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CLINICAL RESEARCH

Prognostic value of right ventricular refractory period heterogeneity in Type-1 Brugada electrocardiographic pattern

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Aims To investigate the prognostic significance of heterogeneity in the refractoriness of right ventricular (RV) outflow tract (RVOT) and RV apex at the electrophysiological study (EPS) in Brugada syndrome (BrS).

Methods and results A cohort of BrS patients (primary prevention) from five Italian centres was retrospectively analysed. Patients with spontaneous or drug-induced Type-1 electrocardiogram (ECG) + symptoms were offered an EPS for prognostic stratification. The primary endpoint was a composite of sudden cardiac death (SCD), resuscitated cardiac arrest, or appropriate intervention by the implantable cardioverter-defibrillator (ICD). Three hundred and seventy-two patients with BrS were evaluated (44 ± 15 years, 69% males, 23% with ICD): 4 SCDs and 17 ICD interventions occurred at follow-up (median 48, interquartile range: 36–60 months). Family history of SCD, syncope, and a spontaneous Type-1 ECG pattern were univariate predictors of the primary endpoint in the whole population. In patients undergoing EPS ($n = 198$, 53%, 44 ± 12 years, 71% males, 39% with ICD), 3 SCD and 15 ICD interventions occurred at follow-up. In this subset, the primary endpoint was not only predicted by ventricular tachycardia/fibrillation inducibility but also by a difference in the refractory period between RVOT and RV apex ($\Delta RP_{RVOT\text{-}apex}$) >60 ms. $\Delta RP_{RVOT\text{-}apex} > 60$ ms remained an independent predictor of SCD/ICD shock at bivariate analysis, even when adjusted for the other univariate predictors, showing the highest predictive power at C-statistic analysis (0.75, 95% confidence interval 0.63–0.86).

Conclusions Heterogeneity of RV refractory periods is a strong, independent predictor of life-threatening arrhythmias in BrS patients, beyond VT/VF inducibility at EPS and common clinical predictors.

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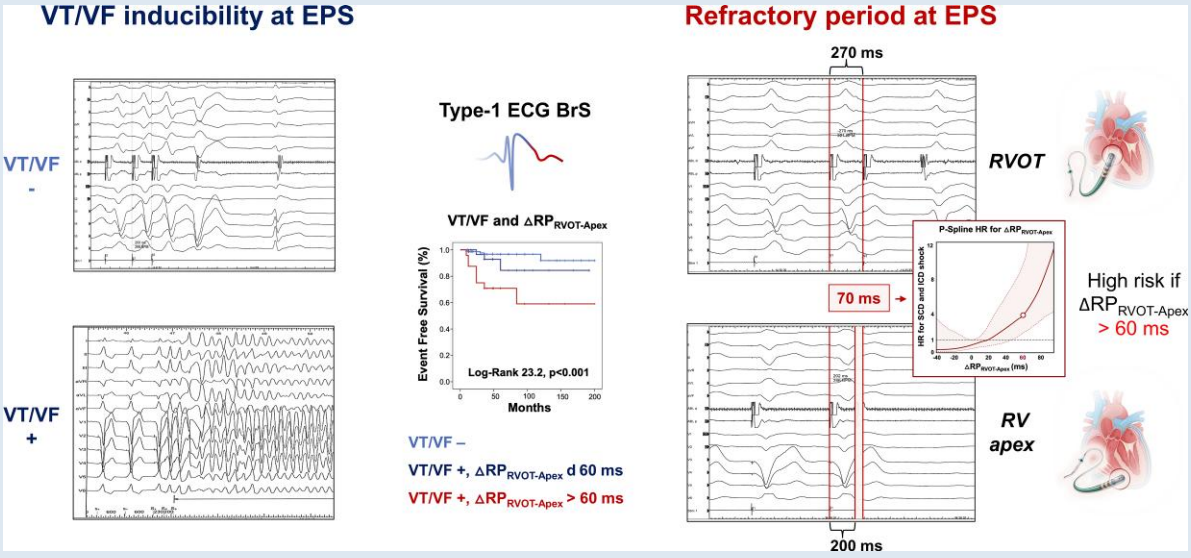
Graphical Abstract



In patients with Type-1 ECG Brugada pattern, the presence of an increased difference in the refractoriness between the right ventricular outflow tract (RVOT) and the apex, mainly driven by an increased refractory period in the RVOT, increases the prognostic discrimination power of the electrophysiological study, currently based only on inducibility of life-threatening arrhythmias. BrS, Brugada syndrome; EPS, electrophysiological study; RP, refractory period; RV, right ventricle; RVOT, right ventricular outflow tract; VF, ventricular fibrillation; VT, ventricular tachycardia.

Keywords Brugada syndrome • Sudden cardiac death • Electrophysiological study • Refractory period

What's new?

- The heterogeneity of right ventricular (RV) refractory periods was assessed at the electrophysiological study (EPS) in a large multicentric Italian cohort of patients with Brugada syndrome (BrS) followed-up for a median of 42 months.
- A difference in the refractory period between RV outflow tract (RVOT) and RV apex (ΔRPRVOT-apex) >60 ms improved risk stratification of patients with BrS beyond ventricular tachycardia/ventricular fibrillation inducibility at EPS and common clinical predictors.
- Prospective trials in larger cohorts should evaluate the value of heterogeneity of RV refractoriness at EPS to test in the future the potential of this novel measure in the decision-making of patients with BrS.

Introduction

Indications for implantable cardioverter-defibrillator (ICD) implantation in primary prevention are still debated in patients with Brugada syndrome (BrS).[1–3] Several models combining clinical factors and ventricular arrhythmias inducibility at the electrophysiological study (EPS) have been proposed to improve prognostic stratification in BrS patients.[4,5]

As recently reviewed, slow discontinuous conduction and dispersion of repolarization in the right ventricle (RV) have been described as specific electrophysiological features and potential arrhythmic substrates of BrS.[6]

Beyond the inducibility of sustained ventricular arrhythmias, we hypothesized that EPS may increase its prognostic predictive power in BrS by providing information related to the heterogeneity of RV refractoriness.

