2 or 3 Brugada ECG found in the DIBrECG group (80.8% vs. 60% in the DIBrS, $p=.026$) (Table 1).

In all cases a total dose of 1 mg/kg of ajmaline was planned. In most cases the drug was infused over 5 ($n=41$, 15.8%) or 10 min ($n=208$, 80%) with no difference in protocols between the groups (Table 2). in all cases the administration of the ajmaline was stopped when a type 1 Brugada pattern was observed resulting in a similar test duration and total dose of ajmaline given in both groups. The peak ST segment elevation measured at 40 and 80 ms from the beginning of the J point were both comparable (Table 2). No severe adverse events were observed. Frequent PVCs were observed in five cases and non-sustained ventricular tachycardia in a single patient.

3.3 | Symptomatic versus asymptomatic cases at baseline

Patients with a personal history of aborted SCD or syncope were defined as symptomatic at baseline. The comparison between symptomatic and asymptomatic patients is detailed in Table S3. Females were over-represented in the symptomatic group (41.1% vs. 27.5%, $p=.05$) while the proportion of baseline ECG showing type II/III Brugada pattern was lower among symptomatic patients (58.9% vs. 73.5%, $p=.034$).

3.4 | Follow up

Survival data was available for all 260 patients. Complete clinical follow up information was available for 228 cases (87.7%) and included 114 patients from each group (Table 3). During a median follow up time of 3.01 years (1.50–5.32), a single event of malignant arrhythmia occurred resulting in SCD of a patient from the DIBrS group. There were two additional cases of non-arrhythmic mortality (malignancy and myocardial infarction), one from each group. Notably, the rate of syncopal events during follow up was three times higher in the DIBrS group than in the DIBrECG group (15.2% vs. 5%, $p=.027$, Table 3).

TABLE 1 Baseline characteristics of patients with drug induced Brugada ECG and drug induced Brugada syndrome.

	All	DI Brugada ECG	DI Brugada syndrome	
	n = 260	*n* = 135	*n* = 125	*p* value
Male sex, *n* (%)	181 (69.9)	106 (78.5)	75 (60.0)	.001
Age, years ± SD	43.4 ± 13.5	42.9 ± 12.2	43.9 ± 14.8	.550
Weight, kg ± SD	74.2 ± 16.1	77.1 ± 14.8	72.6 ± 16.8	.166
Ethnicity				
African, *n* (%)	1 (0.4)	1 (0.7)	0	1
Asian, *n* (%)	0	0	0	
Caucasian, *n* (%)	259 (99.6)	134 (99.3)	125 (100)	
History of AF, *n* (%)	12 (4.6)	8 (5.9)	4 (3.2)	.295
History of syncope, *n* (%)	56 (21.5)	0	56 (44.8)	<.001
Likely reflex mediated	30 (53.6)	0	30 (53.6)	
Likely arrhythmic	8 (14.3)	0	8 (14.3)	
Unexplained	18 (31.1)	0	18 (31.1)	
History of VF, *n* (%)	3 (1.2)	0	3 (2.4)	<.001
Family history, *n* (%)				
Brugada syndrome, *n* (%)	58 (22.3)	0	58 (46.4)	<.001
SCD, *n* (%)	47 (18.1)	0	47 (37.6)	<.001
Baseline ECG morphology				
Normal, *n* (%)	23 (8.8)	9 (6.7)	14 (11.2)	.026
ICRBBB/CRBBB, *n* (%)	36 (13.8)	14 (10.4)	22 (17.6)	
Type 2/3 Brugada, *n* (%)	183 (70.4)	108 (80.8)	75 (60)	
Other, *n* (%)	18 (6.9)	4 (3)	14 (11.2)	
Baseline J elevation (mm)	1.15 ± 0.8	1.33 ± 0.73	1.1 ± 0.8	.191
Baseline T wave inversion	26 (10.7)	10 (7.9)	16 (13.6)	.155
Baseline sinus rhythm	260 (100)	135 (100)	125 (100)	1

Abbreviations: CRBBBB, incomplete right bundle branch block; ICRBBB, incomplete right bundle branch block; SCD, sudden cardiac death.

