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A New Electrocardiographic Marker of Sudden Death in Brugada Syndrome

The S-Wave in Lead I

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ABSTRACT

BACKGROUND Risk stratification in asymptomatic patients remains by far the most important yet unresolved clinical problem in the Brugada syndrome (BrS).

OBJECTIVES This study sought to analyze the usefulness of electrocardiographic parameters as markers of sudden cardiac death (SCD) in BrS.

METHODS This study analyzed data from 347 consecutive patients (78.4% male; mean age 45 ± 13.1 years) with spontaneous type 1 BrS by ECG parameters but with no history of cardiac arrest (including 91.1% asymptomatic at presentation, 5.2% with a history of atrial fibrillation [AF], and 4% with a history of arrhythmic syncope). Electrocardiographic characteristics at the first clinic visit were analyzed to predict ventricular fibrillation (VF)/SCD during follow-up.

RESULTS During the follow-up (48 ± 38 months), 276 (79.5%) patients remained asymptomatic, 39 (11.2%) developed syncope, and 32 (9.2%) developed VF/SCD. Patients who developed VF/SCD had a lower prevalence of *SCN5A* gene mutations ($p = 0.009$) and a higher prevalence of positive electrophysiological study results ($p < 0.0001$), a family history of SCD ($p = 0.03$), and AF ($p < 0.0001$). The most powerful marker for VF/SCD was a significant S-wave (≥0.1 mV and/or ≥40 ms) in lead I. In the multivariate analysis, the duration of S-wave in lead I ≥40 ms (hazard ratio: 39.1) and AF (hazard ratio: 3.7) were independent predictors of VF/SCD during follow-up. Electroanatomic mapping in 12 patients showed an endocardial activation time significantly longer in patients with an S-wave in lead I, mostly because of a significant delay in the anterolateral right ventricular outflow tract.

CONCLUSIONS The presence of a wide and/or large S-wave in lead I was a powerful predictor of life-threatening ventricular arrhythmias in patients with BrS and no history of cardiac arrest at presentation. However, the prognostic value of a significant S-wave in lead I should be confirmed by larger studies and by an independent confirmation cohort of healthy subjects. (J Am Coll Cardiol 2016;67:1427–40) © 2016 by the American College of Cardiology Foundation.

Brugada syndrome (BrS) is characterized by ST-segment elevation in the right precordial leads and an increased risk of ventricular fibrillation (VF) and sudden cardiac death (SCD) (1,2). The real incidence of SCD in these patients is uncertain, and controversy exists with regard to risk stratification in asymptomatic subjects (3–12).

Certain electrocardiographic (ECG) markers of ventricular depolarization and repolarization have been reported to identify high-risk patients with BrS

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BrS = Brugada syndrome

ECG = electrocardiographic

EPS = electrophysiological study

ICD = implantable cardioverter-defibrillator

RBBB = right bundle branch block

RV = right ventricular

RVOT = right ventricular outflow tract

SCD = sudden cardiac death

VF = ventricular fibrillation

(5–12), although conclusions regarding the clinical impact of these markers have been inconsistent. Some studies (13–21) have suggested that the pathophysiological basis of this syndrome is a conduction delay in the right ventricular outflow tract (RVOT).

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The so-called third vector, which is directed upward and somewhat to the right and backward, generates the S-wave in lead I (22). This vector is determined by electrical activation of the basal region of both ventricles and by depolarization of the RVOT. A prominent S-wave in lead I is typically present in cases of congenital heart disease, valvular heart disease, and cor pulmonale that cause right ventricular (RV) enlargement and fibrosis (22). Thus, we hypothesized that a deep and/or large S-wave in lead I in BrS would reveal a conduction delay over the RVOT and could be used to identify high-risk patients.

The purposes of this study, conducted in a large population of patients with BrS, were to verify the usefulness of the previously proposed ECG markers of SCD and to analyze the potential role of the S-wave in lead I as a new prognostic ECG parameter to predict VF/SCD during follow-up.

METHODS

STUDY POPULATION. Of a study population of 655 subjects affected by BrS, we analyzed data from 347 consecutive patients (78.4% male; mean age 45 ± 13.1 years) with spontaneous type 1 BrS ECG phenotype (coved ST-segment elevation >2 mm in at least 1 right precordial lead). These subjects were prospectively enrolled in 4 Italian tertiary cardiology centers since 1999 (Policlinic Casilino, Rome; Città della Salute e della Scienza Hospital, Torino; Policlinic Sandro Pertini, Rome; Cardiology Clinic, Ospedali Riuniti Umberto I-Lancisi-Salesi, Ancona).

The study was approved by the local Institutional Review Boards of each participating institution, and each subject gave consent to participate in the study.

After enrollment, all subjects were prospectively followed with periodic cardiological visits including a resting 12-lead ECG study, performed at least every year or in case of symptoms. We did not include patients with BsS who had a history of VF or aborted SCD at presentation in this study. The family medical history was obtained at the first clinical visit and was considered positive if at least 1 first-degree family member had died suddenly with a type 1 Brugada ECG pattern or before the age of 45 years in the absence of known heart disease. All patients underwent transthoracic echocardiography and Holter ECG monitoring. Genetic testing and cardiac magnetic resonance were carried out at the discretion of the physicians, in line with each center's clinical practice.

ELECTROCARDIOGRAPHIC ANALYSIS. ECG studies were recorded at a paper speed of 25 mm/s and at a standard gain of 1 mV/cm. Two independent cardiologists (C.L. and M.A.) examined and interpreted all ECG tracings by using a magnifying glass, and discrepancies were resolved by consensus. The ECG tracing recorded at the patient's inclusion in the study was used for the analysis, and these tracings were analyzed with no patients receiving antiarrhythmic drugs.

The heart rate and QRS axis were manually calculated. The QRS interval duration and the PR, JT, and QT intervals were measured in the II and V_6 leads with calipers by physicians who were blinded to historical data. A PR interval >200 ms and a QRS interval duration >120 ms were considered abnormal (23). Right bundle branch block (RBBB), left bundle branch block, left anterior fascicular block, and left posterior fascicular block were defined in accordance with current guidelines (23). The presence of a fragmented QRS interval, characterized by fragmentation within the QRS complex, with ≥4 spikes in a single lead or ≥8 spikes in leads V_1, V_2, and V_3 (5), as well as evidence of an epsilon wave in the V_1 lead, were investigated. Considering that fibrosis in patients with nonischemic cardiomyopathy typically involves the epicardial RVOT, in addition to the basal left ventricle, the Tzou criteria (24), including V_1R >0.15 mV, V_6S >0.15 mV, and V_6S:R >0.2 mV, were also analyzed.

