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Brugada syndrome in the young: an assessment of risk factors predicting future events

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Aims To investigate the clinical characteristics, prognoses, and presence of risk factors in young patients with Brugada syndrome (BS).

Methods and results A consecutive cohort of 128 young BS patients (≤25 years old at diagnosis) was analysed. Eighty-eight patients (69%) were asymptomatic, whereas 40 (31%) presented with clinical manifestations of BS. Markers of prognosis and risk were identified upon comparison of these two groups. A history of malignant syncope was strong predictors of ventricular arrhythmic events. Family history of sudden cardiac death (SCD) and mutations in the SCN5A gene did not associate with increased risk. Symptomatic patients presented with significantly abnormal baseline electrical characteristics when compared with the asymptomatic cohort, including spontaneous type I electrocardiograph (ECG) patterns, sinus node dysfunction (SND), first-degree atrioventricular (AV) block, and intra-ventricular conduction delay. The symptomatic group more frequently exhibited atrial arrhythmias. Electrophysiological studies resulted positive more frequently in symptomatic patients, but no risk association for future events could be determined. During the follow-up period (mean: 65 months), 10 arrhythmic events occurred in nine symptomatic patients (event rate: 4.5% per year). No events occurred in the asymptomatic group. Variables significantly associated with arrhythmic events during follow-up were presence of symptoms at diagnosis and spontaneous type I ECG. The presence of atrial arrhythmias and conduction abnormalities was also associated with the risk of arrhythmic events during follow-up.

Conclusion Symptomatic BS in the young age is a rare but malignant condition that can manifest with a spectrum of electrical abnormalities (i.e. SND, atrial tachycardias, AV block, and infra-nodal conduction delay) and result in the extreme cases in lethal arrhythmic events and SCD.

Keywords Brugada syndrome • Clinical characterization • Risk stratification

Introduction

Brugada syndrome (BS), first described in 1992, is a disease that predisposes to sudden cardiac death (SCD) in healthy patients with the absence of structural heart disease.[1] Patients present with a typical electrocardiographic (ECG) patterns characterized by coved-type ST-segment elevation in the right precordial leads (V_1–V_3), with or without right bundle branch block. These diagnostic ECG attributes may present spontaneously, or they may be undetectable until revealed by intravenous administration of a sodium channel blocker.

Patients with BS typically develop symptoms in the fourth or fifth decade of life. Yet, BS has been described in children, as in the first article on this syndrome, and has been linked to SCD in younger cohorts.[1,2] In the last few years, growing evidence has suggested that BS can present in early childhood and manifest as ongoing rhythm abnormalities and SCD.[3–6] Previous studies have identified an increased risk of sudden death in children affected by BS and described symptoms useful for prognosticating the disease.[7] Additionally, our group has previously described the final outcomes of follow-up in patients of <12 years of age (yo).[8] The aim of the

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What's new?

- This study is the largest collection of young patients with BS and their outcome in the mid and long term. It contains information on provocative tests in 128 individuals ≤25 years of age.
- It also constitutes the largest series of ventricular stimulation tests performed in this age group (>70% of patients with positive ajmaline test underwent a ventricular stimulation protocol); this allows to reach statistically significant conclusions in a disease that is rare in the young population.
- Risk criteria for the young population with BS were defined, and the high-risk markers that have been identified can help paediatric cardiologists and electrophysiologist to make management decision in their BS patients.

present study was to investigate risks factors related to BS in younger patient cohorts. To identify predictors for arrhythmic events and SCD, symptomatic and asymptomatic young BS patients were compared.

Methods

Study population

An ongoing prospective cohort has been collected since 1986. Patients with a spontaneous or drug-induced type I ECG have been included in a family registry and prospectively followed. Electrocardiographic findings were considered diagnostic of BS if a coved-type ST-segment elevation ≥2 mm was documented in at least one lead from V1 to V3.[9] This could occur in either the presence or absence of a sodium channel-blocking agent. The present study complies with the Declaration of Helsinki, the research protocol was approved by the UZ Brussel-VUB ethics committee, and informed consent of the subjects (or their parents) has been obtained.

From 1986 to 2015, a total of 1439 patients were tested with ajmaline provocative tests (*Figure 1*). Of these, 560 patients were positive for BS. Patients were included in study cohort if they were ≤25 yo at the time of diagnosis. We identified 128 young patients with BS. This young cohort was further subdivided according to whether patients were asymptomatic or presented with clinical manifestations of the disease (symptomatic) at diagnosis. Clinical or electrical evidence of BS included repetitive brutal syncope, aborted SCD (aSCD), ventricular arrhythmias [ventricular tachycardia (VT) or ventricular fibrillation (VF)], atrial arrhythmias, or sinus node dysfunction (SND). Personal histories of syncope, as well as family histories of BS or unexplained SCD, were noted. Syncope was defined as a non-traumatic and reversible loss of consciousness and was considered of arrhythmia origin if it was abrupt and without an underlying explanation. Patients with clinical diagnosis of vaso-vagal syncope were not considered as symptomatic and excluded from the cohort.

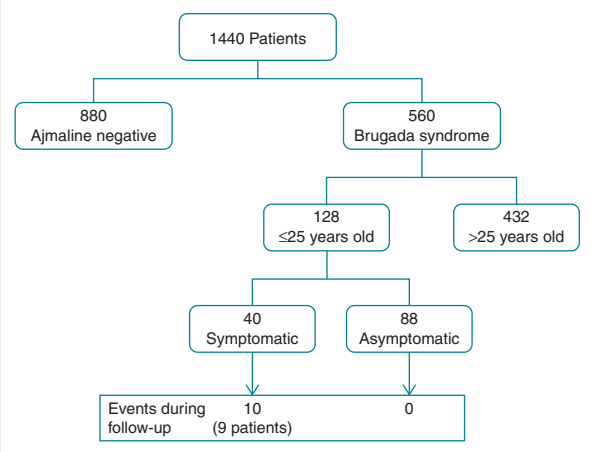

Figure 1 Flow diagram of the study patients.

Forty participants presented with clinical or electrical evidence of BS, and 88 patients were completely asymptomatic and free of conduction anomalies at enrolment.

