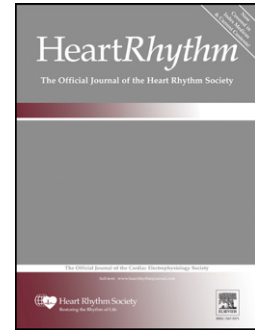


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**Syncope in Brugada Syndrome Patients:
Prevalence, Characteristics and Outcome.**

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Abstract

Background: The report from the 2nd Consensus Committee on BrS suggests that all patients with syncope without a “clear extracardiac cause” should have an implantable cardioverter-defibrillator (ICD). However, a clear extracardiac cause for syncope may be difficult to prove.

Objective: This study aims to characterize syncope in patients with Brugada syndrome (BrS).

Methods: All patients diagnosed with BrS at our institution between 1999 and 2010 have been enrolled in a prospective registry. Patients with suspected arrhythmic syncope (group 1) were compared to patients with non-arrhythmic syncope (group 2) and to patients with syncope of doubtful origin (group 3).

Results: Of 203 pts with BrS, 57 (28% (44 male, 46±12y)) experienced at least one syncope. Group 1 included 23 pts (all received an ICD). In group 2 (17 pts), 3 received an ICD because of positive electrophysiological study. In group 3 (17 pts), 6 received an implantable loop recorder and 6 received an ICD. After a mean follow-up of 65±42 months, 14 pts of group 1 remained asymptomatic, 4 had recurrent syncope and/or 6 an appropriate ICD therapy. In group 2, 9 pts remained asymptomatic, 7 had recurrent neurocardiogenic syncope. In group 3, 7 remained asymptomatic and 9 had recurrent syncope. One patient from each group died from a non cardiac cause.

Conclusions: Syncope occurred in 28% of patients with BrS in the present study. Ventricular arrhythmia rate was 5.5%/year in group 1. In 30%, the etiology of the syncope was questionable. No sudden cardiac death occurred in group 2 and 3.

Key-words: Brugada Syndrome, Ventricular Fibrillation, Sudden Cardiac Death, Channelopathy, Syncope,

Abbreviations

BrS: Brugada Syndrome

ICD: Implantable Cardioverter-Defibrillator

ECG: Electrocardiogram

EPS: Electrophysiological Study

RV: Right Ventricle

VT: Ventricular Tachycardia

VF: Ventricular Fibrillation

ILR: Implantable Loop Recorder

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Introduction:

Risk stratification in patients with Brugada Syndrome (BrS) remains challenging. The report from the 2nd Consensus Committee on BrS suggests that all patients with syncope without a “clear extracardiac cause” should have an implantable cardioverter-defibrillator (ICD)¹. However, a clear extracardiac cause for syncope (i.e. non arrhythmic syncope) may be difficult to prove unless an electrocardiogram (ECG) is recorded during the episode itself. Recent studies have shown that BrS patients have a higher than expected rate of positive head-up tilt-tests, suggesting that they are prone to neurocardiogenic syncope in addition to syncope due to life-threatening ventricular arrhythmia^{2,3}. Distinguishing between these causes of syncope is important since the management is very different⁴.

We aimed to characterize syncope in BrS patients and their outcome.

Methods:

All patients diagnosed with BrS at our institution between 1999 and 2010 had been prospectively enrolled in a registry including: detailed personal history (such as syncope characteristics...), familial history, age at diagnosis, examinations, events during follow-up and therapeutic decision. All patients of this registry who experienced syncope, whether it was the index event or not, were included in this study. To focus on syncope management, we have excluded patients who experienced resuscitated sudden cardiac death as the presenting symptom.

After a meticulous personal and family history and physical examination, all patients had an ECG with Valsalva maneuvers, noninvasive ECG monitoring for at least 24 hours, an exercise test on bicycle and a transthoracic echocardiogram. Some of them had signal averaged ECG (n=22), tilt-test (n=33), electrophysiological study (EPS) (n=47), and a neurological consult (n=19).

Brugada syndrome diagnosis

Clinical diagnosis of BrS was established in the presence of a type 1 ECG pattern, either spontaneously or after a sodium channel blocking agent (flecainide or ajmaline). It was defined by a coved ST-segment elevation ≥ 0.2 mV followed by a negative T-wave being present at least in 2 right precordial leads (from V1 to V3)¹.

