JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 84, NO. 10, 2024

Continuous Rhythm Monitoring With Implanted Loop Recorders in Children and Adolescents With Brugada Syndrome

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ABSTRACT

BACKGROUND Young (<18 years of age) patients with Brugada syndrome (BrS) are often under-represented in BrS studies and their management, especially related to syncopal episodes, remains unclear.

OBJECTIVES This study sought to describe the arrhythmia prevalence among young patients with BrS undergoing continuous rhythm monitoring by implantable loop recorder (ILR) and to assess the etiology behind syncope of undetermined origin.

METHODS A total of 147 patients with BrS with ILR were enrolled in 12 international centers and divided into pediatric (age <12 years; n = 77, 52%) and adolescents (age 13-18 years; n = 70, 48%).

RESULTS Mean age was 11.3 years, 53 patients (36.1%) were female, and 31 (21.1%) had spontaneous type 1 electrocardiograms. Over a median follow-up of 3.6 years (Q1-Q3: 1.6-4.8 years), an arrhythmic event was recorded in 33 patients (22.4%), mainly of nonventricular origin: 15 atrial (10.2%) and 16 bradyarrhythmic events (10.9%). Ventricular arrhythmias occurred in 4 patients, all with spontaneous BrS, and were fever-related in one-half. Among all patients with recurrence of syncope during follow-up, true arrhythmic syncope was documented in 5 (17.8%), and it was due to bradyarrhythmias or atrial arrhythmias in 3 cases (60%).

CONCLUSIONS Continuous rhythm monitoring with ILRs in young patients with BrS detects a broad range of arrhythmias. Ventricular arrhythmias occur predominantly in patients with spontaneous type 1 electrocardiograms and during fever. Despite the young age, bradyarrhythmias and atrial arrhythmias are frequent and represent the cause of arrhythmic syncope in 60% of patients. Young patients with BrS with syncope of undetermined origin may benefit from ILR implant. (*JACC* 2024;84:921-933) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2024.04.070

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AV = atrioventricular

BrS = Brugada syndrome

ECG = electrocardiography

ICD = implantable cardioverter-defibrillator

ILR = implantable loop recorder

P/LP = pathogenic/likely pathogenic

PM = pacemaker

PSVT = paroxysmal supraventricular tachycardia

SCD = sudden cardiac death

VA = ventricular arrhythmia

VF = ventricular fibrillation

VT = ventricular tachycardia

Brugada syndrome (BrS) is an inherited disorder that can cause life-threatening ventricular arrhythmias (VAs) and sudden cardiac death (SCD).[1] In the seminal study, 3 of 8 patients were children and presented with VAs. Yet, BrS is rarely diagnosed during childhood.[2] Despite impressive progress in characterizing BrS in the adult population in the last 30 years,[3,4] very few studies have addressed BrS in the pediatric population. Risk stratification for arrhythmias in children remains a significant challenge due to its complex nature and lack of established evidences.

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Many questions remain unresolved, and numerous issues require attention: 1) aside from the risk of life-threatening VAs, little is known about the incidence of atrial tachyarrhythmias and bradyarrhythmias in this population; 2) the characterization of syncope in pediatric patients is more difficult than in adults and the decision to implant an implantable cardioverter-defibrillator (ICD) is weighted by a higher risk of lifelong device-related complications, occurring in up to 34% of cases;[5-7] and 3) the evidence supporting guidelines recommendation, for what concerns ICD (Class 2a, Level of Evidence: C in case of suspected arrhythmic syncope) or implantable loop recorder (ILR) (Class 2a, Level of Evidence: C in case of syncope of undetermined origin) comes from the adult population.[4,8-13] Applying this recommendation to younger patients is questionable and needs confirmation.

The primary objective of this large multicenter study involving pediatric and adolescent patients with BrS undergoing continuous monitoring with ILRs was 2-fold: 1) to categorize the prevalence of VAs, atrial arrhythmias, and bradyarrhythmias in this population and the clinical benefit of ILR in refining the management of these patients; and 2) to characterize the prevalence of arrhythmic syncope in young patients with BrS and its underlying etiology.

METHODS

STUDY DESIGN. The present study is a retrospective multicenter study investigating the use of ILRs in patients with BrS <18 years of age at the time of ILR implant. The study conforms to the Declaration of Helsinki and was approved by the Ethics Committees of each participating center (approval numbers are reported in the Supplemental Appendix, Supplemental Information section). The data sets generated and/or analyzed during the current study are not publicly available to maintain patient confidentiality but are available from the corresponding author on reasonable request and after the agreement of all the coauthors.

PATIENT POPULATION: INCLUSION AND EXCLUSION CRITERIA. The overall pediatric BrS population at recruiting sites is depicted in Supplemental Figure 1. A total of 400 pediatric patients from the 12 participating centers were screened for inclusion. The present study included only patients <18 years of age at the time of ILR implant, who met all of the following inclusion criteria:

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Review and acceptance occurred under Dr Valentin Fuster's term as Editor-in-Chief.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 5, 2024; revised manuscript received March 27, 2024, accepted April 24, 2024.

1. Diagnosis of BrS, based on a Shanghai score ≥3.5.[4,12,14] Specifically, patients were included in the presence of a spontaneous type 1 electrocardiogram (ECG) (coved-type ST-segment elevation ≥2 mm in ≥1 right precordial leads [V_1-V_3] positioned in the fourth, third, or second intercostal space) or drug-/fever-induced Brugada type 1 ECG plus 1 of the following: 1) arrhythmic syncope or nocturnal agonal respiration; 2) family history of SCD at 45 years of age with negative autopsy; 3) family history of BrS; or 4) a pathogenic or likely pathogenic (P/LP) variant in *SCN5A*.
2. Implantation of an ILR after the diagnosis of BrS, with a follow-up of at least 12 months.