Each patient was initially evaluated with a physical examination, a personal and family medical history work-up, a baseline ECG, and a provocative test with ajmaline in cases of normal baseline ECG. The absence of underlying structural cardiac abnormalities was confirmed in all patients by echocardiography. Most patients were also tested with cardiac magnetic resonance imaging (MRI) or computed tomography (CT).

Events during follow-up included SCD, aSCD, sustained (lasting >30 s) monomorphic VT, sustained polymorphic VT, sustained VF, and VF storm.

Provocative tests

Brugada syndrome diagnosis was based on either spontaneous type I ECGs or the presence of the typical ECG pattern during a provocative test. In the case of a spontaneous diagnostic ECG, the provocative test was not performed. In the case of a normal baseline ECG, an ajmaline intravenous infusion (maximum dose of 1 mg/kg) was administered over a 5 min (min) period. In patients younger than 5 yo, the test was performed under drug sedation by a single intravenous bolus of propofol. All baseline and drug-induced 12-lead ECGs were recorded at a paper speed of 25 mm/s and amplitude of 10 mm/mV, with the right precordial leads positioned at the sternal margin of the third and fourth intercostal space according to the guidelines.[9]

Ajmaline infusion was terminated before reaching the target dose if QRS prolongations was >30% above baseline, frequent premature ventricular beats or type I Brugada ECGs occurred, or in cases that developed high-degree atrioventricular (AV) blocks or sustained ventricular arrhythmias.

All ECGs were analysed before and after ajmaline administration by two independent, experienced electrophysiologists. In cases of disagreement, a third physician was consulted. PR intervals, QRS durations, and QTc intervals (determined using Bazett's formula) were measured in milliseconds (ms). Measurements of each parameter were obtained by averaging three consecutive beats. Maximal ST-segment elevations were measured at the J point in the right precordial leads (V_1–V_3), and analyses of ST-segment elevation were performed in leads V_1 and V_2. The presence of R waves in aVR and QRS fragmentations were identified and noted.[10]

The transmural dispersion of repolarization was assessed by measuring the Tpeak–Tend interval (Tp–e) and Tp–e dispersion.[11] Tp–e intervals were measured in each precordial lead, and the final measurements were obtained from the difference between QT and QT peak intervals (measured from the beginning of the QRS until the peak of the T wave). Tp–e dispersion was defined as the difference between the maximum and minimum Tp–e intervals in precordial leads V1–V6.

ECG measurements were repeated after ajmaline challenge. Ajmaline-induced sustained ventricular arrhythmias were defined as occurrences of sustained VF or sustained VT lasting at least 30 s.

Electrophysiological studies

Electrophysiological studies (EPSs) were performed with the purpose of risk stratification. In individuals <12 yo, studies were performed under propofol sedation. Intravenous accesses were gained using right femoral venipuncture, and single catheters were used to determine baseline intervals and to stimulate the hearts. Baseline intervals were measured, including the AH and HV intervals.

Evaluation of SND was performed in all patients who underwent an EPS. Electrophysiological evaluation of SND included measurement of sinus node recovery time (SNRT), corrected SNRT, and sinoatrial conduction time estimated using the method described by Narula *et al.*[12] The AV conduction system was evaluated by measuring the Wenkebach cycle length and the AV nodal effective refractory period in each case. In patients with either history of palpitations or evidence by Holter monitor of supraventricular tachycardia, an atrial stimulation protocol was also performed. The ventricular stimulation protocol consisted of a maximum of three ventricular extrastimuli, with minimum coupling interval of 200 ms, which were delivered from a single right ventricular site. Results were considered positive in the case of induction of sustained VF or VT.

Genetic tests

Starting in 2010, genetic testing to specifically analyse the SCN5A gene sequence was recommended for all young patients diagnosed with BS. Sequence analyses of SCN5A were performed by extracting genomic DNA from peripheral blood leucocytes using standard protocols. In mutation-positive index cases, family members were also screened for specific SCN5A genetic mutations.

Implantable cardioverter-defibrillator indications

Recommendations made in the Brugada consensus reports were used for establishing an initial diagnosis and for determining candidacy for implantable cardioverter-defibrillator (ICD) therapy.[13] Decisions to place epicardial vs. endocardial ICD leads, and the appropriate location for the ICD generators, were made on the basis of an individual patient's body size, age, and activity level. In this population, initial visits after implantation were scheduled at 1 and 3 months with visits every 6 months in the longer term. Home-monitoring devices allowed a closer follow-up in the paediatric group.

Follow-up

During the follow-up period, arrhythmic event outcomes occurred when individual patients experienced SCD or aSCD, recordings of sustained VT or VF during ECG, Holter monitoring, implantable loop recorder or ICD memory, or appropriate ICD shocks with tracings recorded in the memory.

Statistical analysis

Data were reported as mean ± SD or median, as appropriate, and were analysed with SPSS statistical package version 21 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA). The mean comparisons were performed with unpaired Student's *t*-tests, the Mann–Whitney test, and the Kruskal–Wallis test. Frequencies were cross-tabulated and analysed with χ^2 tests; Fisher's exact tests were used, when appropriate. Time data were presented with mean and range. Hazard ratio (HR), confidence intervals (CI), and *P*-values were calculated in univariate analysis. A multivariate analysis was adjusted on variables with a *P*-value of <0.15 in the univariate analysis, using a Cox model. The cumulative probability of an arrhythmic event or SCD at follow-up was determined with a life-table method of Kaplan–Meier for the different subgroups. The log-rank test was applied. Significance was defined as *P*-values of <0.05.

Results

Demographics, symptoms, and family histories

Among the BS-positive patients enrolled in the study, 128 were ≤25 yo at diagnosis. Of these, 88 individuals (69%) were asymptomatic, whereas 40 (31%) exhibited clinical manifestations of the disease. The demographic profiles, baseline clinical characteristics, and ECG parameters for each group (mean and SD) are given in *Table 1*.

Patients in the asymptomatic group [51% males; mean age at diagnosis 15.88 yo (range: 0.72–24.9)] belonged to 61 different families. Patients in the symptomatic group [65% males; mean age at diagnosis 14.93 yo (range: 0.96–24.47)] belonged to 35 different families. No significant gender predominance was evident, and patient ages at diagnoses were similar between symptomatic and asymptomatic groups.