An electrophysiologic study was performed in 38 (14.6%) patients. It was used three times more in the DIBrS group (25.4% vs. 7.9% in the DIBrECG $p < .001$). Only four patients were found to be inducible, all from the DIBrS group. A total of 32 (14%) patients were implanted with a loop recorder. The rates of implantation were significantly higher among patients with DIBrS (21.9% vs. 6.1%, $p = .001$). Similarly, the proportion of patients that received an ICD was much higher in the DIBrS (11% vs. 1.7%, $p = .004$). Quinidine treatment was initiated in 4 (1.8%) patients, three from the DIBrS group including one VF survivor. One patient (0.9%) from the DIBrECG group received the treatment as well ($p = .662$).

During follow up, a spontaneous type 1 Brugada pattern was identified in 12 (11.3%) and 10 patients (8.9%) from the DIBrS and DIBrECG respectively ($p = .574$). A sub analysis that included only cases followed at a single center that systematically screen with ECG and Holter monitoring (Savigliano, Italy) ($n = 118$) observed 12 patients (10.2%) who developed a spontaneous Brugada type 1 pattern. These patients were compared to those who were not found to have a spontaneous type 1 Brugada ECG during follow up ($n = 106$, 89.2%) (Table S4). While the comparison found no statistically significant differences due to the small sample size of the groups, the rates of a history of syncope, family history of BrS and SCD were all higher in patients that demonstrated a spontaneous type 1 during follow up (meeting the criteria of Brugada syndrome). Moreover, females tended to display spontaneous type 1 Brugada pattern more often during follow up (50% vs. 29.2%, $p = .142$).

History of symptoms at baseline was associated with a higher rate of syncope during follow up, and a higher rate of implantation of loop recorders or defibrillators despite an equal follow up duration (Table S5). However, the likelihood of demonstrating a spontaneous type 1 pattern was similar and the only patient that developed VF during the study follow up was asymptomatic at baseline.

TABLE 2 Ajmaline provocation test.

Parameter	All $n=260$	DI Brugada ECG $N=135$	DI Brugada syndrome $N=125$	p value
Ajmaline administration protocol				
1 mg/kg IV during 5 min	208 (80)	113 (83.7)	95 (76)	.436
1 mg/kg IV during 10 min	41 (15.8)	19 (14.1)	22 (17.6)	.443
Other	2 (0.8)	0 (0)	2 (1.6)	.230
Accumulated ajmaline mg/kg	0.84 ± 0.29	0.81 ± 0.26	0.87 ± 0.30	.353
Test duration, min	5 ± 2.21	4.9 ± 2	5.1 ± 2.4	.609
Peak ST elevation	3.9 ± 1.1	3.8 ± 1.2	4.1 ± 1.5	.177
ST elevation at 40 ms, mm	3.2 ± 1.1	3.2 ± 1.0	3.1 ± 1.2	.797
ST elevation at 80 ms, mm	2.2 ± 1.0	2.2 ± 1.0	2.1 ± 1.0	.485

4 | DISCUSSION

The present study enrolled consecutive patients with a positive ajmaline test (defined as the appearance of Brugada type 1 pattern) and divided them according to the ESC guidelines[1] to those meeting the definition of Brugada syndrome and those who merely have an induced Brugada type 1 ECG. The new diagnostic criteria create a new subpopulation of subjects that are SCB test positive but do not meet the diagnosis of BrS. The prognosis of these particular patients has only been investigated in a handful of studies, and there are no specific recommendations regarding their management.

The most significant observation of our study is that only half of SCB positive patients met the current diagnostic criteria of BrS. Importantly the yield was higher among females. Moreover, only one patient suffered from an arrhythmic event during a median 3 year follow up (an annual rate of 0.119%), which occurred in a patient from the DIBrS group. These result suggest the need for a more selective use of the sodium challenge test and a more structured approach.

