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Baseline intervals in electrocardiogram for risk stratification in Brugada syndrome: A 10-year prospective study

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SOUHRN

Kontext: Stratifikace rizika u syndromu Brugadových (Brugada syndrome, BrS) představuje i nadále značný problém. Cílem této studie bylo změřit vstupní intervaly na klidovém elektrokardiogramu (EKG) kohorty portugalských pacientů a jejich příbuzných prvního stupně, u nichž byla stanovena diagnóza BrS, a identifikovat EKG parametry spojené se vznikem srdečních příhod v období deseti let.
Metody: Byla provedena prospektivní studie, v níž bylo vyšetřeno 107 portugalských pacientů spolu s příbuznými prvního stupně, u nichž byla stanovena diagnóza BrS a kteří byli sledováni po dobu deseti let s cílem zaznamenat jakoukoli srdeční příhodu. Byly vytvořeny podskupiny spontánního typu (spontaneous type 1, SB), indukovatelného typu (inducible type 1, IB) a s normálním EKG. Souhrnný sledovaný parametr srdečních příhod zahrnoval náhlou srdeční smrt (SCD), implantaci kardioverteru-defibrilátoru (implantable cardioverter-defibrillator, ICD) a vhodné (adekvátní) vyslání výboje z ICD.
Výsledky: Celkem u 15 % pacientů byla stanovena diagnóza SB a u 10 % pacientů byl diagnostikován IB; průměrný věk účastníků studie byl 29,9 ± 16 let; 51 % z nich byli muži. Pacienti se SB a IB vykazovali statisticky významně delší intervaly PR než jedinci s normálním EKG ($p < 0,01$, resp. $p = 0,02$). Žádné rozdíly v intervalu PR mezi podskupinami SB a IB nebyly zjištěny ($p = 0,93$). Srdeční příhody byly zaznamenány u 41,5 % pacientů se SB a 18,2 % pacientů s IB. U pacientů s normálním EKG a s normálním výsledkem provokačního testu s flecainidem nebyla zaznamenána žádná srdeční příhoda. Po adjustaci na rodinnou anamnézu SCD a při pozitivním výsledku genetického testu představoval interval PR nezávislý prediktor časnějšího vzniku srdeční příhody (HR 1,06; 95% CI 1,02–1,10; $p < 0,01$). U pacientů s PR > 200 ms byla průměrná doba do vzniku srdeční příhody statisticky významně kratší, přičemž optimální mezní hodnota pro predikci srdeční příhody byla 180 ms.
Závěr: Interval PR představuje na vstupním EKG záznamu významný parametr spojený se vznikem srdečních příhod při BrS. Pro přesné stanovení individuálního rizika se doporučuje zařadit do klinického algoritmu interval PR.

Keywords:
Brugada syndrome
Electrocardiography
Risk stratification

ABSTRACT

Background: Risk stratification in Brugada syndrome (BrS) remains challenging. The aim of this study was to evaluate the baseline intervals in resting ECG of a cohort of Portuguese patients with first-degree relatives diagnosed with BrS and to identify ECG parameters associated with cardiac events (CE) over a 10-year period.
Methods: Prospective study assessing 107 Portuguese patients with first-degree relatives diagnosed with BrS and followed over a decade to detect CE. Subgroups included spontaneous type 1 (SB), inducible type 1 (IB), and normal ECG. CE were a composite endpoint comprising of sudden cardiac death (SCD), implantable cardioverter-defibrillator (ICD) implantation and appropriate ICD shocks.
Results: 15% patients with SB and 10% patients with IB, mean age was 29.9±16 years; 51% were male. SB and IB patients exhibited significantly higher PR intervals than those with normal ECG (p <0.01, p = 0.02, respectively). There were no differences in PR interval between SB and IB (p = 0.93). CE occurred in 41.5% of SB and in 18.2% of IB patients. No CE in patients with normal ECG and normal flecainide provocative test. PR interval was an independent predictor of earlier CE (HR 1.06 CI 95% [1.02–1.10]; p <0.01), adjusted to familiar SCD and positive genetic test. Mean time for a CE was significantly shorter in patients with PR >200 ms and the optimal cutoff value for predicting CE was 180 ms.
Conclusion: The PR interval is a significant parameter in basal ECG associated with CE in BrS. Considering the PR interval in the design of clinical algorithms is recommended for accurate individual risk assessment.