Syncope

Patients with syncope were divided into 3 groups based on clinical data. *Group 1* included patients with presumed arrhythmic syncope (due to self-terminated VT/VF - Figure 1) based on the association of the 4 following criteria: absent or brief (<10 seconds) prodrome, absence of specific triggering circumstance, brief loss of consciousness (<1 min), fast return to consciousness. Though severe trauma (head trauma, facial hematoma, broken bones...), urinary incontinence and/or tonico-clonic activity favored arrhythmic syncope, these factors were neither mandatory nor sufficient to classify these patients in Group 1. *Group 2* included patients with presumed non-arrhythmic syncope, determined by the presence of neurocardiogenic symptoms (sweating, nausea, pallor...) before the loss of consciousness, longer time of unconsciousness (> 1 minute) and absence of severe physical injuries. *Group 3* corresponded to patients with syncope of an uncertain cause because at least one characteristic of group 1 or 2 was missing. Examples include absence of prodrome but in a warm atmosphere, severe physical injuries due to syncope with vasovagal prodrome, and seizure-like symptoms).

Tilt-test

The tilt-test was performed with 10 minutes of supine rest followed by passive head up tilt to an angle of 60 degrees. If no symptoms occurred within 45 minutes nitroglycerin spray was administrated and the test continued for 15 minutes. It was considered positive if it induced

syncope or pre-syncope with or without nitroglycerin spray, whether or not it reproduced the symptoms of the clinical episode. Then 3 types of positive response were defined as: type 1 which was a mixed response (hypotension preceding bradycardia), type 2 with a cardio-inhibitory response (bradycardia preceding hypotension) and type 3 with a vasodepressor response (hypotension without significant bradycardia).

Electrophysiological Study (EPS)

EPS was performed at 2 sites (right ventricular (RV) apex and RV outflow tract), with 2 cycles (600ms and 400ms) with 1, 2 and then 3 extrastimulus down to 200 ms or until induced sustained ventricular arrhythmia. It was considered positive if a ventricular tachycardia (VT) / ventricular fibrillation (VF) > 30 seconds were induced or an external cardioversion was needed.

Questionnaire

Patients with syncope completed a standardized questionnaire (figure 2) that was divided into 4 parts. The first part focused on symptoms before BrS diagnosis. The second part included the description of the syncope : day time, presence or absence of prodromes, seizure-like activity, time unconscious, recovery circumstances, post-syncopal symptoms (weakness, post-episode fatigue, confusion, physical harm...), and presence and observations of any witness. The third part was about similarity and differences between recurrent syncopal events. The fourth and last part was about the treatment received (devices, antiarrhythmic drugs...), advice to avoid syncope, and anxiety about recurrent syncope.

Follow-up:

Patients were followed in the ICD clinic or on an annual basis via clinic or phone calls (with questions about any hospitalization, syncope or new treatment). ICD or implantable loop

recorder (ILR) were interrogated at least every 6 months and the vast majority received ICD with remote monitoring capabilities.

During follow-up, patients were considered to have an arrhythmic event in case of documented ventricular arrhythmia via ICD/ILR log or on Holter-ECG/telemetry/ECG. Sudden death was also classified as an arrhythmic event. In case of recurrent syncope, its characteristics were noted and compared to the initial syncope.

Statistical analysis:

Data were analyzed with the SAS Software package (SAS Institute, Cary, NC, version 9.1 and further versions). Fisher's exact test or Chi square test was used to compare categorical variables. One way-ANOVA (with or without Welch correction) was performed to compare continuous variables when data were normally distributed, whereas we used Kruskal-wallis test if not. A two-sided p-value < 0.05 was considered statistically significant. When applicable, data are expressed as mean \pm SD or median (25th quintile – 75th quintile).

Results:

Of 203 BrS patients (75% male, 44 \pm 12 years of age), 57 (28%) patients (44 male, 46 \pm 12 years of age) experienced at least one syncope. In these 57 patients with syncope, BrS was identified during syncope evaluation (38 pts, 67%), familial screening (8 pts, 14%) or routine ECG (11 pts, 19%). 25% had a familial history of sudden cardiac death and 9 patients (from different families) among the 49 patients tested (18%) had a SCN5A mutation. Three patients from group 1 have transiently been treated with quinidine (Trial), whereas one received quinidine for recurrent ICD shocks and remained on treatment. In group 2, 5 patients received beta-blockers for vaso-vagal syncope (n=4) or hypertension (n=1). None of the patients of group 3 had anti-arrhythmic drug therapy.

The characteristics of the 3 groups are presented in Table 1. Patients with syncope of doubtful origin (group 3) were younger (40 ± 12 years of age) at diagnosis. Circumstances of BrS diagnosis were also different among the 3 groups. Syncope was the main reason in group 1 (87%) but only in 53% of patients from group 2 and 3. There was no difference concerning spontaneous type 1 ECG pattern among the 3 groups (respectively present in 65%, 65% and 59%). The mean degree of maximal ST elevation was also similar between groups (group 1: 0.40 ± 0.2 mV, group 2: 0.32 ± 0.14 mV, group 3: 0.37 ± 0.13 mV), as were other ECG parameters (PR, QRS duration, QRS fragmentation, QTc). Signal averaged ECG (n=22), were positive in 55% of patients (50% in group 1, 33% in group 2 and 75% in group 3).