Exclusion criteria were: 1) the patient was previously diagnosed with sustained arrhythmias; and 2) <50% of required baseline data were available for the patient. None of the patients screened at each participating site was excluded because of the aforementioned exclusion criteria.

DATA COLLECTION AND DEFINITIONS. Patient data, including the indication for ILR implantation and demographic and clinical information (eg, Shanghai score, family history, ECG parameters, genetic test, and electrophysiological study) were collected and analyzed.

The suspected syncopal etiology was defined as follows: 1) arrhythmic syncope: abrupt onset without prodromal symptoms and triggers, short duration, and prompt recovery; 2) vasovagal: syncope associated with typical triggers (eg, pain, fear, long standing), and typical progressive prodromes (pallor, sweating, nausea); and 3) unexplained/unknown origin: when the clinical features did not allow to classify into one of the above forms.[11,15] Tilt table test, Schellong test, and other investigations to achieve a comprehensive characterization of the syncopal episodes before ILR implant were left at the treating physician's discretion, according to guidelines.[11,15]

During follow-up, arrhythmic events were collected and divided in 3 categories, based on current guidelines[16-18]:

1. Bradyarrhythmias of nonvasovagal origin, including: 1) sinus arrest of 3 to 6 seconds if symptomatic, or longer than 6 seconds if asymptomatic; or 2) advanced atrioventricular (AV) block (second-degree type II AV block or third-degree degree AV block). The vasovagal origin of each episode was assessed and ruled out based on the presence of typical triggers and prodromes, and its behavior, (eg, sinus node slowing preceding or occurring concurrently with AV block).
2. Atrial arrhythmias, including: 1) atrial fibrillation (AF)/atrial flutter longer than 6 minutes; or 2) atrial tachycardia or paroxysmal supraventricular tachycardia (PSVT) longer than 30 seconds.
3. VAs, including: 1) monomorphic sustained VT; or 2) sustained polymorphic VT or ventricular fibrillation (VF).[16-18]

All participating centers routinely performed remote monitoring of the device, and patients were systematically contacted within 24 to 48 hours after the arrhythmic event to facilitate the correlation with symptoms. All ILR events were reviewed and adjudicated by expert electrophysiologists. Arrhythmic events were categorized based on date of the first event, frequency of the event, and correlation with the initial symptoms. Data on mortality and cause of death were also recorded. The clinical benefit derived from ILR implantation was defined as the occurrence of arrhythmic events leading to a change in the clinical management of the patient (ie, catheter ablation, initiation of antiarrhythmic and/or anticoagulant drug therapy, pacemaker [PM] or ICD implantation).

ENDPOINTS. The primary endpoint was the occurrence of any ILR-recorded arrhythmia (VTs, atrial tachyarrhythmias, and bradyarrhythmias). Secondary endpoints were initiation of antiarrhythmic and/or anticoagulant medications, atrial or ventricular ablation procedures, PM or ICD implantations. Additionally, predictors of events with clinical benefit from ILR implantation were investigated as well as the incidence of syncope and its correlation with any arrhythmic events.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD when normally distributed or otherwise median (Q1-Q3). Comparisons between groups were undertaken with parametric (Student's *t*-test) or nonparametric (Mann-Whitney *U*) test, respectively. The comparison between categorical variables was performed with the chi-square test and the Fisher exact test, as indicated. Event-free survival probability for the first recorded event was estimated using the Kaplan-Meier method. Univariate linear regression analysis (ORs and 95% CIs) was used to estimate the association between baseline characteristics and events with clinical benefit from ILR implant. The prevalence of different arrhythmia subtypes over the years (0-18) is presented with Loess curves for visual interpretation. A 2-sided *P* value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 23.0 (IBM Corp).

TABLE 1 Characteristics of the Participants at Baseline

	Total (N = 147)	<12 y Pediatric (n = 77)	12-18 y Adolescents (n = 70)	*P* Value
Age at ILR implant, y	11.3 (7.4-15.0)	7.7 (4.1-9.5)	15.2 (13.6-16.4)	<0.001
Female	53 (36.1)	23 (29.9)	30 (42.9)	0.12
Proband status	55 (39.0)	30 (41.1)	25 (36.8)	0.61
Family history of BrS	93 (63.3)	47 (61.0)	46 (65.7)	0.61
Family history of SCD	37 (25.2)	17 (22.1)	20 (28.6)	0.44
Spontaneous Brugada type 1 ECG	31 (21.1)	24 (31.2)	7 (10.0)	**0.002**
Fever-induced Brugada type 1 ECG	34 (23.1)	22 (28.6)	12 (17.1)	0.12
Shanghai score	4 (4-5)	4.5 (4-5.5)	4 (3.5-4.5)	0.28
PR interval, ms	150.4 ± 23.5	148.9 ± 23.1	151.9 ± 23.9	0.44
QRS interval, ms	100 ± 14.9	100.0 ± 16.4	103.2 ± 12.9	0.19
Genetic test	117 (79.6)	68 (88.3)	55 (78.6)	0.12
SCN5A P/LP variant	57/117 (48.7)	32/66 (48.5)	25/51 (49.0)	1.0
VT/VF induction during EP study	10/59 (16.9)	4/28 (14.3)	6/31 (19.4)	0.73
Symptoms before ILR				
Syncope	46 (31.2)	23 (29.9)	23 (32.9)	0.86
Palpitations	13 (8.8)	8 (10.4)	5 (7.1)	0.56
Agonic breathing during the night	2 (1.4)	2 (2.6)	0	—
Epilepsy	6 (4.1)	4 (2.7)	2 (2.8)	0.91
Syncope characterization before ILR, % of all syncope				
Suspected arrhythmic	5 (10.8)	5 (21.7)	0	0.079
Unexplained	41 (89.1)	18 (78.3)	23 (100)	—

Values are median (Q1-Q3), n (%), or n/N (%). **Bold** values are statistically significant.

