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# Number of electrocardiogram leads in the diagnosis of spontaneous Brugada syndrome

**Abbreviated title:** Number of electrocardiogram leads in Brugada syndrome diagnosis

**Marine Arnaud[a], Pauline Berthome[b], Romain Tixier[c], Jean Briand[d], Olivier Geoffroy[e], Xavier Le Guillou[a], Dominique Babuty[f], Jacques Mansourati[g], Laurence Jesel[h], Jean-Marc Dupuis[i], Paul Bru[j], Florence Kyndt[a], Béatrice Guyomarch[a], Aurélie Thollet[a], Nathalie Behar[d], Philippe Mabo[d], Frédéric Sacher[c], Vincent Probst[a], Jean-Baptiste Gourraud[a,*]**

[a] *L'Institut du Thorax, INSERM, CNRS, Université de Nantes, CHU de Nantes, 44093 Nantes, France*

[b] *L'Institut du Thorax, CHU de Nantes, 44093 Nantes, France*

[c] *Service de Cardiologie, Liryc, CHU de Bordeaux, 33600 Pessac, France*

[d] *Service de Cardiologie, CHU de Rennes, 35000 Rennes, France*

[e] *Service de Cardiologie, CHU de La Réunion, 97400 Saint-Denis de La Réunion, France*

[f] *Service de Cardiologie, CHU de Tours, 37000 Tours, France*

[g] *Service de Cardiologie, CHU de Brest, 29609 Brest, France*

[h] *Service de Cardiologie, CHRU de Strasbourg, 67091 Strasbourg, France*

[i] *Service de Cardiologie, CHU d'Angers, 49100 Angers, France*

[j] *Service de Cardiologie, GH La Rochelle, 17019 La Rochelle, France*

* Corresponding author at: L'Institut du Thorax, CHU de Nantes (HGRL), boulevard Jacques Monod, 44093 Nantes CEDEX 1, Nantes, France.

*E-mail address:* jeanbaptiste.gourraud@chu-nantes.fr (J.-B. Gourraud).



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**Summary**

*Background.* – The recently recommended single lead-based criterion for the diagnosis of Brugada syndrome may lead to overdiagnosis of this disorder and overestimation of the risk of sudden cardiac death.

*Aim.* – To investigate the value of a single-lead diagnosis in patients with Brugada syndrome and a spontaneous type 1 electrocardiogram.

*Methods.* – Consecutive patients with Brugada syndrome were included in a multicentre prospective registry; only those with a spontaneous type 1 electrocardiogram were enrolled. Clinical and electrocardiogram data were reviewed by two physicians blinded to the patients' clinical and genetic status.

*Results.* – Among 1613 patients, 505 (31%) were enrolled (79% male; mean age 46 ± 15 years). A spontaneous type 1 electrocardiogram pattern was found in one lead in 250 patients (group 1), in two leads in 227 patients (group 2) and in three leads in 27 patients (group 3). Groups were similar except for individuals in group 3, who presented more frequently a fragmented QRS complex, an early repolarization pattern and a prolonged $T_{peak}$–$T_{end}$ interval. After a mean follow up of 6.4 ± 4.7 years, ventricular arrhythmia, sudden cardiac death or implantable cardiac defibrillator shock occurred in 46 (9%) patients, without differences between groups.

*Conclusion.* – The prognosis of Brugada syndrome with a spontaneous type 1 electrocardiogram pattern does not appear to be affected by the number of leads required for the diagnosis.

**Résumé**

*Contexte.* – Les recommandations diagnostiques du syndrome de Brugada, basées sur une seule dérivation ECG, pourraient mener à diagnostiquer ce syndrome en excès et à surestimer son risque rythmique.

*Objectif.* – Notre objectif est d'évaluer la valeure pronostique d'un diagnostic à une seule dérivation chez les individus présentant un aspect ECG spontané de syndrome de Brugada.