Clinical manifestations

Clinical expressions occurring in symptomatic patients included aSCD ($n = 7$), severe syncope likely related to arrhythmias ($n = 30$), presence of AT ($n = 2$), and SND ($n = 1$). Syncope occurred at rest in 29 patients and during exercise in 1 patient. In two cases (5%), syncope was associated with fever. The average age at first onset of symptoms was 14.76 ± 7.36 yo (range: 1–24).

Recorded evidence of atrial tachycardia during follow-up in the symptomatic group included atrial flutter ($n = 2$) and atrial fibrillation ($n = 5$). In three patients, atrial fibrillation was associated with SND.

Family history

Forty-five young patients (35%) were the index patients in their respective families. Eighteen of these patients were asymptomatic (20%), whereas 27 patients were symptomatic (67%). Family history of SCD was present in 42 (47%) asymptomatic patients and 13 (32%) symptomatic patients ($P = 0.12$).

The ages of the family members who presented with SCD were statistically similar between the two groups. There was no difference in the early presentation of familiar SCD between the two groups. The percentages of patients with two or more family members who presented with SCD were no different between the groups. Overall, a family history of SCD was not significantly associated with the risk of symptomatic disease in young patients with BS.

Analysis of baseline and follow-up electrocardiographic parameters

Electrocardiographic parameters of the symptomatic and asymptomatic BS patients were compared (*Table 1*). Type I ECGs spontaneously presented in at least one ECG taken during diagnoses or

Table 1 Clinical characteristics, family history, and ECG parameters of young asymptomatic and symptomatic patients with BS

Group	Asymptomatic	Symptomatic	*P*-value
Number	88	40	
Male	45 (51)	26 (65)	0.18
Age at diagnosis (year)	15.88 ± 6.39	14.92 ± 6.82	0.44
Family history			
Family history SCD	42 (47)	13 (32)	0.12
Age familiar SCD	33.38 ± 13.55	37.69 ± 21.49	0.39
SCD <20 yo (*n*)	8 (9)	3 (7)	>0.99
SCD <12 yo (*n*)	1 (1)	2 (5)	0.23
≥2 SCD in the family	11 (12)	4 (10)	0.77
SCD in females	8 (9)	3 (7)	>0.99
Electrical characteristics			
Spontaneous ECG type I	4 (4)	12 (30)	<0.001*
Sinus node dysfunction	0 (0)	10 (22)	<0.001*
Maximal PR (ms)	154.73 ± 29.64	181.35 ± 44.72	<0.001*
First-degree AV block	19 (21)	20 (50)	0.001*
Maximal QRS (ms)	101.66 ± 18.34	122.17 ± 35.85	<0.001*
QRS fragmentation	12 (13)	6 (15)	0.79
R ≥ 3 mV aVR	3 (3)	6 (15)	0.05
Tpeak–Tend (ms)	85.37 ± 17.18	90.27 ± 18.12	0.16
Tp–e dispersion (ms)	23.35 ± 15.37	23.33 ± 19.79	0.99
QTc DII (ms)	405.51 ± 28.57	405.56 ± 31.22	0.99
Atrial arrhythmias	0 (0)	7 (17)	<0.001*
Conduction abnormalities	32 (36)	26 (65)	<0.001*

ECG, electrocardiogram; *n*, number; SCD, sudden cardiac death; yo, years old.
Data within parentheses indicate percentages.
*Statistically significant results.

follow-up visits in 4% of asymptomatic and 30% of symptomatic patients ($P < 0.001$). Overall, 18% of the cases of spontaneous type I ECG occurred during a febrile episode, irrespective of the presence of symptoms. Sinus node dysfunction was absent in the asymptomatic group and present in 22% of symptomatic patients ($P < 0.001$). Atrioventricular conduction abnormalities were present more frequently in the symptomatic group. Both the maximal PR intervals and maximal QRS intervals (obtained by comparing all available ECGs from each patient) were longer in the symptomatic group. The symptomatic group had wider mean baseline and maximal QRS durations than the asymptomatic group, with a mean QRS width of >120 ms in lead V2. Significantly more symptomatic patients exhibited frequent prominent R waves (≥3 mm; *Figure 2*) in aVR. Overall, electrical conduction abnormalities were more prevalent in symptomatic patients.

Provocative tests

Ajmaline provocative tests were performed in 84 asymptomatic patients (95%) and 34 symptomatic patients (85%) (*Table 2*). In asymptomatic patients, the main indication for ajmaline challenge was familiar screening. The test was not performed in four patients from the asymptomatic group and six patients from the symptomatic group due to evidence of spontaneous type I ECG.

After the infusion of ajmaline, ECG intervals lengthened in all patients when compared with baseline measurements. The only measurement that presented a significant difference post-ajmaline between the asymptomatic and the symptomatic groups was the QTc duration (443.90 ± 44.88 ms compared with 476.19 ± 77.14 ms, respectively, $P = 0.01$). All test results were positive for BS, as they exhibited increases in the ST elevation and appearances of coved type I patterns. There were no statistically significant differences between the two groups in the magnitude of R-wave elevations in aVR, Tp–e, or Tp–e dispersions.

None of the asymptomatic patients presented with ventricular arrhythmias during the provocative tests. Four symptomatic young patients (range: 5–7 yo) presented with sustained VFs or polymorphic VTs during ajmaline infusions (10% of the symptomatic subcohort and 3% of the entire cohort). All of them received immediate treatment with an infusion of isoproterenol; one required a shock from an external defibrillator for termination. The ventricular arrhythmias lasted, on average, 1–3 min and responded well to isoproterenol-induced sinus acceleration. No patients suffered long-term complications from the provocative tests.