BrS = Brugada syndrome; ECG = electrocardiogram; EP = electrophysiological; ILR = implantable loop recorder; P/LP = pathogenic/likely pathogenic; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

RESULTS

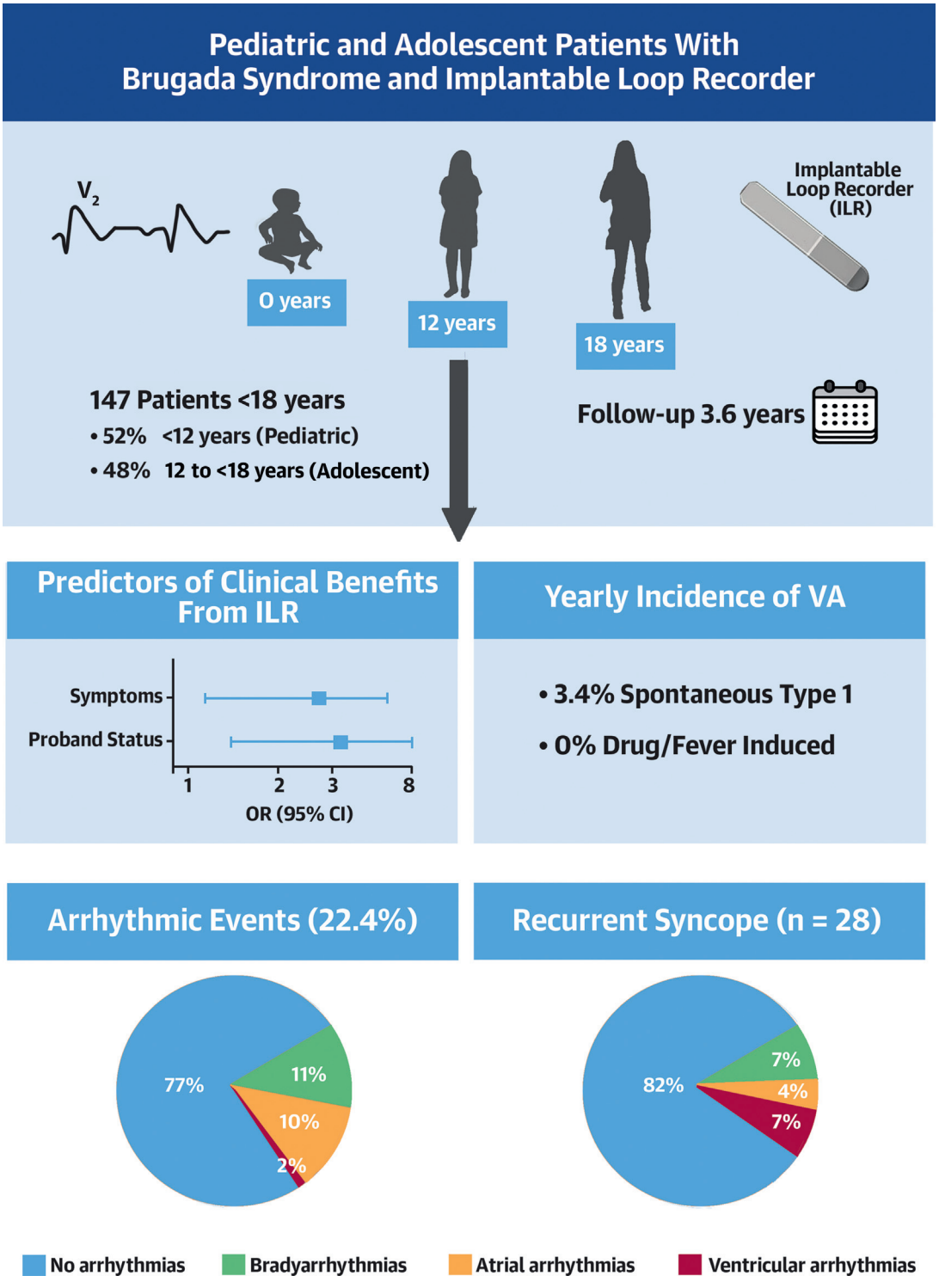
BASELINE CHARACTERISTICS. The study population included 147 patients with BrS, who underwent ILR implantation between 2015 and 2022 at 12 international centers. Median age was 11.3 years (Q1-Q3: 7.4-15.0 years), and 53 were female (36.1%). Seventy-seven patients (52.3%) were children (<12 years of age), whereas the remaining 70 (47.6%) were adolescent (12-18 years of age) at the time of ILR implant. Baseline characteristics are reported in **Table 1**. Sixty-five patients (44.2%) had a spontaneous or fever-induced Brugada type 1 ECG and 93 had a family history of BrS (63.3%). A genetic test was performed in 117 patients (79.6%), and a P/LP *SCN5A* variant was found in 57 (48.7%).

Overall, 67 patients (47.6%) were implanted due to symptoms (ie, syncope, palpitations, epilepsy, nocturnal agonic breath). In patients with syncope (n = 46), the suspected etiology was undetermined in 41 (89.1%) and initially considered arrhythmic in 5 (10.8%). A comparison between symptomatic and asymptomatic patients is presented in Supplemental Table 1. Asymptomatic patients underwent ILR implantation due to family history of SCD, spontaneous type 1 ECG, or family wish.

ARRHYTHMIC EVENTS AT FOLLOW-UP. Over a median follow-up of 43.2 months (Q1-Q3: 19.3-57.2 months), 35 arrhythmic events were recorded in 33 patients (22.4%) (**Central Illustration**, **Table 2**). Specifically, 16 patients (10.9%) experienced a significant bradyarrhythmia (3 advanced AV block and 13 sinus arrest), and 15 patients (10.2%) experienced atrial tachyarrhythmias (5 AF and 10 PSVT). Four patients (2.8%) experienced a VA (3 sustained monomorphic VT, 1 nonsustained VF) (Supplemental Figure 2) with a yearly incidence rate of 0.7% (3.4% among spontaneous type I ECG vs 0% among fever- or drug-induced BrS). Concomitant fever during VAs was reported in 2 cases (50%). The baseline characteristics of these 4 patients are presented in Supplemental Table 2. No patient died during follow-up.