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Background

Brugada syndrome (BrS) is an inherited ion channel disorder distinguished by a unique electrocardiographic (ECG) pattern showing J point elevation of 0.2 mV with coved ST elevation and T wave inversion in at least one right precordial ECG lead, positioned in the second, third or fourth intercostal spaces. This condition is associated with a higher risk of sudden cardiac death (SCD) in the absence of detectable structural heart disease. The ECG pattern can occur spontaneously or be inducible by exposure to drugs such as sodium channel blockers or fever.[1]

Implantable cardioverter-defibrillator (ICD) is indicated in patients with aborted SCD or with syncopal episodes due to ventricular arrythmia.[1] Risk stratification in asymptomatic patients is challenging. Some features such as ECG abnormalities or inducibility of sustained ventricular arrythmias in programmed electrical stimulation (PES) studies appear to be associated with a higher risk of SCD.[2] Fragmented QRS (fQRS), prolongation of PR and QRS intervals or right bundle branch block are described in literature as being related to a higher risk.[2] Nevertheless, the assessment of the independent prognostic efficacy of these baseline ECG abnormalities in long-term follow-up is lacking solid evidence.

The primary aim of this study is to evaluate the resting ECG of a cohort of Portuguese patients with first-degree relatives diagnosed with BrS and to identify ECG parameters associated with cardiac events (CE) over a 10-year period.

Methods

Study design and patient recruitment

We conducted a prospective, longitudinal, observational, single-center study that included 107 consecutive patients with first-degree relatives diagnosed with Brugada syndrome (BrS). These patients underwent three routine ECGs in 2009 for screening of type 1 BrS at a Portuguese center. The diagnosis of index patients was made incidentally during these routine ECG examinations.

ECG analysis

All subjects underwent a standard 12-lead and a high-lead ECG, following specific measurement criteria (paper speed 25 mm/s, gain of 10 mm/1 mV and filter of 0.05–150 Hz) for the initial identification of a spontaneous type 1 Brugada pattern. The type 1 Brugada pattern was defined as a prominent coved ST-segment elevation displaying J-point amplitude or ST-segment elevation ≥2 mm, followed by a negative T wave in right precordial leads (V_1 to V_3). Quantitative ECG parameters of interest included heart rhythm, PR interval (ms), QRS duration (ms), QTc interval (ms), RR interval (ms), QRS axis calculation and presence of fQRS. Conditions that could produce a Brugada-like pattern were excluded.

Patients with a normal baseline ECG were submitted to provocative test with flecainide to diagnose an induced type 1 Brugada pattern based on the clinician judgment at the time. The flecainide provocative test was conducted following established literature guidelines, involving intravenous infusion of flecainide 2 mg/kg over a duration of 10 minutes, accompanied by concurrent electrocardiographic monitoring.

All patients were submitted to genetic testing with an NGS panel (CNV analysis) for the diagnosis of BrS.

Electrophysiological study

A PES was performed whenever it was deemed appropriate, according to the family history and clinician discretion. The PES followed a protocol comprising programmed ventricular stimulation at the right ventricle apex with two pacing cycle lengths (600 and 400 ms) and the introduction of up to three ventricular extrastimuli with a minimum coupling interval of 200 ms. A positive test result was defined as the induction of sustained ventricular arrythmia lasting for more than 30 seconds or requiring termination due to hemodynamic compromise. The detection of inducibility during programmed ventricular stimulation was regarded as a valid indication for ICD implantation before the initiation of follow-up.

Clinical follow-up

After subgroup stratification (spontaneous type 1, inducible type 1 or normal ECG) patients were submitted to clinical follow-up for 10 years. CE were a composite endpoint comprising of SCD, cardiac syncope, detected arrhythmic events and appropriate ICD shocks. Clinical records were used to identify time until event and type of event.

Data management and statistical analysis

Categorical variables were characterized by determining the absolute and relative frequencies, and the continuous variables were expressed as central tendency and dispersion measures according to their distribution after normality testing with the Shapiro–Wilk and Kolmogorov–Smirnov test was performed.

The Chi-squared test was used for between-group comparisons of the categorical variables. To assess differences in the distribution between continuous variables, parametric or non-parametric tests were used according to the type of distribution (Mann–Whitney U test and t-student test for two groups, and Kruskal–Wallis and ANOVA test were used to compare between more than two groups).

A survival analysis was performed through the Kaplan–Meier method to analyze CE (single event) over the 10-year follow-up period according to the presence of first-degree atrioventricular block. A Cox regression was employed to study the hazard impact of variables on the time until cardiac event occurs.

SPSS 29.0 was used for statistical analysis, with a 5% significance level for hypothesis testing.