The definition of Brugada syndrome has evolved since the Brugada brothers' publication in 1992.[11] Their first description was of patients displaying what is nowadays called "the spontaneous type 1 Brugada ECG." Since then, the spontaneous type 1 Brugada ECG persisted as the cornerstone for diagnosis and risk stratification of patients.

The recognition of mutations in the cardiac sodium channel gene SCN5A[12] led to the understanding that this syndrome is primarily an electrical disease. It was later realized that Brugada syndrome may present with absent or intermittent ECG patterns and that the diagnostic ECG can be unmasked by blocking these sodium channels[13,14] allowing a differentiation from idiopathic VF and generating the "drug-induced" type. Since then, there has been a gradual rise in reported cases leading to an increase in the reported prevalence of BrS worldwide, in parallel with increasing proportion of asymptomatic patients referred for SCB challenge.[15]

Determining the prognostic value of a positive SCB challenge test remains difficult. It is well established that the risk of malignant arrhythmia in this group is lower compared to the spontaneous type 1 Brugada group.[16] Nevertheless, the risk for an arrhythmic event is not negligible as evident by the fact that patients with drug induced BrS constituted a third of the largest cohort of BrS patients with arrhythmic events.[9]

Although there is no gold standard for the diagnosis of BrS in the absence of a spontaneous type 1 ECG, it has been suggested that the specificity of SCB challenge to unmask the pattern is imperfect. Similar to any other test, if used in scenarios of low pre-test probability SCB challenge may lead to false positive result.[5,17] Therefore, adequately selecting cases referred to the test is paramount. The ESC formally acknowledged this issue, for the first time, in the 2022 edition of guidelines concerning the prevention of ventricular arrhythmia and sudden cardiac death (SCD).[1] The recommendation is to restrict the utilization of SCB challenge to individuals exhibiting specific symptoms or possessing relevant family history.[1] In a recent review, Wilde et al. endorsed comparable recommendations, asserting that relying solely on the test in cases of type 2 Brugada ECG as an indication raises doubts about its value.[17] Our results support these notions.

4.1 | Drug-induced Brugada ECG versus drug-induced Brugada syndrome

The initial and most noteworthy finding from our study is that approximately half of the cohort fulfilled the criteria essential for a Brugada Syndrome diagnosis. Notably, within our study group, the existence of a type 2 or 3 Brugada pattern at the outset did not serve as a reliable predictor of Brugada syndrome. This implies that, as an isolated observation, it might not be sufficient to warrant the use of the SCB challenge.

Earlier studies have demonstrated a higher incidence of drug-induced Brugada pattern in female patients compared to males.[18] In our study, we noted that females with a positive Ajmaline test were more prone to receive the diagnosis of Brugada syndrome rather than only drug-induced Brugada ECG. This suggests that conducting the test in suspected females is a reasonable approach.

TABLE 3 Events during follow up.

Parameter	All N = 228	DI Brugada ECG N = 114	DI Brugada syndrome N = 114	p value
Syncope, *n* (%)	24 (10.6)	7 (5)	17 (15.2)	.027
Likely reflex mediated	17 (70.8)	5 (71.4)	12 (70.6)	
Likely arrhythmic	5 (20.8)	2 (28.6)	3 (17.6)	
Unexplained	2 (8.3)	0	2 (11.8)	
Implantation of loop recorder, *n* (%)	32 (14)	7 (6.1)	25 (21.9)	.001
Ventricular arrhythmia detected, *n* (%)	0	0	0	NA
Implantation of a defibrillator, *n* (%)	15 (6.58)	2 (1.75)	13 (11.4)	.001
Appropriate therapy	0	0	0	NA
Quinidine Tx, *n* (%)	4 (1.8)	1 (0.9)	3 (2.6)	.662
EPS, *n* (%)	38 (16.7)	9 (7.9)	29 (25.4)	<.001
Positive, *n* (%)	4 (10.5)	0	4 (13.8)	.239
New spontaneous type 1 ECG, *n* (%)	22 (10)	10 (8.9)	12 (11.3)	.574
VF/SCD, *n* (%)	1 (0.4)	0	1 (0.9)	1
Follow up duration (years), median (IQR)	3.09 (1.50–5.32)	3.36 (1.68–5.32)	3.03 (1.25–5.38)	.503