*Méthodes.* – Tous les patients consécutifs atteints de syndrome de Brugada ont été inclus dans un registre prospectif multicentrique. Seuls les patients avec un aspect ECG spontané ont été inclus. Les données cliniques et ECG ont été revues deux fois indépendamment du statut clinique ou génétique.

*Résultats.* – Parmi 1613 patients, 505 (31 %) ont été inclus (79 % d'hommes ; age moyen 46 ± 15 ans). L'aspect ECG de Brugada était retrouvé dans un dérivation pour 250 patients (groupe 1), deux dérivations pour 227 patients (groupe 2) et trois dérivations pour 27 patients (groupe 3). Hormis une augmentation de QRS fragmenté, de repolarisation précoce et un allongement de l'intervalle pic-terminaison de l'onde T dans le groupe 3, les groupes étaient comparables. Au cours d'un suivi moyen de 6,4 ± 4,7 années, 46 (9 %) arythmies ventriculaires, morts subites ou chocs de défibrillateur sont survenus sans différence d'incidence entre les groupes.

*Conclusions.* – Le pronostic des patients atteints d'un syndrome de Brugada spontané n'est pas modifié par le nombre de dérivations ECG utilisées pour en faire le diagnostic.

**KEYWORDS**

Brugada syndrome;

Diagnosis;

Electrocardiogram;

Leads

**MOTS CLÉS**

Syndrome de Brugada ;

Diagnostic ;

Électrocardiogramme ;

Dérivations

*Abbreviations:* DNA, deoxyribonucleic acid; ICD, implantable cardiac defibrillator; SCD, sudden cardiac death; TPE, $T_{peak}$–$T_{end}$ interval; VA, ventricular arrhythmia; VF, ventricular fibrillation.

## Background

Brugada syndrome is a rare inherited disorder, predisposing to sudden cardiac death (SCD) by ventricular fibrillation (VF), despite a structurally normal heart [1]; it has been consistently reported as a Mendelian disease, with an autosomal dominant mode of inheritance and incomplete penetrance [2-4]. To date, 23 genes have been associated with the Brugada syndrome, and *SCN5A* gathers the majority of the mutations [3, 5]. However, the genotype/phenotype studies conducted in families with *SCN5A* mutations illustrate the complex mode of inheritance of Brugada syndrome [6]. This genetic complexity has recently been confirmed by the identification of common polymorphisms strongly associated with the Brugada syndrome [7].

As a consequence, diagnosis of Brugada syndrome is only based on a specific, but labile, aspect on the electrocardiogram, known as a type 1 electrocardiogram pattern, which consists of a coved ST-segment elevation in the right precordial leads > 0.2 mV, ending with a negative T wave [1]. This aspect can be revealed or enhanced by a sodium channel-blocking agent [8]. While previous guidelines required the presence of a type 1 electrocardiogram pattern in at least two right precordial leads, the last consensus conference additionally proposed to accept the diagnosis of Brugada syndrome in patients with only one lead showing the typical aspect [1]. This criterion was modified as a result of one small single tertiary centre study, and given the potential consequences of Brugada syndrome diagnosis, it seems important to validate this new diagnostic criterion in an independent cohort of patients [9].

The aim of the present study was to evaluate the validity of Brugada syndrome diagnostic criteria in a large cohort of patients with Brugada syndrome and a spontaneous type 1 electrocardiogram pattern.

## Methods

### Study population

Consecutive patients were recruited between 1993 and 2016 through the Nantes Reference Centre and its network (15 French tertiary centres). Patients were enrolled in the study in the presence of Brugada type 1 electrocardiogram pattern at baseline, as defined in the latest guidelines [1]. All clinical data previously defined as predictors of arrhythmia were considered, and the analysis was done retrospectively on the electrocardiogram collected previously.

