Defining Electrocardiographic Criteria to differentiate Non-Type 1 Brugada ECG variants from normal incomplete RBBB patterns in the young SCD-SOS cohort

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Abstract

Aims: We assessed the prevalence of non-type 1 Brugada pattern (T1BrP) in children and young adults from the SCD-SOS cohort and the diagnostic yield of non-expert manual and automatic algorithm ECG measurements.

Methods: Cross-sectional study. We reviewed 14662 ECGs and identified 2226 with a rSr'-pattern in V1-V2. Among these, 115 were classified by experts in hereditary arrhythmic-syndromes as having or not non-T1BrP, and were compared with measurements of 5 ECG-derived parameters based on a triangle formed by r'-wave (d(A), d(B), d(B)/h, β-angle) and ST-ascent, assessed both automatically and manually by non-experts. We estimated intra and interobserver concordance for each criterion, calculated diagnostic accuracy and defined the most appropriate cut-off values.

Results: A rSr'-pattern in V1-V2 was associated with higher PQ interval and QRS duration, male gender and lower BMI. The manual measurements of non-T1BrP criteria were moderately reproducible with high intra-observer and moderate interobserver concordance coefficients (ICC:0.72-0.98, and 0.63-0.76). Criteria with higher discriminatory capacity were: distance d(B) (0.72;95%CI0.65-0.80) and ST-ascent (0.87;95%CI0.82-0.92), which was superior to the 4 r'-wave criteria together (AUC0.74). We suggest new cut-offs with improved combination of sensitivity and specificity: d(B)≥1.4mm and ST-ascent≥0.7mm (Sensitivity1-82%;Specificity71-84%), that can be automatically measured to allow classification in 4 morphologies with increasing non-T1BrP probability.

Conclusion: rSr'-pattern in precordial leads V1-V2 is a frequent finding and the detection of non-T1BrP by using the aforementioned 5 measurements is reproducible and accurate. In this study, we describe new cut-off values that may help untrained clinicians to identify young individuals who may require further work-up for a potential Brugada Syndrome diagnosis.

Keywords: Non-type 1 Brugada pattern, rSr' pattern, athlete's ECG, children and young adults

Introduction

Brugada syndrome (BrS) is a channelopathy associated with an increased risk of sudden cardiac death (SCD) secondary to ventricular fibrillation in the absence of unequivocal structural abnormalities. The classic electrocardiographic (ECG) abnormalities constitute the distinctive feature of the BrS: Type-1 Brugada Pattern (T1BrP) ("coved-type") is the only diagnostic pattern, while non-T1BrP ("saddle-back type") is considered only suggestive of BrS(1). In individuals with the latter, the diagnosis of BrS can be made if a T1BrP occurs with provocative drug testing using intravenous administration of sodium-channel blockers(2).

Given that SCD in young patients is a hallmark of this syndrome, prompt and accurate recognition of non-T1BrP is essential to identify patients with an indication for provocative drug challenge and subsequent risk stratification and management.

The true prevalence and burden of non-T1BrP in children and the young adult population is currently unknown. This may be due to: (i) the dynamic nature of ECG patterns in this population, and (ii) the fact that non-T1BrP typically presents with a rSr' pattern in precordial leads V1-V2 that may be confused with incomplete bundle branch block (iRBBB) and may correspond to a normal variant or a typical athlete's ECG.

In 2012, *Bayés de Luna et al* (3) published the morphologic criteria for defining typical saddle-back pattern on the Consensus Report on Brugada pattern diagnosis. The characteristic r'-wave was defined as having a high take-off of at least 2mm and be followed by a minimum ST-ascent ≥0.5mm. In addition, four ECG criteria utilizing measurements of the angles and distances of the triangle formed by the ascending and descending branch of the r'-wave were recently recognized as accurate differentiators between non-T1BrP and normal variant/healthy athletes pattern(4). To our knowledge, an evaluation of non-T1BrP criteria on a young population cohort without BrS diagnosis has not yet been performed.

We aimed to (i) determine the prevalence of rSr' pattern in precordial leads in children and young adults, (ii) assess the diagnostic yield of experts and non-experts in hereditary arrhythmic syndromes for the identification of non-T1BrP in individuals with a r'-wave in precordial leads V1 and V2 who

may warrant further evaluation for Brugada Syndrome, and (iii) define a group of simple manually measured parameters that can help non-experts to accurately identify non-T1BrP individuals.

Methods

Design and study population

From February 2012 to May 2013, 14,667 children and young adults (aged 40 years-old or less) of the central region of Portugal participated in the Sudden Cardiac Death-Screening Of risk factorS (SCD-SOS) survey (NCT01845909). This survey included a 12-lead ECG that was undertaken by 14,662 individuals, and a previously validated (5) questionnaire about symptoms, personal and family history that was filled by 11,878 participants who were willing to provide more information (see **Supplementary Material 1**). The SCD-SOS protocol was approved by the local Ethics Committees (355/Sec/10/03/2011): Comissão de Ética do Centro Hospitalar de Coimbra, Instituto Português do Ritmo Cardíaco e Comissão Nacional de Protecção de Dados.

