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Stratification du risque de mort subite chez les patients présentant un syndrome de Brugada et un aspect de repolarisation précoce

Romain Tixier

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Né le 22 avril 1990 à Fontenay-Aux-Roses (92)

**STRATIFICATION DU RISQUE DE MORT SUBITE CHEZ
LES PATIENTS PRESENTANT UN SYNDROME DE
BRUGADA ET UN ASPECT DE REPOLARISATION
PRECOCE**

Directeur de thèse

Monsieur le Professeur Frédéric SACHER

Jury

Monsieur le Professeur Jean-Michel HAISSAGUERRE, président

Monsieur le Professeur Pierre BORDACHAR

Madame le Docteur Méléze HOCINI

Monsieur le Docteur Jean-Baptiste GOURRAUD, rapporteur

Monsieur le Docteur Josselin DUCHATEAU

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INTRODUCTION: RISK STRATIFICATION IN BRUGADA SYNDROME

Brugada syndrome (BrS) is an inherited arrhythmia syndrome affecting ionic channels mainly located in the anterior right ventricular outflow track^{1,2}. Most patients remain asymptomatic for life but a minority can develop palpitations, syncope or nocturnal agonal respiration due to ventricular tachycardia (VT) or fibrillation (VF), potentially leading to Sudden Cardiac Death (SCD). While therapeutic management in symptomatic BrS is well defined, consisting of Implantable Cardiac Defibrillator (ICD) implantation³, risk stratification in asymptomatic BrS remains challenging due to a lower rate of events in this young and healthy population with long life expectancy compared to a significant ICD devices morbidity⁴. Furthermore, nowadays newly diagnosed BrS patients are mainly drug induced and/or asymptomatic patients^{5,6} addressed from family screening or systematic ECG screening which need us to improve risk stratification and management of this category of patients. This is a review of known risk stratification criteria.

SYMPTOMS

Symptomatic patients either with history of aborted SCD or history of typical arrhythmic syncope are a group at very high risk of arrhythmias recurrence⁷. In the first cohort of 334 BrS patients described in by Brugada et al.¹, after an average follow-up of 33±39 months, the annual rate of arrhythmias recurrences was 8.8% in patients with history of syncope and 13.7% in patients with history of aborted SCD. The FINGER study⁸ analyzed 1029 BrS patients during a median follow-up of 31.9 months, the annual rate was 1.9% in patients with history of syncope and 7.7% in patients with history of aborted SCD. In the Sieira and al. study published in 2017, the annual rate of arrhythmias recurrence was 2.2% in patients with history of syncope and 11.1% in patients with history of aborted SCD.

These differences could be explained by the fact that initial cohorts included patients at higher risk, by recruitment bias or by center effect. Our cohort of 1613 BrS patients followed during a median period of 5.2[1.9;9.6] years showed an annual rate of recurrence of 8% among spontaneous BrS ECG pattern patients with history of aborted SCD, 2.2% among spontaneous BrS ECG pattern patients with history of syncope, 10.5% among induced BrS ECG pattern patients with history of SCD, 1.1% among induced BrS ECG pattern patients with history of syncope. These high rates of recurrence justify the implantation of defibrillation devices in symptomatic patients despite their potential complications.

On the other hand, asymptomatic patients are at lower risk of arrhythmic event since overall annual rates of occurrence range are between 0.5% and 0.8%. However, one should not forget this still represents more than 100 times the risk in general population⁶ which emphasize the necessity of a more precise risk stratification among these asymptomatic patients.

AGE

Annual rates of ventricular arrhythmias recurrences are made on assumption that events rates are constant over time. In our cohort of 1613 patients, annual rate of event was 2.0% in patients younger than 17, 1.0% in patients between 17 and 59 and 0.3% in patients older than 59.

There is only few data concerning young patients, especially under 18, so prevalence of BrS in children isn't precisely defined, and even if BrS in children is rarer than in adults, fatal arrhythmic event can occur even at young age^{1,7,9}, more likely during a fever episode¹⁰. In a small cohort of 95 patients under 19, Corcia and al.¹¹ found, after a median follow-up of 33.8[9.0;97.7] months, an overall 1.9% annual rate of events, 6.9% in previously symptomatic patients and 0.28% in asymptomatic patients. When BrS is symptomatic in children, it seems to be a far more severe form of the disease.

In elderly patients, some data suggests a lower risk after 60 years old¹², data from our cohort supports this assumption. However, patients over 60 presenting with symptoms and newly diagnosed with BrS should undergo ICD implantation as recommended by latest expert consensus report.

Therefore, the period between 30 and 50 seems to represent the critical period for arrhythmias events. Mean age of first event is reported around 40, events are rarer before 20 or after 60 years old¹³. One hypothesis relies on testosterone levels¹⁴.

GENDER CONSIDERATION

Despite equal genetic transmission of affected genes, all large studies showed that BrS is 8 to 10 times more prevalent in males than in women. Furthermore, women seem to display less severe form of BrS than men.

In the largest cohort of BrS women with 494 female patients, Berthome and al.¹⁵ showed that women were less symptomatic at baseline (69% vs. 77%, $p < 0.001$), showed less frequently spontaneous BrS pattern ECG (17% vs. 29%, $p < 0.001$), and had a lower annual rate of arrhythmia events (0.5% in asymptomatic women with spontaneous BrS ECG pattern, 0.4% in women with induced BrS ECG pattern). Also, mean age at first event was higher in women than in men (48.6 ± 17.8 years vs. 43 ± 14.2 years, $p < 0.001$). In multivariate analysis, predictors of arrhythmias recurrence were proband status (HR 10.2, $p = 0.01$), aborted SCD (HR 69.4, $p < 0.0001$), syncope (HR 6.8, $p = 0.02$), QRS fragmentation (HR 20.2, $p = 0.02$, leading to an annual rate of arrhythmias recurrence of 3.8% in asymptomatic women with fragmented QRS in this study) and QRS duration above 120ms (HR 4.7, $p = 0.03$).

Another study from Sieira and al.¹⁶ comparing 228 women and 314 men affected by BrS found an annual rate of arrhythmias recurrence of 0.7% in women and 1.9% in men. Clinical presentation was also more favorable in women in this study with less symptomatic

patients and less spontaneous BrS pattern ECG in the women group. Predictors of recurrence were aborted SCD (HR 25.4, $p < 0.01$) contrary to the presence of syncope (HR 1.4, $p = 0.69$), and presence of SND (HR 9.1, $p = 0.04$).