Clinical follow-up was collected prospectively either from the referring cardiologists or directly from the patients. Only syncopes likely to be caused by arrhythmia were considered in the study, including nocturnal agonal respiration and unexplained nocturnal enuresis. The endpoint of the study was defined as the occurrence of ventricular arrhythmia (VA), implantable cardiac defibrillator (ICD) shock or SCD.

The study was conducted according to European guidelines for clinical and genetic research. Informed written consent was obtained from each patient who agreed to participate in the clinical and genetic study.

## Electrocardiogram analysis

All electrocardiograms were analysed by two physicians who were blinded to clinical presentation and genetic results. In case of disagreement, a third physician was consulted. Brugada syndrome was defined as a coved ST-segment elevation > 0.2 mV in a right precordial lead (V1, V2, V3) [1]. Only the third and fourth intercostal spaces were considered for this study.

Heart rate, P-wave duration, PR interval, QRS duration, $T_{peak}$–$T_{end}$ interval (TPE) and QT interval were measured using Image J software (National Institutes of Health, Bethesda, MD, USA; http://rsb.info.nih.gov/ij), as described previously [10].

The maximum value of TPE in the precordial lead, a fragmented QRS complex, early repolarization pattern, ST-segment elevation in peripheral leads and aVr sign were considered, as described previously [2, 10]. Diagnosis of sinus node dysfunction was based on the presence of documented symptomatic bradycardia (either sinus bradycardia, sinus arrest or junctional escape), diagnosed on electrocardiogram or Holter electrocardiogram, as described previously [10].

## Electrophysiological study

An electrophysiological study was performed according to the clinical recommendations of the referring cardiologists, with at least two extrastimuli, a minimum coupling interval of 200 ms and at least one right ventricular site. The electrophysiological study was considered positive in case of occurrence of VF or sustained ventricular tachycardia.

## Mutational analysis of *SCN5A*

Genomic DNA was extracted from peripheral blood leukocytes using standard protocols. All 28 exons of *SCN5A* were amplified by polymerase chain reaction with intronic primers. Polymerase chain reaction products were screened for an *SCN5A* mutation using denaturing high-performance liquid chromatography deoxyribonucleic acid (dHPLC-DNA) sequencing. We verified that these DNA variants were disease-causing mutations, rather than polymorphisms, by generally accepted criteria [11]; this included their presence in highly conserved regions of *SCN5A* and their absence from 200 control individuals.

### Statistical analysis

Continuous data are presented as mean ± standard deviation or median (interquartile range) based on the distribution. Categorical variables are presented as count (percentage). One-way analysis of variance (ANOVA) tests were performed to test for statistical differences in continuous variables between groups. The $\chi^2$ test 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 and 95% confidence intervals) was used to evaluate the risk of cardiac events. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

Among 1613 patients with Brugada syndrome, 505 (31%) presented at least one electrocardiogram with a spontaneous type 1 electrocardiogram pattern, including 398 (79%) men and 107 (21%) women. Mean age at diagnosis was 46 ± 15 years. At diagnosis, 117 (23%) patients were symptomatic, including 32 (6%) aborted SCDs. An ICD was implanted in 191 (38%) patients. Global characteristics of the population are described in Table 1. A spontaneous type 1 electrocardiogram pattern was observed in one lead in 250 (50%) patients, in two leads in 227 (45%) patients and in three leads in 28 (5%) patients, defining groups 1, 2 and 3 respectively (Fig. 1). No significant clinical differences were observed between these three groups (Table 1).

### Electrocardiogram variables

In the whole population, a fragmented QRS complex was observed in 12 (2%) patients. We additionally identified an early repolarization pattern in 41 (9%) patients, and a prolonged TPE (> 100 ms) in 304 (60%) patients. Among the three groups, these three variables presented with statistical differences. Group 3 presented more frequently a fragmented QRS complex (3 [11%] vs 6 [2%] and 3 [1%] in groups 1 and 2, respectively; $P = 0.03$), an early repolarization pattern (7 [21%] vs 19 [8%] and 15 [6%] in groups 1 and 2, respectively; $P = 0.02$) and a prolonged TPE interval (22 [79%] vs 136 [54%] and 146 [64%] in groups 1 and 2, respectively; $P = 0.01$).