Beyond the factors incorporated in the diagnostic criteria, no individual variable exhibited an independent association with the diagnosis of Brugada syndrome. This lack of association could be attributed to a greater prevalence of a family history of sudden cardiac death (SCD) and Brugada Syndrome (BrS) among females referred to the test, leading to an elevated pretest probability of a "true positive" outcome. While this observation may indicate a referral bias and a potentially lower threshold for Ajmaline challenge tests in males, it also suggests that refining the indications for the test could enhance its specificity.

4.2 | Arrhythmic events in patients with a positive ajmaline test

Among the 228 patients in our cohort with comprehensive follow-up data, only one experienced an arrhythmic event over a 3-year period. This patient met the diagnostic criteria of Brugada syndrome. Our results suggest a lower risk of SCD among patients with a drug induced Brugada pattern. The arrhythmic event rate of 0.119% per year is significantly lower than previous reports.[6,19] While it is well established that the risk in patients with drug induced Brugada ECG is lower than in those with spontaneous type 1 pattern, few studies have focused specifically on the former population[6] and most reports included mixed groups.[20–22] The relatively limited number of events could stem from our relatively brief 3-year follow-up period. Nevertheless, the lower annual rate is probably attributable to differences in the characteristics of the studied population. This is supported by the higher proportion of patients with a history of aborted SCD and family history of SCD included in cohorts reported by Rizzo et al.[19] and Sieira et al.,[6] all markers of a higher risk for SCD. The incidence of malignant arrhythmic events in our study resembled those observed in cohorts of asymptomatic patients with drug-induced Brugada syndrome.[16] Moreover, a minority of individuals in our cohort were symptomatic at the time of the test, and only three were survivors of cardiac arrest. Intriguingly, none of these patients experienced a recurrence during the 3-year follow up period.

The sole intervention provided to all patients in our cohort involved education, with a focus on avoiding arrhythmic triggers. Our study did not aim to assess the effectiveness of this approach or determine its adequacy in specific cases. Indeed, future studies are necessary to enhance risk stratification for these patients and to develop a more organized and selective approach for employing the SCB challenge.

4.3 | Study limitations

This is a retrospective and observational analysis of patients with a positive ajmaline challenge test. While ajmaline is acknowledged as the most sensitive sodium blocker challenge test, it may not be the most specific, and we did not include other commonly used sodium channel blockers in our study. The relatively brief follow-up duration

limits the prognostic significance of our findings, and a more prolonged follow-up period is certainly warranted. Furthermore, as prolonged ECG monitoring was not a routine part of the follow up we cannot rule out the possibility that the syncopal events, particularly those not clearly reflex mediated, were in fact the result of non-sustained arrhythmia. Our study cohort may potentially constitute a population with a lower a priori risk than previously documented. Importantly, our cohort did not include Asian patients, a population with a higher prevalence of BrS, however, it was assembled from various specialized centers across Europe, making it representative of current practices. Additionally, it is essential to note the absence of genetic testing in our study.

5 | CONCLUSION

Over a 3-year follow-up period, the likelihood of sudden cardiac death (SCD) in individuals with a positive ajmaline test is remarkably low, even when meeting the revised diagnostic criteria for Brugada syndrome. Employing the ajmaline challenge should be reserved for high-risk cases with a substantial pre-test probability of Brugada syndrome. Educating patients on the importance of arrhythmic triggers is prudent and should be encouraged in all cases.

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This research did not receive any form any source.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interests for this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Sheba medical center Institutional Review Board (IRB) committee as well as by the local IRBs in all participating centers. All participants signed informed consent forms.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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