The arrhythmic event distributions stratified according to the symptom status and age are presented in **Table 2** and **Figure 1**. The incidence of arrhythmias in each age group is presented in **Figure 2**. The

CENTRAL ILLUSTRATION **Arrhythmias and Arrhythmic Syncope in Young Brugada Patients With Implantable Loop Recorders**



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In our large cohort of pediatric patients with Brugada syndrome (147 patients from 12 international centers) monitored continuously with an implantable loop recorder (ILR) for 3.6 years, 22.4% of the patients experienced an arrhythmic event. Arrhythmic syncope occurred in 18% of patients. The presence of symptoms and proband status were significant predictors of clinical benefit from ILR implant. VA = ventricular arrhythmia.

TABLE 2 Follow-Up Outcomes Comparison Between Patients Younger and Older Than 12 Years of Age

	Total (N = 147)	<12 y Pediatric (n = 77)	≥12 y Adolescents (n = 70)	HR	Lower 95%CI	Upper 95% CI	*P* Value
Arrhythmic events							
Overall arrhythmias, number of patients	33 (22.4)	13 (16.9)	20 (28.6)	0.5	0.3	1.0	**0.05**
Bradyarrhythmic events	16 (10.9)	5 (6.5)	11 (15.7)	0.3	0.1	1.0	**0.05**
Atrial tachyarrhythmias	15 (10.2)	7 (9.1)	8 (11.4)	0.6	0.2	1.8	0.45
Ventricular tachyarrhythmias	4 (2.8)	2 (2.6)	2 (2.8)	1.1	0.1	16.1	0.86
Arrhythmic death	0	0	0	–	–	–	–
	Total (N = 147)	**<12 y Pediatric (n = 77)**	**≥12 y Adolescents (n = 70)**	**OR**	**Lower 95%CI**	**Upper 95% CI**	***P* Value**
Clinical benefit from ILR	22 (15.0)	9 (11.7)	13 (18.6)	0.6	0.2	1.4	0.25
PM implantation	0	–	–	–	–	–	–
ICD implantation	7 (4.8)	4 (5.2)	3 (4.3)	1.2	0.3	5.7	0.79
Drug therapy initiation	0	–	–	–	–	–	–
Atrial arrhythmias ablation	13 (8.8)	6 (7.8)	7 (10)	0.7	0.2	2.4	0.64
Ventricular arrhythmias ablation	3 (2.0)	2 (2.6)	1 (1.4)	–	–	–	–

Values are (%) unless otherwise indicated. Bold values are statistically significant. Univariate Cox regression (upper part) and logistic regression (lower part) analysis for predictors of arrhythmias, comparing patients with symptoms and those without symptoms.

ICD = implantable cardioverter-defibrillator; PM = pacemaker; other abbreviations as in Table 1.

incidence of bradyarrhythmias progressively increased with age, whereas atrial arrhythmias peaked at 10 to 12 years of age and VAs started to decrease after the age of 16.

CLINICAL BENEFIT FOLLOWING ILR-DETECTED ARRHYTHMIAS. An ICD was implanted in 7 patients (4.8%). No patient was started on antiarrhythmic or anticoagulant medications, but 16 patients (10.8%) were referred for catheter ablation: 13 patients underwent atrial arrhythmias ablation (8 AV nodal re-entrant tachycardia/AV re-entrant tachycardia ablation, 5 AF ablation) and 3 patients underwent VT ablation. One patient presented with right ventricular outflow tract VT, which was successfully ablated from the endocardium, whereas 2 patients presented with bundle branch re-entrant VT.

PREDICTORS OF CLINICAL BENEFIT FROM ILR IMPLANT. At univariate linear regression analysis (Table 3), the presence of symptoms before ILR implant (OR: 2.9; 95% CI: 1.1-7.4; $P = 0.026$), and proband status (OR: 3.3; 95% CI: 1.3-8.6; $P = 0.013$) were found to be associated with clinical benefit from ILR implant.

The Kaplan-Meier distribution stratified by age and syncope is presented in Figure 3.