No significant differences were observed in all other depolarization and repolarization variables. The electrocardiogram characteristics are summarized in Table 2.

## Electrophysiological study

An electrophysiological study was performed in 223 (44%) patients, without differences between the three groups: 102 (41%), 107 (47%) and 14 (50%) patients in groups 1, 2 and 3, respectively. Ventricular tachyarrhythmia was induced in 91 (18%) patients, without differences between the three groups: 40 (16%), 46 (20%) and 5 (18%) patients in groups 1, 2 and 3, respectively ($P = 0.84$).

## Genetic analysis

Genetic screening for *SCN5A* mutation was positive in 147 patients (29%), without differences between the three groups: 72 (29%), 67 (30%) and 8 (29%) patients in groups 1, 2 and 3, respectively ($P = 0.99$).

## Follow-up

Mean follow-up was 6.4 ± 4.7 years, without differences between the three groups: 6.2 ± 4.7, 6.5 ± 4.7 and 7.2 ± 4.9 years in groups 1, 2 and 3 respectively ($P = 0.47$). During follow-up, an event occurred in 46 (9%) patients: SCD or VA in 20 (4%) patients; and ICD shock in 26 (5%) patients. None of the VAs was identified with Holter monitoring. Event occurrence was similar in the three groups: 22 (9%) in group 1; 22 (10%) in group 2; and 2 (7%) in group 3 (Table 3). Kaplan-Meier cardiac event-free survival was similar in the three groups ($P = 0.87$; Fig. 2).

# Discussion

Our study demonstrates a similar prognosis in Brugada syndrome diagnosed with one, two or three leads. These results reinforce the diagnostic electrocardiogram criteria in current use [1].

In a study by Richter et al. [9], only 65 patients presented with a spontaneous electrocardiogram pattern. All other patients were diagnosed using sodium channel blocker challenge (either flecainide, ajmaline or procainamide). Compared with symptomatic patients with a spontaneous electrocardiogram pattern, asymptomatic patients with a drug-induced electrocardiogram pattern present with a very low risk of arrhythmia [2]. Indeed, in the study by Richter et al. [9], only 15 events occurred in the whole population during follow-up. Given the small number of arrhythmic events and the subgroup analysis, the authors could not draw definite conclusions about the prognosis of such patients.

## Role of a spontaneous electrocardiogram pattern

In Brugada syndrome, the identification of a spontaneous aspect of Brugada syndrome on electrocardiogram has been consistently associated with VA occurrence, ranging from 0.81%/year in asymptomatic patients to 2.3%/year in symptomatic patients [12-14]. Additionally, we have previously demonstrated that a spontaneous electrocardiogram pattern in an asymptomatic patient may lead to a cumulative risk of VF reaching 12% at 10 years [15]. Although some alternatives, such as catheter ablation, have emerged, the only proven efficient therapy to prevent this risk is ICD implantation [1, 16, 17]. Given the extreme consequences without ICD implantation and potential inconvenience after implantation, identification of patients with the highest risk of SCD is the main challenge in Brugada syndrome [12, 15, 18]. The definition of the Brugada electrocardiogram pattern is crucial to this risk stratification and the care of patient.

In previous studies, the Brugada syndrome electrocardiogram pattern was defined using at least two right precordial leads, in accordance with the previous guidelines [19]. We have demonstrated for the first time that the risk is similar using one or two leads, in a large cohort of patients (250 vs 227 patients, respectively, with 22 events in both groups). These results allow validation of the new guidelines for the diagnosis of Brugada syndrome.