The presence of an S-wave in leads I, II, and III was examined. The amplitude (mV) from the isoelectric line to the nadir of the S-wave and the duration (ms) from the beginning to the end of the S-wave in leads I, II, and III were measured with calipers. The area (mm^2) of the S-wave was calculated as the product of the amplitude and duration.

The QTc interval in lead II was calculated by Bazett's method. The corrected JT interval was obtained by subtracting the QRS interval duration from the QTc interval in leads II and V_6 (12). The T_{peak}-T_{end} interval in leads V_2 and V_6 was defined as the interval from the peak of a positive T-wave or the nadir of a negative T-wave to the end of the T-wave (12). An early repolarization pattern was defined as an elevation of the J-point of at least 1 mm above the baseline level in ≥2 consecutive leads, either as QRS interval slurring or notching in the inferior (II, III, aVF) or lateral (I, aVL, and V_4 to V_6) leads (11).

ELECTROPHYSIOLOGICAL STUDY AND ELECTROANATOMIC MAPPING. Electrophysiological studies (EPSs) were performed in accordance with current guidelines (25), using a protocol that included ventricular premature stimulation at the apex and at the outflow tract at 2 pacing cycle lengths (600 and 400 ms), with up to 2 or 3 extrastimuli. Results of EPS were defined as positive when VF leading to collapse and requiring shock was induced. Twelve patients undergoing EPS were randomly selected for detailed electroanatomic mapping of the right ventricle. This testing was performed during normal sinus rhythm, with a 4-mm Navistar tip, a 3.5-mm NaviStar-ThermoCool tip, a 3.5-mm NaviStar-ThermoCool SorroundFlow tip, or a 3.5-mm-tip NaviStar-ThermoCool SmartTouch catheter (Biosense Webster, Inc., Diamond Bar, California), using the CARTO 3 EP Navigation System (Biosense Webster, Inc.), which enables simultaneous creation of maps using different parameters, such as local activation time, bipolar signal voltage, and unipolar signal voltage maps.

In the bipolar maps, tissue was defined as normal when the voltage amplitude was ≥1.5 mV, scar tissue was defined by voltage amplitude <0.5 mV, and the low-voltage electroanatomic border zone was defined by voltage amplitude >0.5 and <1.5 mV (26). In the unipolar maps, electroanatomically normal tissue was defined by voltage amplitude ≥5.5 mV, scar tissue by voltage <3.5 mV, and the low-voltage electroanatomic border zone by voltage >3.5 and <5.5 mV (27). Abnormal electrograms were defined as electrograms that have the following: 1) low voltage (≤1 mV); 2) split electrograms or fractionated electrograms with multiple potentials and ≥2 distinct components, with >20 ms isoelectric segments between peaks of individual components; and 3) wide duration (>80 ms) or late potentials, with distinct potentials extending beyond the end of the QRS complex. The RVOT for electroanatomic mapping is defined superiorly by the pulmonic valve and inferiorly by the RV inflow tract and the top of the tricuspid valve (28).

Automatic implantable cardioverter-defibrillators (ICDs) were implanted in accordance with current guidelines (25). In patients with ICDs, analysis of arrhythmias and appropriate shocks was also performed.

CLASSIFICATION OF CLINICAL EVENTS. Patients with BrS were divided into 3 groups according to clinical events during follow-up: asymptomatic, syncope, and VF/SCD. The group of patients who remained asymptomatic included subjects who developed syncope presumed to be of neurally mediated origin, without documentation of ventricular arrhythmias by resting ECG study and/or Holter monitoring. The group with VF/SCD included subjects who experienced SCD, aborted SCD, spontaneous VF, or sustained polymorphic ventricular tachycardia or with VF/fast ventricular tachycardia (>200 beats/min) episodes recorded by the implanted ICD. In the group with syncope, we considered episodes of loss of consciousness to be caused by ventricular tachyarrhythmias only after exclusion of other causes, such as neurally mediated syncope (6).

STATISTICAL ANALYSIS. Categorical variables were summarized as frequencies and percentages and were analyzed by the chi-square test. Continuous variables were summarized as mean ± SD. Differences between groups were evaluated by Student *t* test or Wilcoxon rank sum test, as appropriate, for continuous variables. The analysis of variance (ANOVA) test was adopted for comparisons among more than 2 groups. Receiver-operating characteristic (ROC) curves were drawn to identify optimal discriminative cutoff values for variables that differed among the groups in the prediction of VF/SCD during follow-up. The curve point with the highest sum of specificity and sensitivity was labeled as the optimized cutoff point and was used in odds ratio (OR), sensitivity, and specificity analyses. Univariate analysis was performed to individuate predictors associated with VF/SCD. Multivariate analysis using Cox proportional hazard regression analysis was also performed to individuate independent risk factors for VF/SCD.

Selection of variables for inclusion in the multivariate model was made on the basis of a stepwise (backward; p removal = 0.1) approach. The colinearity test was performed in case of predictors that could be interrelated to one another. If a strong correlation was found between variables, only 1 of them was chosen, on the basis of the best Akaike information criterion for inclusion of any single variable in the model.

The effect of independent risk factors on major adverse events during follow-up was evaluated using the log-rank test and described using a Kaplan-Meier curve. Interobserver variability was assessed using the kappa statistic and proportion agreement. Fleiss's agreement scale was used to interpret kappas, with values >0.75 considered excellent, 0.40 to 0.75 considered fair to good, and <0.40 considered poor. A 2-tailed p value <0.05 was considered statistically significant. Statistical analyses were performed using R software (R-3.1.2 for Windows [R Foundation for Statistical Computing, Vienna, Austria]) and were confirmed by an independent statistician who used different software (StataCorp LP for Windows, College Station, Texas).

RESULTS

STUDY POPULATION. Demographic and clinical characteristics of the study population are summarized in Table 1. Genetic testing was carried out in 107 (30.8%) subjects and showed *SCN5A* mutations in 32 (29.9%) patients. Cardiac magnetic resonance was performed in 22 (6.3%) patients and showed structurally normal hearts, except for 1 case of mild left ventricular hypertrophy, 1 case of mild hypokinesis of the RV apex, and 1 case of scar in the apical segment of the interventricular septum. ICD implantation was performed in 98 patients. Eighteen patients (5.2%) had a history of persistent or paroxysmal atrial fibrillation (AF). At presentation, 14 patients had a history of syncope, and 18 had a history of symptomatic AF. One patient was symptomatic for both syncope and AF.

During the follow-up period of 48 ± 38.6 months, 276 (79.5%) patients remained asymptomatic, 39 (11.2%) developed syncope, and 32 (9.2%) had VF/SCD. Twenty-two patients presenting with neurally mediated syncope were classified as asymptomatic.

Among subjects who developed VF/SCD during follow-up, 3 died suddenly, 14 had aborted SCD, and 15 had appropriate ICD shocks in response to VF episodes. Two of these 32 patients had syncope at presentation.