The present study aims at assessing the clinical usefulness of a combined approach including clinical data and EPS in patients with either spontaneous or drug-induced Brugada Type-1 electrocardiogram (ECG) pattern.

Methods

This was a retrospective multicentric study (Pisa, Arezzo, Lido di Camaiore, Siena, and Naples) on patients with a diagnosis of BrS, without a history of cardiac arrest or sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). Any underlying structural or functional cardiac abnormality was excluded. The study was approved by Institutional Ethics Committee of each participant centre.

Brugada Type-1 ECG pattern was defined as the presence of coved ST-segment elevation ≥0.2 mV in ≥1 lead from standard/modified V1–V3 assessed in basal conditions, during drug challenge, or at 12-lead 24-h Holter monitoring.[1]

Genetic testing limited to sodium voltage-gated channel alpha subunit 5 (SCN5A) variants was recommended to all patients and only pathognomonic variants were collected.

Family history of BrS (first- or second-degree relatives)[7] or juvenile sudden cardiac death (SCD) before the age of 40 years,[5] and history of syncope, palpitations, or nocturnal agonic breathing were collected.[8] Syncope was anamnestically defined by referring cardiologists after exclusion of signs suggesting a vasovagal origin. 'Symptoms' were defined as the presence of syncope and/or palpitations, and/or nocturnal agonic breathing.

Electrophysiological study was proposed to all individuals with spontaneous Brugada Type-1 ECG pattern, regardless of symptoms, and to symptomatic subjects with drug-induced Brugada Type-1 ECG pattern. As for 'symptomatic patients', we considered those with a high suspicion of arrhythmic events based on anamnestic evaluation.

An ICD was implanted in patients with syncope and spontaneous Brugada Type-1 ECG pattern or with a positive EPS study according to recommendations of the second consensus BrS conference.[1,9]

Electrophysiological study

Electrophysiological study included basal measurements of conduction intervals, ventricular programmed stimulation (VPS), and collection of ventricular effective refractory periods (VERP) at two sites in the RV, namely the apex and the RV outflow tract (RVOT).

In all centres, VPS was performed with a drive of 8–10 beats (basic cycle lengths of 600 and 400 ms) and up to two extrastimuli anticipated in 10 ms decrements up to the shortest coupling interval that resulted in ventricular capture from the RV apex and the RVOT.[8,10]

Electrophysiological study was assumed as 'positive' in case of sustained VT or VF induction (duration up to 30 s), with clinical symptoms or collapse, or requiring direct current-shock. Ventricular effective refractory periods were defined as the longest interval between two stimulated beats that failed to achieve ventricular capture. Ventricular effective refractory period values were collected using a drive of 600 ms and a single extrastimulus from the RV apex and RVOT. In all centres, programmed electrical stimulation from the RV apex and RVOT was performed at twice the diastolic threshold strength and a pulse of 2 ms duration.

Study follow-up and clinical endpoints

All patients were followed through in-office or remote follow-up visits every 12 months or in case of symptoms or ICD interventions until March 2021. The primary endpoint was a composite of SCD, resuscitated cardiac arrest, or appropriate ICD therapies for sustained VT or VF (antytachicardia algorithms or endocardial shocks). A secondary endpoint including inappropriate ICD therapies or related complications was also evaluated.

Statistical analysis

Statistical analysis was performed using SPSS (version 25.0, IBM Statistics) and R statistical software (version 3.4.0). A two-tailed *P*-value $\leq$0.05 was considered significant.

Quantitative data were expressed as mean $\pm$ standard deviation (SD) or median and interquartile range (IR) according to distribution (Shapiro–Wilk test) and compared by independent *t*-test or Mann–Whitney *U* test. Discrete variables were expressed as numbers and/or percentages and compared by χ^2 or Fisher exact tests.

Kaplan–Meier method was performed to build the survival curves with log-rank statistic used for comparison, while Cox proportional hazard regression model (univariate and bivariate analysis) was used for event analysis over time, with the risk quantified as a hazard ratio (HR) with 95% confidence interval (CI). The list of risk factors included in survival analysis, in line with the literature, includes: age at diagnosis, male sex, family history of SCD, presence of spontaneous Type-1 ECG, symptoms (syncope/agonic nocturnal breathing), presence of a pathogenic SCN5A mutation, VT/VF at EPS, and a metric of heterogeneity in endocardial VERP between the apex and the RVOT at EPS (as explained below). Considering the number of events in our population, we limited multivariate analysis to a bivariate analysis to reduce the risk of overfitting models.

Cubic spline interpolation was used for an exploratory assessment of the prognostic relationship between a covariate and the hazard risk. The optimal prognostic threshold was then chosen by using the maximally selected rank statistics.

For event prediction, C-statistics analysis was used (ranges from 0.5 as no discrimination to 1.0 as maximum discrimination ability). The Integrated Brier score (IBS) was employed to evaluate the accuracy of a predicted survival function (ranges between 0.0 and 1.0, with lower values being better and 0.0 being the best possible value).

Results

A cohort of 372 patients with Type-1 ECG pattern was finally evaluated (Pisa $n=111$, Arezzo $n=52$, Lido di Camaiore $n=165$, Siena $n=21$, and Naples $n=23$). The clinical characteristics of the population are reported in *Table 1*.

Patients (age at diagnosis 44 ± 15 years) were mainly males (69%). A family history of BrS and SCD was present in 26 and 28% of patients, respectively; symptoms and syncope were present in 46 and 25% of cases, respectively. Patients had spontaneous and drug-induced Type-1 ECG pattern in 49 and 51% of cases, respectively. A total of 167 genetic samples (45%) were collected, finding 55 (33% of those evaluated) SCN5A pathognomonic variants.