It should be noted that, in these two studies, spontaneous BrS pattern ECG does not appear to be a predictor of arrhythmias recurrence.

Possible hypothesis explaining these gender differences in BrS are a smaller *Ito* current in the RVOT in women¹⁷ and differences in testosterone levels^{14,18,19}.

FAMILY BACKGROUND

Majority of large studies had failed to highlight a relation between family history of SCD and future personal risk of VF^{8,9,20-24}, even considering only SCD in first relative or SCD in first relative at a young age^{25,26}.

In a 2017 Sieira and al.²⁷ study designed to build a risk stratification score, although globally a history of family SCD was not statistically associated with future arrhythmic events, considering SCD in first degree relative younger than 35 years old only conferred a three-fold VF risk (HR 2.9; 95% CI [1.2;7.0], $p = 0.02$).

However, in 2 studies from 2016⁹ and 2017¹¹, by the same group of authors, focalizing on risk assessment in young patients, family history of SCD was not statistically related to future rhythmic events no matter age of occurrence or level of degree-relative.

GENETIC ASPECTS

Genetic testing is positive in up to 35% of BrS patients and in most cases (75%) it involves one of the 300 known mutations of the SCN5A gene^{28,29} (encoding the alpha subunit of the cardiac sodium channel Nav1.5).

Few small studies reported correlation between genetic and risk of arrhythmic event in BrS^{30,31}. Nevertheless, relationship between presence, type or precise site of SCN5A mutations and risk of arrhythmic event has not been made in large cohorts of BrS patients^{8,13,21,32}.

Furthermore, whereas BrS was considered as a monogenic disease with an autosomal dominant mode of transmission with incomplete penetrance, recent findings, studying genotype/phenotype correlations among individuals of BrS families, highlighted the fact that BrS inheritance could be much more complex with presence of multiple genetic factors modulating the risk of presence of BrS ECG phenotype²⁹.

ECG CHARACTERISTICS

BRUGADA ECG PATTERN

Showing a spontaneous BrS ECG pattern has been constantly related to a greater risk of arrhythmic events in large Brugada cohorts^{5,8,20}.

In the FINGER study, among asymptomatic patients, showing a spontaneous BrS ECG pattern was associated with a 0.81%/year risk versus a 0.35%/year risk in induced BrS ECG pattern patients, among patients with previous history of syncope, risk varied between 2.3%/year in spontaneous BrS ECG pattern patients and 1.44% in induced BrS ECG pattern patients⁸.

In a study published in 2016, focusing on prognosis of drug induced BrS patients, Sieira and al.³³ showed an annual arrhythmic recurrence rate of 0.4% in asymptomatic induced BrS ECG pattern patients vs. 1.2% in asymptomatic spontaneous BrS ECG pattern patients. It should be noted that during follow-up, 13.7% of initially drug induced BrS ECG pattern showed a spontaneous BrS ECG pattern, reminding BrS ECG pattern is fluctuant over time and risk assessment should be repeated on regular basis.

Besides, evaluation of BrS ECG pattern burden by 24-hours 12-leads ECG monitoring could be useful to improve risk stratification as it was retrospectively linked to a greater risk of ventricular arrhythmias³⁴ but another study did not find this relationship³⁵ and real life application could be technically difficult.

Concerning fever-induced BrS ECG pattern patients, a retrospective study from Mizusawa³⁶ reported an annual risk, after a 43.6±37.4 months follow-up, ranging from 3.0% in patients with previous history of VF, 1.3% in patients with previous history of syncope, to 0.9% in asymptomatic patients.

FRAGMENTED QRS

Fragmented QRS (fQRS), defined by the presence of an abnormal QRS complex fragmentation with ≥ 4 spikes in 1 or ≥ 8 spikes in all of the leads V1, V2 and V3³⁷ has been repeatedly linked to a worst prognosis^{20,37-41}. In order to assess properly the presence or absence of fQRS, special attention should be made about ECG filters since it requires low pass filter with high frequency cut-off (150Hz).

In our cohort of BrS patients, the presence of fQRS was associated with a greater risk of ventricular events (HR 3.37; 95% CI [1.37;8.32], $p=0.008$). Fragmented QRS were found only in 1.5% (N=25) of BrS patients, but among those 25 patients, 5 had recurrences of ventricular arrhythmias.

As previously mentioned, in Berthome and al.¹⁵ study, in women, fQRS was found to be an independent risk factor in multivariate analysis (HR 20.2, $p=0.02$, leading to an annual rate of arrhythmias recurrence of 3.8% in asymptomatic women with fragmented QRS in this study).

Two 2017 meta-analysis by Meng and al.⁴² and Rattanawong and al.⁴³ highlighted a three to four fold risk in fQRS patients (respectively HR 3.88; 95% CI [2.26;6.65], $p<0.00001$ and HR 3.36; 95% CI [2.09;5.38], $p<0.001$).

VENTRICULAR LATE POTENTIALS

Ventricular Late Potentials (LP) are based on the analysis, using signal average ECG, of the total filtered QRS duration, the root mean square voltage of the 40ms terminal portion of the QRS (RMS_{40}) and the duration of the low amplitude electric potential component ($<40\mu V$) of the terminal portion of the QRS (LAS_{40}). LP are considered positive when 2 of 3 criteria are met.

A Yoshioka study⁴⁴ reported, in BrS patients, a prolonged total filtered QRS duration, a prolonged LAS_{40} and a diminution of RMS_{40} at night compared with the day.

One study⁴⁵ with 11 BrS patients reported differences in modifications of these parameters compared to healthy individuals during Isoproterenol infusion. In BrS patients decreased RMS_{40} and prolonged LAS_{40} were reported after Isoproterenol infusion, whereas total filtered QRS duration was unchanged. This could be consistent with an intraventricular conduction disturbance of low amplitude revealed during Isoproterenol infusion.

A 43 BrS patients prospective study⁴⁶ reported an increased arrhythmic risk in BrS patients with positive LP (HR 10.9, 95% CI [1.1;104.3], $p=0.038$).

However, further prospective data from bigger studies is needed in order to confirm these results.