ECG screening and definition of cases with non-T1BrP

(i) rSr' pattern cases - For the ECG screening, all 14,662 digital ECGs included in the SCD-SOS cohort were manually reviewed for evidence of any r'-wave in leads V1 and V2 (defined as ≥ 0.5mm (0.5mV)), by one investigator (MC) and subsequently confirmed by two others (AC and RP). 2527/14662 (17.2%) ECGs met this criterion. Among them, 5 were reclassified as Type-1 Brugada pattern, 49 as complete RBBB and the remaining 2473 as an rSr' pattern. ECGs were available in a graphical software package (ECGDB, Dotlogic, Portugal) that allows exportation of the raw average and rhythm ECG signals to Excel files. The raw signal was used to automatically compute the necessary features from the ECG signal, through an analysis tool developed by the investigators in Excel for this purpose. This tool enabled automatic calculation of the required wave points and diagnostic criteria (**Figure 1**), namely: r'-wave identification - including the segment location at upslope and downslope of r′-wave and the isoelectric line; d(A), the duration of the base of the triangle at 0.5mV from r'-wave high take-off; d(B) and h – respectively, the duration and height of the triangle at the isoelectric line; β-angle – angle from r'wave upslope and downslope. A Python programming tool created by one of the investigators was used to extract the diagnostic criteria from all 14662 raw signal files. MC & AC reviewed all the ECGs in which the initial manual r'-wave assessment and the Excel algorithm did not match and a third investigator (RP) revised the ECGs where MC & AC were not in agreement (**Figure**

2). After reclassification of the ECGs based on the algorithm output, 2226 cases of rSr' pattern in V1-V2 were included for analysis. A similar number of ECGs were discarded after being considered as having rSr' pattern by either investigator visual assessment (n=369) or the Excel algorithm (n=384). There were diverse reasons behind the need to reclassify and discard ECGs: fragmented QRS, inconsistent r'wave when it was absent in at least one QRS in V2 or the majority of QRS in V1 or when r'wave was confounded with a variation in ST-segment, r'wave height less than 0.5mm and artifacts in V1 and V2. The flowchart used for the validation of the algorithm by the investigators is depicted in **Figure 2**. Clinical and ECG characteristics of individuals with a rSr'-pattern in V1-V2 were compared with those without it.

(ii) non-T1BrP cases - using the algorithm, a terminal r'-wave of at least 2mm (0.2mV) in height in precordial leads V1-V2, and either d(A)≥3.5mm and/or a β-angle≥58º in any of the precordial V1 and V2 leads (2 criteria), were identified in 23 ECGs, thus fulfilling the first criterion for non-T1BrP, as described by *Bayes de Luna et al*. (3). ECGs not meeting either of the two criteria were classified as normal variant rSr' pattern/athlete's ECG. All cases of non-T1BrP were mixed in a 1:4 proportion with ECGs classified by the algorithm as rSr' pattern normal variant/athlete's. This mixed sample (total 115 ECGs) was blindly and independently reviewed by two experts in hereditary arrhythmic syndromes (RP and WJY) (**Figure 2**), who re-classified the ECGs as non-T1BrP *versus* rSr' pattern normal variant/athlete's ECG. A third expert (PL) was the final referee who resolved any disagreements between the 2 authors. These non-T1BrP cases were used as a reference for evaluation of r'-wave criteria accuracy. We compared the frequency of non-T1BrP cases according to *Bayes de Luna et al.* (3) and *Serra et al.* (4) criteria, the latter defined by a terminal r'-wave of at least 2mm in height and either d(A)≥4mm and/or a β-angle≥36.8º. The complete version of *Serra* criteria also included d(B)≥1.5mm and/or d(B)/h ≥ 1.

ECG measurements - interobserver and intraobserver concordance

For all 115 ECGs, the four previously described parameters (d(A), d(B), d(B)/h and β-angle) and ST-ascent (**Figure 1**), were manually measured by two non-expert investigators (MC and AC), by using a ruler and a protractor. The same ECGs but in a different file order were re-printed and the

measurements repeated by both investigators. The inter and intraobserver concordance were assessed with intraclass correlation coefficients (ICC) and 95% confidence intervals (95%CI), for the two rounds of estimates performed by both investigators, between non-expert' assessments and between the means of all manual measurements and the algorithm estimates.

Other electrocardiographic alterations that may be observed in Brugada Syndrome were also assessed by these two non-experts and one expert (WJY), who solved the disagreements between the other two investigators. These extra criteria included the alpha angle, which is the angle between a vertical line and the downslope of the r-wave; whether downslope of r' coincides with the beginning of ST; mismatch between V1 and V6 QRS duration, which may be longer in right precordial leads; the presence of fragmented QRS complexes, early repolarization in inferior leads, and T-wave morphology.(6) QTc was calculated with the Bazett formula, using the values of QT interval and heart rate that were obtained using the recorder's automatic measurement software (VERITAS ECG algorithm, Mortara Instrument). Prolonged QTc was defined as >460ms in females, >450ms in males and > 450ms in children with less than 13 years-old independently of gender (7)

Statistical analysis and criteria accuracy estimates

Statistical analysis was performed using Stata 13.0 software. Shapiro-Wilk test for normality was used to assess the distribution of continuous variables. Continuous variables with normal distribution are expressed as means ± standard deviation (SD) and means and standard errors (SE) for non-parametric variables were obtained by bootstrapping 5000 times. To compare the distribution of continuous variables we used Student's t-test. Categorical variables were described as numbers of cases and percentages, and we used chi-squared tests to determine whether the presence of clinical and ECG features differed between groups analyzed. To express the strength of these relations, we obtained the odds ratios (OR) with 95% confidence intervals (CI) through univariate logistic regression. Multivariate logistic regression was used to evaluate the association of clinical and ECG variables with the presence of rSr'-pattern in V1-V2. Finally, we performed Non-parametric Receiver Operating Curves (ROC) analysis to assess discrimination capacity of criteria measured by the algorithm. We calculated C-statistics (AUC – Area Under the Curve with a 95%CI) and computed sensitivities (Se), specificities (Sp) and likelihood ratios for the cut-offs defined by *Bayes de Luna et al.* and *Serra et al*. and defined

the best cut-off points according to the highest proportion of correctly classified individuals in our sample. Values automatically calculated by the algorithm and manually measured with a ruler and a protractor were rounded to the nearest 0.1 and 0.5 millimeters, respectively. A p-value < 0.05 was regarded as significant and two-tailed tests were applied.