Electrophysiological study

Electrophysiological study was proposed to 212 (57% of the whole population) BrS subjects; of them, seven patients were excluded for

Table 1 Clinical characteristics of patients with Brugada syndrome

	All patients ($n=372$)	No EPS ($n=174$)	EPS ($n=198$)	*P*-value
Age at diagnosis, years	44 ± 15	44 ± 17	43 ± 13	0.999
Males	257 (69)	117 (67)	140 (71)	0.501
Family history of Brugada syndrome	98 (26)	59 (34)	39 (20)	0.002
Family history of SCD	105 (28)	44 (25)	61 (31)	0.250
Spontaneous Type-1 ECG	185 (49)	66 (38)	119 (60)	<0.001
Symptoms	170 (46)	68 (39)	102 (52)	0.017
Syncope	94 (25)	36 (21)	58 (29)	0.057
Presyncope	51 (14)	24 (14)	27 (14)	0.965
Palpitations	87 (23)	31 (18)	56 (28)	0.017
Agonic nocturnal breathing	10 (3)	3 (1.7)	7 (3.5)	0.310
Genetic testing performed	175 (47)	72 (41)	103 (52)	0.048
SCN5A mutation[a]	55 (31)	24 (33)	31 (30)	0.502
Cardiovascular risk factors				
Hypertension	64 (17)	31 (18)	33 (17)	0.785
Diabetes	12 (3)	7 (4)	5 (3)	0.559
Dyslipidaemia	35 (9)	11 (6)	24 (12)	0.074
Smoke	59 (16)	20 (12)	39 (20)	0.033

Data are given as mean ± standard deviation or number (percentage). ECG, electrocardiogram; SCD, sudden cardiac death; SCN5A, sodium voltage-gated channel alpha subunit 5.

[a]% are related to patients with a genetic sampling.

lack of consent and seven for incompleteness of the VERP assessment due to programmed ventricular stimulation performed only at the RV apex in four patients, unavailability of VERP for both sites of pacing for VF induction with single extrastimulus either at the apex (two patients) or the RVOT (one patient). Data from EPS were finally analysed in 198 patients (53% of the whole population) with VERP available for both RV pacing sites.

Patients studied with EPS compared with those who did not (*Table 1*) had more frequently a spontaneous Type-1 ECG pattern (73 vs. 56%, $P < 0.001$), a family history of SCD (42 vs. 27%, $P = 0.036$) and a history of syncope (42 vs. 25%, $P = 0.041$). As expected, patients who underwent EPS were more likely to be implanted with an ICD (39 vs. 6%, $P < 0.001$).

Out of 198 patients, 52 (27%) had a positive EPS (*Table 2*): all patients but one (regular VT) had VF inducible with two extrastimuli. Overall, VERP assessed at the RV apex and RVOT were 220 ± 39 and 244 ± 44, respectively. Ventricular effective refractory periods assessed at the RV apex was shorter, while that measured at the RVOT was longer in VT/VF inducible patients compared with non-inducible patients (VERP RV apex 210 ± 17 vs. 223 ± 43 ms, $P = 0.034$; VERP RVOT 259 ± 36 vs. 239 ± 45 ms, $P = 0.005$, respectively) (*Table 2*). As for the difference between RVOT and RV apex ($\Delta RP_{RVOT\text{-}apex}$), a longer $\Delta RP_{RVOT\text{-}apex}$ mean values were observed in inducible compared with non-inducible patients [40 (10–80) vs. 10 (0–20) ms, $P < 0.001$]. Furthermore, a $\Delta RP_{RVOT\text{-}apex} > 60$ ms was more likely in patients with positive EPS (45 vs. 8%, $P < 0.001$). Patients with a positive EPS also showed a higher prevalence of appropriate ICD shocks (15 vs. 5%, $P = 0.025$). Out of 53 inducible patients, 20 (38%) had inducibility at the apex and 33 (62%) at the RVOT ($P = 0.002$). With regard to the induction site, no differences were found between patients with $\Delta RP_{RVOT\text{-}apex} > 60$ ms or ≤60 ms ($P = 0.31$).

At univariate logistic regression analysis, a positive EPS was predicted by the family history of SCD (odds ratio, OR 1.99, 95% CI 1.03–3.82, $P = 0.039$), the presence of spontaneous Type-1 ECG pattern (OR 2.21, 95% CI 1.11–4.39, $P = 0.024$), and a $\Delta RP_{RVOT\text{-}apex} > 60$ ms (OR 9.78, 95% CI 4.28–22.35, $P < 0.001$). At multivariate logistic regression analysis, only $\Delta RP_{RVOT\text{-}apex} > 60$ ms (OR 8.01, 95% CI 3.41–18.78, $P < 0.001$) remained an independent predictor of a positive EPS.