Table 2 summarizes the clinical characteristics of the subgroups. In particular, the patients who developed VF/SCD during follow-up more frequently had a positive EPS result ($p < 0.0001$), a family history of SCD ($p = 0.03$), and AF episodes ($p < 0.0001$) than did patients who developed syncope or remained asymptomatic (Table 2).

ELECTROCARDIOGRAPHIC FINDINGS. Interobserver variability for ECG parameters indicated good agreement. Online Table 1 shows the interobserver variability for each ECG parameter in detail.

TABLE 1 Clinical Characteristics of the Study Population

Male/female	272/75
Age, yrs	45 ± 13.1
Family history of SCD	71 (20.5)
SCN5A gene mutation (analyzed: n = 107)	32 (29.9)
Asymptomatic	316 (91.1)
History of syncope	14 (4.0)
History of AF	18 (5.2)
Positive EPS (performed: n = 186)	77 (41.4)
ICD recipients	98 (28.2)

Values are n, mean ± SD, or n (%). Note that 1 patient was symptomatic both for syncope and AF.

AF = atrial fibrillation; EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death.

ECG findings of the study population are presented in Table 3. The mean amplitude of the R-wave in lead V_1 and the S-wave in lead V_6 did not significantly differ among patients who developed VF/SCD or syncope and those who remained asymptomatic during follow-up (Table 3). The prevalence of V_1R >0.15 mV, V_6S >0.15 mV, and V_6S/R >0.2 mV was similar in the 3 groups (Table 3). The mean amplitude and duration of the S waves in lead II and III were similar among patients in the different groups (Table 3).

Overall, the S-wave in lead I was present in 205 patients (59.1%), including all but 1 of those patients who had VF/SCD (96.9%). The mean amplitude of the S-wave in lead I was higher among patients who developed VF/SCD (0.21 ± 0.08 mV) than in patients who developed syncope (0.082 ± 0.07 mV; $p < 0.0001$) and remained asymptomatic (0.077 ± 0.06 mV; $p < 0.0001$) (Figure 1A). Similarly, the mean duration of the S-wave in lead I was longer in the VF/SCD group (52.8 ± 20.1 ms) than in the syncope (20.8 ± 20.3 ms; $p < 0.001$) and asymptomatic groups (20.2 ± 20.1 ms; $p < 0.001$) (Figure 1B). Moreover, the mean amplitude duration area of the S-wave was higher in patients with VF/SCD (2.9 ± 1.7 mm^2) than in those with syncope (0.92 ± 0.91 mm^2) and in those who remained asymptomatic (0.77 ± 0.76 mm^2; $p < 0.001$) (Figure 1C). There was no statistically significant correlation between the degree of ST-segment elevation and the S-wave characteristics in lead I.

ROC curves for the amplitude, duration, and amplitude duration area of the S-wave in lead I were calculated to have an optimized cutoff point in the prediction of VF/SCD during follow-up. The optimized cutoff point was 0.075 mV for the amplitude of the S-wave in lead I, 25 ms for S-wave duration, and 0.69 mm^2 for the product of depth and duration (Figure 2A to 2C). For use in clinical practice, these cutoff values were approximated to ≥0.1 mV (amplitude), ≥40 ms (duration), and ≥1 mm^2 (amplitude duration area), respectively, and they were distinctly used to identify a "significant" S-wave in lead I.

The S-wave amplitude ≥0.1 mV, duration ≥40 ms, and area ≥1 mm^2 in lead I had a sensitivity of 90.6%, 96.9%, and 96.9%, respectively; a specificity of 62.2%, 61.1%, 69.5%, respectively; a negative predictive value of 98.5%, 99.5%, and 98.7%, respectively; a positive predictive value of 19.6%, 20.5%, and 23.2% respectively; and a diagnostic accuracy of 64.8%, 65.1%, and 71.5%, respectively, for VF/SCD during follow-up. An S-wave in lead I with amplitude ≥0.1 mV, duration ≥40 ms, and area ≥1 mm^2, was present in 135 (42.7%), 120 (37.9%), and 115 (36.4%) of

the 316 patients who were completely free of symptoms at presentation. Sensibility, specificity, positive and negative predictive values, and diagnostic accuracy were similar to those observed in the total study population.

Figures 3 and 4 present some ECG tracings of patients with BrS with and without a significant S-wave in lead I.

CLINICAL AND ELECTROCARDIOGRAPHIC CHARACTERISTICS ASSOCIATED WITH AN S-WAVE IN LEAD I. Clinical, genetic, and ECG data of patients with and without a significant S-wave in lead I were analyzed (**Table 4**). Patients with a significant S-wave in lead I were relatively younger and more likely to develop VF/SCD during follow-up. ECG parameters did not differ between groups, apart from a longer QRS interval duration in leads V_2 and II and a higher incidence of complete RBBB and first atrioventricular block in patients with a significant S-wave in lead I.

ELECTROPHYSIOLOGICAL STUDIES AND ELECTROANATOMIC MAPPING. EPSs were performed in 186 patients (53.6%) and resulted in VF induction in 77 (41.4%). RV electroanatomic mapping (210 ± 73 points) was performed in 8 patients with S waves in lead I and in 4 patients without S waves. In all patients, activation started in the lower septum and subsequently diverged toward the tricuspid annulus and RVOT. The mean endocardial activation time was significantly longer in patients with BrS who had S waves in lead I compared with patients without S waves (102.0 ± 41.2 ms vs. 51.5 ± 31.4 ms; $p < 0.05$). Within the group with S waves in lead I, significant delays were evident in the anterolateral RVOT, representing a line of conduction delay of 41.2 ± 24.3 ms versus 8.4 ± 3.7 ms over this region (**Figure 5**). Fragmented electrograms exhibiting relatively low voltage, prolonged duration, and late polyphasic potentials were present in significantly more of the patients with S waves in lead I (7 patients vs. 1 patient). These abnormal electrograms and the areas of low voltage were localized exclusively over the anterior aspect of the RVOT.