S-WAVE IN LEAD D1 (S1 PATTERN)

Conduction delay in RVOT is a suggested pathophysiological basis in BrS⁴⁷⁻⁵⁰. Calo and al.²⁴ hypothesized that a deep or large S1 pattern could reflect conduction delay in RVOT and therefore constitute an attractive tool for risk assessment. They included 347 patients without previous history of SCD (78.4% male; mean age 45 ± 13.1 years; mean follow-up was 48 ± 38.6 months), in whom 59.1% showed a S1 pattern. Amplitude, mean

duration and mean amplitude duration area of S1 were significantly higher in patients who developed arrhythmic events compared to patients who presented a syncope than in patients who remained asymptomatic. For clinical practice proposed cut-off were amplitude ≥ 1 mV, duration ≥ 40 ms and mean amplitude area ≥ 1 mm². Interestingly, invasive RV mapping was performed in some patients with (8) and without (4) S1 pattern showing significantly longer endocardial activation time in S1 patients with significant delays in RVOT, more fragmented and abnormal electrograms, lower mean voltage in RVOT and bigger areas of abnormal voltage, localized exclusively in the RVOT region.

EARLY REPOLARIZATION PATTERN (ERP)

ERP is defined by elevation of J-point ≥ 0.1 mm (0.1 mV) in ≥ 2 contiguous inferior (DII, DII and VF) and/or lateral (D1, VL, V4-V6) leads in which J-point is the peak of an end QRS notch and/or the onset of an end QRS slur⁵¹. ERP is a common ECG finding seen in 2-5% of the general population but BrS patients seem to display ERP more frequently than general population.

BrS and ERP are often gathered into “J-wave syndrome” appellation⁵² since both syndromes shared some clinical and pathophysiological mechanisms. Both of them are associated with life threatening ventricular arrhythmias, occurring predominantly in young male patients without structural heart disease, and triggered by short-coupled premature ventricular complex during sleep or low level of physical activity⁵³⁻⁵⁵. In both syndromes, ECG patterns are dynamic and accented by vagal tone, corporal temperature. During electrical storm, administration of B-adrenergic agonists, quinidine or temporary pacing lead to an amelioration of symptoms in both cases.

Nevertheless, differences should be noticed: regions in which ECG abnormalities are seen are different since BrS pattern is found in right precordial leads corresponding to the right ventricular outflow track while ERP is found in inferior and/or lateral leads

corresponding to inferior and/or lateral left ventricle walls; sodium blocker test leads to an increase of BrS pattern and decrease of ER pattern; incidence of late potential signal on average ECG and incidence of atrial fibrillation are higher in BrS patients compared to ERP patients. Furthermore, precise pathophysiological mechanisms underlying BrS and ERP are not fully understood as it remains a matter of debate between the depolarization and the repolarization hypotheses.

Controversial data exist about value of ERP in BrS patients. Among the five main first studies exploring arrhythmic risk of ERP in BrS patients 3 of them reported higher arrhythmic risk in ERP patients, one reported higher risk in inferolateral ERP only and the other one did not. These five studies were gathered into a meta-analysis by Georgopoulos et al., aggregating a total of 1375 patients, reporting that patients with BrS displaying ERP had a statistically higher risk of arrhythmic events compared to those without ERP and that an inferolateral pattern was at higher risk but without statistical significance.

REPOLARIZATION DISPERSION

T_{peak-Tend} (T_{pe}) interval is calculated by the difference between QT interval duration (measured between QRS onset and end of T-wave) and QT peak interval duration (measured between QRS onset and T-wave peak) on leads V1 to V4. It has been proposed has a marker of repolarization dispersion between endocardium and epicardium. Maury and al.⁵⁶ showed in a 325 BrS patient cohort that increased T_{pe} interval was an independent predictor of arrhythmic occurrences (OR 9.61; 95% CI [3.13;29.41], p<0.0001) using a 100ms cut-off value. These observations were as well made in previous smaller study^{57,58}. Besides, in a recent meta-analysis⁵⁹ studying T_{pe} interval for risk stratification in different cardiac diseases in general population, T_{pe} interval prolongation was associated with arrhythmic or mortality outcomes in general population with highest risk in the subgroup of BrS patients constituted from 6 different studies (OR 5.68; 95% CI [1.57;20.53], p=0.001).

T-Wave Alternans (TWA), defined by beat-to-beat fluctuation in T-wave amplitude, reflects also repolarization dispersion and high TWA variation has been linked to worst prognosis in BrS patients in some studies^{60,61} but confirmation is needed.

AVR SIGN

In a 2007 study⁶², the aVR sign, defined as R wave ≥ 0.3 mV or R/q ≥ 0.75 in lead aVR, has been described as a risk factor for recurrence of arrhythmias in BrS patients. The R wave amplitude or R/q ratio in lead aVR was significantly greater in patients experiencing a recurrence, since 84% of BrS patients with presence of aVR sign but only 27% of BrS patients without aVR sign had events during follow-up. It should be noted that these results are based only on a 24 patients cohort.

SINUS NODE DYSFUNCTION

Sinus Node Dysfunction (SND) is clinically defined by sinus bradycardia according to age and activity, sinus pauses ≥ 2.5 seconds and/or chronotropic incompetence (impossibility to reach 85% of age predicted maximum heart rate during exercise). SND has sometimes been linked to rhythmic events in particular in young patients^{9,11} and women¹⁶. Nonetheless, further investigation in large studies is needed to confirm this hypothesis.

PROGRAMMED ELECTRICAL STIMULATION (PES)

Controversial data exists about the use of PES in risk stratification for BrS patients. Although some data, especially first papers from Brugada and al.^{22,23}, initially suggests its prognostic significance, following studies failed to confirm a link between positive PES and occurrence of arrhythmias in BrS⁸. In the PRELUDE study²⁰, in a total of 308 patients, 41%

were inducible using a stimulation protocol with up to 3 extrastimuli in 2 sites (RV apex and RVOT). After a mean follow-up of 36 ± 8 months, no statistical difference was found between induced patients and non-induced patients regarding arrhythmias recurrence ($p=0.67$). Using a 2 extrastimuli protocol, inducibility rate dropped to 20.5%, but in this subgroup no statistical difference was neither found ($p=0.89$). Consequently, the Expert Consensus Paper in 2013 dropped indication for ICD implantation after PES induced arrhythmia from IIa to IIb³. Notably, questions were raised about patients in whom PES should be performed, stimulation protocols used, outcomes definition, and PES reproducibility.