Results

Clinical characteristics of individuals with rSr'-pattern in V1-V2

From a total of 14662 individuals who had an ECG performed as part of the SCD-SOS survey, 2226 (15.2%) displayed a rSr'-pattern in precordial leads V1 and V2. There were 49 (0.31%) with complete right bundle branch block (RBBB) and 5 (0.03%) had a Type-1 Brugada pattern and were excluded from the analysis. Among individuals with rSr' pattern, the mean age was 20.3±0.1 years-old, ranging from 4 to 40 years-old, and of whom 673 (30.2%) were children (<18 years-old). Compared with individuals without a rSr' pattern, they were slightly younger, more frequently male, had lower body mass index and were more frequently involved in sports practice (**Table 1**).

Symptom-wise, in the total cohort, 4441 (23.5%) individuals reported transient loss of consciousness, 310 (16.5%) reflex syncope, 52 (11.8%) had unexplained syncope and 401 (21.5%) palpitations. Sudden death in relatives before the age of 50 years was present in 149 (9.8%) of patients with an r'-wave in V1-V2. In the multivariate analysis, after adjusting for age and physical activity, PQ interval (OR 1.004 per ms; 95%CI 1.002-1.007, p<0.001), QRS duration (OR 1.039 per ms; 95%CI 1.033-1.044, p<0.001), male gender (OR 1.429; 95%CI 1.269-1.610, p<0.001) and BMI (OR 0.872 per Kg/m^2; 95%CI 0.855-0.889, p<0.001) were independently associated with the presence of r'-wave in precordial leads V1-V2 (**Supplementary Material 2**). Unexplained syncope, palpitations and family history of sudden death were not associated with a rSr'-pattern in the young SCD-SOS population.

Non-T1BrP cases – prevalence and description of clinical and ECG characteristics

In the total cohort, the prevalence of *Bayes de Luna* and *Serra* criteria measured by the algorithm were 0.16% (n=23), and 0.10% (n=15), respectively. When considering at least one of the four *Serra et al*. electrocardiographic criteria, the prevalence was 1.00% (n=146). Among the 115 ECGs selected using the Excel algorithm (23 *Bayes de Luna* non-T1BrP & 92 normal variants/athlete heart ECGs), experts in hereditary arrhythmic syndromes identified 46 (40.0%) with a pattern suggestive of non-T1BrP (**Figure 3**). There was agreement in 76.5% of the cases. The arbiter (PL) had a concordance of 80.9% with one expert and 95.6% with the other. There were no differences in clinical characteristics

of individuals with and without non-T1BrP (**Table 2**). Manual measurements performed by two non-experts showed significantly higher values of criteria d(A), d(B), d(B)/h, β-angle and ST-ascent in non-T1BrPs cases defined by experts, comparing to those in rSr' pattern normal variant/athlete's. There were no statistically significant differences in the remaining extraordinary ECG characteristics assessed by non-experts (**Table 2**).

r'-wave criteria reproducibility

When comparing the manual measurements performed by two investigators, the interobserver concordance was moderate, while high intraobserver concordance coefficients were observed for both investigators (MC and AC). On the other hand, concordance coefficients between the means of all manual measurement and algorithm estimates were also moderate. (**Table 3**)

r'-wave criteria accuracy and re-definition of cut-off values

In non-T1BrPs cases defined by experts, the algorithm estimates of the criteria d(A), d(B), d(B)/h, β-angle and ST-ascent were significantly higher, comparing to those in rSr' pattern normal variant/athlete's. All measurements were significantly associated with non-T1BrP (**Supplementary Material 3**) and depicted high AUC ≥0.70 (**Central Illustration**).

The classic *Bayes de Luna et al.* criteria defined by a r'-wave having a high take-off of at least 2mm and either d(A)≥3.5mm and/or a β-angle≥58º in any of the precordial V1 and V2 leads showed poor discrimination capacity (AUC 0.59; 95%CI 0.51-0.66) when measured by the algorithm, especially due to loss of sensitivity (30.4%), and despite high specificity (87.0%). The discrimination capacities of the four revised *Serra et al.* criteria, namely d(A)≥4mm (AUC 0.56; 95%CI 0.50-0.63; Se 19.6%; Sp 92.8%), d(B)≥1.5mm (AUC 0.58; 95%CI 0.48-0.67; Se 45.6%; Sp 69.6%), d(B)/h>1 (AUC 0.53; 95%CI 0.48-0.58; Se 10.9; Sp 95.6%) and β-angle≥36.8º (AUC 0.51; 95%CI 0.47-0.54; Se 4.4%; Sp 97.1%) were also poor, mainly due to lower sensitivity comparing to previously published data.(4) ROC analysis facilitated the identification of new non-T1BrP criteria cut-off values with enhanced sensitivity (≥42.7%), high specificity (71.2-84.5%) and optimal high likelihood ratios (2.12-5.29): d(A) ≥ 100ms

(2.5mm), d(B) ≥ 56ms (1.4mm), d(B)/h ≥ 0.7, β-angle ≥ 18.5º and ST-segment elevation ≥ 0.7mm (**Central Illustration**).