Tilt-tests were more frequently positive in group 2. The 3 positive tilt tests in group 1 (38%) were a mixed response. In group 2, 7 patients (50%) had a mixed response, 2 (14%) had a cardio-inhibitory response with asystole and 2 (14%) had a vasodepressor response. In group 3, the 3 positive tilt-tests (27%) had a mixed response. Only 56% of the patients with a suspected arrhythmic syncope (group 1) who underwent an EPS were inducible. ICD implantation was performed in all 23 patients from group 1. Three patients from group 2 were implanted with an ICD: 3 had inducible EPS (including 1 with a familial history of SCD). In group 3, 6 patients were implanted; all had a positive EPS. Two of these patients had a syncope labeled as “severe” but did not fulfilled the 4 criteria to be classified in group 1 and 1 had a familial history of SCD.

Of the 17 patients in group 3, 6 (35%) received an ILR.

Characteristics of syncope are summarized in Table 2. Thirty-eight patients (67%) experienced syncope before BrS diagnosis. Patients with suspected arrhythmic syncope (group 1) had their first syncope at older age (74% after 30 years of age) compared to patients from group 2 and 3. Syncope occurred equally at rest or during daily activity but not during

exertion /stress in the 3 groups. Five patients (21%) from group 1 experienced short prodrome (lightheadedness <10 seconds) before syncope including 2 patients with further VF during follow-up. Obviously, prodromes were much more frequent in group 2 and 3 (94% and 82% respectively, $p < 0.01$) because of the clinical definition of the 3 groups however they were generally longer and clinically different (nausea, sweating...). Interestingly when the etiology of syncope was doubtful (group 3), patients were more often anxious (63%), whether they had a device (8/12) or not (2/5), about the possibility of having a new syncope.

Follow-up

No patient was lost to follow-up. The median follow-up period was 53 months (36 - 93) and the mean follow-up 65 ± 42 months (table 3).

The mean arrhythmic event rate per year in our 57 patients with syncope was 1.9% (5 VF and 1 VT with a cycle length of 330 ms) and 5.5% per year in the arrhythmic syncope group (group 1). All appropriate shocks occurred in group 1 (6/23). 20/ 57 (35%) patients had recurrent syncope with neurocardiogenic cause for 15 (75%) patients. Clinical characteristics of syncope in BrS patients (association of the absence (or brief <10 sec) of prodromes, absence of particular circumstances, brief loss of consciousness (<1 min.) and quick return to consciousness) had a sensitivity of 100%, a specificity of 67%, a positive predictive value of 26% and a negative predictive value of 100% to predict ventricular arrhythmia at 5 years in this study.

In group 1, 14 patients remained asymptomatic, 6 had appropriate ICD therapy (5.5% / year) with syncope prior ICD discharge in 2. Among patients with arrhythmic events, 2/4 had negative EPS (2 other patients with appropriate ICD therapy did not have EPS). Two other patients had further syncopal events not associated with cardiac arrhythmia. The recurrent syncopes were typically vaso-vagal, different from the initial one. However tilt-test was negative for these 2 patients. One patient died from a noncardiac cause.

In group 2, 9 patients remained asymptomatic, 7 had recurrent typical neurocardiogenic syncope, 1 died from a noncardiac cause (ICD log without arrhythmia).

In group 3, 7 patients remained asymptomatic, 9 had recurrent syncope clinically vaso-vagal in 6 (with an ICD in 1 not showing any arrhythmia) and similar to the initial one in 3 (without arrhythmia shown by ICD log in 1 and ILR in 2 pts but with a final diagnosis of epilepsy in 1 –figure 3). One patient died due to a violent fight confirmed by the autopsy.

Among the 32 patients with ICD, 9 patients (28%) had complication. Inappropriate shocks occurred in 8 patients (25%): lead fracture (n=5), T wave oversensing (n=2) and sinus tachycardia (n=1). One patient had endocarditis resulting in surgical device extraction.

Discussion:

Prevalence of syncope in Brugada syndrome patients is 28%. Of these episodes, clinical features suggested an arrhythmic cause in 40% of patients, a non-arrhythmic cause in 30%, and in 30% the cause was doubtful. Clinical characteristics of syncope in BrS patients (association of the absence (or brief <10 sec) of prodromes, brief loss of consciousness (<1 min.), absence of triggering circumstance, and quick return to consciousness) had an excellent sensitivity and negative predictive value (100%) to predict the absence of ventricular arrhythmia during a 5 year follow-up. Patients with syncope not having these characteristics had a benign prognosis. We think these clinical features may replace the term “clear extra-cardiac cause” from the 2nd consensus conference on BrS¹.