Table 2 Patients' characteristics according to a negative or positive electrophysiological study

	EPS− ($n = 146$)	EPS+ ($n = 52$)	*P*-value
Age, years	43 ± 13	45 ± 12	0.360
Males	99 (68)	41 (79)	0.133
Family history of Brugada syndrome	31 (21)	8 (15)	0.363
Family history of SCD	39 (27)	22 (42)	0.036
Spontaneous Type-1 ECG	81 (56)	38 (73)	0.039
Symptoms	75 (51)	27 (52)	0.945
Syncope	37 (25)	21 (42)	0.041
Presyncope	22 (15)	5 (10)	0.325
Palpitations	46 (32)	10 (19)	0.091
Agonic nocturnal breathing	4 (3)	3 (6)	0.382
Genetic testing performed[a]	75 (51)	28 (54)	0.759
SCN5A mutation	22 (30)	9 (32)	0.845
VERP RV apex, ms	223 ± 43	210 ± 17	0.034
VERP RVOT, ms	239 ± 45	259 ± 36	0.005
$\Delta RP_{RVOT\text{-}RVapex}$, ms	10 (0–20)	40 (10–80)	<0.001
$\Delta RP_{RVOT\text{-}RVapex} > 60$ ms	11 (8)	23 (45)	<0.001
SCD	0 (0)	3 (6)	0.017
ICD implanted	36 (24)	42 (81)	<0.001
Appropriate ICD shock	7 (5)	8 (15)	0.025
Inappropriate ICD shock	3 (9)	4 (10)	0.865

Data are given as mean ± standard deviation or number (percentage). ECG, electrocardiogram; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; RV, right ventricle; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; SCN5A, sodium voltage-gated channel alpha subunit 5; VERP, ventricular effective refractory period.
[a]% are related to patients with a genetic sampling.

Implantable cardioverter-defibrillators

As a primary prevention strategy, 89 patients (24%) received an ICD (64 transvenous ICD, 23 subcutaneous ICD) that was programmed according to current medical practice.

Patients with ICD had more frequently a family history of SCD (44 vs. 23%, $P < 0.001$), a history of syncope (51 vs. 17%, $P < 0.001$), a

Table 3 Patients' characteristics according to the absence or presence of sudden cardiac death/appropriate implantable cardioverter-defibrillator shock

All patients ($n = 372$)	SCD/ICD intervention− ($n = 351$)	SCD/ICD intervention+ ($n = 21$)	*P*-value
Age at diagnosis, years	43 ± 15	45 ± 12	0.583
Males	241 (69)	16 (76)	0.682
Family history of SCD	92 (26)	13 (62)	0.002
Syncope	83 (24)	11 (52)	0.007
Spontaneous Type-1 ECG	168 (48)	17 (81)	0.003
Patients with genetic testing ($n = 167$)	$n = 154$	$n = 13$	
SCN5A mutation[a]	48 (31)	7 (54)	0.124
Patients undergoing EPS ($n = 198$)	$n = 180$	$n = 18$	
VT/VF at EPS[a]	43 (24)	11 (61)	0.002
VERP RV apex, ms	221 ± 40	207 ± 20	0.146
VERP RVOT, ms	241 ± 44	271 ± 32	0.007
$\Delta RP_{RVOT\text{-}RVapex}$, ms	10 (0–40)	70 (35–90)	<0.001
$\Delta RP_{RVOT\text{-}RVapex}$ >60 ms[a]	23 (13)	11 (61)	<0.001

Data are given as mean ± standard deviation or number (percentage). ECG, electrocardiogram; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; RV, right ventricle; RVOT, right ventricle outflow tract; SCD, sudden cardiac death; SCN5A, sodium voltage-gated channel alpha subunit 5; VERP, ventricular effective refractory period; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a]% to be referred to patients with genetic testing or who underwent EPS.

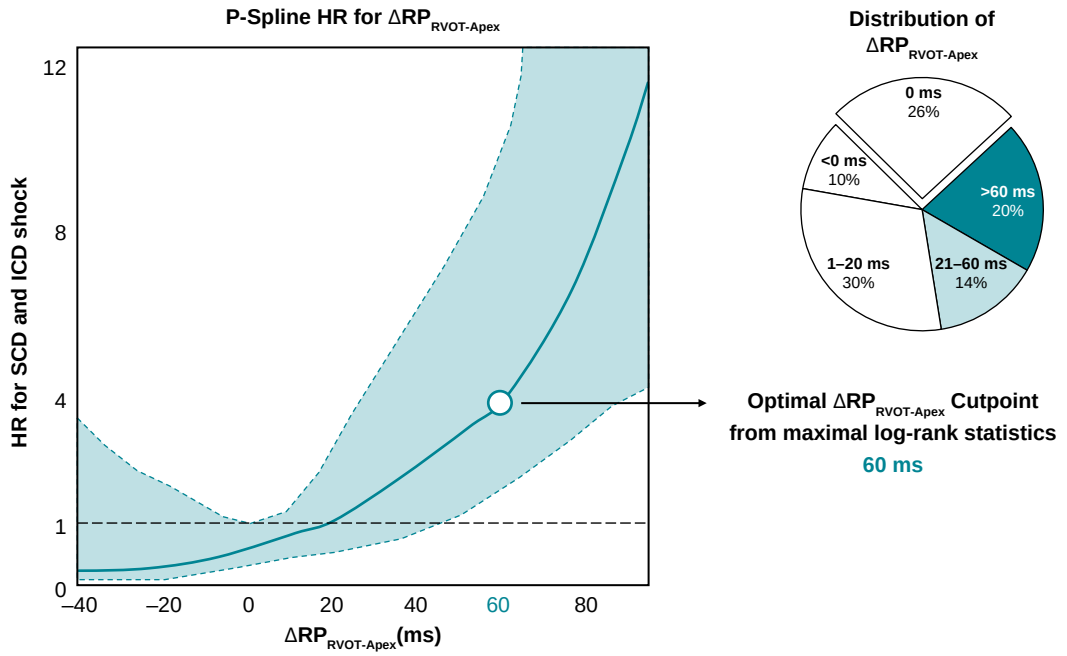


Figure 1 P-spline HR curve of SCD/appropriate ICD shock related to $\Delta RP_{RVOT\text{-}RVapex}$. The continuous curve represents the P-spline describing hazard ratio (HR) for sudden cardiac death (SCD) or aborted appropriate ICD shocks as a function of $\Delta RP_{RVOT\text{-}RVapex}$, while the dashed lines represent the 95% CIs. While a higher risk of events is already evident with a $\Delta RP_{RVOT\text{-}RVapex} > 20$ ms, above a $\Delta RP_{RVOT\text{-}RVapex}$ of 60 ms the HR for SCD/appropriate ICD shocks steeply increases. This cutpoint corresponds to the optimal cutpoint identified by the maximal log-rank statistic analysis. In the upper-left panel the distribution of different $\Delta RP_{RVOT\text{-}RVapex}$ intervals is also displayed.

positive EPS (53 vs. 2%, $P < 0.001$), and a $\Delta RP_{RVOT\text{-}apex} > 60$ ms (34 vs. 7%, $P < 0.001$).