The mean voltage in the RVOT was lower in the patients with S waves (1.6 ± 0.8 mV vs. 3.7 ± 1.4 mV; $p < 0.05$), particularly in the anterolateral region (0.9 ± 0.4 mV vs. 3.5 ± 1.2 mV; $p < 0.05$). In patients with S waves in lead I, the mean areas of abnormal bipolar and unipolar voltage were 4.8 ± 3.6 cm^2 and 11.3 ± 6.8 cm^2, respectively, whereas in patients without S waves, the mean areas of abnormal bipolar and unipolar voltage were 0.6 ± 1.2 cm^2 and 3.7 ± 6.7 cm^2, respectively. Details of the electroanatomic maps are available in Online Table 2. **Figure 5** shows

TABLE 2 Clinical Characteristics in Subgroups, According to Symptoms

	Asymptomatic (n = 276)	Syncope (n = 39)	VF/SCD (n = 32)	p Value
Male	217 (78.6)	27 (69.2)	28 (87.5)	NS
Age, yrs	45.1 ± 13.8	44.7 ± 15.3	40.6 ± 14.2	NS
Family history of SCD	50 (18.1)	14 (35.9)	7 (21.8)	0.03
SCN5A gene mutation	22/78 (28.2)	8/17 (47)	2/12 (16.6)*†	0.009
Positive EPS	47/139 (33.8)	19/30 (63.3)	11/17 (64.7)‡	<0.001
VF/fast polymorphic VT	40/7	16/3	9/2	
ICD recipients	46 (16.7)	25 (64.1)	27 (84.4)§	<0.001
ICD recipients with appropriate shock (VF)	0 (0)	0 (0)	15 (46.8)‡§	<0.001
AF	8 (2.9)	3 (7.7)	7 (21.9)‡	<0.001
Quinidine administration	2 (0.7)	1 (2.6)	12 (37.5)‡§	<0.001

Values are n (%), mean ± SD, or n/N (%) tested. The p values refer to the distribution of electrocardiographic parameters among the 3 groups (analysis of variance for quantitative variables; chi-square test for qualitative variables). *p < 0.05 for VF/SCD versus syncope; †p <0.05 for VF/SCD versus asymptomatic; ‡p <0.001 for VF/SCD versus asymptomatic; §p < 0.001 for VF/SCD versus syncope.

NS = not significant; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

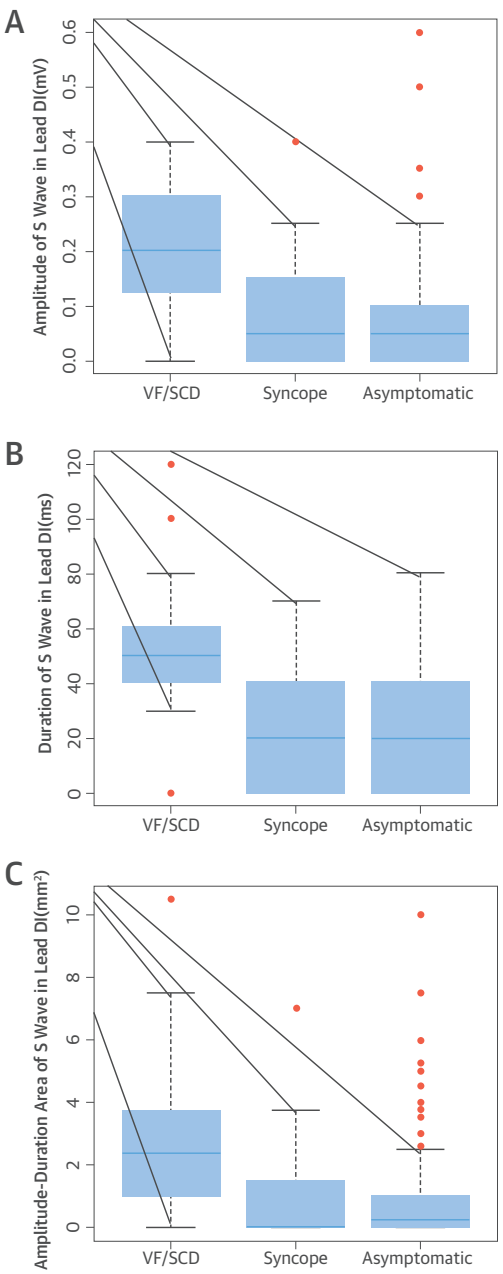
TABLE 3 Electrocardiographic Parameters

	Asymptomatic (n = 276)	Syncope (n = 39)	VF/SCD (n = 32)	p Value
First-degree AV block	38 (13.8)	7 (17.9)	6 (18.8)	NS
QRS duration in lead II, ms	94.5 ± 20.3	99.1 ± 19.6	97.8 ± 19.6	NS
QRS duration in lead V_2, ms	109 ± 20.3	115.1 ± 19.6	115.6 ± 19.6*	NS
Complete RBBB	23 (8.3)	6 (15.4)	4 (12.5)	NS
Incomplete RBBB	26 (9.4)	5 (12.8)	6 (18.7)	NS
LAFB	47 (17)	5 (12.8)	1 (3.1)	NS
fQRS	69 (25)	5 (12.8)	11 (34.4)	NS
Epsilon wave in lead V_1	6 (2.2)	1 (2.6)	1 (3.1)	NS
V_1R >0.15 mV	139 (50.4)	16 (41.0)	23 (71.8)	NS
V_6S >0.15 mV	155 (56.2)	29 (74.3)	23 (71.8)	NS
V_6S/R >0.2 mV	117 (42.4)	21 (53.8)	18 (56.2)	NS
V_1R amplitude, mV	0.17 ± 0.15	0.15 ± 0.14	0.26 ± 0.20	NS
V_6S amplitude, mV	0.23 ± 0.21	0.25 ± 0.21	0.31 ± 0.29	NS
S-wave in lead I				
S presence	154 (55.8)	20 (51.4)	31 (96.9)†‡	<0.0001
S amplitude ≥0.1 mV	103 (37.3)	16 (41)	29 (90.6)†‡	<0.0001
S duration >40 ms	89 (32.2)	14 (35.9)	29 (90.6)†‡	<0.0001
S amplitude duration area ≥1 mm^2	83 (30.1)	13 (33.3)	29 (90.6)†‡	<0.0001
DII S amplitude, mV	0.28 ± 0.27	0.37 ± 0.36	0.31 ± 0.29	NS
DII S duration, ms	41.2 ± 33.2	37.3 ± 22.5	48.5 ± 45.2	NS
DIII S amplitude, mV	0.28 ± 0.26	0.36 ± 0.33	0.31 ± 0.24	NS
DIII S duration, ms	41.4 ± 24.2	41.3 ± 24.4	37.1 ± 35.2	NS
Early repolarization pattern	22 (7.9)	6 (15.4)	2 (6.2)	NS
QTc in lead DII, ms	395.1 ± 33.4	402 ± 32.5	397.7 ± 32.9	NS
T_p-T_e in lead V_2, ms	72.2 ± 21.8	75 ± 14.2	90 ± 25.4‡§	0.044
T_p-T_e in lead V_6, ms	82.6 ± 15.1	78.6 ± 11.1	88.4 ± 13.5‡§	NS

Values are n (%) or mean ± SD. The p value refers to distribution of electrocardiographic parameters among the 3 groups (analysis of variance for quantitative variables; chi-square test for qualitative variables). *p < 0.05 for FV/SCD versus asymptomatic; †p < 0.001 for VF/SCD versus syncope; ‡p < 0.001 for VF/SCD versus asymptomatic; §p < 0.05 for VF/SCD versus syncope.