The study protocol was approved by the Institutions' Ethics Committee and conforms to the 1975 Declaration of Helsinki. A patient consent form was signed for every participant in the study.

Results

Patient characteristics and ECG parameters

A total of 107 patients, from three different families, underwent ECG for screening of BrS in our department in

the year of 2009. No phenocopies of Brugada pattern were identified. In 12.7% (16) a spontaneous type 1 Brugada pattern was detected and in 10% (11) the ECG was normal but a provocative test with flecainide was positive.

The parameters in baseline ECG that significantly differ between groups were PR interval and QRS interval (**Table 1**).

Both patients with spontaneous type 1 Brugada pattern (202.5±32.8 vs 150.2±29.3 ms; p <0.01) and induced type 1 Brugada pattern (177.3±33.5 vs 150.2±29.3 ms; p = 0.02) had significantly higher PR intervals in comparison with patients with normal ECG. No differences were found in PR interval between patients with spontaneous and induced type 1 Brugada pattern (p = 0.93).

QRS interval was significantly higher in patients with spontaneous type 1 Brugada pattern in comparison with patients with normal ECG (110.0±16.3 vs 89.5±15.6 ms; p <0.01). No differences were found between other groups regarding QRS interval.

SCN5A mutations were identified in 34.6% (n = 37) of patients, among whom 4.7% (n = 5) had a normal ECG and tested negative on provocative flecainide testing, while 9.3% (n = 10) had a normal ECG and did not undergo provocative testing.

EPS was performed in 63% (16) patients with spontaneous type 1 and in 55% (6) patients with induced type 1 Brugada pattern. No differences were found between spontaneous or induced Brugada pattern regarding AH (p = 1.0) and HV (p = 0.52) intervals. Three patients had a positive EPS study, all of them with spontaneous type 1 Brugada pattern, leading to ICD implantation.

Clinical follow-up

No patients were lost in follow-up. CE at the 10-year follow-up occurred in 7.5% of the study population. Among patients with a type 1 Brugada pattern, CE occurred in 35.7% (5) of cases. Specifically, 3 patients underwent ICD implantation due to arrhythmic events/syncope, 1 patient experienced an appropriate ICD shock, and 1 SCD.

In patients with an induced type 1 Brugada pattern, 20% (2) experienced CE (2 patients underwent ICD implantation due to an arrhythmic event). No CE were reported in the population with a normal ECG.

The mean time taken for a CE to happen was 302 months (95% confidence interval 298 to 305). The time to the event was significantly shorter in the group with PR >200 ms (p <0.01) (**Fig. 1**).

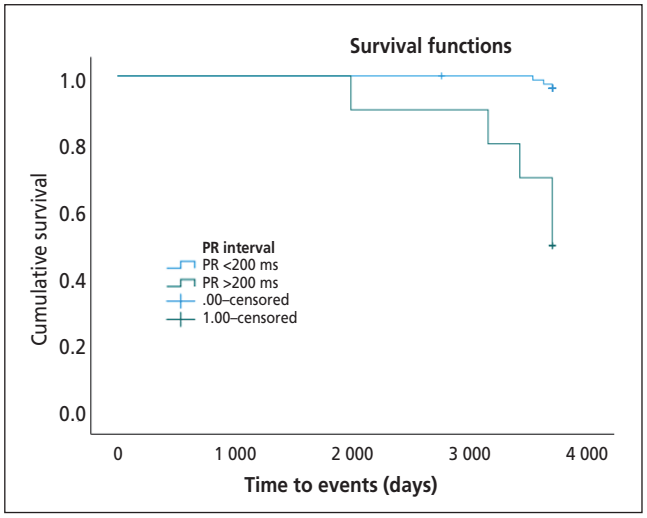

Fig. 1 – Kaplan–Meier curve showing the association between first-degree atrioventricular block and clinical outcomes. Blue line – PR interval <200 ms; green line – PR interval >200 ms.