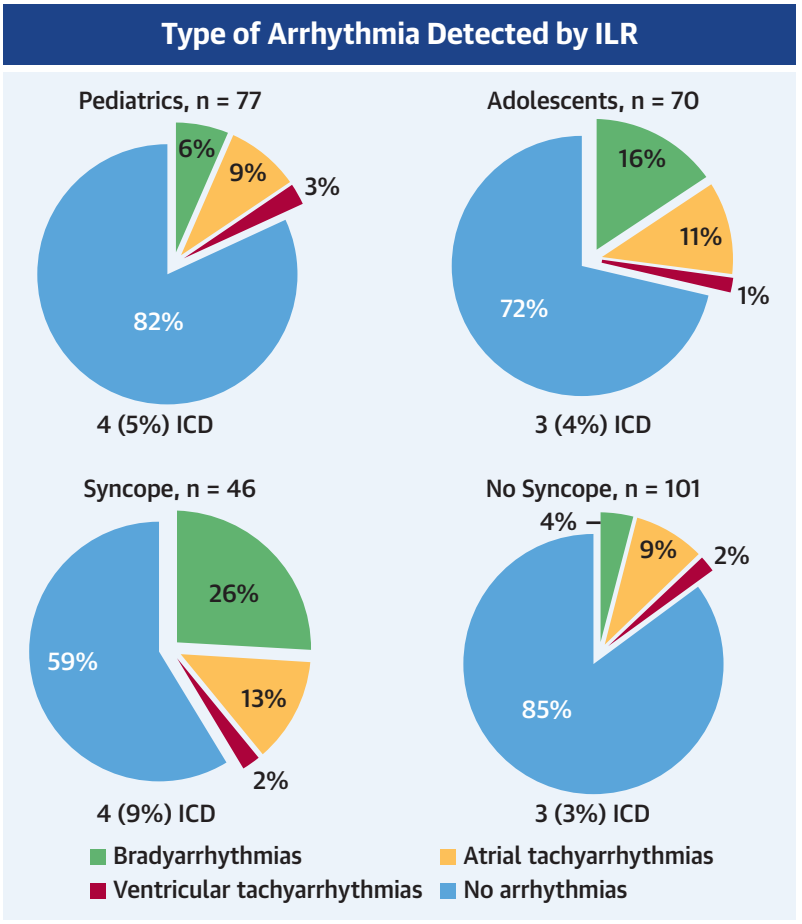
CHARACTERIZATION OF SYNCOPE. Over a median follow-up of 43.2 months (Q1-Q3: 19.3-57.2 months), syncope recurrence was experienced by 28 patients (60.8% of those whose ILR was implanted due to syncope) (Figure 4). Of them, a symptom-correlated arrhythmia was found in 5 cases (17.8%) (arrhythmic syncope), whereas no arrhythmia during the syncopal episode was documented in the remaining 23 (82.1%). Among the arrhythmic syncope, the underlying etiology was a bradyarrhythmia in 2 patients (40%, 2 cases paroxysmal high-degree AV block), VA in 2 cases (40%, 1 nonsustained VT, 1 sustained VT) and atrial arrhythmia in the remaining 1 case (20%, 1 AF). An asymptomatic arrhythmia was recorded in 7 of 28 patients (21.4%) with syncope recurrence (Figure 4).

DISCUSSION

The current study not only includes the largest cohort of young patients with BrS ever reported, but it is also the first large multicenter study describing pediatric and adolescent patients with BrS undergoing continuous rhythm monitoring with an ILR.

The main findings are: 1) continuous rhythm monitoring with ILRs in BrS pediatric patients can detect a broad range of heart rhythm disturbances including life-threatening arrhythmias; 2) VAs occur predominantly in patients with spontaneous type 1 ECG and in one-half of cases are fever-related; 3) despite the young age, bradyarrhythmias and atrial tachyarrhythmias are frequent, affecting 1 of 5 young patients with BrS, especially adolescents, with type 1 ECG and history of syncope; and 4) among young patients with BrS with unexplained syncope,

FIGURE 1 Arrhythmias in Different Subgroups



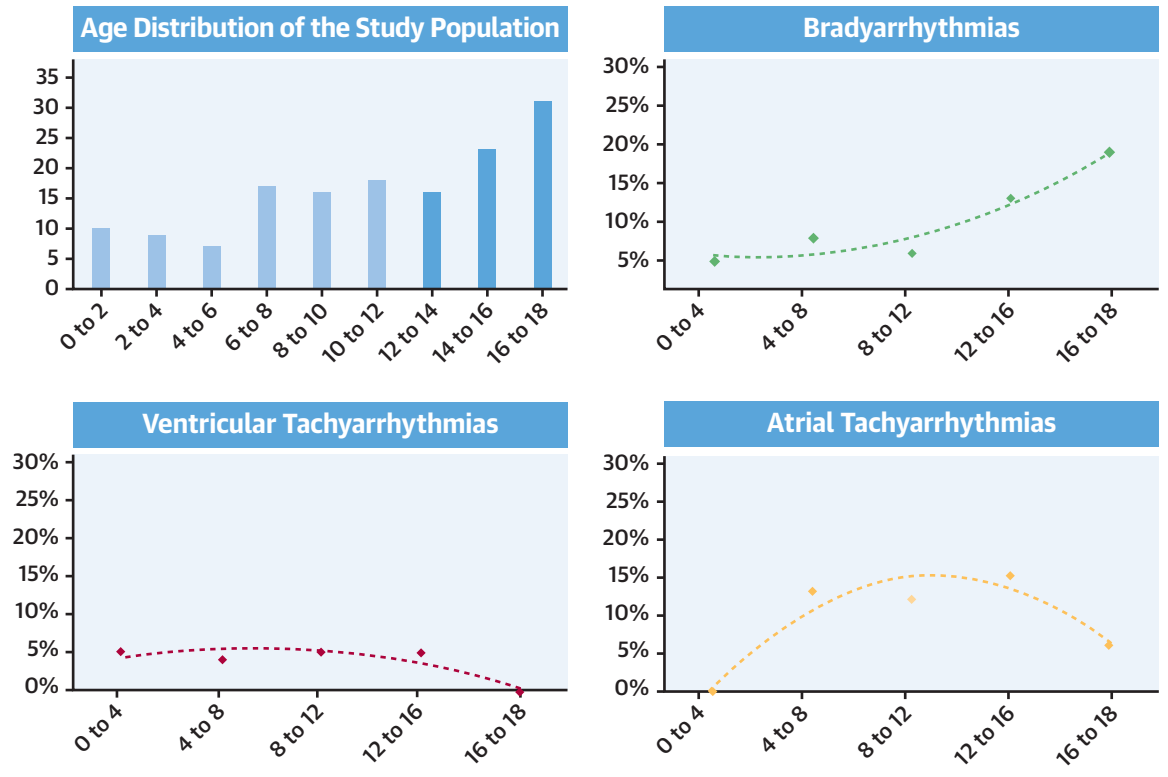
Type of arrhythmia detected at implantable loop recorder (ILR) monitoring, stratified according to the symptom status and age at baseline. ICD = implantable cardioverter-defibrillator.

the etiology is arrhythmic in <20% of cases, highlighting the benefit of a continuous rhythm monitoring-based strategy in this population.