AV = atrioventricular; fQRS = fragmented QRS; LAFB = left anterior fascicular block; RBBB = right bundle branch block; T_p-T_e = T_{peak}-T_{end}; other abbreviations as in Tables 1 and 2.

FIGURE 1 Box Plot of Results Obtained for S Waves in Lead I in Patients Who Presented With VF/SCD, Developed Syncope, and Remained Asymptomatic During Follow-Up



(A) Amplitude of the S-wave in lead I. **(B)** Duration of the S-wave in lead I. **(C)** Product of amplitude and duration of the S-wave in lead I. The box width is proportional to the square root of the number of observations in the group. The **bottom** and **top of the box** represent the first and the third quartiles; the **band inside the box** represents the median value; the **ends of the whiskers** represent, respectively, the lowest datum within 1.5 interquartile range of the lower quartile and the highest datum within 1.5 interquartile range of the upper quartile. Outliers are presented as **small circles**. SCD = sudden cardiac death; VF = ventricular fibrillation.

electroanatomic mapping in patients with and without S waves.

CLINICAL AND ELECTROCARDIOGRAPHIC CHARACTERISTICS ASSOCIATED WITH VENTRICULAR FIBRILLATION AND SUDDEN CARDIAC DEATH. Univariate and multivariate analyses for prediction of VF/SCD during follow-up are presented in Table 5. A strong correlation was found among the amplitude, duration, and amplitude duration area of the S-wave in lead I ($r = 0.73$ for correlation between the amplitude and duration of the S-wave in lead I; $p < 0.000001$; $r = 0.88$ for correlation between amplitude and amplitude duration area of the S-wave in lead I; $p < 0.000001$; $r = 0.77$ for correlation between duration and amplitude duration area of the S-wave in lead I; $p < 0.000001$). Considering the strong correlation found among these variables, only S-wave duration ≥40 ms was chosen, on the basis of the best Akaike information criteria, for inclusion of any single variable in the model. Multivariate analysis showed that the following 2 parameters were independent risk factors for VF/SCD: S-wave duration ≥40 ms and AF (Table 5).

The Central Illustration shows a Kaplan-Meier analysis of freedom from VF/SCD events during follow-up in patients with an S-wave in lead I versus those without an S-wave. The patients with an S-wave in lead I had a significantly worse prognosis than did the others ($p < 0.0001$). A similar trend was found for S waves in lead I with amplitude ≥0.1 mV ($p < 0.0001$), duration ≥40 ms ($p < 0.0001$), and area ≥1 mm^2 ($p < 0.0001$).

DISCUSSION

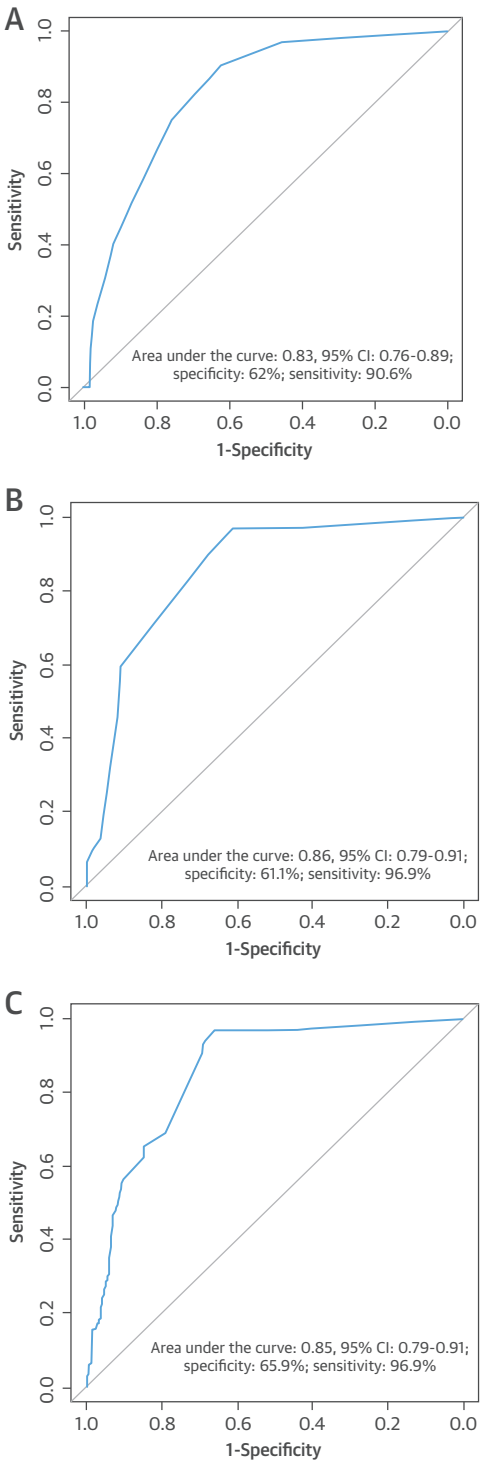
MAIN FINDINGS. We studied a large population of patients with BrS with long-term follow-up (48 ± 38.6 months), to analyze the usefulness of ECG parameters as markers of SCD. The following results were observed:

1. The most powerful marker for VF/SCD was a significant S-wave (≥ 0.1 mV and/or ≥40 ms) in lead I, which showed a sensitivity of 90.6% and 96.9%, a specificity of 62.2% and 61.1%, a negative predictive value of 98.5% and 99.5%, and a positive predictive value of 19.6% and 20.5%, respectively.
2. In the multivariate regression analysis, the duration of the S-wave in lead I ≥40 ms (hazard ratio: 39.1) and AF (hazard ratio: 3.7) were independent predictors of VF/SCD during follow-up.
3. Electroanatomic mapping in 12 patients showed that the endocardial activation time was

significantly longer in patients with BrS who had S waves in lead I compared with patients without S waves. This difference in activation time was mostly the result of a significant delay in the anterolateral RVOT.