The etiology of syncope based on clinical judgment was difficult to assess in a significant proportion of BrS patients (30% - group 3). Unfortunately, none of the ancillary investigations were able to identify patients at higher risk of ventricular arrhythmia after syncope. The role of EPS in BrS risk stratification remains controversial⁵. In our series, no statistical difference was observed in term of inducibility between group 1, 2 and 3 (56% vs 19% vs 43%; p =

0.12); however, the population was limited. On the 6 patients from group 1 who experienced ventricular arrhythmias during follow-up, only 2 of 4 with EPS were inducible. Hence, the utility of EPS for risk stratification in the setting of syncope seems limited. The predictive value of tilt-test is also limited with 38% of patients from group 1 having a positive test and 22% of patients from group 2 having a negative test. Two patients from the arrhythmic group (group 1) had a recurrent syncope not related to ventricular arrhythmia, emphasizing that the presence of both ventricular arrhythmia and neurocardiogenic syncope in patients with BrS is not rare³. Take et al⁶ recently showed that positive results of a Head-Up Tilt-test in BrS with syncope might incorrectly indicate syncope associated with VF as being benign vagal syncope.

During a mean follow-up of 65 ± 42 months, the annual event rate in BrS patients with syncope was 1.9%. However, only patients from group 1 experienced an arrhythmic event, which represented an event rate of 5.5%/year. Brugada et al reported an event rate of 8.9%/year in syncopal patients⁷. In one of our previous multicenter studies⁸ dealing only with BrS patient implanted with an ICD, this event rate was 3%/year for patients implanted because of syncope. In the largest study published to date, Probst et al.⁹ (FINGER study) reported an event rate of 1.9%/year for patients with syncope which is one third the rate we found in patients from group 1. Prior reports did not standardize the evaluation of the cause of syncope, which may explain the variability in event rates. Given the absence of objective criteria in many cases (the “clear extra-cardiac cause” required by the 2nd consensus conference¹), it is tempting to want to protect patients with an ICD when the cause of syncope is unclear. However, ICD therapy can also lead to significant harms, so refining risk stratification in this population is critical.^{8, 10}

Comparisons between groups

The first syncopal event in Group 1 occurred frequently (74%) after 30 yo whereas it occurred before 40 years of age in 64% patients from group 2 (Table 2). The older age at the time of arrhythmic syncope could be explained by the need for sufficient maturation of the pathologic substrate to generate VF, which is not a requirement for neurally mediated syncope. However, no age threshold accurately discriminated between syncope types.

Absence of prodrome was in favor of arrhythmic syncope, but 5 patients (21%) from the first group described brief prodromes (<10 seconds) such as lightheadness. They were related to the initiation of a ventricular arrhythmia as it can be seen during VF induction at EPS when loss of consciousness occurred only 10 to 15 seconds after VF initiation. In a recent study, Take et al.⁶ concluded that syncope with prodrome, especially blurred vision, suggests a benign etiology however 2/32 patients with VF experienced this prodrome in their study. They found that the combination of fragmented QRS, abnormal respiration and absence of blurred vision had excellent accuracy to diagnose patients with VF (sensitivity 84.4%, specificity 82.7%).

The arrhythmic syncopes were usually impressive which explains why the circumstances of BrS diagnosis were more often syncope than familial screening or routine examination in group 1. It is also the reason why familial BrS is more frequent in group 2 and 3.

Asthenia is generally thought to be a sign of neurocardiogenic syncope however in this study, 43% patients of group 1 felt fatigue after syncope (table 2). This is probably due to low cerebral flow during ventricular arrhythmia.

Despite being non significant, more people were anxious about the possibility of having a new syncope in group 3 (63%) compared to patients with arrhythmic syncope (40%) or neurocardiogenic syncope (21%). If the medical team easily reassured patients from group 2,

patients from group 1 became often less anxious when they knew the origin of their syncope. Even if this origin was potentially life-threatening, they felt better partly because of the ICD. However patients from groups 3 remained in the doubt which increased anxiety. Finding the etiology is extremely important and the use of ILR should be widespread in this situation.

Therapeutic decision

Whereas there is consensus that ICD therapy is indicated for patients with clear arrhythmic syncope (group 1), and not indicated for patients with neurocardiogenic syncope (group 2), management of those whose cause of syncope is unclear (group 3) has been challenging. We offered an ILR to every patient in this group who was not implanted with an ICD, as previously reported by others^{11, 12}. Among the 17 group 3 patients, 12 had continuous rhythm monitoring available (6 by ICD implanted because of positive EPS and 6 with an ILR). In 3 patients, the implanted device recorded no arrhythmia during recurrent syncopal events with similar characteristics to the previous episodes. This validated withholding ICD therapy in the 2 patients with an ILR and raised questions about ICD replacement for the one with an ICD implanted because of positive EPS. It is our opinion that an ILR should be offered to any BrS patient with a syncope which clinical characteristics fit with group 3 (unknown origin).