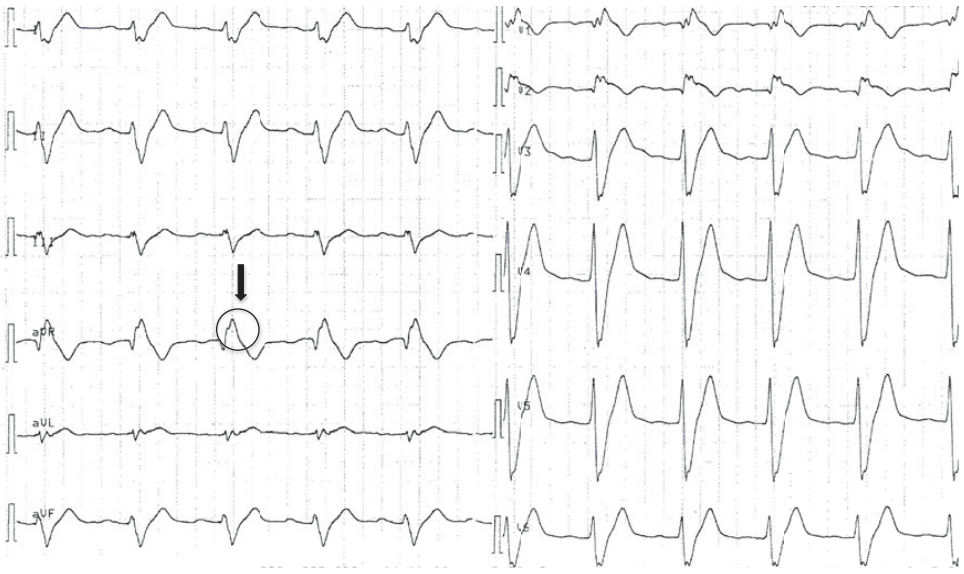

Figure 2 Twelve-lead ECG of 15 yo male who presented with aborted sudden death and was diagnosed with BS. Note the prominent R wave in lead aVR with spontaneous QRS fragmentation in aVR (late phase of QRS complex), V1, and V2 with saddle back type of ST elevation.

Table 2 Results of provocative test of asymptomatic and symptomatic patients

Group	Asymptomatic			Symptomatic			*P*-value[a]
	Baseline	After ajmaline	*P*-value	Baseline	After ajmaline	*P*-value	
Provocative test (*n*)	88	84 (95)		40	34 (85)		
PR (ms)	151.95 ± 27.63	193.86 ± 36.20	<0.001*	155.69 ± 35.65	196.15 ± 39.30	<0.001*	0.78
QRS (ms)	91.63 ± 16.18	135.52 ± 44.37	<0.001*	101.19 ± 23.73	149.23 ± 23.81	<0.001*	0.13
QTc (ms)	406.89 ± 27.24	443.90 ± 44.88	<0.001*	401.40 ± 25.73	476.19 ± 77.14	<0.001*	0.01*
R in aVR (mm)	1.25 (0–5)[b]	2.67 (0–7)[b]	<0.001*	1.76 (0–5)[b]	2.90 (0–5)[b]	<0.001*	0.53
Tp–e (ms)	85.29 ± 17.64	103.13 ± 17.94	<0.001*	83.20 ± 13.75	100.40 ± 25.24	<0.005*	0.56
Tp–e dispersion (ms)	21.66 ± 14.20	23.63 ± 15.65	0.38	18.57 (0–40)[b]	26.66 (0–50)[b]	0.03*	0.44
Sustained polymorphic VT/VF		0 (0)			4 (10)		<0.001*

Values are expressed in mean ± SD.
[a]Range.
[b]*P*-values in the intergroup comparisons of the increment in ECG parameters after the pharmacological test.

Electrophysiological study

An EPS was performed for risk stratification in 70 (79%) asymptomatic and 28 (70%) symptomatic patients, as shown in *Table 3*. The baseline interval measurements included AH, with no statistically significant differences between groups, and HV, which was longer in the symptomatic patients (47.04 ± 13.20 ms vs. 41.98 ± 7.08 ms; $P < 0.05$). The atrial stimulation protocol could not identify subclinical abnormalities in the AV nodal conduction system, other than prolonged HV interval. Supraventricular tachycardias were induced and ablated in five symptomatic patients [one atrial tachycardia, one atrial flutter, and three AV nodal re-entrant tachycardia (AVNRT)] and in one asymptomatic patient (one AVNRT). Sustained VF or polymorphic VT was induced in six symptomatic patients (21%) and was not induced in any asymptomatic patients ($P < 0.01$).

Genetic characteristics

Genetic testing was performed in 20 out of 40 symptomatic patients (50%), with 9 positive results (45%). This high diagnostic yield in the genetic test compared with the literature may be justified by the presence of advanced electrical disease in this group, including SND, conduction abnormalities, and atrial arrhythmias.

On the other hand, the genetic screen for mutations in the SCN5A gene was performed in 33 (37%) asymptomatic patients,

Table 3 Electrophysiological parameters and genetic data in asymptomatic and symptomatic young patients

Group	Asymptomatic	Symptomatic	*P*-value
EPS	70/88 (79)	28/40 (70)	0.26
EPS_AH	92.15 ± 18.35	95.06 ± 40.70	0.71
EPS_HV	41.98 ± 7.08	47.04 ± 13.20	<0.02*
Induction of A arrhythmias	5 (7)	1 (3)	0.67
Induction of V arrhythmias	0 (0)	6/28 (21)	<0.01*
Genotype			
Performed	33/88 (37)	20/40 (50)	0.24
SCN5A mutation positive	24/33 (72)	9/20 (45)	0.07
ICD			
ICD implantation	0/88 (0)	34/40 (85)	<0.001*
Follow-up			
Age last follow-up (year)	21.03 ± 8.49	20.51 ± 9.87	0.76
Length of follow-up (year)	5.16 (0–19.57)[a]	5.59 (0–31.37)[a]	0.68

A, atrial; EPS, electrophysiology study; V, ventricular.
Data within parentheses indicate percentages.
[a]Range.
*Statistically significant results.

and 72% of these tested positive for a mutation. The higher genetic yield in the asymptomatic group (72%) when compared with the asymptomatic group (45%) can be explained by the fact that genetic screening for the later group was very frequently preceded by the identification of a familiar mutation. Moreover, in those cases with no familiar mutation identified, the test was not usually performed in the younger generations if members were asymptomatic.

The yield in the genetic testing is higher when considering specific patients' characteristics: positive genetic results were found in 75% of patients with a spontaneous type I ECG pattern (6 out of 8 tested patients), 68% of patients with conduction abnormalities (19 out of 28 tested patients), 67% of patients with atrial arrhythmias (2 out of 3 tested patients), and 60% of patients with SND (3 out of 5 tested patients).