The addition of the degree of ST-ascent to the 4 aforementioned parameters presented an AUC of 0.87 (95%CI 0.82-0.92) for the diagnosis of non-T1BrP by experts, comparing to an AUC of 0.74 (95%CI 0.68-0.80) when only the 4 parameters were considered. The criteria showing the higher AUC were d(B) (0.72; 95%CI 0.65-0.80) and the ST-ascent (0.87; 95%CI 0.82-0.92). Finally, among ECGs classified by experts as "probable non-T1BrP" we found: a) benign morphology with a d(B)<1.4mm and ST-ascent<0.7mm in V1-V2 in 4.3% of the cases; b) probable benign morphology with a d(B)≥1.4mm and ST-ascent<0.7mm in 2.2%; c) possible non-T1BrP morphology with a d(B)<1.4mm but a ST-ascent≥0.7mm in 23.9%; and d) probable non-T1BrP morphology with d(B) ≥1.4mm and a ST-ascent≥0.7mm in 69.6% of the cases. Therefore, we propose a new classification of rSr'-pattern into four morphologies, with increasing non-T1BrP probability (**Central Illustration**).

Discussion

R'-wave in V1-V2 was a frequent finding in our young population which implies careful evaluation is necessary to avoid errors in non-T1BrP identification. The manual measurement of non-T1BrP criteria is reproducible and accurate. Criteria with higher discriminatory capacity were: d(B) (AUC 0.72) and the ST-ascent (AUC 0.87), and using the measurement of the degree of ST-ascent had a higher discriminatory capacity of non-T1BrP identified by experts, when comparing to using the other 4 parameters together (AUC 0.74). Moreover, the criteria d(B) ≥ 56ms (1.4mm) and ST-ascent ≥ 0.7mm (Sensitivity 61-82%; Specificity 71-84%) can be automatically measured by a busy clinician to allow classification in a spectrum of 4 morphologies with increasing probability of corresponding to non-T1BrP pattern (**Central Illustration**). We also define new cut-offs with higher sensitivity and specificity for the remaining criteria: d(A) ≥ 100ms (2.5mm), d(B)/h ≥ 0.7 and β-angle ≥ 18.5º.

The typical Brugada rSr' pattern may be confused with benign and pathological clinical conditions(6)(8). In fact, the rSr' pattern is a relatively frequent ECG finding, that was previously described to be present in 3 to 7% of subjects without apparent cardiovascular disease(9)(10)(11). We detected a much higher incidence of rSr'-pattern in precordial leads V1-V2 (15.2%) in the young-adult population of the SCD-SOS cohort, and we have found an independent association of the pattern with male gender and low BMI, possibly indicating the influence of anatomical or hormonal factors. We hypothesize that a lower BMI would be associated with less retrosternal fat, thus bring the right-ventricle outflow tract closer to V1-V2 leads and increasing the probability of a r'-wave on the surface ECG. Our findings are in line with results from *Bussink et al.* (9) and *Pecini et al.*, who have also described an association of iRBBB with male gender(12). On the other hand, we hypothesize that the observed longer PQ and QRS duration in rSr' pattern individuals may suggest the existence of concomitant conduction abnormalities.

The non-T1BrP may be distinguished from athletes' ECG or iRBBB normal variant by careful examination of the resting ECG using consensus criteria. (3) These criteria showed an accuracy of 86% in a computerized analysis of Brugada ECGs in a Japanese population, comparing to iRBBB normal variants (13). Other r'-wave characteristics to identify non-T1BrP in ECG leads V1-V2 were described

in that document, the most accurate being the β-angle and the d(A) distance (3). *Serra* and collaborators (4) studied these 2 ECG criteria, as well as d(B) and d(B)/h for the differential diagnosis of non-T1BrP *versus* rSr' pattern of healthy athletes, and estimated AUCs between 0.91 and 0.96. They calculated an interobserver concordance overall coefficient of 0.87. However, in our real-world cohort of young-adults, these criteria did not perform as well (AUC of 0.51-0.58) and therefore we had to define new criteria. These differences may be specific of this population of patients with confirmed BrS and non-T1BrP and/or may be explained by the fact that previous authors who studied these criteria have performed measurements using mathematical programming tools for scale adjustment and segment extraction, implying new cut-off points should be validated for other types of measuring procedures. In contrast, in addition to developing an algorithm that allowed precise measurements of the r'-wave parameters, we also performed manual estimates using a ruler and a protractor after printing the ECGs. We intended to study a more practical approach to these criteria, as a proof of concept that these measurements could be easily and accurately made by non-expert physicians.

Although d(A) distance and β-angle have been more widely studied by previous authors (10)(3)(14), in our cohort, d(B) and ST-ascent had higher discriminatory capacity. In patients with Brugada syndrome, early repolarization in the epicardium results in a transmural voltage gradient which manifests as ST-elevation on the 12-lead ECG (15). An ST-ascent ≥0.7mm had a specificity of 84.5% and a sensitivity of 82.0% for referral for a Brugada drug-challenge by an expert. Previous studies have shown that J point or ST-segment elevation is one of the strongest independent predictors of a Brugada-type response to sodium channel blocker testing (16). Furthermore, *Shahrzad et al.* have shown that a baseline ST-elevation in V2 ≥1.7 mm is an independent predictor of a positive response to provocative testing (specificity 82%, sensitivity 60%) (17). Therefore, besides the new cut-off values for manual measurement, we propose a new classification for assessment of non-T1BrP for children and young adults: a) benign morphology with a d(B)<1.4mm and ST-ascent<0.7mm, b) probable benign morphology with a d(B) ≥1.4mm and ST-ascent <0.7mm, c) possible non-T1BrP morphology with a d(B)<1.4mm and ST-ascent ≥0.7mm d) probable non-T1BrP morphology with a d(B) ≥1.4mm and ST-ascent≥0.7mm (**Central Illustration**).