However, this is not a therapeutic device and patients from group 2 and 3 have to be aware to seek medical attention promptly in case of recurrent syncope. As for all BrS patients, they should treat any fever and avoid contra-indicated drugs.

Limitations

Several limitations exist concerning the methodology. The monocentric and small population is one limit; however, all patients have been interviewed and examined by the same medical team. This study is based on a retrospective analysis of prospectively collected data (through a registry) as the vast majority of studies on Brugada syndrome. The 3 different groups have

been defined based on clinical history and not on ECG during syncope. Therefore, some patients from group 1 may not have a true arrhythmic syncope (only 6 patients experienced ventricular arrhythmia during 5 years follow-up). Due to the same limitation, we cannot be 100% sure that patients without ILR/ICD implant did not experience asymptomatic non sustained VT/VF despite their good outcome. However, it was a choice to be as close as possible of the clinical practice. Finally, only 33/57 BrS patients had a tilt-test because this examination became systematic in our Brugada syndrome work-up during the year 2007. Finally, a follow-up of 5 years remains short for Brugada syndrome patients who have a normal life expectancy in the absence of VF episode.

Conclusions:

Syncope is common (28%) in patients with Brugada syndrome. Clinical features obtained from a standardized history allow distinction between suspected arrhythmogenic and non-arrhythmogenic causes of syncope in 70% of cases. A strategy of initially providing ICD therapy only to patients with arrhythmogenic syncope appears to be safe and effective at 5 years. An ILR may provide a diagnosis in patients in whom the cause of syncope is doubtful.

References

1. Antzelevitch C, Brugada P, Borggrefe M. et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation*. 2005 Feb 8;111(5):659-70
2. Letsas K, Efremidis M, Gavrielatos G, Filippatos G, Sideris A and Kardaras F. Neurally Mediated Susceptibility in Individuals with Brugada-Type ECG Pattern. *PACE* 2008; 31: 418-421
3. Yokokawa M, Okamura H, Noda T. et al. Neurally Mediated Syncope as a Cause of Syncope in Patients with Brugada Electrocardiogram. *J Cardiovasc Electrophysiol*. 2009 Sep 28
4. Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J*. 2009 Nov;30(21):2631-71.
5. Paul M, Gerss J, Schulze-Bahr E, et al. Role of programmed ventricular stimulation in patients with Brugada syndrome: a meta-analysis of worldwide published data. *Eur Heart J*. 2007 Sep;28(17):2126-33.
6. Take Y, Morita H, Toh N, et al. Identification of high-risk syncope related to ventricular fibrillation in patients with Brugada syndrome. *Heart Rhythm*. 2011 Nov 26. [Epub ahead of print]
7. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, and Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. *Circulation*. 2002 Jan 1;105(1):73-8.
8. Sacher F, Probst V, Iesaka Y. et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. *Circulation*. 2006 Nov 28;114(22):2317-24
9. Probst V, Veltmann C, Eckardt L, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. *Circulation*. 2010 Feb 9;121(5):635-43.
10. Sacher F, Probst V, Bessouet M, et al. Remote implantable cardioverter defibrillator monitoring in a Brugada syndrome population. *Europace*. 2009 Apr;11(4):489-94.
11. Champagne J, Philippon F, Gilbert M, et al. The Brugada syndrome in Canada: a unique French-Canadian experience. *Can J Cardiol*. 2007 Oct;23 Suppl B:71B-75B.

12. Kubala M, Aïssou L, Traullé S, Gugenheim AL, Hermida JS. Use of implantable loop recorders in patients with Brugada syndrome and suspected risk of ventricular arrhythmia. *Europace*. 2011 Oct 6.

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Figure Legends:

Figure 1 : Self terminated VF recorded by an ICD (Lumax VR-T, Biotronik) in Brugada syndrome patients leading to syncope. The ICD log is composed of 3 channels. On the top line the V channel represents the interpretation of the patient's rhythm by the device (sensed marker). On the middle line, the FF (farfield) channel displays the tracings recorded between the device can and the distal coil. On the bottom line, the V channel represents the electrogram recorded by the distal bipole of the ICD lead.

Figure 2: Syncope questionnaire.

Figure 3 : Implantable Loop Recorder (Reveal, Medtronic) log showing muscular artefacts (asterisks) registered during loss of consciousness with tonico-clonic movement. The triangle identifies the manual activation of the device by the patient's wife.