Out of total 89 ICD implants, 52 patients were implanted due to VT/VF inducibility during EPS, 35 patients due to syncope and spontaneous Type-1 electrocardiographic pattern, and 2 patients due to a family history of SCD, non-sustained VT during EPS, and symptoms (presyncope and palpitations).

Device-related complications occurred in 13 ICD recipients, with two infections, four lead fractures, and eight inappropriate shocks.

Survival analysis

In the whole population, 21 patients experienced the primary endpoint, with 4 SCD, no case of resuscitated cardiac arrest, and 17 VT/VF appropriately treated by the ICD during a median follow-up of 48 months (IR 36–60 months) (*Table 3*). The cumulative incidence of SCD and ICD appropriate interventions was 0.27 and 1.9%, respectively. Patients experiencing the primary endpoint had more frequently a family history of SCD ($P = 0.002$), a history of syncope ($P = 0.007$) and a spontaneous Type-1 ECG pattern ($P = 0.003$).

Considering the subset who underwent EPS, 18 patients experienced the primary endpoint, with 3 SCD, no case of resuscitated cardiac arrest, and 15 appropriate ICD intervention during follow-up (48 IR 27–84 months). Comparing patients experiencing or not the primary endpoint, no difference was observed regarding VERP at the apex (207 ± 20 vs. 221 ± 40 ms, $P = 0.15$), while a longer VERP at the RVOT (271 ± 32 vs. 241 ± 44, $P = 0.007$), and a longer $\Delta RP_{RVOT\text{-}apex}$ were observed in patients with events [70 (35–90) vs. 10 (0–40), $P < 0.001$] (*Table 3*). A higher risk of events was observed in patients with a positive EPS (61 vs. 24%, $P = 0.004$), or with a $\Delta RP_{RVOT\text{-}apex} > 60$ ms (61 vs. 13%, $P < 0.001$). The distribution of $\Delta RP_{RVOT\text{-}apex}$ in BrS patients and the relationship (*P*-Spline HR analysis) between $\Delta RP_{RVOT\text{-}apex}$ and the risk of events is displayed in *Figure 1*. The risk of events start to rise above a $\Delta RP_{RVOT\text{-}apex}$ of 20 ms, but the optimal prognostic cutpoint was identified as 60 ms by using the maximally selected rank statistics (sensitivity 61%, specificity 87%, positive predictive value 32%, negative predictive value 96%, accuracy 85%). Notably, patients with a $\Delta RP_{RVOT\text{-}apex} > 60$ ms compared with those with a $\Delta RP_{RVOT\text{-}apex} \leq 60$ ms had a both a longer VERP at RVOT (298 ± 19 vs. 234 ± 42 ms, $P < 0.001$) and a shorter VERP at the RV apex (202 ± 16 vs. 224 ± 41, $P < 0.001$). A $\Delta RP_{RVOT\text{-}apex} > 60$ ms was more frequently observed in patients with a spontaneous rather than drug-induced Type-1 ECG (25 vs. 6%, $P < 0.001$).

At Kaplan–Meier analysis, the family history of SCD (*Figure 2A*), the presence of syncope (*Figure 2B*), and spontaneous Type-1 ECG pattern (*Figure 2C*) were all associated with a higher risk of experiencing the primary endpoint. As for symptoms, the presence of presyncope or palpitation was not associated with events (all $P > 0.05$).

A higher risk of events was also observed in patients with a pathogenic SCN5A mutation, but without a family history of BrS (to avoid any referral bias, Supplementary material online, *Figure S1*).

In patients undergoing EPS, inducibility of VF/VT at EPS (*Figure 3A*) and $\Delta RP_{RVOT\text{-}apex} > 60$ ms (*Figure 3B*) stratified the risk of events. The prognostic power of EPS was improved by using the $\Delta RP_{RVOT\text{-}apex} > 60$ ms. Indeed, the primary endpoint occurred more frequently in patients in whom a positive EPS was accompanied by $\Delta RP_{RVOT\text{-}apex} > 60$ ms (*Figure 3C*).

At Cox proportional hazard univariate analysis (*Table 4*), family history of SCD, history of syncope/agonic nocturnal breathing, a spontaneous Type-1 ECG pattern, a positive EPS (VT/VF inducibility), and a $\Delta RP_{RVOT\text{-}apex} > 60$ ms at EPS were all univariate predictors of the primary endpoint (all $P < 0.05$). At bivariate analysis (*Table 5*),