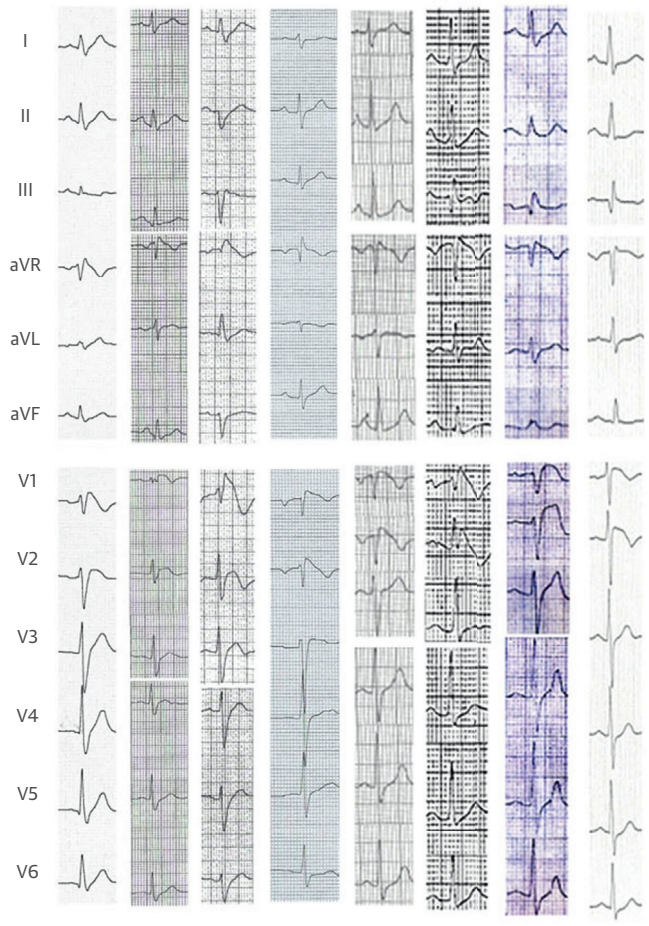
In our study, a deep and/or large S-wave in lead I strongly correlated with malignant ventricular arrhythmias during follow-up. The presence of a significant S-wave in lead I could be related to delayed activation in the RVOT. In fact, ventricular depolarization, described as a QRS complex on ECG tracings, occurs in 3 consecutive phases that give rise to the generation of 3 vectors. The third vector, generating the S-wave in lead I, represents the depolarization of basal parts of the septum and right ventricle, particularly the pulmonary conus region. A large and prominent S-wave in leads I and V_6 in adults is a diagnostic criterion for RBBB (23). However, an $S_IS_{II}S_{III}$ pattern and an $S_IR_{II}R_{III}$ pattern with a QRS interval <0.12 s can be produced by RV enlargement or zonal RV block (22). Furthermore, some rare types of distal RBBB, without impairment of conduction over the main right bundle branch, can be observed in patients with tetralogy of Fallot after transatrial or transventricular repair, in cardiomyopathy with chronic lung disease, and in atrial septal defect, in which stretching of Purkinje fibers and/or muscle causes delayed activation of the RVOT. Horowitz et al. (29) found that after repair of tetralogy of Fallot, some patients had RBBB caused by vertical ventriculotomy along the RVOT. In these patients, the activation delays with fragmented endocardial electrograms were restricted to the anterobasal region of the RVOT and produced wide slurred S waves in leads I and V_6. In an experimental study (30), the damage to part of the RV specialized conductive tissue distal to the anterior papillary muscle determined a very slight increase in QRS interval duration, with the greatest modification in lead I, where the ventricular complex changes from a QR to an RS configuration. More recently, vectorcardiographic analysis of patients with BrS type 1 showed peculiar characteristics in comparison to healthy subjects with incomplete and complete RBBB (31). This study clearly demonstrated that the wide S-wave in the left lead does not indicate a typical RBBB morphology, but rather represents a right end conduction delay in the RVOT. Thus, it can be hypothesized that the localization and amount of delayed activation in larger or smaller masses of ventricular tissue in the RVOT could be related to the area of the S-wave in lead I and produce variable morphology and the presence or absence of RBBB in these patients.

FIGURE 2 Receiver-Operating Characteristic Curves for Amplitude and Duration of the S-Wave in Lead I



(A) Receiver-operating characteristic curve for amplitude of the S-wave in lead I. **(B)** Receiver-operating characteristic curve for duration of the S-wave in lead I. **(C)** Receiver-operating characteristic curve for the product of the amplitude and duration of the S-wave in lead I. CI = confidence interval.

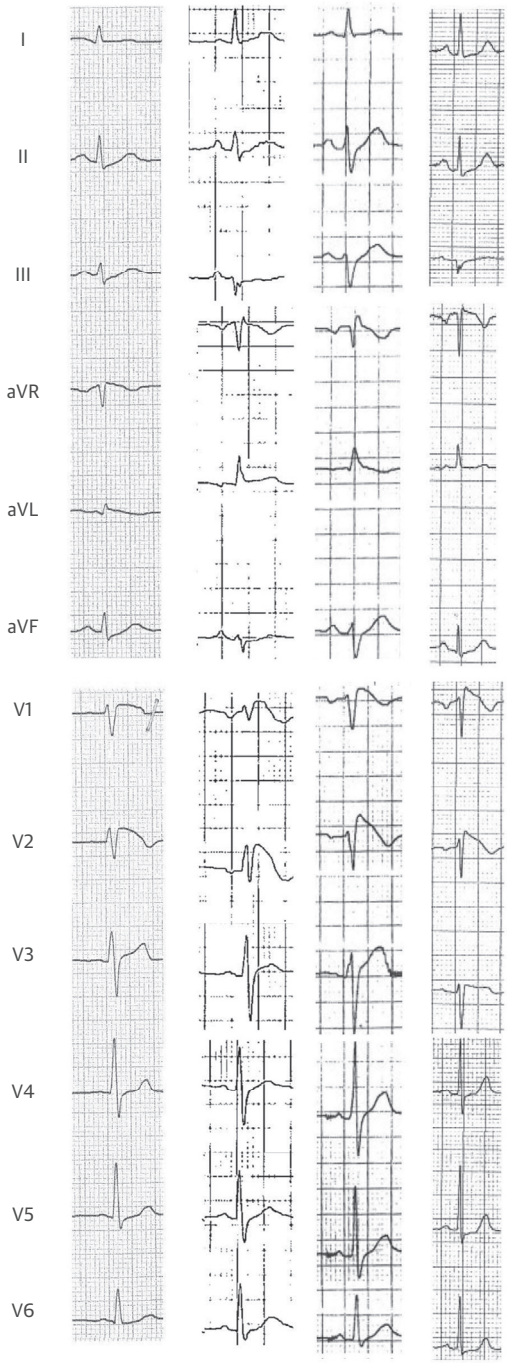
FIGURE 3 ECGs of Patients With BrS That Show the Spontaneous Coved-Type Pattern and a Significant S-Wave in Lead I



Twelve-lead surface electrocardiograms (ECGs) taken from 8 subjects with Brugada syndrome (BrS) showing the typical "coved-type" pattern in leads V_1 to V_2. Note the prominent S-wave in lead I without the presence of a "true" right bundle branch block.