## Impact of a three-lead electrocardiogram pattern

In group 3 (diagnosis using three right precordial leads) the clinical presentation appeared slightly

different, including an increase in some electrocardiogram variables associated with prognosis. In this group of patients we observed more frequently a prolonged TPE interval, an early repolarization pattern and a fragmented QRS complex [20-22]. Those variables, affecting both depolarization and repolarization, may describe a more advanced phenotype. However, the prognosis seems similar in the three groups of patients, even if the limited sample size ($n$ = 28) may limit conclusions being drawn about the prognosis of this group.

### Study limitations

Although our study has the largest population of patients with Brugada syndrome ever described, the subgroup analysis, particularly in group 3, may limit the statistical significance of our results. Moreover, as the use of the second intercostal space is quite recent in Brugada syndrome, it was not investigated in the present study, to avoid introducing putative bias into the analysis. The diagnosis was therefore performed in either the third or fourth intercostal space. Lastly, the type 1 electrocardiogram pattern is highly variable over time. This dynamic aspect is not taken into account during the recording of a single 12-lead electrocardiogram. Although the electrocardiogram has been selected as the more consistent with Brugada syndrome, some patients may be misclassified. In particular, a longer follow-up period may increase the likelihood of recording a spontaneous pattern in more than one electrocardiogram lead.

## Conclusions

The prognosis of Brugada syndrome with a spontaneous type 1 electrocardiogram pattern does not appear to be affected by the number of diagnostic leads. However, patients with a type 1 electrocardiogram pattern in three leads have an increased prevalence of electrocardiogram depolarization or repolarization abnormalities. In view of our results, the new definition of Brugada syndrome appears to be acceptable, as the prognosis of patients with only one diagnostic lead is similar to that of those with two or three leads. Finally, we failed to correlate the number of diagnostic leads with the severity of the disease, and this variable could not be used to evaluate the arrhythmic risk of the patients.

## Acknowledgements

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## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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**Figure legends**

**Figure 1.** Brugada electrocardiogram pattern, according to the number of positive leads at diagnosis. The electrocardiogram was recorded at 25 mm/s and 10 mV/mm. Only a coved ST-segment elevation > 2 mV was considered as a type 1 electrocardiogram (lead V2 in group 1; leads V1 and V2 in group 2; all three leads in group 3).

**Figure 2.** Cardiac event-free survival, according to the number of positive leads at diagnosis. The red curve represents group 1, the green curve represents group 2 and the blue curve represents group 3. RPL: right precordial lead.

**Table 1** Clinical characteristics of patients with Brugada syndrome, according to the number of positive leads at diagnosis.

| | Group 1 (*n* = 250) | Group 2 (*n* = 227) | Group 3 (*n* = 28) | Overall population (*n* = 505) | *P* |
|---|---|---|---|---|---|
| Male sex | 194 (78) | 183 (81) | 21 (75) | 398 (79) | 0.64 |
| Age (years) | 46 ± 15 | 46 ± 13 | 51 ± 18 | 46 ±1 5 | 0.26 |
| Index patient | 218 (87) | 208 (92) | 22 (79) | 448 (89) | 0.06 |
| Familial Brugada syndrome | 45 (18) | 37 (16) | 5 (18) | 87 (17) | 0.79 |
| Familial SCD | 63 (25) | 52 (23) | 7 (25) | 122 (24) | 0.86 |
| Coronary artery disease | 8 (3) | 7 (3) | 2 (7) | 17 (3) | 0.40 |
| Valvulopathy | 2 (1) | 0 (0) | 0 (0) | 2 (0) | 0.55 |
| EPS positive | 40 (16) | 46 (20) | 5 (18) | 91 (18) | 0.84 |
| EPS not performed | 148 (59) | 120 (53) | 14 (50) | 282 (56) | |
| *SCN5A* mutation | 72 (29) | 67 (30) | 8 (29) | 147 (29) | 0.99 |
| Symptoms | | | | | |
| Syncope | 41 (16) | 39 (17) | 5 (18) | 85 (17) | 0.82 |
| SCD | 19 (8) | 10 (4) | 3 (11) | 32 (6) | 0.87 |
| SVT | 7 (3) | 4 (2) | 3 (11) | 14 (3) | 0.05 |
| Management | | | | | |
| ICD | 87 (35) | 91 (40) | 13 (46) | 191 (38) | 0.3 |
| Beta-blocker | 16 (6) | 12 (5) | 4 (14) | 32 (6) | 0.18 |
| Hydroquinidine | 17 (7) | 8 (3) | 1 (3) | 26 (5) | 0.27 |
| Amiodarone | 3 (1) | 2 (1) | 1 (4) | 6 (1) | 0.45 |
| Follow-up (years) | 6.2 ± 4.7 | 6.5 ± 4.7 | 7.2 ± 4.9 | 6.4 ± 4.7 | 0.47 |