BrS, CHILDREN, AND VAs. The first VA event for patients with BrS occurs generally between the fourth and fifth decades of life, and only 4.3% of all patients with BrS experience their first event before 16 years of age.[19-22] Because of the rarity of this entity, the outcome and management of pediatric patients with BrS are inconsistently described in the published data. Previous small mostly single-center published data are concordant in showing a lower incidence of ventricular events in young patients with BrS, along with a lower prevalence of spontaneous type 1 ECG as compared to the adult population.[5-7,19,23-25] Additionally, similarly to adults, the spontaneous type 1 ECG is strongly associated with the risk of life-threatening arrhythmias.[5-7,19,23-25] Michowitz et al[19] have previously reported on high-risk pediatric BrS in a smaller cohort of patients. In their study, only pediatric patients with previous ventricular arrhythmic events were included and 65% of the total population (57 pediatric patients) had type 1 ECG.

Our study gives a unique opportunity to assess the arrhythmic risk and to characterize syncopal events by continuous rhythm monitoring in this peculiar patient population. Ventricular arrhythmias in our

FIGURE 2 Age Distribution



Distribution of study population according to the age groups and arrhythmias distribution in different age groups. The numbers on the x-axis represent the years of age at the time of implantable loop recorder implant (top left) and at the time of the arrhythmic event (remaining panels).

TABLE 3 Predictors of Clinical Benefit From ILR Implantation

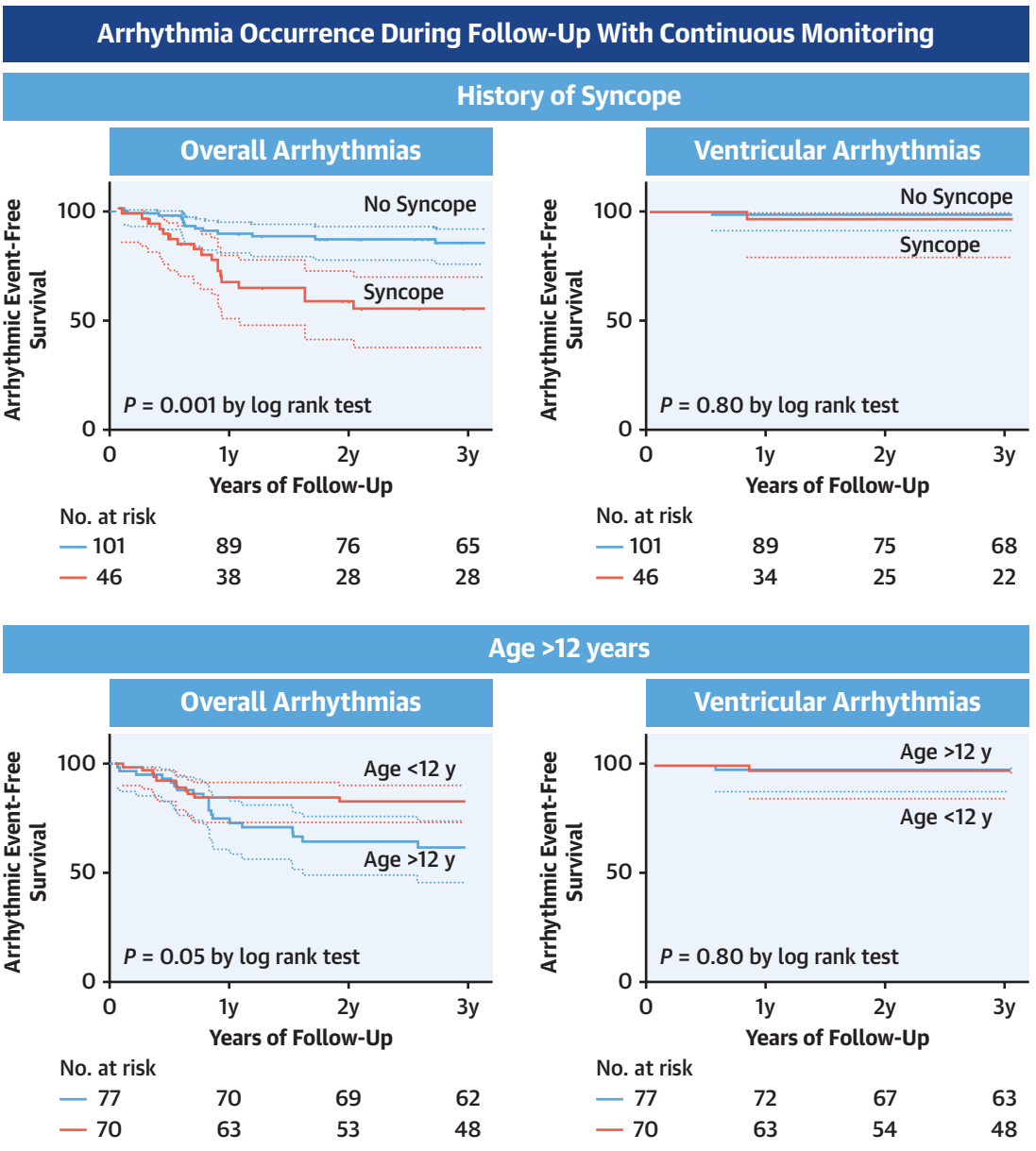
	Univariate Analysis			
		95% CI		
All Arrhythmic Events	OR	Lower	Upper	*P* Value
Female	0.8	0.3	2.1	0.65
Age <12 y	0.6	0.2	1.4	0.58
ILR for syncope	2.1	0.8	5.2	0.13
ILR for palpitations	1.8	0.5	7.2	0.39
ILR for symptoms	2.9	1.1	7.4	0.026
Proband status	3.3	1.3	8.6	0.013
Family history of BrS	0.7	0.3	1.6	0.36
Family history of SCD	1.9	0.8	4.9	0.19
Shanghai score	1.1	0.7	1.7	0.66
Fever-induced type 1 ECG	2.2	0.9	5.7	0.12
Spontaneous type 1 ECG	1.1	0.4	3.3	0.84
SCN5A P/LP variant	1.9	0.7	5.6	0.24
Positive EP study	3.9	0.9	16.2	0.060