ROLE OF RIGHT VENTRICULAR CONDUCTION DELAY IN BRUGADA SYNDROME. The depolarization hypothesis for the arrhythmogenic substrate of BrS is supported by several histological, imaging, ECG, and electrophysiological observations. In 1989, Martini et al. (32) described the presence of histopathological changes in patients with resuscitated VF, apparent absence of heart disease, and an ECG pattern reminiscent of BrS. In 2001, Corrado et al. (13) found a 14% rate of SCD in patients with type I BrS, and all these patients had arrhythmogenic RV dysplasia, except for 1 patient without evidence of structural heart disease, a finding suggesting an overlap between BrS and

FIGURE 4 ECGs of Patients With BrS That Show a Spontaneous Coved-Type Pattern Without a Significant S-Wave in Lead I



Twelve-lead surface electrocardiograms (ECGs) taken from 4 subjects with Brugada syndrome (BrS) showing the typical "coved-type" pattern in leads V_1 to V_2. Note the absence of prominent S-wave in lead I.

arrhythmogenic RV cardiomyopathy. Coronel et al. (14) published a combined electrophysiological, genetic, histopathological, and computational study of a patient with clinical evidence of BrS who underwent heart transplantation for incessant VF. In this patient, conduction slowing secondary to interstitial fibrosis caused the ECG signs and was the origin of VF. A subsequent study confirmed the presence of concealed structural abnormalities by endomyocardial biopsy in patients with BrS (33). It has been suggested that the cause of these myocardial structural abnormalities, such as severe reactive fibrosis and altered expression of gap junction proteins, can be related to reduced *SCN5A* expression (34). Recently, it has been observed that BrS is associated with the epicardial surface, interstitial fibrosis, and reduced gap junction expression in the RVOT (35). Furthermore, Zhang et al. (36), using noninvasive ECG imaging, showed that slow discontinuous conduction and steep dispersion of repolarization were present in the RVOT of patients with BrS, whereas the control group with only RBBB had delayed activation in the entire right ventricle, without ST-segment elevation, fractionation, or repolarization abnormalities on electrograms.

Several studies, using ECG studies, late potentials, and electrophysiological mapping, have reported depolarization abnormalities and conduction delay in patients with BrS (3,5-10,13-21,35,36). First-degree atrioventricular block has been associated with SCD or appropriate ICD therapies in BrS (6). Prolonged QRS interval duration in the precordial leads and fragmented QRS intervals have been shown to be markers for future major cardiac events (3,5-8), even though a prolonged QRS interval duration was not found to be of prognostic value in a recent review (37). Moreover, epsilon-like waves were observed in approximately 10% of patients with BrS. Finally, abnormal late potentials were found in patients BrS, and the presence of these potentials seems to indicate increased arrhythmic risk (9).

Delayed activation at the RVOT was reported on endocardial and epicardial mapping (13-21,35). Nagase et al. (15) found the presence of late potentials on signal-averaged ECG studies and demonstrated the correlation between these late potentials and delayed abnormal electrograms in the epicardium of the RVOT. Postema et al. (16) observed that BrS is characterized by wide and fractionated electrograms at the RV endocardium. The same group confirmed that the dominant pathophysiological mechanism for the type 1 ECG pattern is related to local depolarization abnormalities in the right ventricle using ECG studies, vectorcardiograms, and body surface potential maps (17). Lambiase et al. (18), by high-density mapping in patients with BrS, demonstrated that zones of significant regional delays were present in the anterolateral free wall of the RVOT and that these areas were critical in VF initiation. More recently, it was observed that the conduction delay in the right ventricle was significantly larger in patients with documented VF than in patients with syncope and without any symptoms (19), and the induction of VF depended on the severity of the depolarization abnormality (20). The role of these areas of slow conduction as key markers of SCD in BrS is reinforced by the observation that electroanatomic maps of the right ventricle in patients with BrS who have recurrent VF episodes showed a prominent delayed depolarization with low voltage and fractionated electrograms (21,35). These electrograms were exclusively present over the anterior epicardial region of the RVOT and their ablation determined prevention of VF and, in the majority of the patients, the disappearance of the Brugada ECG pattern (21,35).

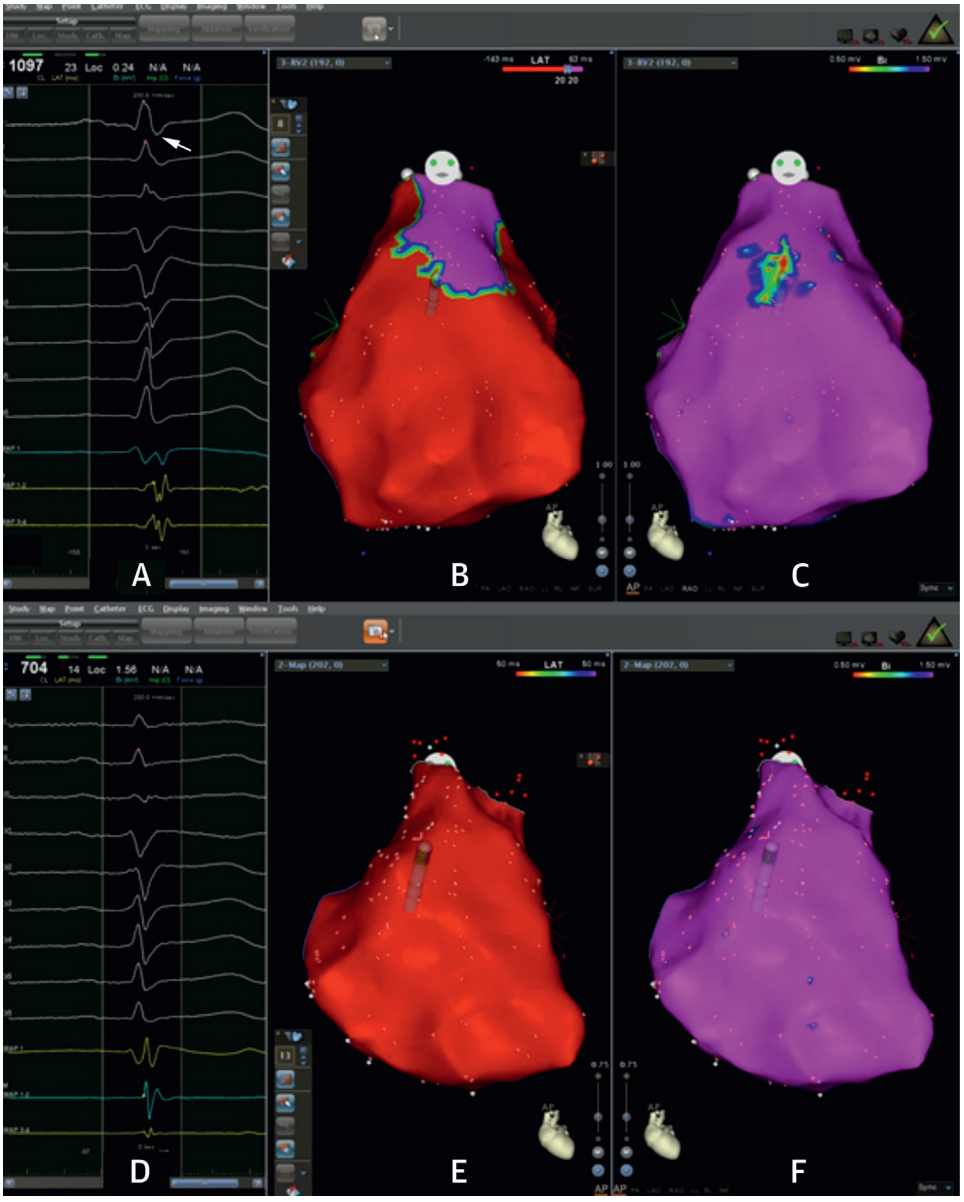
In our study, electroanatomic mapping showed that the endocardial activation time (mostly because of a significant delay in the anterolateral RVOT) was significantly longer in patients with S waves in lead I compared with patients without S waves. Fragmented