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Table 1: Baseline characteristics of the 3 groups (EPS : electrophysiological study, SAECG: signal averaged ECG; y: years of age)

	Group 1 Arrhythmic syncope	Group 2 No-arrhythmic syncope	Group 3 Doubtful syncope	Total	P
No, n	23	17	17	57	
Age at diagnosis, y	50 ±10	47 ±12	40 ±12	46 ±12	p=0.03
Gender, n %					p=0.4
<i>Men</i>	20 (87%)	12 (71%)	12 (71%)	44 (77%)	
<i>Women</i>	3 (13%)	5 (29%)	5 (29%)	13 (23%)	
Family history, n %					
<i>SCD < 45 y.o.</i>	6 (26%)	4 (25%)	4 (25%)	14 (25%)	p=0.7
<i>Brugada Syndrome</i>	1 (4%)	3 (19%)	7 (41%)	11 (20%)	p=0.05
Circumstances at diagnosis, n %					p=0.03
<i>Syncope</i>	20 (87%)	9 (53%)	9 (53%)	38 (67%)	
<i>Family history</i>	1 (4%)	2 (12%)	5 (20%)	8 (14%)	
<i>Routine examination</i>	2 (9%)	6 (35%)	3 (17%)	11 (19%)	
Genetic Testing (SCN5A)	20	15	14	49	p=0.9
<i>Mutation, %</i>	4 (20%)	2 (13%)	2 (14%)	9 (18%)	-
Spontaneous Type 1 pattern, n %	15 (65%)	11 (65%)	10 (59%)	36 (63%)	p=0.9
Mean ST elevation (mV)	0.40 ±0.2	0.32 ±0.14	0.37 ±0.13	0.37 ±0.17	p=0.3
Tilt test, n	8	14	11	33	0,12
<i>Positive</i>	3 (38%)	11 (79%)	3 (27%)	17 (52%)	p=0.03
<i>Type 1</i>	3	7	3	13	
<i>Type 2</i>	0	2	0	2	
<i>Type 3</i>	0	2	0	2	
EPS, n	17	16	14	47	
<i>Inducible, n %</i>	9 (56%)	3 (19%)	6 (43%)	14 (28%)	p=0.12
SAECG, n	8	6	8	22	
<i>≥ 2 positive criteria</i>	4 (50%)	2 (33%)	6 (75%)	12 (55%)	p=0.29