Univariate logistic regression analysis for predictors of arrhythmias.
Abbreviations as in Table 1.

cohort were rare and exclusively observed in patients with spontaneous type 1 ECG, confirming the low risk of VAs among pediatric patients with non-spontaneous type 1 ECG. This may offer reassurance for patients and their families. Notably, the ECG phenotype and their related arrhythmic risk may change after puberty and these patients should be therefore closely monitored over time.[19,26,27]

The reason behind the different behavior of the disease between adults and children and before and after puberty is still a matter of debate. The role of testosterone in the development of Brugada ECG pattern and VF may explain the low event rate in pediatric patients, which is confirmed by the fact that there is no male predominance in pediatric patients with BrS and the age-related response to ajmaline test.[23,28-30] Our study shows a high rate of *SCN5A* P/LP variants (48.7%) in BrS pediatric patients, which is in line with a previous report on a smaller cohort of patients.[31]

FIGURE 3 Arrhythmic Event-Free Survival

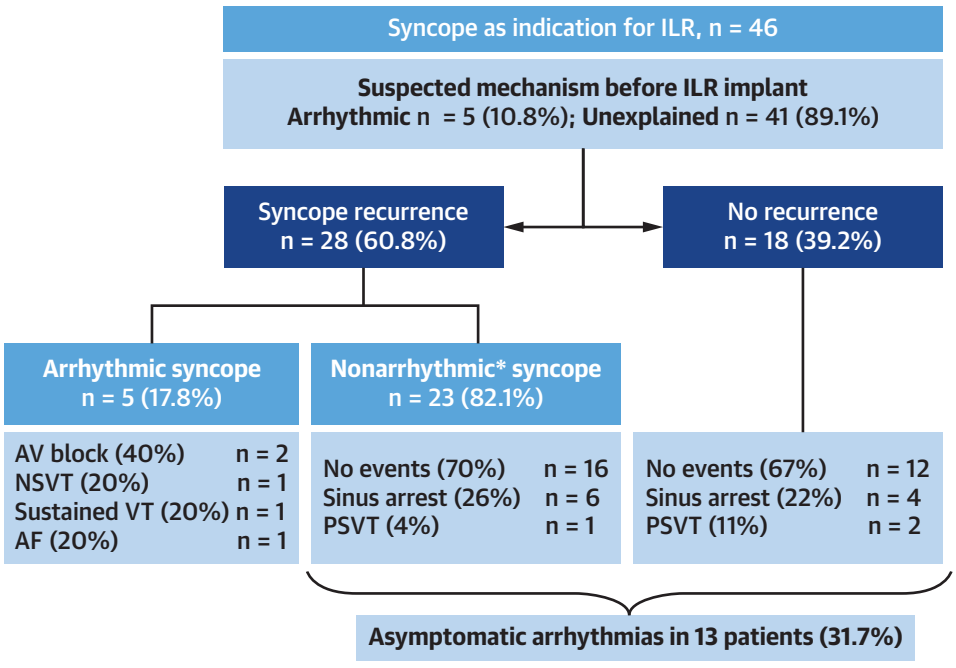


Arrhythmic event-free survival stratified according to age. (Left) Overall arrhythmias (atrial tachyarrhythmias, ventricular arrhythmias, and bradyarrhythmias). (Right) Ventricular arrhythmias.

CONTINUOUS RHYTHM MONITORING IN CHILDREN WITH (AND WITHOUT) BrS. Very few small studies including <12 patients can be found in the literature describing the use of ILR among children without known cardiomyopathy, mostly in the assessment of syncope.[32,33] Similarly, very little data are present in literature regarding the utility of ILRs among children with inherited arrhythmia syndromes.[34-37]

Our study highlights the fact that among pediatric patients with BrS, and no previous ventricular event, in case of cardiac symptoms, or proband status, the use of an ILR may be reasonable as the detection of

FIGURE 4 Syncope During Follow-Up



Characterization of syncope by implantable loop recorder (ILR). *No correlation between events and syncope. AF = atrial fibrillation; AV = atrioventricular; NSVT = nonsustained ventricular tachycardia; PSVT = paroxysmal supraventricular tachycardia; VT = ventricular tachycardia.

arrhythmic event is high (>30%) and predominantly related to bradyarrhythmias and atrial arrhythmias. Additionally, it is crucial to understand that in symptomatic patients with BrS, the absence of arrhythmic events is as significant as their presence. Identifying no arrhythmias can provide substantial reassurance to both the patient and their family, thereby positively affecting their quality of life.[38,39] Although the ILR may assist physicians in the characterization of symptoms complained by young patients with BrS, a comprehensive history collection and thorough evaluation of each syncopal event, including circumstances and patient's and family's event description, remain of paramount importance in guiding the decision-making process.

BrS AND SYNCOPE. In previous studies focusing on VA in pediatric patients with BrS, one-half of the patients, experiencing an arrhythmic event, reported syncope in the past.[5] On the other hand, in previous small studies addressing the etiology of syncope in young patients with BrS, this was due to vasovagal causes in more than one-half of the cases.[40] Based on guidelines, in the presence of suspected arrhythmic syncope, an ICD should be implanted.[4,11,12] However, 2 caveats should be considered. First, in adult patients, the predictive value of "suspected" arrhythmic syncope is relatively low: only up to 15% of patients with arrhythmic syncope experience sustained VAs 9 years after ICD implantation.[41] Second, inappropriate shocks and device-related complications are not infrequent, especially in young patients, being present in up to 34% at 7 years of follow-up.[5-7] This complexity is compounded by the fact that the diagnosis of arrhythmic syncope mostly relies on patients' memory and their ability to describe the event, which can be limited in young children.[42,43] Current guidelines suggest that instead of an ICD, an ILR should be considered in patients with recurrent episodes of unexplained syncope (Class 2a, Level of Evidence: C).[11,12] Our study contributes to the field of syncope in pediatric patients with BrS because it describes the course of pediatric patients with syncope and BrS and it accurately characterizes each of these patients with an ILR. Overall, our study confirms that syncopal episodes should be carefully investigated in young patients with BrS, before deciding to implant an ICD.