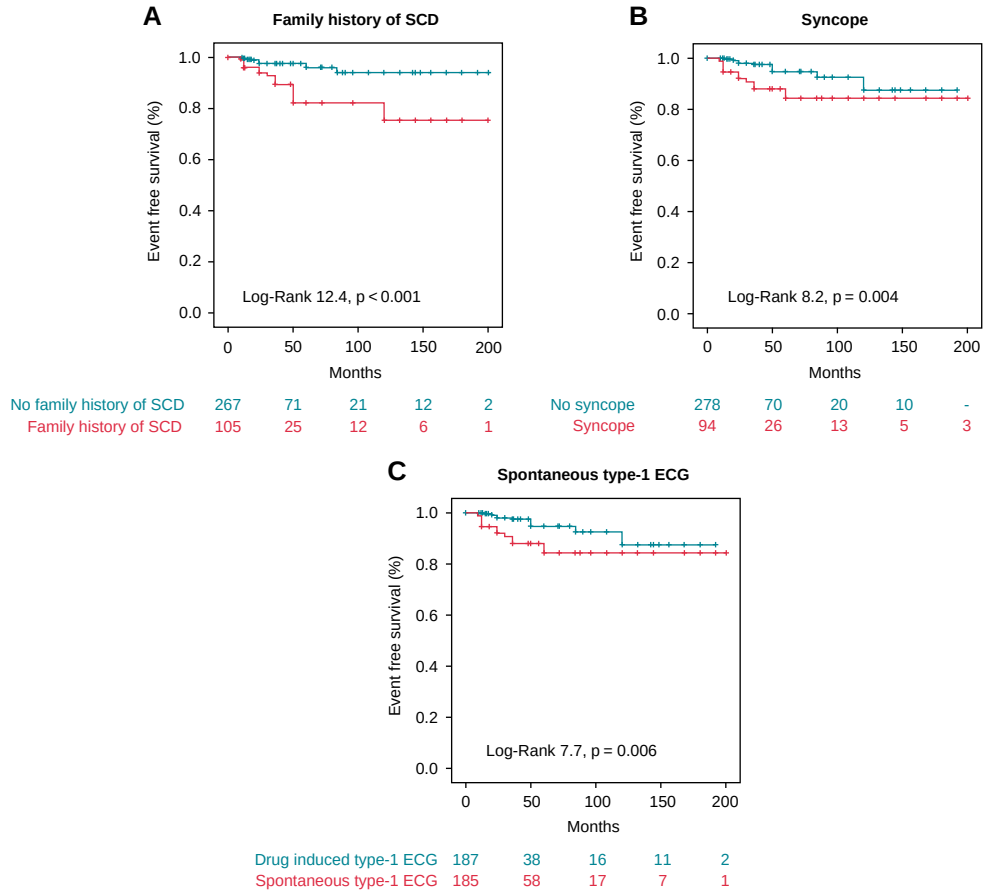


Figure 2 Kaplan–Meier curves of traditional risk factors for Brugada syndrome. Family history of sudden cardiac death (SCD, *A*) and syncope (*B*) and spontaneous Type-1 ECG pattern (*C*) were all adverse prognostic factors associated with SCD and ICD appropriate shock in patients with Brugada syndrome.

$\Delta RP_{RVOT\text{-}apex} > 60$ ms remained an independent predictor of events, even when adjusted for the family history of SCD, history of syncope, and a positive EPS.

At discrimination analysis by C-statistic, the strongest model was the one using $\Delta RP_{RVOT\text{-}apex} > 60$ ms as a covariate, with a C-statistics (95% CI) of 0.75 (0.63–0.86), followed by those using VT/VF inducibility at EPS, 0.67 (0.54–0.79), family history of SCD, 0.66 (0.54–0.78), a spontaneous Type-1 ECG pattern, 0.65 (0.57–0.73), and a history of syncope, 0.64 (0.51–0.76). Overall, a model including clinical variables (family history of SCD, syncope, and spontaneous Type-1 ECG pattern) and EPS variables (VT/VF inducibility and $\Delta RP_{RVOT\text{-}apex} > 60$ ms) provide a very high prognostic precision with C-statistic 0.88 (0.81–0.92).

The accuracy of the $\Delta RP_{RVOT\text{-}apex} > 60$ ms model was also confirmed by IBS analysis: indeed, models based on $\Delta RP_{RVOT\text{-}apex} > 60$ ms and family history of SCD showed the lowest IBS (0.15), followed by VT/VF inducibility at EPS (0.25), family history of SCD, history syncope (0.29), and a spontaneous Type-1 ECG pattern (0.54).

Discussion

The heterogeneity of right ventricular (RV) refractory periods was assessed at EPS in a large multicentric Italian cohort of patients with BrS. The difference in the refractory period between RVOT and RV apex ($\Delta RP_{RVOT\text{-}apex}$) > 60 ms improved risk stratification beyond VT/VF inducibility at EPS and common clinical predictors. If confirmed in larger cohorts, the assessment of the heterogeneity of RV refractory periods may help clinical decision-making on whether or not to prescribe more aggressive therapeutic options (e.g. an ICD) to BrS patients in primary prevention.

In our cohort, the family history of SCD, the presence of syncope, or nocturnal agonic breathing, a spontaneous Type-1 ECG pattern, and a positive EPS were confirmed to be predictors of life-threatening arrhythmic events.[5,11–14] Delise *et al.*[5] proposed a multiparametric approach, in which the addition of VT/VS inducibility at EPS to accepted clinical predictors increased the prognostic discriminative capability of the model. Indeed, a VT/VS inducibility at EPS predicted arrhythmic events also in our population, but the assessment of RV refractoriness heterogeneity during EPS added further precision to the EPS model. In fact, patients with VT/VF inducibility but with a short ΔRP RVOT-apex (≤60 ms) at EPS showed a similar risk of events than patients without VT/VF inducibility. Furthermore, at bivariate analysis, VT/VF inducibility was no longer predictive of SCD/appropriate ICD shocks when adding to the model $\Delta RP_{RVOT\text{-}apex} > 60$ ms, which instead remained an independent predictor of survival. Of note, mean $\Delta RP_{RVOT\text{-}apex}$ values were significantly higher in patients with inducible ventricular arrhythmias compared with non-inducible ones.