Implantable cardioverter-defibrillator implantation

An ICD was implanted in 34 symptomatic patients (85%). The indications for ICD implantations included aSCD ($n = 6$, 18%), inducible ventricular arrhythmias observed during either provocative tests or EPSs ($n = 8$, 23%), and high risk ($n = 20$, 59%), due to either multiple occurrences of severe syncope recalling arrhythmic events in the setting of a positive genetic tests and/or a family history of malignant BS disease. The mean age of ICD implantation was 17.83 ± 8.6 yo. Thirteen patients (38%, mean age 12.37 ± 6.91 yo) underwent epicardial lead implantation with an abdominal system.

Follow-up

After a mean follow-up period of 64 months (range: 0–376 months), 10 events were observed in nine symptomatic patients (22%), corresponding to an annual event rate of 4.5. Interestingly, we could not identify any event related to fever, but we have to note that patients are usually admitted and aggressively treated with antipyretics during febrile periods.

The clinical profile of the symptomatic patients who presented with events during the follow-up period is given in *Table 4*. Seventy-eight per cent ($n = 7$) were male, with a mean age at presentation of 12.14 yo (range: 2–24 yo). Fifty-five per cent ($n = 5$) initially manifested with aSCD. Abnormal baseline ECGs were present in 78% ($n = 7$) of these patients, 6 (67%) exhibited spontaneous type I ECGs, 6 (67%) exhibited first-degree AV blocks (AVB), one additionally presented with intermittent second-degree AVB, and two (22%) exhibited atrial fibrillation.

The only two patients who died in our cohort were a couple of siblings in whom the BS was initially described.[1] Both presented with spontaneous type I ECGs and several episodes of severe syncope and aSCD. The female sibling died suddenly at 2 yo without an ICD. His brother received an ICD but died at 18 yo in VF electrical storm.

Interestingly, the mean time lapsing from ICD implantation to VF occurrence was 1 year. A later arrhythmia event, 5.6 years after ICD implantation, occurred in one patient.

No asymptomatic patients presented with arrhythmic events during a mean follow-up time of 62 months (range: 0–234 months).

Three patients presented with VT event during follow-up (Patients 6, 7, and 9 from *Table 4*). Patient 6 had monomorphic VT and underwent an epicardial ablation of an anterior RVOT substrate at age 22. Patient 9 presented with repetitive shocks due to a monomorphic and polymorphic VT and underwent a substrate percutaneous ablation targeting post-QRS potentials in the posterior RVOT endocardium at age 14. Both patients were non-inducible after ablation, and neither of them recurred after the procedure.

A Kaplan–Meier survivorship analysis shows the statistical difference in the outcome of symptomatic vs. asymptomatic patients during follow-up after initial diagnosis: 9 patients presented life-threatening events from the 40 symptomatic patients (22%) vs.

Table 4 Characteristics of symptomatic patients who presented events during follow-up

Pt	Prob	Gen	Age dx	Sympt	aECG	Ind	Gene	ICD	Age ICD	Event FU	Ev age	FU	Age FU
1	Yes	F	2.3	SCD	Yes	n.d.	n.d.	No	No ICD	SCD	2.6	0.3	2.6
2	Yes	M	3.2	SCD	Yes	n.d.	n.d.	Yes	17.6	VF storm/ICD shock	18.2	15	18.2
3	Yes	M	24.4	Syncope	Yes	Yes	n.d.	Yes	26.5	VF/ICD shock	26.7	14.6	39.0
4	Yes	M	15.3	SCD	No	Yes	n.d.	Yes	15.3	VF/ICD shock	15.9	8.1	23.4
5	No	M	24	Syncope	Yes	n.d.	Positive	Yes	24.1	VF/ICD shock	26.3	6.7	30.7
6	Yes	F	16.5	SCD	No	No	Negative	Yes	16.5	MVT/ICD pace	22.1	5.6	22.1
7	Yes	M	8.2	Syncope	Yes	No	n.d.	Yes	8.2	VT/ICD shock	8.7	4.4	12.6
8	Yes	M	15.3	Syncope	Yes	No	Negative	Yes	15.4	VF/ICD shock	15.5	2.1	17.4
9	Yes	M	13	SCD	Yes	n.d.	n.d.	Yes	13.3	VT/ICD shock	14.1	1.5	14.5

Age dx, age at diagnosis (years); AECG, abnormal electrocardiogram; Age ICD, age at ICD implantation (years); Age FU, age at last follow-up (years); Ev age, event age (years); Event FU, event at follow-up; F, female; FU, length of follow-up (years); Gen, Gender; Gene, genetic test; ICD, internal cardio-defibrillator; Ind, inducibility in electrophysiology study; M, male; n.d., not done; Prob, proband; Pt, patient; Sympt, symptom; SCD, sudden cardiac death; VF, ventricular fibrillation; MVT, monomorphic ventricular tachycardia.

no life-threatening event in the 88 asymptomatic patients (log-rank $P < 0.001$; *Figure 3*).

Follow-up of the high-risk patients with an ICD indicated that seven patients underwent appropriate ICD shocks (20%) for eight episodes of malignant ventricular arrhythmias. One patient experienced a monomorphic VT that was terminated by ICD pacing. On the other hand, eight patients with ICD (23%) experienced inappropriate shocks due to lead dysfunctions ($n = 3$), supraventricular tachycardia ($n = 3$), and T-wave over-sensing ($n = 2$). Furthermore, six patients (17%) experienced device-related complications including lead fractures ($n = 3$), lead dislocations ($n = 1$), device migrations ($n = 1$), and system infections ($n = 1$).

Univariate and multivariate analysis were performed to investigate additional clinical variables associated with occurrence of life-threatening events at follow-up. The univariate analysis showed that a spontaneous type I ECG (HR 10.24, $P = 0.01$) and the presence of conduction abnormalities (HR 5.01, $P = 0.045$) were associated with events during follow-up. The multivariate analysis determined that a spontaneous type I ECG was the only predictive variable for arrhythmic events (HR = 8.07, CI 1.32–52.98, $P = 0.029$).

When considering the patients' age instead of the length of follow-up for the Kaplan–Meier analysis, the presence of symptoms (log-rank $P < 0.01$) and a spontaneous type I ECG (log-rank <0.01) were significantly associated with life-threatening arrhythmic events. In this same analysis, atrial arrhythmias and conduction abnormalities also showed a positive association (log-rank $P = 0.17$ and 0.29, respectively). *Figure 4* shows these different survival curves related to patients' age in years.