Table 1 – Patients' characteristics and baseline ECG evaluation according to the subgroup of Brugada syndrome study

Variables	Spontaneous type 1 Brugada pattern (n = 16)	Inducible type 1 Brugada pattern (n = 11)	Normal ECG (n = 80)	*p*-value
Patients' characteristics				
Age (years) Median (IQR)	31.0±16.2	34.5±12.3	28–29±16.4	0.76#
Male sex, n (%)	11 (68,80%)	5 (45.50%)	39 (48.80%)	0.32*
History of syncope, n (%)	1 (6.30%)	1 (9.10%)	1 (3.80%)	0.17*
Positive genetic test, n (%)	15 (93.80%)	7 (63.60%)	15 (18.80%)	<0.01*
History of sudden cardiac death in the first degree relatives, n (%)	2 (15.4%)	2 (20.00%)	0 (0.00%)	<0.01*
ECG parameters				
PR interval (ms) Median (IQR)	202.5±32.8	177.3±33.5	150.2±29.3	<0.01#
QRS interval (ms) Median (IQR)	110.0±16.3	100.0±28.4	89.5±15.6	<0.01#
QTc interval (ms) Mean (SD)	397.6±41.3	392.8±28.4	409.8±29.3	0.76$
Fragmented QRS, % (n)	4 (25.00%)	4 (36.40%)	25 (31.30%)	0.81*
EPS parameters				
AH intervals (ms) Mean (SD)	106.3±34.9	88.5±9.2		1.00%
HV intervals (ms) Mean (SD)	48.2±9.9	45.2±6.3		0.52%

ICD – implantable cardioverter-defibrillator; IQR – interquartile range; SD – standard deviation; # Kruskal–Wallis test, * Chi-squared test; $ ANOVA test, % independent t test.

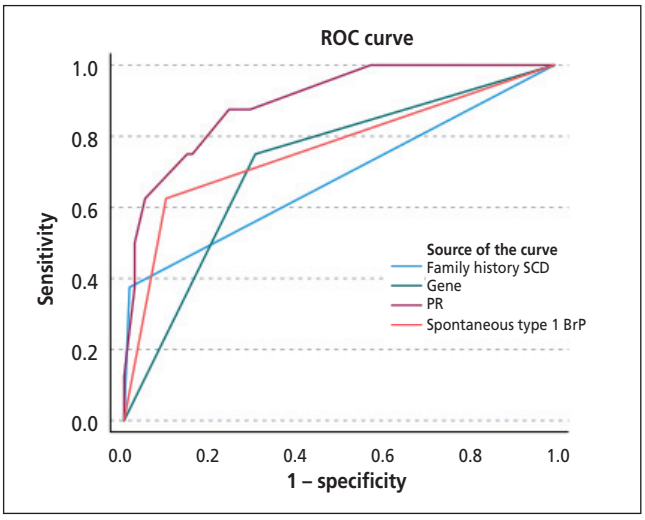

Fig. 2 – ROC curve analysis for the multivariate logistic regression analysis and discriminant analysis models. Blue line – family history of sudden cardiac death (AUC 0.681); red line – spontaneous type 1 Brugada pattern in basal ECG (AUC 0.764); green line – positive genetic test (AUC 0.723); purple line – PR interval in basal ECG (AUC 0.898).

Multivariate Cox regression analysis demonstrated that PR interval was an independent predictor of earlier CE (HR 1.06 95% CI [1.02–1.10]; p <0.01) (**Table 2**), adjusted to other significant clinical variables such as familiar SCD, spontaneous type 1 Brugada pattern, and positive genetic test.

The Receiver Operating Characteristic curve (ROC) analysis demonstrated that the PR interval exhibits a highly predictive effect concerning CE (area under the curve [AUC] 0.896; p <0.01; 95% CI 0.79–1.00). In the multivariate analysis, the PR interval (AUC 0.896) emerged as a superior predictor of CE when compared to familial SCD (AUC 0.681), spontaneous type 1 Brugada pattern (AUC 0.764), and positive genetic test (AUC 0.723) (**Fig. 2**).

The optimal cutoff value for predicting CE, determined by maximizing Youden's index (J = 0.581; sensitivity 87.5%; specificity 92.4%), was identified at 180 ms in our analysis of the diagnostic test results.

Discussion

This study offers a detailed long-term follow-up of individuals with BrS, emphasizing the significance of ECG parameters in assessing risk, particularly the PR interval.

In BrS, the *SCN5A* gene is frequently implicated, with loss-of-function mutations linked to an elevated risk of bradycardia and atrioventricular (AV) conduction disorders.[3] First-degree AV block on the baseline ECG is identified as an independent predictor of severe arrhythmic events, serving as a valuable prognostic marker.[4,5] This block may indicate a heightened risk due to a more pronounced reduction in sodium current (INa), leading to increased myocardial electrical instability.[6] Yet, there's uncertainty regarding BrS patients with a normal PR interval or without first-degree AV block, and their risk during follow-up.[7] This study establishes that the risk threshold falls below the level for a first-degree atrioventricular