Data are expressed as number (%) or mean ± standard deviation. EPS: electrophysiological study; ICD: implantable cardiac defibrillator; SCD: sudden cardiac death; SVT: supraventricular tachycardia.

**Table 2** Electrocardiographic variables, according to the number of positive leads at diagnosis.

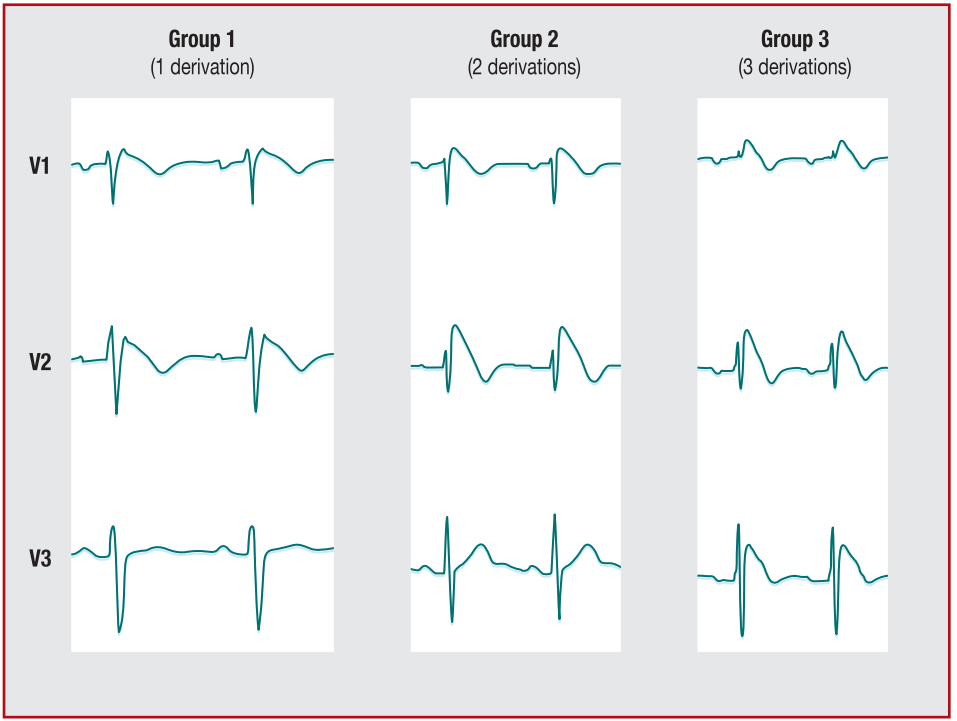
| Variable | Group 1 ($n$ = 250) | Group 2 ($n$ = 227) | Group 3 ($n$ = 28) | Overall population ($n$ = 505) | $P$ |
|---|---|---|---|---|---|
| Peripheral type 1 | 24 (10) | 23 (10) | 4 (14) | 51 (10) | 0.67 |
| Type 1 atrioventricular block | 68 (27) | 55 (24) | 8 (29) | 131 (26) | 0.69 |
| QRS > 120 ms in D2 | 49 (20) | 49 (22) | 10 (36) | 108 (21) | 0.15 |
| TPE > 100 ms | 136 (54) | 146 (64) | 22 (79) | 304 (60) | 0.01 |
| QTc > 460 ms | 14 (6) | 17 (7) | 5 (18) | 36 (7) | 0.06 |
| Early repolarization pattern | 19 (8) | 15 (7) | 7 (21) | 41 (8) | 0.02 |
| Fragmented QRS complex | 6 (2) | 3 (1) | 3 (11) | 12 (2) | 0.03 |
| aVr sign | 51 (20) | 50 (22) | 4 (14) | 105 (21) | 0.68 |
| Sinus node dysfunction | 6 (2) | 2 (1) | 0 (0) | 8 (2) | 0.47 |