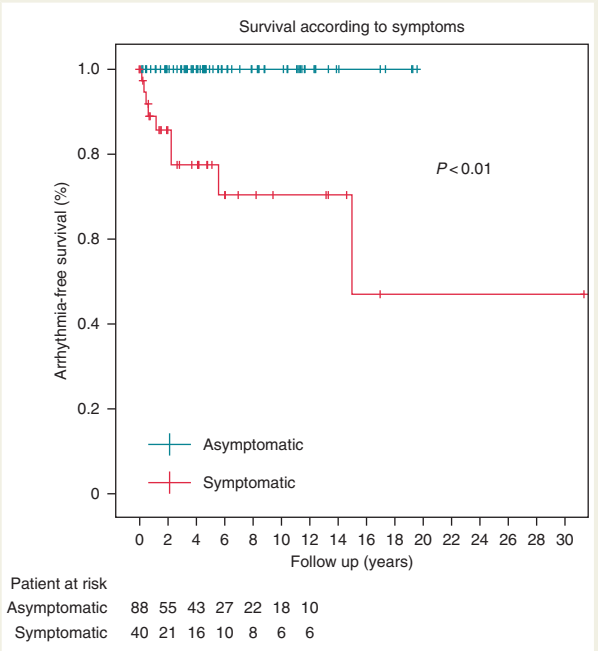

Figure 3 Kaplan–Meier survivorship analysis of arrhythmic event-free survival according to the presence and absence of symptoms from initial diagnosis time along follow-up time (in years).

Discussion

There are two main challenges facing young patients with BS. First, BS is a rare disease in young patients (0.0098%) compared with adult populations (0.14–0.7%).[13,14] Second, the true incidence rate of symptomatic disease expressions, beyond the ECG-induced patterns, remains unknown. This results in a lack of recommendations for the management of children and adolescents newly diagnosed with BS. Moreover, the value of induced VT/VF has never been tested in younger patients.

Data gathered from this case series showed that asymptomatic patients identified by familiar screening, notwithstanding their genetic status or family history of SCD, remain at low risk in the long term. However, these patients require close follow-up to rule-out future onset of clinical electrocardiographic or symptomatic manifestations, especially during febrile episodes.

In the symptomatic group for whom the disease presented clinically by arrhythmias or syncope, risk of future arrhythmic events appeared very high. Risk should be evaluated in these patients

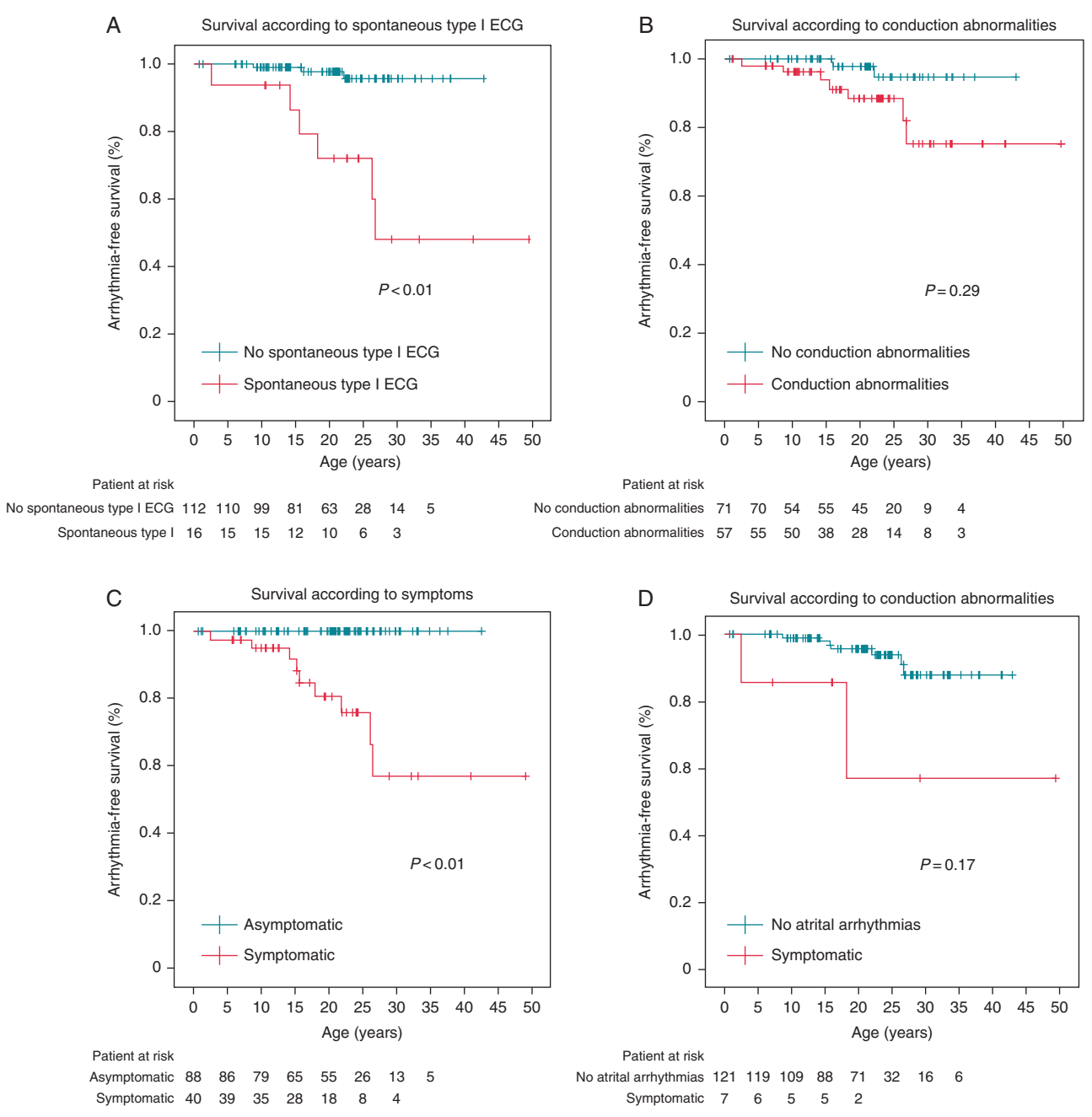

Figure 4 Kaplan–Meier arrhythmia-free survival according to age at follow-up (years). Kaplan–Meier survivorship analysis of arrhythmic event-free survival according to (*A*) spontaneous type I ECG, (*B*) symptoms, (*C*) atrial arrhythmias, and (*D*) conduction abnormalities.

based on several clinical parameters. First, the vast majority of symptomatic young patients were male. Second, baseline ECG abnormalities were markers of active disease and risk of future events, in particular the presence of a spontaneous type I ECG. While on revision of the present manuscript, the paper by Andorin *et al.*[15] was published online describing similar findings on a multicentric European study including 106 patients below age 19. In their study, the event rate during a mean follow-up of 54 months was 9.4%. As in our study, the presence of symptoms at diagnosis and type I Brugada ECG were predictive of arrhythmic events during follow-up, whereas a positive family history and the presence of SCN5A mutations were not.