ATRIAL TACHYARRHYTHMIAS AND BRADYARRHYTHMIAS. Atrial arrhythmias are not infrequently reported among young patients with BrS, because they are often the presenting sign of the disease.[40,44] In recent

studies, the occurrence of atrial arrhythmias was found to range between 10% and 39%.[19,40] These data are in line with our study, reporting 10.2% of patients experiencing atrial arrhythmias (67% PSVT and 33% AF) and confirming the association between BrS and an "atrial phenotype" among certain patients.[45-47]

For what concerns the prevalence of bradycardia, this becomes often concealed after ICD implantation and it is thus under-reported in this population.[48] Among patients without continuous rhythm monitoring, AV block can be present in nearly 3% of patients with BrS and is often associated with syncope. As for sinus node dysfunction, although this can be asymptomatic and of apparently little clinical relevance, it is strongly associated in the pediatric population with increased risk of SCD.[5] Therefore, its diagnosis can help in risk stratification. The prevalence of advanced AV block and sinus node dysfunction in our study population was 2.0% and 8.8%, respectively. These findings importantly support the current guidelines-based recommendation on the utility of ILR in BrS with respect to symptom correlation and arrhythmia detection.[49]

Concerning the clinical consequences of the diagnosed arrhythmia, it is noteworthy, though not entirely unexpected, that in our cohort, no new medications were initiated—neither antiarrhythmic nor anticoagulant drugs, which contrasts with the management of older patients where both approaches are commonly adopted.[13] Many arrhythmias were indeed managed with a "first-line" ablation strategy. Equally remarkable is the use of ICDs in patients with bradyarrhythmias. The appropriateness and benefits of this strategy for young patients remain uncertain, because there are no clear guidelines recommending the best treatment approach. Further investigation is required to weigh the advantages and disadvantages of this decision and to determine whether the risks associated with ICDs as compared with a PM are outweighed by a long-term reduction in life-threatening events.

STUDY LIMITATIONS. Our study presents certain limitations, including the absence of a prospective design and the lack of predefined criteria for ILR implantation. Nevertheless, there are no guidelines-based recommendation to guide ILR implant in pediatric patients and prospective studies are warranted to confirm our findings. The low prevalence of spontaneous type 1 ECG, although in line with previous studies, may be considered as a limitation of our study and the study results cannot be entirely generalized to this specific population. The duration of 3-year follow-up period can be considered relatively brief, which could potentially result in underestimating event rates, especially considering the young age of the patient population. Due to the low event rate, no multivariable linear regression analysis was performed for the predictors of clinical benefit from ILR implantation. Additionally, because of the low rate of VA in the study population, no conclusive remark can be drawn on the risk assessment of future VAs. Even if the syncopal episode was related to an ILR-recorded bradyarrhythmias or atrial arrhythmia, the prognostic value of this finding in predicting future ventricular events is unknown. Further studies with very long-term follow-up are needed to clarify this issue.

CONCLUSIONS

Continuous rhythm monitoring with ILRs in young patients with BrS detects a broad range of heart rhythm disturbances including life-threatening arrhythmias. VAs occur predominantly in patients with spontaneous type 1 ECG and in one-half of cases are fever-related. Despite the young age, bradyarrhythmias and atrial arrhythmias are overall frequent and represent the cause of arrhythmic syncope in 60% of patients. This study supports the use of ILRs to assist clinicians in decision-making for managing pediatric patients with BrS, especially those with unexplained syncope.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was fully supported by a research grant of the Swiss National Science Foundation (PZ00P3_180055). Dr Özkartal has received research grants from Medtronic and Philips; and has received speaker fees from MicroPort CRM. Dr P. Brugada has received compensation for teaching purposes from Biotronik. Dr de Asmundis has received research grants on behalf of the center from Biotronik, Medtronic, Abbott, LivaNova, Boston Scientific, AtriCure, Philips, and Acutus Medical; and has received compensation for teaching purposes and proctoring from Medtronic, Abbott, Biotronik, LivaNova, Boston Scientific, AtriCure, Acutus Medical, and Daiichi-Sankyo. Dr Tondo has served on the Advisory Boards of Medtronic and Boston Scientific; and has received lecture and grant travel fees from Medtronic, Abbott Medical, Boston Scientific, and AtriCure. Dr Auricchio has served as a consultant to Boston Scientific, Cairdac, Corvia, MicroPort CRM, EPD-Philips, and Radcliffe Publisher; has received speaker fees from Boston Scientific, Medtronic, and MicroPort CRM; has participated in clinical trials sponsored by Boston Scientific, Medtronic, and EPD-Philips; and has intellectual properties with Boston Scientific, Biosense Webster, and MicroPort CRM. Dr Conte has received a research grant (PZ00P3_180055) from the Swiss National Science Foundation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients <18 years old with BrS, ILRs identified a 22% incidence of arrhythmic events and 18% incidence of arrhythmic syncope; 60% of the latter were nonventricular.

TRANSLATIONAL OUTLOOK: Future research should explore the incidence and types of arrhythmias in broad, unselected pediatric patients with BrS.

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KEY WORDS adolescent, atrial arrhythmias, bradyarrhythmias, Brugada syndrome, implantable loop recorder, pediatric, rhythm monitoring, sudden cardiac death, syncope, ventricular arrhythmias, young

APPENDIX For supplemental figures, tables, and the reference numbers of ethical committee approvals, please see the online version of this paper.