There are some limitations to our study. We do not know the BrS diagnostic yield if this sample of individuals with presumed non-T1BrP were referred for drug provocative testing, and the new classification of non-T1BrP morphologies still requires to be tested in a validation cohort. However, to our knowledge, this is the first study analyzing non-T1BrP specific criteria in a young population cohort without the diagnosis of BrS. Additionally, the rSr' patterns in precordial leads may be associated with other rarer conditions such as Arrhythmogenic Right Ventricle Dysplasia, and multiple causes of right ventricle enlargement that cannot be excluded unless an imaging exam such as an echocardiogram, or a cardiac magnetic resonance are performed (14).

In conclusion, we showed that a rSr'-pattern in precordial leads V1-V2 is a frequent finding, and that the manual measurement of 5 ECG criteria is reproducible and accurate for the detection of non-T1BrP when the r'-wave is 2mm or more in height. We believe that these criteria will help untrained clinicians to identify individuals who should be referred for further assessment in a hereditary arrhythmia syndrome clinic.

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Supplementary Material 1: The SCD-SOS questionnaire (translated to English)

Supplementary Material 2: Multivariate analysis of the characteristics of individuals with r'-wave in leads V1-V2

	Odds Ratio	CI 95%	p-value
PQ interval (ms)	1.004	1.002-1.007	<0.001
QRS duration	1.039	1.033-1.044	<0.001
Male	1.429	1.269-1.610	<0.001
BMI (kg/m²)	0.872	0.855-0.889	<0.001
Age (years-old)	1.003	0.993-1.014	0.496
Sports practice	1.024	0.918-1.142	0.668

Legend: BMI – Body Mass Index, kg – kilogram, m² - squared meter, ms - milliseconds

Supplementary Material 3: Algorithm measurements of non-T1BrP criteria

R' wave diagnostic criteria	Algorithm measurements (mean ± SE)			
	Non-T1BrP (n=46)	Normal variant/Athlete's ECG (n=69)	OR (CI 95%)	p-v
d(A) in V1-V2 (in mm)	3.6 ± 0.3	2.3 ± 0.1	1.4 (1.16-1.70)	<0
d(B) in V1-V2 (in mm)	1.6 ± 0.1	1.2 ± 0.0	3.2 (1.60-6.64)	0.
d(B)/h in V1-V2	0.7 ± 0.0	0.5 ± 0.0	5.5 (2.13-14.03)	<0
β-angle in V1-V2 (in °)	19.1 ± 1.3	13.0 ± 0.8	1.1 (1.03-1.11)	<0
ST-ascent in V1-V2 (in mm)	1.1 ± 0.1	0.4 ± 0.0	11.7 (5.3-25.8)	<0

Legend: * measurements performed in leads V1, V2 or both. β - beta, d(A) – distance A, d(B) – distance B, h – height, mm – millimeters, ms - milliseconds

Tables

Table 1: Clinical and electrocardiographic characteristics of individuals with r'-wave in leads V1-V2

	r'-wave in V1-V2 (n=2226)	No r'-wave in V1-V2 (n=12436)	OR (CI 95%)	p-value
Age (years-old)	20.3±0.1	20.6±0.0	0.99 (0.98-1.00)	0.047
Male	52.1%	41.2%	1.56 (1.42-1.70)	<0.001
BMI (kg/m²)	21.6±0.1	22.5±0.0	0.91 (0.90-0.93)	<0.001
Sports practice	54.0%	49.6%	1.19 (1.08-1.31)	<0.001
Time spent per week in sports practice (minutes)	311.4±8.0	292.9±3.3	1.02 (1.00-1.04)	0.025
Heart rate (bpm)	71.3±0.3	71.5±0.1	1.00 (1.00-1.00)	0.711
PQ interval (ms)	149.7±0.5	147.2±0.2	1.00 (1.00-1.01)	<0.001
QRS duration (ms)	97.2±0.2	93.2±0.1	1.04 (1.03-1.04)	<0.001
Prolonged QTc *	1.4%	0.9%	1.00 (1.00-1.01)	0.005
TLOC**	23.5%	27.1%	0.82 (0.73-0.92)	0.001
Reflex syncope**	16.5%	17.9%	0.91 (0.80-1.04)	0.155
Unexplained syncope**	11.8%	15.3%	0.74 (0.54-1.01)	0.057
Palpitations**	21.5%	22.7%	0.93 (0.83-1.05)	0.256
Sudden death in relatives before 50 years-old	9.8%	11.1%	0.87 (0.72-1.04)	0.135

Legend: * QTc >460ms in females, >450ms in males and > 450ms in children with less than 13 years-old independently of gender (7), ** previous history of, bpm – beats per minute, ms – milliseconds, TLOC – transient,

Table 2: Clinical and electrocardiographic characteristics of individuals with and without non-T1BrP