Table 2: Characteristics of the syncope in the 3 groups

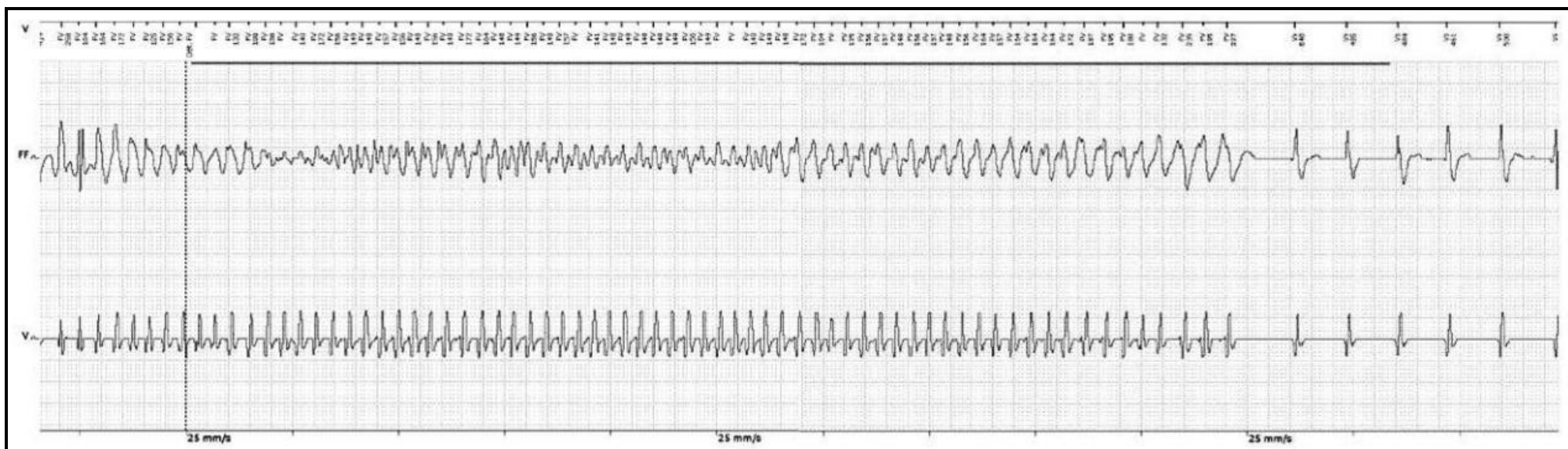
	Group 1 Arrhythmic syncope	Group 2 Non-arrhythmic syncope	Group 3 Doubtful syncope	Total	p-value
N°, n	23	17	17	57	
Age at 1st syncope, n %					p= 0.03
< 15 y	2 (9%)	5 (29%)	1 (6%)	8 (15%)	
15-30 y	4 (17%)	1 (6%)	8 (47%)	13 (23%)	
30-40 y	7 (30%)	5 (29%)	6 (35%)	18 (31%)	
> 40 y	10 (44 %)	6 (35%)	2 (12%)	18 (31%)	
Syncope before BrS diagnosis, n %	15 (65%)	11 (65%)	12 (70%)	38 (67%)	p=0.9
Circumstances, n %					p=0.9
<i>Activity</i>	12 (52%)	10 (59%)	9 (53%)	31 (54%)	
<i>Rest</i>	11 (48%)	7 (41%)	8 (47%)	26 (46%)	
<i>Day time</i>	19 (82%)	13 (76%)	14 (82%)	46 (80%)	
<i>Night time</i>	4 (18%)	4 (24%)	3 (18%)	11 (20%)	
Prodrome, n %	5 (21%)	16 (94%)	14 (82%)	35 (62%)	p<0.01
Severe Trauma, n %	10 (44%)	0	7 (41%)	17 (30%)	p=0.5
Witness, n %	17 (74%)	12 (71%)	12 (75%)	41 (73%)	p=1
Return to consciousness, n %					p=0.2
<i>Spontaneously</i>	16 (70%)	7 (41%)	9 (53%)	32 (56%)	
<i>After stimulation</i>	7 (30%)	10 (59%)	8 (47%)	25 (44%)	
State after return to consciousness, n %					p=0.7
<i>Neurological deficit</i>	0	2 (12%)	1 (6%)	3 (6%)	
<i>Incontinence</i>	4 (17%)	0	2 (12%)	6 (10%)	
<i>Asthenia</i>	10 (43%)	9 (53%)	7 (41%)	26 (46%)	
<i>No change of state</i>	9 (40%)	6 (35 %)	7 (41%)	22 (38%)	
Anxiety, n %	8 (40%)	3 (21%)	10 (63%)*	21 (42%)*	0.08

*1 patient from Group 2 and one from Group 3 died from a non cardiac cause before the end of follow-up. The percentage is based on 16 patients in these 2 columns.

Table 3: Outcome during follow-up in the 3 groups (ICD: Implantable Cardioverter Defibrillator; ILR: Implantable Loop Recorder)

	Group 1	Group 2	Group 3	Total	P
	Arrhythmic syncope	No arrhythmic syncope	Doubtful syncope		
No, n	23	17	17	57	
Follow up, mean,	57 ± 34	80 ± 46	60 ± 45	65 ± 42	p=0.2
<i>Median, (months)</i>	72 (46-106)	57 (39-77)	44 (19-108)	53 (36-93)	p=0.2
Outcome, n %					
Recurrent Syncope	4 (17%)	7 (41%)	9 (53%)	20 (35%)	p=0.05
- <i>Similar features</i>	2 (50%)	7 (100%)	3 (33%)	12 (60%)	
- <i>Different features</i>	2 (50%)	0 (0%)	6 (66%)	8 (40%)	
Asymptomatic	14 (60%)	9 (53%)	7 (41%)	30 (52%)	
Ventricular Arrhythmia	6 (26%)	0	0	6 (10%)	
- <i>With syncope</i>	2 (33%)	0	0	2 (3%)	
Death	1 (5%)	1 (6%)	1 (6%)	3 (5%)	
Patients with ICD, n %	23 (100%)	3 (18%)	6 (35%)	32 (56%)	p<0.01
<i>No syncope</i>	19 (83%)	2 (66%)	4 (66%)	25 (78%)	
<i>Appropriate shock</i>	5	0	0	5 (16%)	
<i>Inappropriate shock</i>	7	0	1	8 (25%)	
<i>ATP</i>	1	0	0	1 (3%)	
Patients with ILR, n%	0	0	6 (35%)	6 (10%)	p<0.01
<i>Syncope</i>	0	0	2 (33%)	2 (33%)	

Figure 1



ACCEPTED MANUSCRIPT

Syncope questionnaire filled by Brugada syndrome patients.