Sieira and al. in 2015 published a study⁶³ with 404 patients with a mean follow up of 74.3 ± 57.3 months. Ventricular arrhythmias were induced in 18.1% of patients using stimulation protocol with up to 3 extrastimuli in the RV apex. PES inducibility was related to arrhythmias recurrence (HR 8.3; 95% CI [3.6;19.4], $p<0.01$).

A meta-analysis from Sroubek and al. in 2016⁶⁴ pooling 1312 patients without personal history of aborted SCD found that, after adjustments for age, sex, cohort, ECG and symptoms presentation, a positive PES with up to 2 extrastimuli was related with more arrhythmia events in BrS patients (HR 2.66; 95% CI [1.44;4.89], $p=0.002$). Using a 2 extrastimuli protocol, inducibility rate was 21%. After linear regression, a third extrastimulus was not statistically associated with arrhythmias recurrence. In asymptomatic patients with spontaneous BrS ECG pattern, recurrence rate was 0.78% in the non-induced group and 1.7% in the induced group which could change patient management, leading to discuss ICD indication.

Thus, PES should only be performed to precise risk stratification in asymptomatic patients with intermediate risk according to clinical status such as asymptomatic patients with spontaneous BrS ECG pattern. An aggressive stimulation protocol increase sensitivity but could lead to a diminution of specificity, stimulation in 2 RV sites (RVOT and apex) and with up to 2 extrastimuli seems to represent a good compromise. PES positivity is defined

by induction of sustained ventricular arrhythmia (VF or VT lasting more than 30 seconds or requiring external shock). PES negativity does not correctly identify low risk patients and risk stratification should be assessed according to clinical status. Reproducibility is still a matter of concern since in the PRELUDE study ventricular arrhythmias were induced in only 34% of previously inducible patients²⁰ contrary to another study from Gasparini and al.⁶⁵ that found a reproducibility rate of 82% but with only 21 patients included.

PROPOSED COMPOSITE SCORES

In order to help risk stratification in asymptomatic patients, composite scores could be useful given the fact that single risk factors aren't able to correctly enough discriminate low risk and high risk patients^{26,66}.

In 2014 a score has been proposed by Kawazoe and al.⁶⁷ with clinical data and mainly ECG criteria. History of syncope, QRS duration in V6, r-J interval in V1 and Tpe dispersion were included. Nevertheless, even if this score has a good performance (AUC 0.845, sensibility 97.1% and specificity 63%), it was retrospectively built on data from only 143 patients whom 140 were males and provides a future VF probability without precise time range. Furthermore, rely on electrical data such as QRS duration or Tpe dispersion, whose precise measurement are known to be tough in real life⁶⁸⁻⁷⁰, in order to decide whether or not an ICD should be implanted, sometimes in young patients, might be tricky.

Another score has been as well proposed by Sieira and al.²⁷ to assessed risk of arrhythmias recurrences in BrS patients (Table 1A). A score ≥ 2 conferred an arrhythmic risk greater than 6% at 5 years (9.2%) and has been proposed as a cut off for ICD implantation by the authors since it's the cut off used in hypertrophic cardiomyopathy (Table 2B). Despite such a score is needed to simplify assessment of arrhythmic risk and management in BrS patients, it is not certain that it allows a correct discrimination of intermediate risk patients representing the group in need for a more accurate risk assessment.

Table 1A: Proposed score model for risk stratification

| Risk factor | Points |
|----------------------------|---------------|
| Spontaneous Type 1 ECG | 1 |
| Early familial SCD (<35yo) | 1 |
| Inducible PES | 2 |
| Syncope | 2 |
| Sinus Node Dysfunction | 3 |
| Aborted SCD | 4 |

Table 1B: Event free survival rate according to the score model group

| Score | 1 year | 5 years | 10 years | p |
|--------------|---------------|----------------|-----------------|----------|
| 0 | 100% | 98.4% | 97.2% | |
| 1 | 100% | 96.4% | 96.4% | 0.79 |
| 2 | 97.4% | 90.8% | 90.8% | 0.02 |
| 3 | 88.7% | 83.4% | 83.4% | <0.01 |
| 4 | 91.4% | 75.2% | 70.1% | <0.01 |
| ≥5 | 79.3% | 68.2% | 61.4% | <0.01 |

Finally, a score for risk assessment in patients under 19 years old has as well been elaborated¹¹ using presence of symptoms (4 points), spontaneous BrS ECG pattern (3 points), SND and/or atrial tachycardia (2 points) and conduction abnormalities (1 points). However, a cut-off of 4 points is considered to discriminate low risk and high risk patients but due to the construction score the results are mainly driven by symptoms which lowers its clinical utility.

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EARLY REPOLARIZATION PATTERN IS NOT RELATED WITH VENTRICULAR ARRHYTHMIAS IN BRUGADA PATIENTS

ABSTRACT

Introduction: *Brugada syndrome (BrS) is an inherited arrhythmia syndrome with an increased risk of syncope and sudden death. The risk stratification of BrS patients remains challenging. An Early Repolarization pattern (ERP) has been suggested to increase the risk of ventricular arrhythmias. The aim of this study was to investigate the association between BrS and ERP with arrhythmic events in the largest cohort of BrS patients ever described.*

Methods: *Consecutive patients affected with BrS were recruited from 15 tertiary centers in France between 1994 and 2015. Data were prospectively collected with an average follow-up of 6.1 ± 4.6 years. ECGs were reviewed by 2 physicians blinded to clinical status. ERP was defined as a 0.1 mV J wave elevation in at least 2 inferior and/or lateral leads.*

Results: *A total of 1613 patients (mean age 45 ± 15 years; 1119 males, 69%) were enrolled in this study. Three hundred and twenty-three patients (20%) were symptomatic at baseline (66 (4%) aborted sudden cardiac death (SCD) or documented VT, 257 (16%) syncope). Four hundred and eleven patients (25%) presented a spontaneous type 1 ECG. Implantable cardiac defibrillator (ICD) was implanted in 477 patients (30%). At baseline, ERP has been found in 117 patients (7%): 76 patients (5%) presented QRS slurring, 33 (2%) QRS notching and 8 (0.5%) both. ERP were more frequent in male than in female (81% male, $p=0.004$). No significant difference was found in the age, family history of SCD or symptoms or spontaneous type 1 ECG. During follow-up of 6.1 ± 4.6 years, 84 of 1496 patients without ERP (6%) and 7 of the 117 patients with ERP (6%) underwent arrhythmic events (1 SCD, 5 appropriate ICD therapy and 1 ventricular arrhythmia). Patients with ERP had not a*

significantly higher rate of arrhythmic events than patients without ERP (HR: 1.16; 95% CI: 0.54-2.51; p= 0,7).