		Non-T1BrP (n=46)	Normal variant/ Athlete's ECG (n=69)	OR (CI 95%)	p-value
Clinical characteristics					
Male gender		76.1%	71.0%	1.30 (0.55-3.05)	0.549
Age (years-old, mean ± SE)		23.1 ± 0.9	22.4 ± 0.6	1.02 (0.96-1.10)	0.493
BMI (kg/m², mean ± SE)		22.0 ± 0.4	21.9 ± 0.3	1.02 (0.88-1.17)	0.829
Sports practice		61.4%	52.2%	1.45 (0.67-3.15)	0.344
TLOC		18.2%	26.9%	0.60 (0.24-1.54)	0.293
Manual measurements using a ruler and a protactor (mean ± SE)					
d(A) in V1-V2 (in mm)		2.7 ± 0.2	1.7 ± 0.1	1.88 (1.38-2.57)	<0.001
d(B) in V1-V2 (in mm)		1.6 ± 0.1	1.1 ± 0.1	3.13 (1.69-5.81)	<0.001
d(B)/h in V1-V2		0.5 ± 0.1	0.4 ± 0.0	3.42 (1.38-8.51)	0.008
β-angle in V1-V2 (in °)		24.3 ± 1.3	17.2 ± 0.9	1.07 (1.04-1.11)	<0.001
ST-ascent in V1-V2 (in mm)		1.2 ± 0.1	0.5 ± 0.0	15.2 ± 6.8	<0.001
Alpha angle in V1-V2 (in °)		16.2 ± 1.1	15.2 ± 1.0	1.01 (0.98-1.04)	0.554
Descending arm of r' coincides with beginning of ST		52.2%	43.5%	1.42 (0.67-3.00)	0.361
QRS duration longer in V1 than in V6		32.6%	34.8%	0.91 (0.41-2.00)	0.809
Fragmented QRS		10.9%	8.7%	1.28 (0.37-4.47)	0.698
Early repolarization in inferior leads		0%	0%	-	
Prolonged QTc*		0%	1.4%	-	0.412
T-wave morphology	**Negative**	46.7%	43.1%	0.87 (0.57-1.32)	0.517
	Positive	45.6%	47.4%		
	Biphasic	7.6%	9.5%		

Legend: * QTc >460ms in females, >450ms in males and > 450ms in children with less than 13 years-old independently of gender (7)

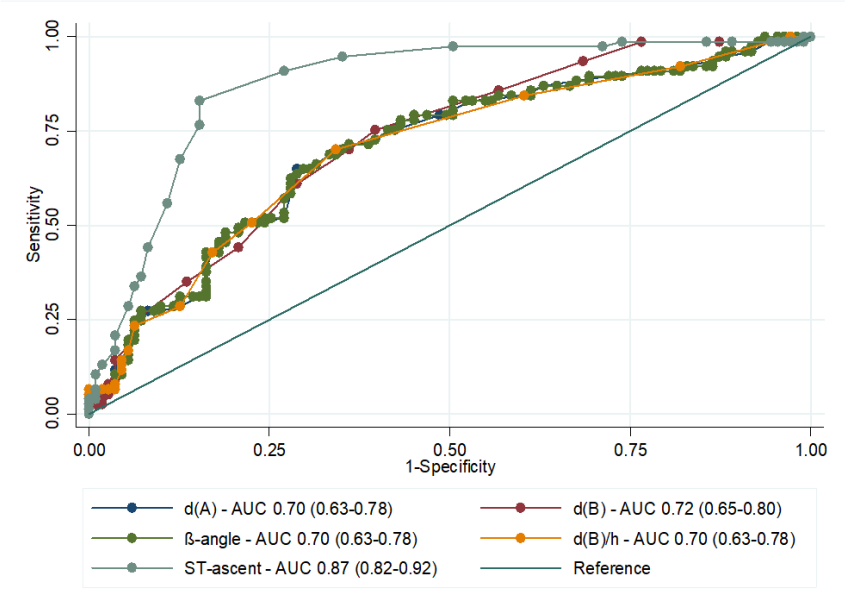
Table 3: Intraclass concordance coefficients for r' wave diagnostic criteria

R' wave diagnostic criteria	Interobserver concordance ICC (CI 95%)	Intraobserver concordance (MC) ICC (CI 95%)	Intraobserver concordance (AC) ICC (CI 95%)	Manual-algorithm concordance ICC (CI 95%)
d(A) in V1-V2	0.76 (0.62-0.84)	0.88 (0.84-0.91)	0.95 (0.93-0.96)	0.62 (0.42-0.74)
d(B) in V1-V2	0.63 (0.53-0.71)	0.72 (0.58-0.81)	0.90 (0.86-0.92)	0.65 (0.56-0.73)
d(B)/h in V1-V2	0.63 (0.49-0.74)	0.76 (0.70-0.82)	0.85 (0.80-0.88)	0.58 (0.42-0.69)
β-angle in V1-V2	0.73 (0.39-0.86)	0.89 (0.85-0.92)	0.91 (0.88-0.93)	0.70 (0.20-0.86)
ST-ascent in V1-V2	0.74 (0.66-0.80)	0.87 (0.83-0.90)	0.98 (0.97-0.98)	0.75 0.68-0.81)

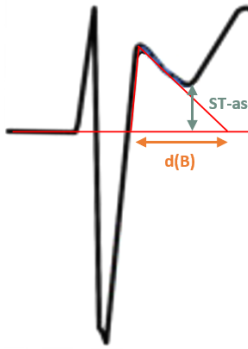
Legend: Concordance coefficients between two non-expert investigators (interobserver), between two rounds of estimates performed by each of them (intraobserver) and between the means of all manual measurements and algorithm estimates. AC – Antonio Creta, β – beta, CI – confidence interval, ICC – intraclass concordance coefficients, d(A) – distance A, d(B) – distance B, h – height, MC – Mafalda Carrington, mm – millimeters, ms - milliseconds

Figures

Central Illustration



Leads V1-V2	Sensitivity	Specificity	Positive likelihood ratio
d(A) ≥ 100 ms (2.5mm)	64.9%	71.2%	2.25
d(B) ≥ 56 ms (1.4mm)	61.0%	71.2%	2.12
d(B)/h ≥ 0.7	42.7%	82.9%	2.50
β-angle ≥ 18.5º	42.9%	83.8%	2.64
ST-ascent ≥ 0.7mm	82.0%	84.5%	5.29