A. Syncope History

1. *At what age did you suffer your first spell of loss of consciousness (syncope)?*

- Age in years: _____

2. *How many episodes of syncope did you have before you were diagnosed with Brugada syndrome?*

- 1
- More than one: specify number _____

B. Description of Syncope

4. *What circumstances, if any, are associated with your spells of loss of consciousness (check all that apply)?*

- Rest
- Activity (specify type): _____

- Daytime
- Night time
- Exertion
- Emotional Stress

5. *What symptoms do you notice before you lose consciousness?*

- Sweating, paleness, dizziness, dimmed vision, clamminess
- Chest palpitations
- Anxiety
- Other (specify): _____

6. *Were you injured as a result of losing consciousness?*

- Yes
- No

7. *If yes, did the injury result in hospitalization?*

- Yes
- No

8. *Did someone else witness your spell?*

- Yes: how did they describe the event to you?

- No

9. *Approximately how long were you unconscious?*

- Less than 1 minute
- 1 to 5 minutes
- More than 5 minutes

10. *How did you regain consciousness?*

- Spontaneously (no assistance)
- Someone stimulated you (shaking, tapping)
- Needed CPR (chest compressions)

11. *Was the episode associated with any of:*

- Biting your tongue?
- Losing control of your bladder?
- Prolonged fatigue after regaining consciousness?
- Difficulty speaking or moving arm(s) and/or leg(s)?
- None of these

C. Further episodes

12. *Have you experienced loss of consciousness since you were diagnosed with Brugada syndrome?*

- Yes
- No

13. *If Yes, was this episode(s) similar to the previous one(s)?*

- Yes
- No

14. *If you have an implantable defibrillator (ICD), have you received a shock associated with an episode of loss of consciousness?*

- Yes
- No
- Not applicable

D. Treatment

15. *What treatment(s) have been prescribed by your cardiologist for management of Brugada syndrome?*

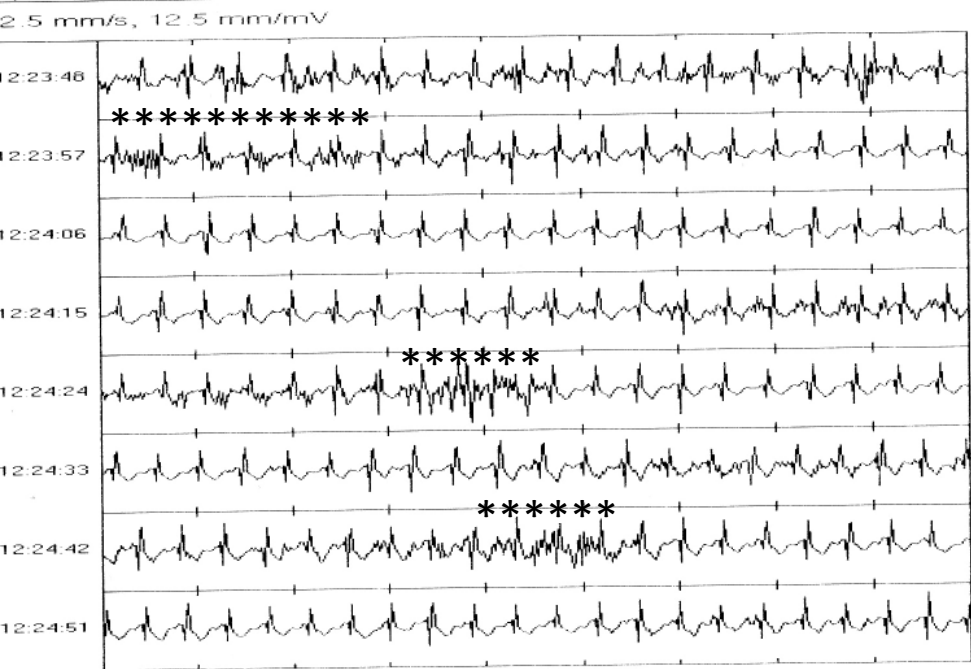
- Implantable defibrillator
- Medications (specify): _____
- Counselling regarding avoiding future syncope

16. *Do you worry about future episodes of syncope?*

- Yes
- No

Figure 3

Reveal(R) Plus Modèle 9526
Amplification: x4 (+/- 0.4 mV)
Mode d'enregistrement: 3 épisodes patient, 5 épisodes automatiques
2 min.
Episode patient 1 de 3 enregistré 02 Oct 2007
15:58 25 Mars 2008
Programmateur 2090 9809v60
(c) Medtronic, Inc. 2003
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Reveal(R) Plus Modèle 9526
Amplification: x4 (+/- 0.4 mV)
Mode d'enregistrement: 3 épisodes patient, 5 épisodes automatiques
42 min.
Episode patient 1 de 3 enregistré 02 Oct 2007
15:58 25 Mars 2008
Programmateur 2090 9809v60
(c) Medtronic, Inc. 2003
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