Conclusion: *In the largest cohort of BrS patients ever described, ERP does not seem to be a marker of arrhythmic event.*

INTRODUCTION

Brugada Syndrome (BrS) is an inherited arrhythmia syndrome first described in 1992 by Pedro and Josep Brugada¹ affecting ionic channels mainly located in the anterior right ventricular outflow track. Most patients remain asymptomatic for life but a minority can develop palpitations, syncope or nocturnal agonal respiration due to ventricular tachycardia (VT) or fibrillation (VF), potentially leading to Sudden Cardiac Death (SCD). While therapeutic management in symptomatic BrS is well defined, consisting of Implantable Cardiac Defibrillator (ICD) implantation^{2,3}, risk stratification in asymptomatic BrS remains challenging due to a lower rate of events in this young population⁴ compared to a significant ICD devices morbidity^{5,6,7}. The Early Repolarization Pattern (ERP) is a common electrocardiographic (ECG) finding seen in 2-5% of the general population which was considered benign until it was linked to idiopathic VF in 2008^{8,9,10}. These 2 syndromes are often gathered into the same J-waves syndromes entity since they share some cellular and ionic similarities^{11,12}. ERP has been suggested to increase the risk of ventricular arrhythmias in BrS and its prognosis significance have already been discussed in several studies but existing data on the risk linked to ERP in BrS remain controversial^{6,13-18}. The aim of this study was to investigate the association of the ERP with arrhythmic events in the largest cohort of BrS patients ever described.

METHODS

Consecutive patients affected with BrS were prospectively recruited from 15 tertiary centers in France between February 1994 and July 2015, gathered into the same database held by Nantes University Hospital Center, FRANCE. The data collected were: gender, age at diagnosis, proband status, personal history of symptoms (syncope, documented sustained ventricular arrhythmia or aborted SCD), ECG characteristics, family history of asymptomatic or symptomatic BrS, family history of SCD, presence of ICD in primary or secondary prevention, presence of programmed electrical stimulation at diagnosis and its result, genetic analysis of SCN5A results. All subjects underwent trans-thoracic-echocardiography and if necessary exercise treadmill test or coronary angiography used at treating physician discretion in order to rule out any structural heart disease.

All 12-leads ECG were recorded, according to international standards, at a paper speed of 25 mm/s, amplitude of 10 mm/mV and with 0.16-150Hz filters. ECG were analyzed by two different physicians blinded to clinical status, in case of disagreement, a third lecture by another electrophysiologist physician was performed. BrS was confirmed in presence of spontaneous or induced (Flecainide 2mg/kg I.V. or Ajmaline 1mg/kg I.V.) type 1 ECG which was defined using latest international recommendations by ST segment elevation ≥ 2 mm (0.2 mV) in ≥ 1 right precordial leads (V1-V3) positioned in the 4th, 3rd, or 2nd intercostal space². ERP was defined, using latest expert consensus report, by elevation of J-point ≥ 0.1 mm (0.1 mV) in ≥ 2 contiguous inferior (DII, DII and VF) and/or lateral (D1, VL, V4-V6) leads in which J-point is the peak of an end QRS notch and/or the onset of an end QRS slur¹⁹. All ECG were analyzed using ImageJ software (National Institutes of Health, Bethesda, Maryland, USA). The following variables were measured: heart rate, P wave duration in D2, PR interval duration in lead D2²⁰, QRS duration in all derivations²¹, QT and QTc using Bazett formula in lead D2, S wave duration and depth in leads D1 and D2²², maximal Tpeak-Tend interval in leads V1 to V6²³, QRS fragmentation²⁴, amplitude of ST

elevation in case of BrS in leads V1 to V3, amplitude of J-point elevation and characterization of ST-segment (horizontal or downward sloping) in case ERP in inferior and/or lateral leads²⁵. When 2 or more ECG were available for the same patient, ECG with the most pronounced BrS and/or ERP features was selected.

During follow-up, an arrhythmic event was defined by occurrence of syncope, documented sustained VT, appropriate ICD shock, SCD or aborted SCD.

Ethics committees from every center have approved the study, data storage and use was approved by the French Data Protection Authority and consents were obtained for all subjects.

STATISTICAL ANALYSIS

Continuous data are presented as mean (\pm standard deviation) or median [25th,75th] based on the distribution. Categorical variables are presented as counts (proportions). The t-test and Mann-Whitney-U tests were performed to test for statistical differences in continuous parameters between the two groups. The chi-square or Fisher's exact test (based on expected frequency) were used to compare categorical variables between groups. The Kaplan-Meier method estimator was used to assess the time to a first cardiac event. Cox proportional-hazards regression analysis [with hazard ratios (HR) and confidence intervals (CI)] were used to evaluate the independent risk of clinical and genetic factors of interest for first cardiac events. The mean event rate per year was evaluated by the number of events occurring during the follow-up divided by the number of patients multiplied by the average duration of follow-up. A P-value <0.05 was considered statistically significant. Data analyses were performed using SAS (SAS version 9.4; SAS Institute Inc., Cary, NC).

RESULTS

A total of 1613 patients (45 ± 15 years, 68% male), members of 1260 different families, were enrolled in the study. Demographic data and clinical status at inclusion are shown in table 1. 323 (20%) were symptomatic at baseline. Spontaneous type 1 ECG was found in 411 (25%) patients. ERP was seen in 117 patients (7%), mean J-point elevation was 0.18 ± 0.078 mV, 14 patients (12%) had a >0.2 mV J-point elevation, 14 (12%) had inferolateral ERP (Figure 1). Their ECG characteristics are shown in table 2. Clinical and ECG differences between BrS patients with and without ERP are shown in table 3. There was no difference between the two groups regarding age, probands status, symptoms, family history of SCD, presence of ICD, presence of SCN5A mutation, positive SVP, sinus node dysfunction, P wave >120 ms, PR interval >200 ms, QRS duration >90 ms, QTC >460 ms, maximum Tpeak-Tend >100 ms, spontaneous type 1 ECG, presence of BrS in peripheral lead, maximum V1 and V2 ST elevation or fragmented QRS. There were statistical differences regarding sex gender (81% male in the ERP group, $p=0,004$), heart rate ($p=0,001$), maximum V3 ST elevation ($p=0.04$) and presence of AvR sign (14% in the non-ERP group versus only 6% in the ERP group, $p=0,01$).