Other conduction abnormalities that have been identified to risk related to patients' age have been conduction abnormalities and presence of atrial arrhythmias. The presence of prominent R waves in lead aVR and Tp–e dispersions have been identified more frequently in symptomatic patients, but the low numbers of patients prevent from reaching statistically significant conclusions. Finally,

provocative tests showed intra-patient differences with respect to ECG parameters, but no risk factor could be identified inter-groups.

In the 10 patients identified as high risk due to the induction of sustained ventricular arrhythmias (polymorphic VTs or VFs) during either provocative tests ($n = 4$) or EPS ($n = 6$), all received an ICD implantation. However, none of the ajmaline-induced ventricular arrhythmias presented with events during the follow-up period. Thus, the significance of ventricular arrhythmic induction by ajmaline infusion remains unclear and requires further investigation. Two out of six patients with positive EPS (33%) results received appropriate shock during the follow-up period, occurring at 26.6 and 15.9 yo, respectively.

The current management practice of our group includes testing sinus node function, AV nodal conduction, presence of atrial arrhythmias, and ventricular vulnerability with an EPS in most of the patients above the age of 12 years with a clear diagnosis of BS. This remains controversial in the young population, in particular if asymptomatic, and is not the policy in many paediatric electrophysiology groups around the world. Our group considers that gathering data on paediatric EPS has helped advance our understanding of the disease behaviour in this age group and will help as the base for future clinical guidelines.

Genetic screening for mutations in the SCN5A gene was useful for diagnostic confirmations and family stratifications of BS. However, mutations in SCN5A were not independent risk markers for phenotypic expressions of the disease.

During the last few years, there has been increasing evidence of the role of ablation in BS.[16] De Wilde and Nademanee[17] showed that radiofrequency ablation of late potentials and fractionated electrograms in the RVOT of BS patients can reduce arrhythmia vulnerability and the ECG manifestation of the disease. These late potentials can be also recorded in signal-averaged electrocardiograms and usually disappear after ablation.[18]

Recent studies in adults with BS show evidence that quinidine reduces inducibility in BS patients and protect against future events.[19–21] In the paediatric age, Probst *et al.*[7] reported a group of four symptomatic children who were treated with quinidine and did not present arrhythmic events or recurrence of symptoms during a mean follow-up of 2 years. More recently, the study of Andorin *et al.* showed that 72% (8 out of 11) of young BS patients treated with hydroquinidine remained asymptomatic during follow-up.[15] Hydroquinidine seems an effective option in asymptomatic young BS patients with spontaneous type I ECG to avoid future events. In young symptomatic BS patients with recurrent events, it may also reduce the incidence of appropriate shocks. In view of the high percentage of device-related complications, some groups propose this therapy as an alternative to ICD implant in high-risk patients. The fact that remains difficult to accept in the light of present literature is that almost 30% of symptomatic patients on quinidine therapy presented with potentially lethal arrhythmic events during follow-up. At this point, we consider that larger scale studies are needed in young symptomatic BS patients to probe its efficacy to protect against lethal arrhythmia events in the long term.

With present technology, ICD implantation during childhood remains an unideal treatment, because it is associated with significant morbidity and requires battery exchanges over time. The present case series indicated a 24% incidence of life-saving appropriate shocks in high-risk patients. However, this percentage was offset by the same percentage of inappropriate shocks and 17% of system-related complications.

Conclusions

Symptomatic BS during the first years of life was a rare occurrence. However, in those presenting early with electrical abnormalities (hallmarks of BS), the risk of SCD and life-threatening arrhythmias increased to >20%. Baseline ECG abnormalities recorded at younger ages, namely, the presence of spontaneous type I ECGs, conduction abnormalities, and clinical atrial arrhythmias and SND, were reliable indicators of susceptibility for future ventricular arrhythmias. Many of the risk parameters previously identified for adults, such as presence of R waves in aVR and T-wave dispersions, were also present with more frequency in the symptomatic group. Implantable cardioverter-defibrillator indications in younger patients should be carefully considered on individual bases due to high long-term risks of system dysfunctions and inappropriate shocks.

Conflict of interest: P.B. has received honoraria and speaker fees from Biotronik and Boston Scientific.