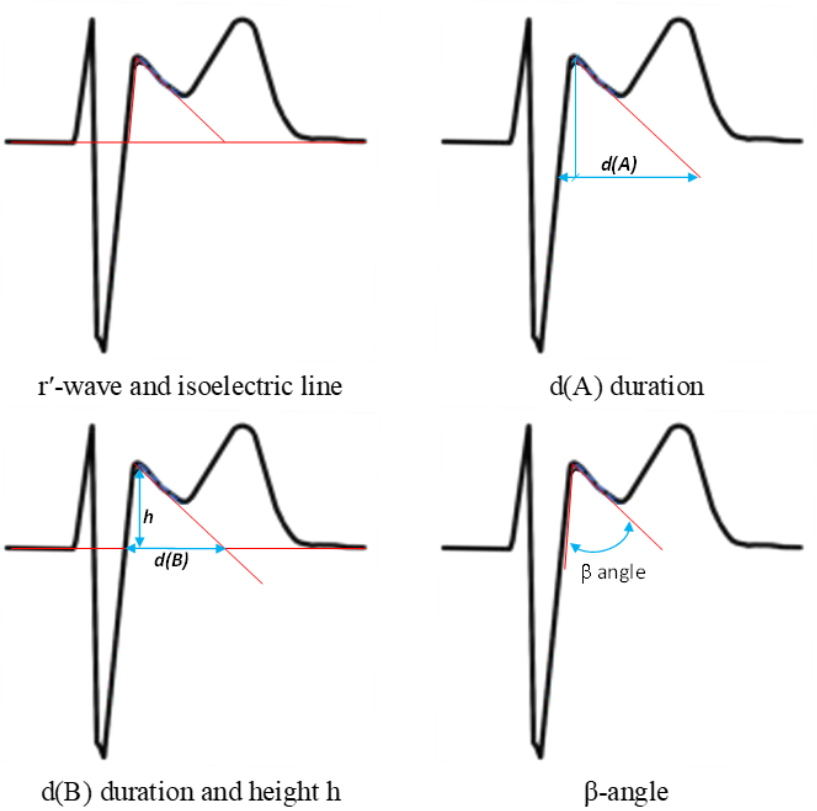


	Normal varia (n=50)
Benign morphology (n=38) d(B) < 1.4mm ST-ascent < 0.7mm	64.0% (32)
Probable benign morphology (n=16) d(B) ≥ 1.4mm ST-ascent < 0.7mm	20.0% (10)
Possible non-T1BrP morphology (n=17) d(B) < 1.4mm ST-ascent ≥ 0.7mm	2.0% (1)
Probable non-T1BrP morphology (n=44) d(B) ≥ 1.4mm ST-ascent ≥ 0.7mm	14.0% (7)

Legend: Left panel - Accuracy of non-T1 BrP electrocardiographic criteria. Right panel - A new classification for assessment of non-T1BrP for children and young adults: 4 classes of morphologies with increasing probability of corresponding to non-T1BrP pattern based on automatically measurements.

AUC - Area Under the Curve (95% Confidence interval), β - beta, d(A) – distance A, d(B) – distance B, h – height, mm – millimeters, ms – milliseconds, Non-T1BrP – Non-Type 1 Brugada pattern.

Figure 1: Non-Type 1 Brugada pattern criteria (*adapted from *Serra et al.* (4))



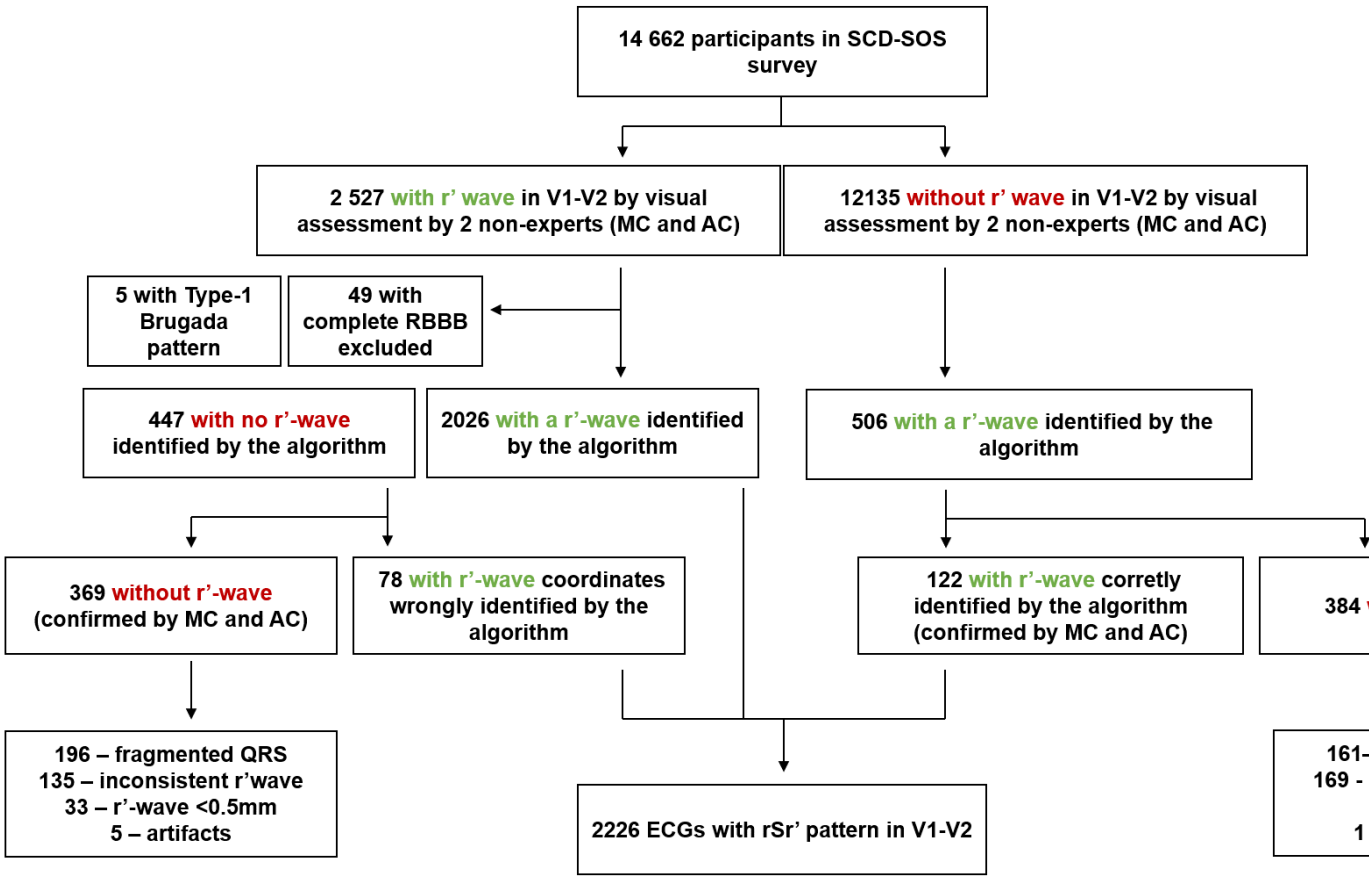
r'-wave and isoelectric line | d(A) duration