During a median follow-up of 5.2[1.9;9.6] years, 7 (7%) arrhythmic events occurred in the ERP group (5 appropriate ICD therapies, 1 SCD and 1 documented VT) vs. 84 (6%) in the non-ERP group. Data about BrS patients showing ERP with symptoms during follow-up are shown in table 4. None of these patients were displaying inferolateral ERP nor a >2 mm J-point elevation and 5 of them were already symptomatic at baseline.

Using univariate Cox proportional hazard regression analysis, and as shown in figure 2, ERP had not a significantly higher rate of arrhythmic events than patients without ERP (HR: 1.16; 95% CI: 0.54-2.51; $p= 0,7$).

Figure 3 shows event rates in BrS patients according to ECG presentation and symptoms at baseline.

DISCUSSION

In our study, which is so far the largest cohort of Brugada patients with 1613 individuals followed for a median period of 5.1 years, ERP was seen in 7% of BrS patients, which is slightly more than the incidence observed in the general population, but was not related to a significantly higher rate of arrhythmic events in BrS patients. Interestingly, in BrS patients with ERP who became symptomatic during follow-up, none of them were displaying inferolateral ERP or >2mm J-point elevation which are yet characteristics considered at higher risk.

Among the five main previous studies exploring arrhythmic risk of ERP in BrS patients, results were controversial: 3 of them reported higher arrhythmic risk in ERP patients, one reported higher risk in inferolateral ERP only and the other one did not.

Definition of ERP in these five studies was the same as the definition we used in our protocol and as recommended in the latest consensus report.

These five studies were gathered into a meta-analysis by Georgopoulos et al.²⁶ reporting that patients with BrS displaying ERP had a statistically higher risk of arrhythmic events compared to those without ERP and that an inferolateral pattern was at higher risk but without statistical significance. These studies had fewer patients than ours since their total of patients was 1375 and the largest one, by Kamakura et al. had 460 patients.

In the Letsas et al.¹⁵ study, which did not find a statistical relation between ERP and arrhythmic events in BrS patients, patient's characteristics were globally similar as the one included in our cohort with 30% of symptomatic BrS including 2.8% of personal aborted SCD or VF history, a male proportion of 70%, a spontaneous type 1 ECG proportion of 45%; ERP proportion was 12% with 31% of inferior ERP, 51% of lateral ERP and 17% of inferolateral ERP; the rate of arrhythmic event was 7% during a smaller follow-up of 3.7 ± 2.3 years.

The Takagi et al.¹⁴ study reported a higher arrhythmic risk in BrS patients showing inferolateral ERP (95% CI:1.4-10.2; p=0.003), ERP was also found in 12% of the BrS patients which were more symptomatic at baseline (42%) with 18% with personal aborted SCD history, were mainly male (94%) and showed a higher proportion of spontaneous type 1 ECG (63%).

In the Kamakura et al.¹⁷ study, only probands were included, 17% had personal aborted SCD history, male proportion was 95%, spontaneous type 1 ECG proportion was 74%, ERP was only found in 10% of BrS patients but all of them showed inferolateral ERP; despite that, event rate remained similar as our study (7%) during a smaller follow up of 4.1±1.3 years.

In the Kawata et al.¹⁸ study the 49 patients included were only symptomatic patients with personal history of aborted SCD, male proportion was 94%, spontaneous type 1 ECG proportion 74%, ERP proportion 63% with 29% of inferolateral ERP, 29% of descending or horizontal ST-segment and a mean J-point amplitude of 0.228±0.122 mV. During a follow-up of 7.6±3.8 years, 71% of patients had another arrhythmic event.

In the Tokioka et al.¹⁶ study, patients were also mainly male (95%), 21,5% were symptomatic at baseline, 5.3% with personal history of aborted SCD, 63% had a spontaneous type 1 ECG, 25% showed an ERP, all of them in the inferolateral leads, there was a 10% rate of arrhythmic events during a follow-up of 3.8±3.7 years.

Differences between these previous results and our study could thus be explained by the fact that majority of patients included in our cohort are lower risk patients at baseline. Particularly, as shown in table 5, in the Kamakura, Kawata and Tokioka studies, which reported higher risk in ERP patients, patients included seem to were at very high risk regarding ERP and/or BrS characteristics with a high proportion of male, spontaneous BrS type 1 ECG, symptomatic BrS patients especially with high proportion of previous aborted

SCD, ERP in inferolateral leads and/or with a >2mV J-point elevation, characteristics which are known for worsening patients' prognostic^{4,7,13,25,27-29}.

Furthermore, with only 7 patients becoming symptomatic during follow-up among ERP patients, we could have lacked statistical power.

Likewise, studies reporting a higher arrhythmic risk in ERP patients are all Japanese studies. The other one, which don't report a higher arrhythmic risk in ERP patients is about European patients, like this study. Maybe Asiatic and European patients aren't part of a homogeneous population considering BrS and/or ERP characteristics. In this case, risk stratification strategy could differ.

BrS and ERP are often gathered into "J-wave syndrome" appellation¹² since both syndromes share some clinical and pathophysiological mechanisms. Both of them are associated with life threatening ventricular arrhythmias, occurring predominantly in young male patients without structural heart disease, and triggered by short-coupled premature ventricular complex during sleep or low level of physical activity. In both syndromes, ECG patterns are dynamic and accented by vagal tone, fever and hypothermia. During electrical storm, administration of B-adrenergic agonists, quinidine or temporary pacing lead to an amelioration of symptoms in both cases. Nevertheless, differences should be noticed: regions in which ECG abnormalities are seen are different since BrS pattern is found in right precordial leads corresponding to the right ventricular outflow track while ER pattern is found in inferior and/or lateral leads corresponding to inferior and/or lateral left ventricle walls; sodium blocker test leads to an increase of BrS pattern and decrease of ER pattern; incidence of late potential signal on average ECG and incidence of atrial fibrillation are higher in BrS patients compared to ERP patients. Furthermore, precise physiopathological mechanisms underlying BrS and ERP are not fully understood as it remains a matter of debate between the depolarization and the repolarization hypotheses^{19,30-34}.

Some limitation concerning this work should be noticed, BrS and ERP are dynamic ECG pattern, while all BrS patients in our cohort were confirmed with either spontaneous or drug induced type 1 ECG, some patients showing intermittent ERP pattern could have been misclassified.