References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;**20**:1391–6.
2. Priori S, Napolitano C, Giordano U, Collisani G, Memmi M. Brugada syndrome and sudden cardiac death in children. *Lancet* 2000;**355**:808–9.
3. Skinner JR, Chung S-K, Montgomery D, McCulley CH, Crawford J, French J *et al.* Near-miss SIDS due to Brugada syndrome. *Arch Dis Child* 2005;**90**:528–9.
4. Suzuki H, Torigoe K, Numata O, Yazaki S. Infant case with a malignant form of Brugada syndrome. *J Cardiovasc Electrophysiol* 2000;**11**:1277–80.
5. Chockalingam P, Rammeloo L, Postema P, Hruda J, Clur SA, Blom N *et al.* Fever-induced life-threatening arrhythmias in children harboring a SCN5A mutation. *Pediatrics* 2011;**127**:e239–44.
6. Wedekind H, Smits JP, Schulze-Barh E, Veldkamp MW, Bajanowski T, Borggrefe M *et al.* A de-novo mutation in the SCN5A gene associated with early onset of sudden infant death. *Circulation* 2001;**104**:1158–64.
7. Probst V, Denjoy I, Meregalli P, Amirault JC, Sacher F, Mansourati J *et al.* Clinical aspects and prognosis of brugada syndrome in children. *Circulation* 2007;**115**:2042–8.
8. Conte G, Dewals W, Sieira J, de Asmundis C, Ciconte G, Chierchia GB *et al.* Drug-induced brugada syndrome in children: clinical features, device-based management, and long-term follow-up. *J Am Coll Cardiol* 2014;**63**:2272–9.
9. Priori SG, Wilde AA, Horie M, Cho Y, Behr E, Berul C *et al.* Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace* 2013;**15**:1389–406.
10. Babai Bigi MA, Aslani A, Shahrzad S. aVR sign as a risk factor for life-threatening arrhythmic events in patients with Brugada syndrome. *Heart Rhythm* 2007;**4**:1009–12.
11. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, Dorantes Sánchez M, Dorticós Balea F, Zayas Molina R *et al.* Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol* 2006;**47**:1828–34.
12. Narula OS, Shantha N, Vasquez M, Towne WD, Linhart JW. A new method for measurement of sinoatrial conduction time. *Circulation* 1978;**58**:706–14.
13. Hermida JS, Lemoine JL, Aoun FB, Jarry G, Rey JL, Quiret JC. Prevalence of the Brugada syndrome in an apparently healthy population. *Am J Cardiol* 2000;**86**:91–4.
14. Yamakawa Y, Ishikawa T, Uchino K, Mochida Y, Ebina T, Sumita S *et al.* Prevalence of right bundle-branch block and right precordial ST-segment elevation (Brugada-type electrocardiogram) in Japanese children. *Circ J* 2004;**68**:275–9.

15. Andorin A, Behr ER, Denjoy I, Crotti L, Dagradi F, Jesel L *et al.* The impact of clinical and genetic findings on the management of young patients with Brugada Syndrome. *Heart Rhythm* 2016;**13**:1274–82.
16. Brugada J, Pappone C, Berruezo A, Vicedomini G, Manguso F, Ciconte G *et al.* Brugada syndrome phenotype elimination by epicardial substrate ablation. *Circ Arrhythm Electrophysiol* 2105;**8**:1373–81.
17. De Wilde AA, Nademanee K. Epicardial substrate ablation in brugada syndrome. *Circ Arrhythm Electrophysiol* 2015;**8**:1306–8.
18. Aizawa Y. A post-QRS potential in Brugada syndrome. *J Am Coll Cardiol* 2008;**51**:1720–1.
19. Hermida JS, Denjoy I, Clerc J, Extramiana F, Jarry G, Milliez P *et al.* Hydro-quinidine therapy in Brugada syndrome. *J Am Coll Cardiol* 2004;**43**:1853–60.
20. Bouzeman A, Traulle S, Messali A, Extramiana F, Denjoy I, Narayanan K *et al.* Long-term follow-up of asymptomatic Brugada patients with inducible ventricular fibrillation under hydroquinidine. *Europace* 2014;**16**:572–7.
21. Belhassen B, Rahkovich M, Michowitz Y, Glick A, Viskin S. Management of Brugada syndrome: thirty-three-year experience using electrophysiologically guided therapy with class IA antiarrythmic drugs. *Circ Arrhythm Electrophysiol* 2015;**8**:1393–402.

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The double adenosine test: a simple and non-invasive tip to unmask unapparent pre-excitations: an example of Mahaim fibres

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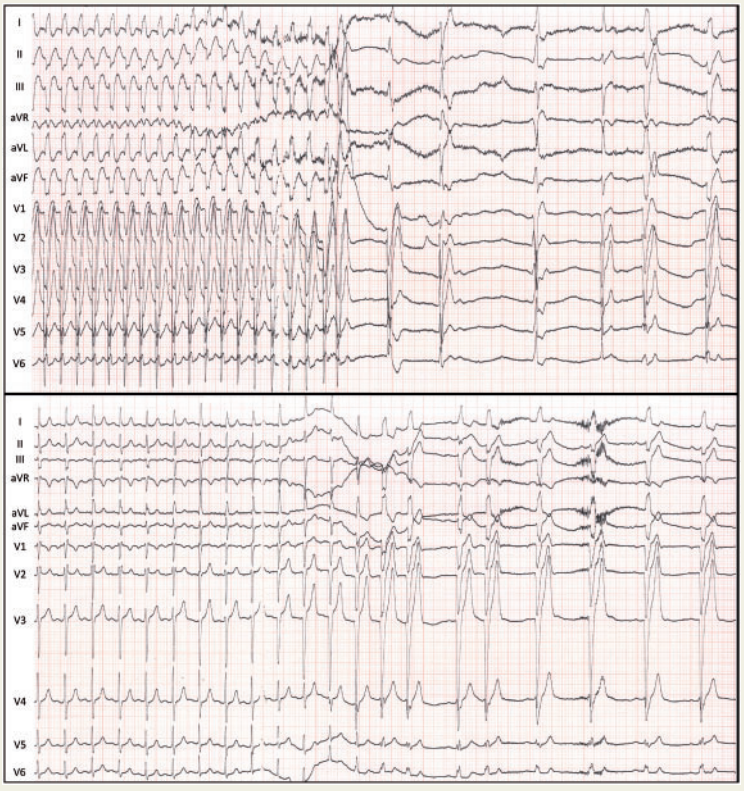
We report the case of a 16-year-old youth who was admitted for a wide QRS tachycardia caused by an atypical atriofascicular bypass tract (the so-called 'Mahaim fibers'). These bypass tracts give rise to antidromic atrioventricular re-entrant tachycardias, in which the bypass tract serves as the anterograde limb of the circuit and the atrioventricular node as the retrograde limb of the re-entrant circuit. Unfortunately, in these patients, it is easy to make a misdiagnosis of supraventricular tachycardia with functional left bundle branch block or even of ventricular tachycardia. Indeed, due to the slow and decremental conduction properties of these bypass tracts, the baseline ECG is either normal or shows only subtle pre-excitation. Herein, we describe a simple tip, consisting of two successive administrations of adenosine [during ongoing tachycardia (upper panel) and during sinus rhythm (lower panel)], to make a non-invasive and definite diagnosis of this condition. Importantly, the use of this method to unmask an accessory pathway capable of anterograde conduction is not limited to the diagnosis of Mahaim fibres. Indeed, it can be used more generally in patients presenting with paroxysmal supraventricular tachycardia whenever the ECG following tachycardia termination does not definitely rule out the presence of an accessory pathway.



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