d(B) duration and height h | β-angle

r'-wave characteristics in precordial leads V1-V2	Cut-off values*
d(A) - duration of the base of the triangle between the upslope and the downsloap of the r'-wave at 0.5mV from the high take-off	**≥ 160ms (4mm)**
d(B) - duration of the base of the triangle at the isoelectric line	**≥ 60ms (1.5mm)**
d(B)/h - ratio of base/height of the triangle at the isolectric line	**≥ 1**
β-angle - formed between the r'-wave upsloap and the downsloap	**≥ 36.8º**

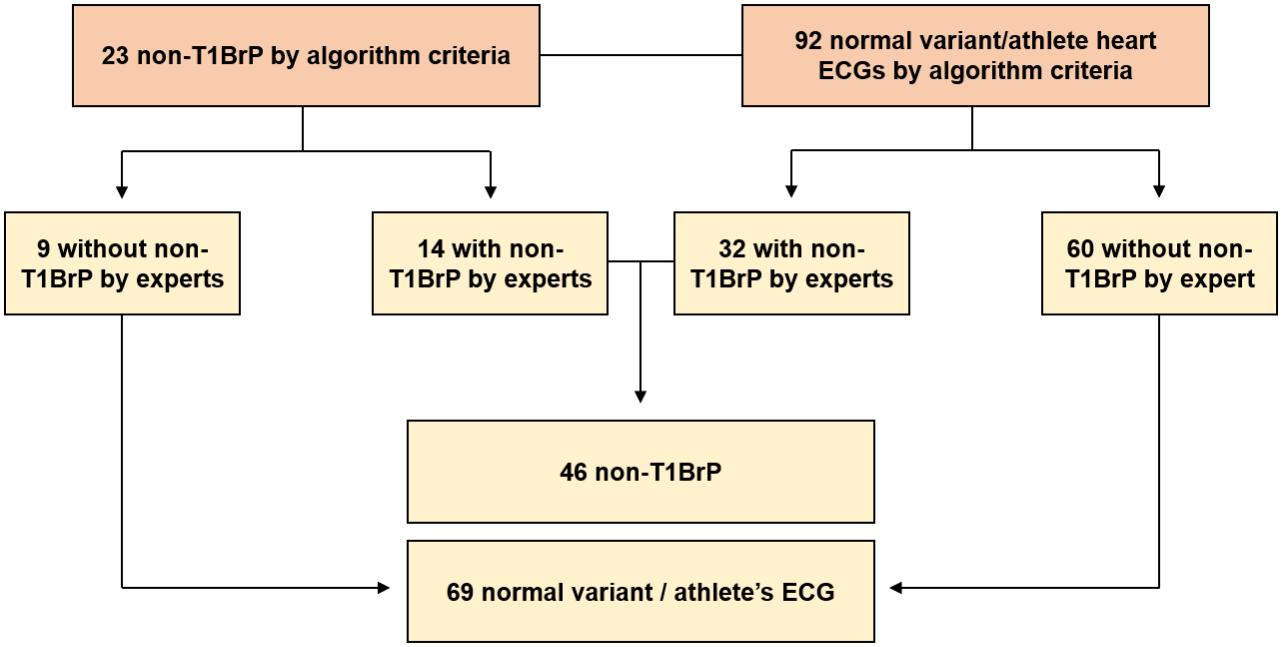
Legend: β - beta, d(A) – distance A, d(B) – distance B, h – height, mm – millimeters, ms - milliseconds

Figure 2: Flowchart for the validation of the algorithm by the investigators



Legend: AC – Antonio Creta, ECG – electrocardiogram, MC – Mafalda Carrington, mm – millimeters, SCD-SOS – Sudden Cardiac Death-Screening of risk factors.

Figure 3: Diagram of expert's classification of the ECGs selected by the algorithm



Legend: orange – classification based on automatic measurements of the Excel algorithm of *Bayes de Luna* et al. criteria; yellow: classification performed by experts in hereditary arrhythmic syndromes. ECG – Electrocardiogram; Non-T1BrP – Non-Type 1 Brugada pattern.