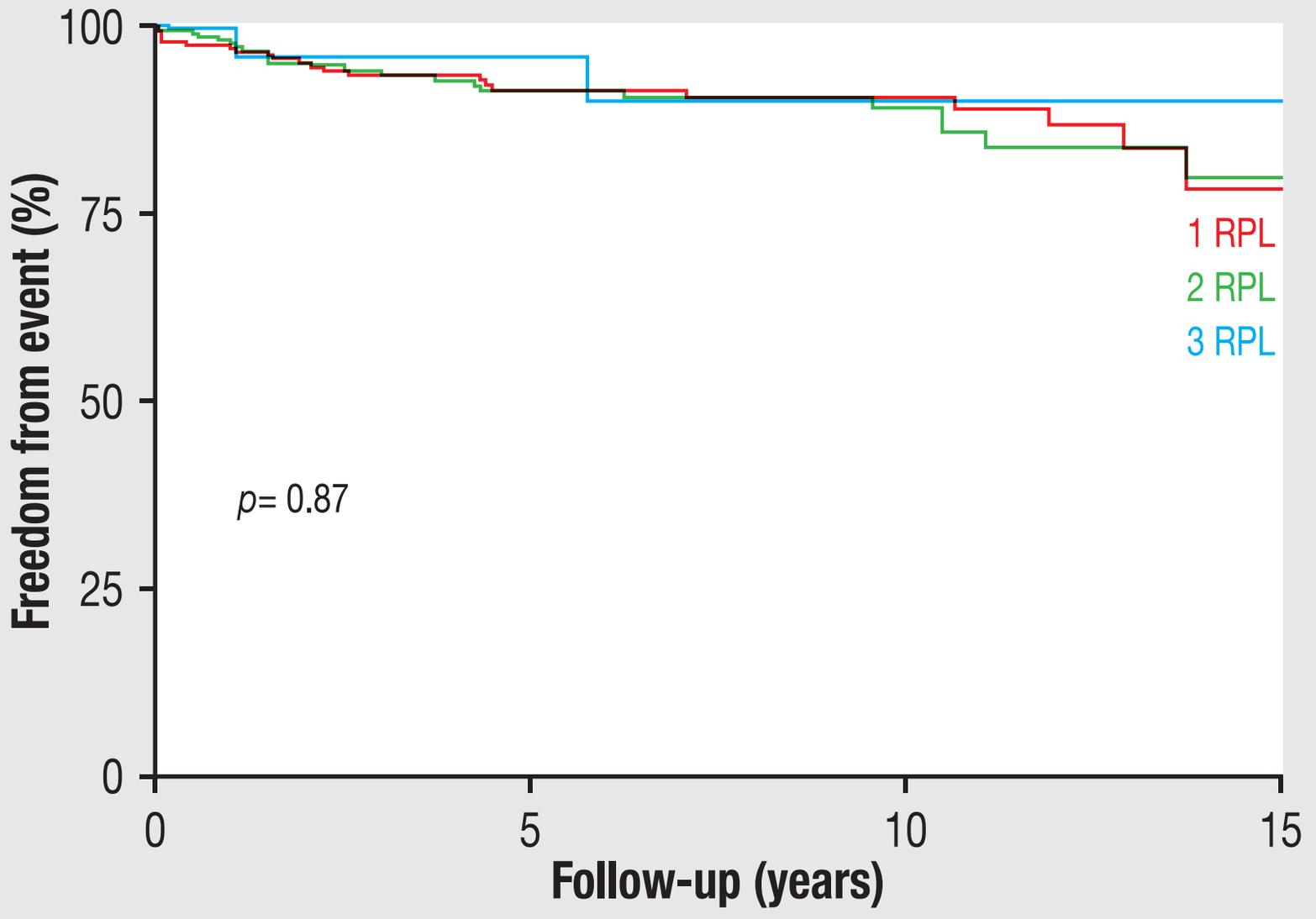
Data are expressed as number (%). QTc: corrected QT interval; TPE: $T_{peak}$–$T_{end}$ interval.