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TABLES AND FIGURES

Table 1: Population characteristics

| Variables | Patients (N=1613) |
|---------------------------------------|--------------------------|
| Age (years) | 45±15 |
| Males | 1119 (69%) |
| Probands | 1187 (74%) |
| Symptomatic | 323 (20%) |
| Syncope | 257 (16%) |
| Ventricular arrhythmia or aborted SCD | 66 (4%) |
| Family history of SCD | 492 (31%) |
| Spontaneous type 1 ECG | 411 (25%) |
| ERP | 117 (7%) |
| ICD | 477 (30%) |
| SCN5A mutation | 355 (22%) |
| Positive PES | 214 (13%) |
| Median follow-up (years) | 5.1[1.9;9.6] |
| Patients with ≥1 arrhythmic event | 91 (6%) |

SCD: Sudden Cardiac Death. **ERP:** Early Repolarization Pattern. **ICD:** Implanted Cardiac Defibrillator. **PES:** Programmed Electrical Stimulation

Table 2: ERP characteristics

| Variables | Patients (N=117) |
|-----------------------------------|-------------------------|
| ERP aspect | |
| Notching | 33 (28%) |
| Slurring | 76 (65%) |
| Both | 8 (7%) |
| Mean J point elevation (mV)* | 0.18±0.078 |
| J point elevation > 2mV* | 14 (12%) |
| ERP localization | |
| Lateral ERP | 66 (56%) |
| Inferior ERP | 37 (32%) |
| Inferolateral ERP | 14 (12%) |
| ST segment characteristics | |
| Horizontal ST segment | 72 (62%) |
| Downward slopping ST segment | 45 (38%) |

*N=115 (2 missing data). **ERP**: Early Repolarization Pattern.

Table 3: Clinical and ECG characteristics in BrS patients with or without ERP

| Variables | Without ERP (N=1496) | With ERP (N=117) | p |
|---------------------------------------|----------------------|------------------|-------|
| Clinical characteristics | | | |
| Age (years) | 45±15 | 44±14 | 0,68 |
| Males | 1024 (68%) | 95 (81%) | 0,004 |
| Probands | 1098 (73%) | 89 (76%) | 0,53 |
| Symptomatic | 298 (20%) | 25 (21%) | 0,74 |
| Syncope | 238 (16%) | 19 (16%) | - |
| Ventricular arrhythmia or aborted SCD | 60 (4%) | 6 (5%) | - |
| Family history of SCD | 459 (31%) | 33 (28%) | 0,58 |
| ICD | 437 (29%) | 40 (34%) | 0,26 |
| SCN5A mutation | 323 (22%) | 32 (27%) | 0,35 |
| Positive PES | 193 (13%) | 21 (18%) | 0,3 |
| ECG characteristics | | | |
| Heart Rate (bpm) | 71±14 | 68±12 | 0,001 |
| Sinus node dysfunction | 17 (1%) | 1 (1%) | 0,78 |
| P wave duration >120ms in D2 | 60 (4%) | 5 (4%) | 0,89 |
| PR interval >200ms in D2 | 274 (18%) | 29 (25%) | 0,09 |
| QRS duration in V2 >90ms | 903 (60%) | 76 (65%) | 0,33 |
| QTc duration in D2 >460ms | 71 (5%) | 3 (3%) | 0,28 |
| Maximum Tpeak-Tend >100ms | 633 (42%) | 52 (44%) | 0,65 |
| Spontaneous type 1 | 377 (25%) | 34 (29%) | 0,36 |
| Type 1 in peripheral lead | 54 (4%) | 4 (3%) | 0,92 |
| V1 ST elevation in type 1 ECG (mV) | 0.14±0.28* | 0.11±0,10 | 0,33 |
| V2 ST elevation in type 1 ECG (mV) | 0.21±0.17* | 0.23±0.16 | 0,2 |
| V3 ST elevation in type 1 ECG (mV) | 0.09±0.12* | 0.11±0.09 | 0,04 |
| Fragmented QRS | 23 (2%) | 2 (2%) | 0,7 |
| AvR sign | 214 (14%) | 7 (6%) | 0,01 |
| Follow-up | | | |
| Median follow-up (years) | 5.2[1.9;9.6] | 3.8[1.8;9.2] | 0,17 |
| Patients with ≥1 arrhythmic event | 84 (6%) | 7 (6%) | 0,7 |

*N=1495 (1 missing data). **SCD**: Sudden Cardiac Death. **ICD**: Implantable Cardiac Defibrillator. **PES**: Programmed Electrical Stimulation. **BrS**: Brugada Syndrome

Table 4: Demographic and clinical data in symptomatic BrS + ERP patients during follow-up

| | Proband | Sex | Age | Symptoms | SND | Spontaneous BrS Pattern | PES | ICD | Family History of SCD | SCN5A | ERP Aspect | Infero-lateral ERP | J point elevation >2mV |
|---|---------|-----|-----|----------|-----|-------------------------|-----|-----|-----------------------|-------|------------|--------------------|------------------------|
| 1 | Yes | M | 37 | None | No | No | - | No | No | + | slurring | No | No |
| 2 | Yes | M | 44 | Syncope | No | Yes | ∅ | Yes | No | + | both | No | No |
| 3 | Yes | F | 50 | SCD | No | Yes | ∅ | Yes | No | - | slurring | No | No |
| 4 | Yes | M | 42 | Syncope | No | Yes | + | Yes | No | - | slurring | No | No |
| 5 | Yes | M | 33 | SCD | No | Yes | - | Yes | No | + | slurring | No | No |
| 6 | No | M | 23 | Syncope | Yes | No | - | Yes | Yes | + | slurring | No | No |
| 7 | No | M | 56 | None | No | Yes | + | Yes | Yes | + | slurring | No | No |

∅: No PES performed. **SCD**: Sudden Cardiac Death. **SND**: Sinus Node Dysfunction. **PES**: Programmed Electrical Stimulation. **ICD**: Implantable Cardiac Defibrillator. **ERP**: Early Repolarization Pattern.