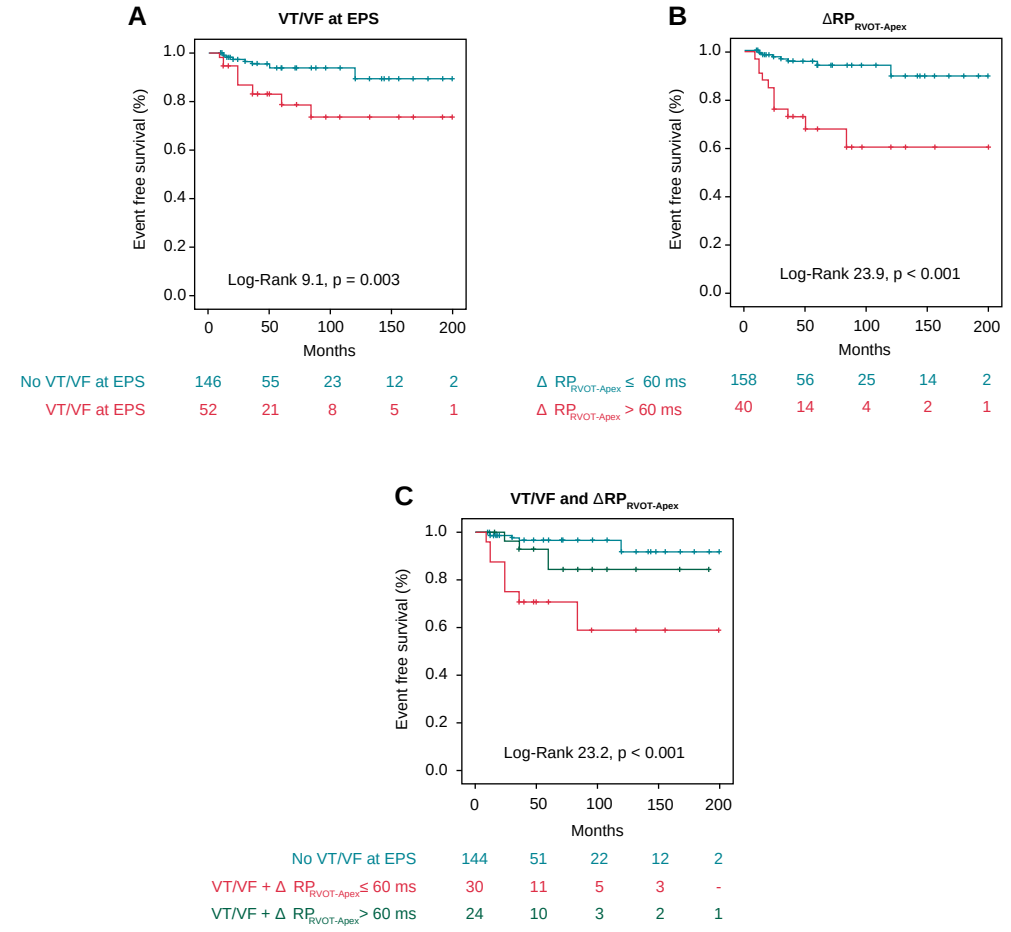


Figure 3 Prognostic significance of VT/VF inducibility and the difference in the refractory period between the right ventricle outflow tract and apex ($\Delta RP_{RVOT\text{-}RVapex}$). In patients undergoing EPS ($n = 198$), VT/VF inducibility (*A*) and a difference in the refractoriness between the right ventricular outflow tract and the apex (*B*) were predictors of SCD and ICD shocks. Notably, patients with a positive EPS (VT/VF inducibility) but a $\Delta RP_{RVOT\text{-}RVapex} \leq 60$ ms showed a similar risk of events compared with patients with a negative EPS, while those with a positive EPS and a $\Delta RP_{RVOT\text{-}RVapex} > 60$ ms were found to be at a higher risk (*C*).

The longer $\Delta RP_{RVOT\text{-}apex}$ in inducible patients seems mainly driven by longer VERP at the RVOT than a shorter VERP at the apex in our population. Lambiase *et al.*[15] reported a significant conduction delay in the RVOT compared with the RV body and apex in BrS subjects. The same region of delayed conduction gave rise to wavefront fragmentation and functional block that led to initiation of polymorphic VT/VF. These findings may explain our observation that a greater $\Delta RP_{RVOT\text{-}apex}$, mainly driven by a longer VERP assessed at the RVOT, was observed particularly in inducible patients. A reduction of VERP was also observed, especially in patients with an increased $\Delta RP_{RVOT\text{-}apex} > 60$ ms. Data from PRELUDE study[12] showed that a VERP <200 ms, assessed only at the RV apex, represents a significant risk factor of arrhythmic events during follow-up.

The association between an increased VERP in the RVOT and the risk of arrhythmias is in line with what was observed in Scn5a+/– mouse model presented by Martin *et al.*[16] Indeed, VERP is influenced also by the recovery of a critical number of activatable sodium channels to favour resumption of excitability, and they may be critically decreased in the RVOT (increasing VERP), thus reverting the physiological gradient between the apex and RVOT in high risk individuals. Overall, our findings suggest that the heterogeneity of refractoriness rather than the evaluation of refractoriness in a single site could represent an additional parameter to improve predictivity of EPS in BrS and further refine risk stratification. Noteworthy, no correlation was found regarding the induction site between patients with $\Delta RP_{RVOT\text{-}apex} > 60$ ms and those without.

Concerning the mechanisms and the substrate underlying the observed heterogeneity of refractoriness, several authors reported the presence of delayed and discontinuous conduction in the RVOT in patients with BrS,[6,17] likely caused by abnormal active membrane processes and electric coupling.[4,6] Although originally reported as a primary electrical disorder in the absence of overt structural disease, there is growing evidence that various degrees of structural alterations may be found by imaging,[18] endomyocardial biopsy,[19] or autopsy studies.[20] Based on this evidence, BrS was suggested to be reclassified as a combination of structural and electrical defects, paving the way to a new risk stratification approach. It is plausible that the presence of a structurally abnormal myocardium at the RVOT would explain the increased refractoriness observed in our patients, with longer values being associated with increased arrhythmic susceptibility, especially when refractoriness is concomitantly reduced at the RV apex.