**Table 3** Follow-up of patients with Brugada syndrome, according to the number of positive leads at diagnosis.

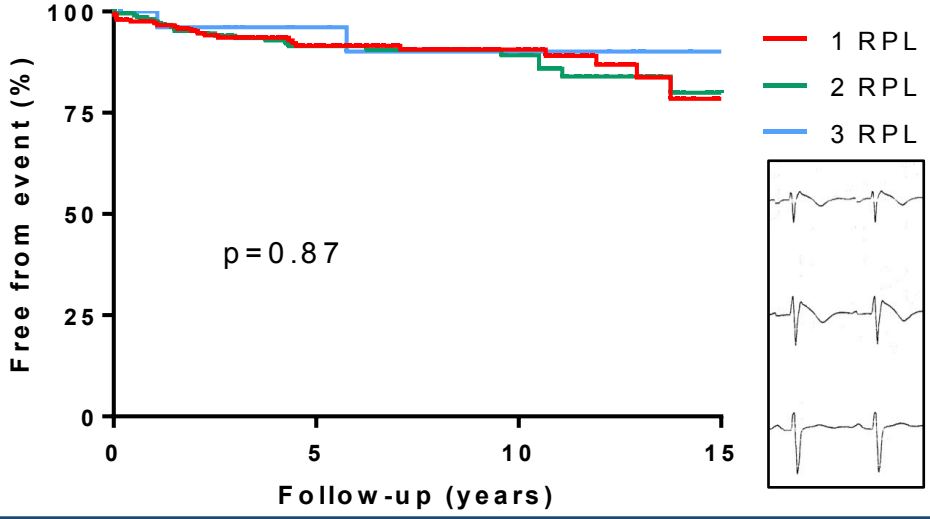
| Variable | Group 1 ($n$ = 250) | Group 2 ($n$ = 227) | Group 3 ($n$ = 28) | Overall population ($n$ = 505) | $P$ |
|---|---|---|---|---|---|
| Event | 22 (9) | 22 (10) | 2 (7) | 46 (9) | 0.87 |
| SCD or VA | 8 (4) | 11 (5) | 1 (4) | 20 (4) | |
| ICD shock | 14 (6) | 11 (5) | 1 (4) | 26 (5) | |

Data are expressed as number (%). EPS: electrophysiological study; ICD: implantable cardiac defibrillator; SCD: sudden cardiac death; VA: ventricular arrhythmia.


Group 1
(1 derivation)
Group 2
(2 derivations)
Group 3
(3 derivations)
V1
V2
V3




| N at risk | 0 | 5 | 10 | 15 |
|---|---|---|---|---|
| 1 RPL | 250 | 127 | 64 | 9 |
| 2 RPL | 227 | 121 | 61 | 10 |
| 3 RPL | 28 | 17 | 7 | 2 |


100
75
50
25
0
Free from event (%)
p=0.87
0
5
10
15
Follow-up (years)
1 RPL
2 RPL
3 RPL