Table 5: Main clinical and ECG characteristics differences between previous studies investigating ERP in BrS patients and our cohort of BrS patients

| | Our study | Letsas | Kamakura | Takagi | Tokioka | Kawata |
|---------------------|------------------|---------------|-----------------|---------------|----------------|---------------|
| Males | 69% | 79% | 95% | 94% | 95% | 94% |
| Symptoms | 20% | 30% | 37% | 42% | 21.5% | 100% |
| Aborted SCD or VF | 4% | 2.8% | 17% | 18% | 5.3% | 100% |
| Spontaneous BrS ECG | 25% | 45% | 74% | 63% | 63% | 74% |
| Inferolateral ERP | 12% | 17% | 100% | 19% | 100% | 29% |

SCD: Sudden Cardiac Death. **VF:** Ventricular Fibrillation. **BrS:** Brugada Syndrome. **ERP:** Early Repolarization Pattern.

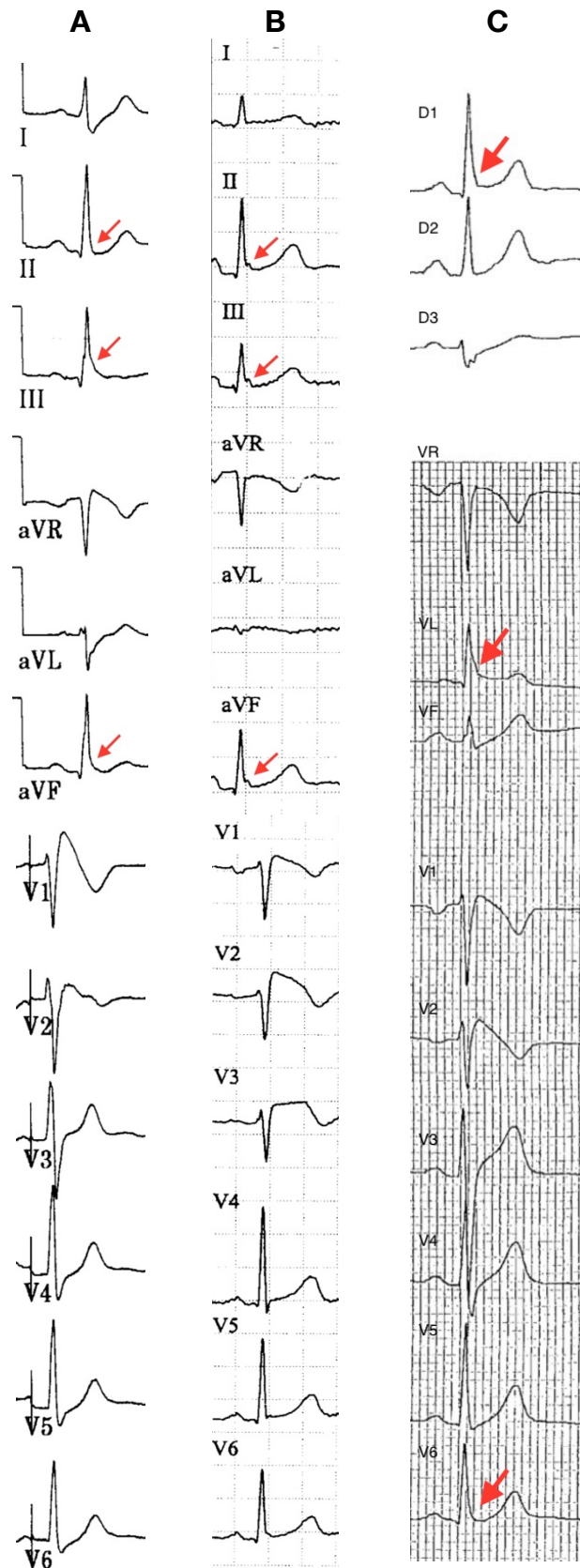
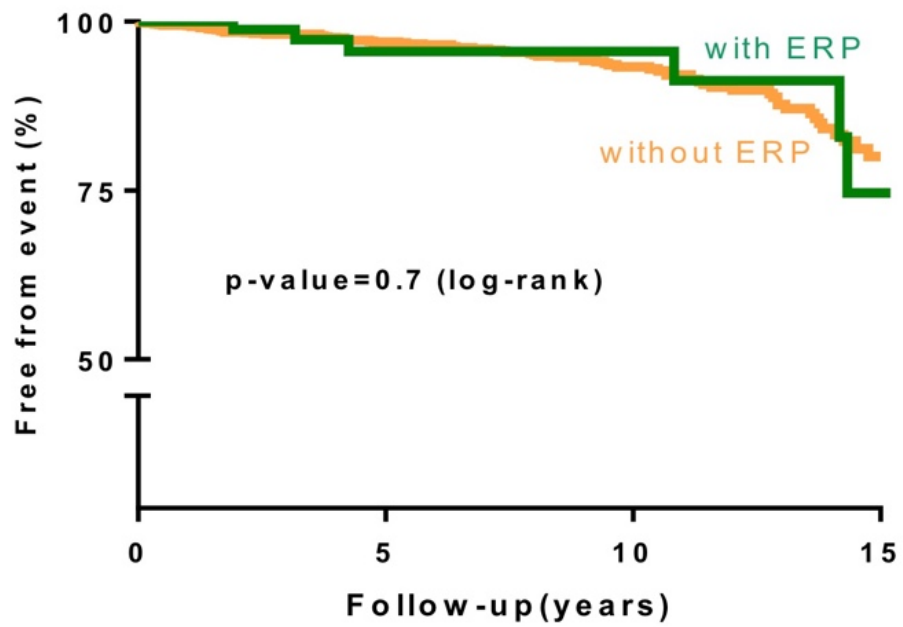


Figure 1: Spontaneous Brugada ECG pattern associated with **A.** Slurred Inferior Early Repolarization Pattern (ERP) **B.** Notched inferior ERP and **C.** Slurred lateral ERP.

Figure 2: Cardiac event-free survival according to presence or absence of Early Repolarization Pattern (ERP)



Nb at risk (free from event (% +/- SD))

| | | | | |
|--------------------|-------------|--------------------|--------------------|-------------------|
| without ERP | 1496 (100%) | 776 (95,5 +/- 0,6) | 352 (92,8 +/- 0,9) | 62 (81,1 +/- 2,1) |
| with ERP | 117 (100%) | 48 (95,7 +/- 2,2) | 25 (95,7 +/- 2,2) | 4 (78,9 +/- 9,3) |

Figure 3: Event rate cohort according to BrS pattern type and symptoms. **BrS:** Brugada Syndrome. **FU:** Follow-up (years) **SCD:** Sudden Cardiac Death.