Table 2 – Clinical and ECG characteristics by family

Variables	Family 1 (n = 36)	Family 2 (n = 49)	Family 3 (n = 22)
Patients' characteristics			
SCN5A mutation, n (%)	11 (30.6%)	22 (44.9%)	4 (18.2%)
CE events 10-year follow-up, n (%)	2 (5.6%)	6 (12.2%)	1 (4.5%)
ECG parameters			
Normal ECG and negative provocative test, n (%)	10 (27.8%)	6 (12.2%)	2 (9.1%)
Normal ECG and provocative test not performed, n (%)	15 (41.7%)	31 (63.3%)	16 (72.7%)
Spontaneous type 1 BrP, n (%)	5 (13.9%)	9 (18.4%)	2 (9.1%)
Inducible type 1 BrP, n (%)	6 (16.7%)	3 (6.1%)	2 (9.1%)

BrP – Brugada pattern in ECG.

Table 3 – Multivariate Cox regression for predictors of time to cardiac events

Variables	*p*-value	HR	95% confidence interval	
			Lower	Upper
PR interval	<0.01	1.06	1.02	1.10
f-QRS	0.41	0.39	0.04	3.72
Induced type 1	0.03	60.86	1.62	2 283.15
Spontaneous type 1	0.02	139.36	1.96	9 912.75
Positive genetic testing	0.05	39.56	1.05	1 486.02
Familiar history of SCD	<0.01	79.87	3.85	1 657.64

HR – hazard ratio; SCD – sudden cardiac death.

block, but questions about dynamic PR interval fluctuations and their correlation with developing prolonged PR intervals or first-degree AV blocks in successive follow-ups remain unanswered.

Consistent with existing literature, our findings emphasize the predictive value of a family history of SCD, the presence of spontaneous type 1 Brugada pattern, and positive genetic testing as robust indicators for anticipating CE.[2,4] Symptomatic patients weren't in our study, but syncope is a clear risk factor acknowledged by various studies. Within 4 to 7 years after being diagnosed with BrS, 17% to 62% of patients may experience an arrhythmic event that can lead to SCD.[8,9]

Besides first-degree AV block,[9] other ECG markers have been identified as indicators of increased risk in asymptomatic BrS patients. These include fQRS,[10] prolonged QRS,[11,12] ST-segment elevation after exercise,[13] a prolonged T-peak–T-end interval,[14] prominent R wave in aVR (aVR sign),[15,16] wide and deep S wave in lead I and II,[17,18] the presence of T-wave alternans.[19] Our study found that a prolonged QRS was linked to the diagnosis of BrS but did not indicate a worse prognosis. Additionally, the presence of fQRS was not associated with arrhythmic events in our study. These findings underscore the need for a better understanding of the risk stratification in this population and the importance of developing improved tools.

In this cohort, a positive PES was not associated with CE over a decade of follow-up. The use of PES to evaluate the risk of asymptomatic BrS patients remains a topic of debate and is challenging to determine [1], with varying findings in the literature.[1,8,20,21] Adverse events in asymptomatic BrS patients are relatively low,[20,21] and implantation of prophylactic ICD in this group is not without risk.[22] ICD implantation may be considered in selected asymptomatic BrS patients with inducible ventricular fibrillation during PES (recommendation IIb).[1] The PRELUDE registry in the United States, studying 308 patients over an average of 34 months, found that induced ventricular arrhythmias didn't identify high-risk patients.[8] Conversely, an Italian study of 404 asymptomatic patients over 20 years revealed that PES was valuable in predicting rhythmic events, particularly in those with a type 1 Brugada pattern, whether spontaneous or induced by sodium channel blockers.[23]

BrS has a higher prevalence in males, and there's a scarcity of studies on risk stratification in women.[24–26] Our population, predominantly female, supports these findings also in this gender.

Conclusion

In this population, a longer PR interval was identified as the most significant ECG parameter associated with a higher risk of adverse outcomes in first-degree relatives diagnosed with BrS and followed for over 10 years. The PR interval, with its independently predictive capability for adverse arrhythmic events, coupled with its practicality and widespread availability, establishes it as a valuable tool for augmenting the precision of risk stratification in individuals with BrS.

Limitations

The present study has limitations predominantly related to inclusion of only a small cohort of a single center in Europe. It is also important to refer that not all patients with normal ECG were submitted to provocative test and selection for PES study was performed only based on clinical judgment. The study does not include patients with type 2 and type 3 BrS.

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Conflict of interest

The authors have nothing to declare.

Funding

The authors have nothing to declare.

Ethical statement

This study has received ethics commission approval from Tondela-Viseu Hospital Center.

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