Table 4 Univariate predictors of sudden cardiac death/appropriate implantable cardioverter-defibrillator shock

	Univariate analysis		
	Hazard ratio	95% CI	*P*-value
Age at diagnosis, years	1.01	0.98–1.04	0.604
Males	1.38	0.50–3.76	0.533
Family history of SCD	4.25	1.76–10.28	0.001
Spontaneous Type-1 ECG	4.18	1.39–12.41	0.010
Symptoms (syncope/agonic nocturnal breathing)	4.36	1.42–13.35	0.009
SCN5A mutation	2.39	0.80–7.10	0.112
VT/VF at EPS	3.65	1.45–9.07	0.005
$\Delta RP_{RVOT\text{-}RVapex} > 60$ ms	7.72	2.98–19.95	<0.001

CI, confidence interval; ECG, electrocardiogram; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; RP, refractory period; RV, right ventricle; RVOT, right ventricle outflow tract; SCD, sudden cardiac death; SCN5A, sodium voltage-gated channel alpha subunit 5; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 5 Predictive value of $\Delta RP_{RVOT\text{-}RVapex}$ at bivariate analysis for sudden cardiac death and appropriate implantable cardioverter-defibrillator shock

	Bivariate analysis		
	Hazard ratio	95% CI	*P*-value
$\Delta RP_{RVOT\text{-}RVapex} > 60$ ms	6.66	2.55–17.41	<0.001
Family history of SCD	2.68	1.02–7.01	0.045
$\Delta RP_{RVOT\text{-}RVapex} > 60$ ms	7.68	2.93–20.08	<0.001
Symptoms (syncope/agonic nocturnal breathing)	1.04	0.39–2.72	0.944
$\Delta RP_{RVOT\text{-}RVapex} > 60$ ms	6.17	2.31–16.48	<0.001
Spontaneous Type-1 ECG pattern	2.16	0.60–7.78	0.239
$\Delta RP_{RVOT\text{-}RVapex} > 60$ ms	5.84	1.87–18.24	0.002
VT/VF at EPS	1.64	0.53–5.12	0.392

CI, confidence interval; ECG: electrocardiogram; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; RP, refractory period; RV, right ventricle; RVOT, right ventricle outflow tract; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

The arrhythmogenesis in BrS patients implies the occurrence of early re-excitation phenomena that would require early recovery for refractoriness. It is plausible that the presence of a structurally abnormal myocardium at the RVOT would explain the increased endocardial refractoriness observed in our patients, with longer values being associated with increased arrhythmic susceptibility, especially when refractoriness is concomitantly reduced at the RV apex, as previously highlighted in the PRELUDE.[12] Not surprisingly, arrhytmogenic effects of increased VERP dispersion have been observed also in experimental models of long QT syndrome and ischaemic cardiomyopathy.[21,22]

Beyond the endocardial gradient of VERP across the RV found in our study, a transmural dispersion of repolarization has been described in BrS as well as in other ion channelopathies.[23] This transmural heterogeneinty may further increase the risk of reentry tachyarrhytmias. Whether this gradient might be higher in patients with prolonged endocardial VERP or $\Delta RP_{RVOT\text{-}apex}$ is a topic of great interest that should be explored in future studies. Finally, it is noteworthy to consider the combination of shortened action potential duration and lengthened VERP, especially in the RVOT, as key mechanism of electric vulnerability.[16] Overall, we believe that VERP heterogeneity could then favour arrhythmogenicity by altering action potentials recovery or affecting conduction characteristics, conditions critical to the initiation of reentrant arrhythmias.

Study limitations

The first limitation of the study is its retrospective design, with potential heterogeneities among the five Italian centres. However, EPS indication, VPS protocol with two extrastimuli at the RV apex and RVOT, and management of ICD implantation were the same between centres and complied with international guidelines.

The measurement of the VERP heterogeneity was possible only when VERP was assessed at both the RV apex and the RVOT. Indeed, seven patients were excluded from the study for VERP being measured only at one site. As previously reported by Sroubek *et al.*[10] in a large pooled analysis, patients induced by one extrastimulus represent a small part of the inducible population (2%), and should be considered at higher risk according to the presence of other accepted risk factors.

As previously reported, we also defined appropriate ICD shocks as fast VT/VF terminated by ICD intervention. However, 'appropriate ICD shock' should only be assumed as a surrogate of SCD (especially VT), considering that some of those arrhythmic events may spontaneously terminate without a risk of death. Furthermore, having the cases of SCD in our series occurred out of the hospital the ECG was not available and thus we cannot exclude that non arrhythmic conditions may have caused SCD. However, patients' age, lack of relevant comorbidities, and Brs diagnosis make the probability of ventricular arrhythmias highly likely. Of note, in two cases of SCD an ICD had been implanted (after a positive EPS) and multiple shocks were delivered without resuscitation.

Finally, the relatively low number of events in our population is a limitation in evaluating the prognostic value of risk factors. However, our study reflects a 'real-world' situation including a large population of 'primary prevention' BrS patients and the low incidence of events is in line with previous published cohorts.[5,12] Given that BrS patients present a lifelong arrhythmic risk, a longer follow-up is notwithstanding advisable.

Conclusions

Risk stratification in BrS remains a significant challenge. Our study showed for the first time that a $\Delta RP_{RVOT\text{-}apex} > 60$ ms, easily achievable during EPS, is independently associated with an increased risk of SCD/appropriate ICD shocks at follow-up. These findings, to be confirmed in larger studies with different cohorts and a prospective design, may increase the prognostic value of EPS and improve risk stratification of BrS patients deserving more aggressive therapeutic options.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: None declared.

Data availability

Data are available from the corresponding author upon reasonable request.

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