TABLE 4 Clinical and Electrocardiographic Characteristics of Patients With and Without Significant S Waves in Lead I

	Significant S (n = 171)	No Significant S (n = 176)	p Value
Male	141 (82.4)	131 (74.4)	NS
Age, yrs	43 ± 13	47 ± 13	0.014
Family history of SCD	28 (16.3)	43 (24.4)	NS
SCN5A gene mutation	20 (11.7)	12 (6.8)	NS
Positive EPS	42 (24.6)	35 (19.9)	NS
AF	11 (6.4)	7 (3.9)	NS
Asymptomatic	123 (71.9)	153 (86.9)	<0.0001
Syncope	17 (9.9)	22 (12.5)	<0.0001
VF/SCD	31 (15.1)	1 (0.57)	<0.0001
First-degree AV block	34 (18.1)	17 (9.7)	0.007
QRS duration in lead II, ms	99 ± 18	91 ± 18.6	<0.0001
QRS duration in lead V_2, ms	112 ± 19	108 ± 20	0.001
Complete RBBB	24 (14)	9 (5.1)	0.008
LAFB	21 (12.3)	31 (17.6)	NS
fQRS	40 (23.4)	45 (25.6)	NS
Epsilon wave in lead V_1	6 (3.5)	2 (1.1)	NS
Early repolarization pattern	9 (5.3)	21 (11.9)	0.04
QTc in lead II, ms	396 ± 33	396 ± 32	NS
T_p-T_e in lead V_2, ms	71 ± 15	68 ± 15	NS
T_p-T_e in lead V_6, ms	82 ± 15	79 ± 15	NS

Values are n (%) or mean ± SD.
Abbreviations as in Tables 1 to 3.

FIGURE 5 Electroanatomic Mapping Using CARTO (Biosense Webster, Inc., Diamond Bar, California)



Anterolateral view of activation, voltage, and some electrograms in a patient with a significant S-wave in lead I **(A to C)** and without an S-wave **(D to F)**. **(A and D)** A single QRS interval at a paper speed of 200 mm/s, including the 12 surface leads (the **arrow** indicates the S-wave in lead I in **A**). The last 3 channels show the local QRS interval, as recorded with the mapping catheter (unipolar recording in **blue**; distal and proximal bipolar recording in **yellow**). **(B and C)** The activation time and the voltage map, respectively, in a patient with an S-wave. **(E and F)** The activation time and the voltage map, respectively, in a patient without an S-wave. On the activation map, a color-coded scale from **red** to **purple** represents earliest to latest activation. On the voltage map, **purple** represents normal endocardium (amplitude ≥1.5 mV); **red** is dense scar (amplitude ≤0.5 mV); and the range between **purple** and **red** is the border zone (signal amplitudes between 0.5 and 1.5 mV). The patient with a significant S-wave showed abnormal electrograms over the anterolateral region of the right ventricular outflow tract, late activation **(purple)** in the local activation time map, and low voltage **(red)** in the bipolar voltage map.

TABLE 5 Probability of VF/SCD During Follow-Up Depending on Clinical and Electrocardiographic Parameters at Presentation: Univariate and Multivariate Analysis

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Male	0.44	0.13–1.46	0.18	–	–	–
Age	0.96	0.93–0.99	0.018	–	–	–
Syncope	1.50	0.36–6.35	0.57	–	–	–
Family history of SCD	1.32	0.56–3.15	0.52	–	–	–
Positive EPS	1.57	0.72–3.48	0.26	–	–	–
AF	5.53	2.30–13.40	0.00015	3.70	1.59–8.73	0.0024
SCN5A mutation	0.68	0.45–1.02	0.06	–	–	–
First AV block	1.50	0.57–4.00	0.41	–	–	–
QRS duration >120 ms	1.90	0.80–4.93	0.14	–	–	–
fQRS	1.90	0.89–4.13	0.09	–	–	–
Epsilon	1.40	0.19–10.6	0.72	–	–	–
V_1R >0.15 mV	2.40	0.47–12.4	0.29	–	–	–
V_6S >0.15 mV	0.52	0.18–1.48	0.22	–	–	–
V_6S/R >0.2 mV	3.30	0.61–18.2	0.17	–	–	–
S amplitude ≥0.1 mV in lead II	0.52	0.18–1.48	0.22	–	–	–
S duration ≥40 ms in lead II	0.79	0.24–2.67	0.71	–	–	–
S amplitude ≥0.1 mV in lead III	0.99	0.22–4.46	0.99	–	–	–
S duration ≥40 ms in lead III	1.56	0.31–8.10	0.59	–	–	–
S-wave in lead I						
S presence	20.90	2.84–154.60	0.003	–	–	–
S amplitude ≥0.1 mV	12.60	3.80–41.90	<0.0001	13.30*	4-05–43.72	<0.0001
S duration ≥40 ms	38.00	5.16–280.7	<0.0001	39.10*	5.34–287.1	<0.0001
S area ≥1 mm^2	16.80	5.05–55.8	<0.0001	17.10*	1.59–8.69	<0.0001
Early repolarization	0.70	0.17–3.13	0.68	–	–	–
QTc	1.001	0.99–1.01	0.66	–		–
T_p-T_e in lead V_2	1.028	1.013–1.042	<0.0001	–		–
T_p-T_e in lead V_6	1.025	1.002–1.048	0.03	–	–	–

Akaike information criterion for various models: Model 1 (AF + S amplitude ≥0.1 mV): 183.1; Model 2 (AF + S duration ≥40 ms): 170.1; Model 3 (AF + S amplitude duration area ≥1 mm^2): 181.2. *Considering the strong correlation found among these variables, only S-wave duration ≥40 ms was chosen, on the basis of the best Akaike information criterion.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1, 3, and 4.

electrograms exhibiting relatively low voltage, prolonged duration, and late polyphasic potentials were significantly more likely to be present in the group with S waves in lead I.

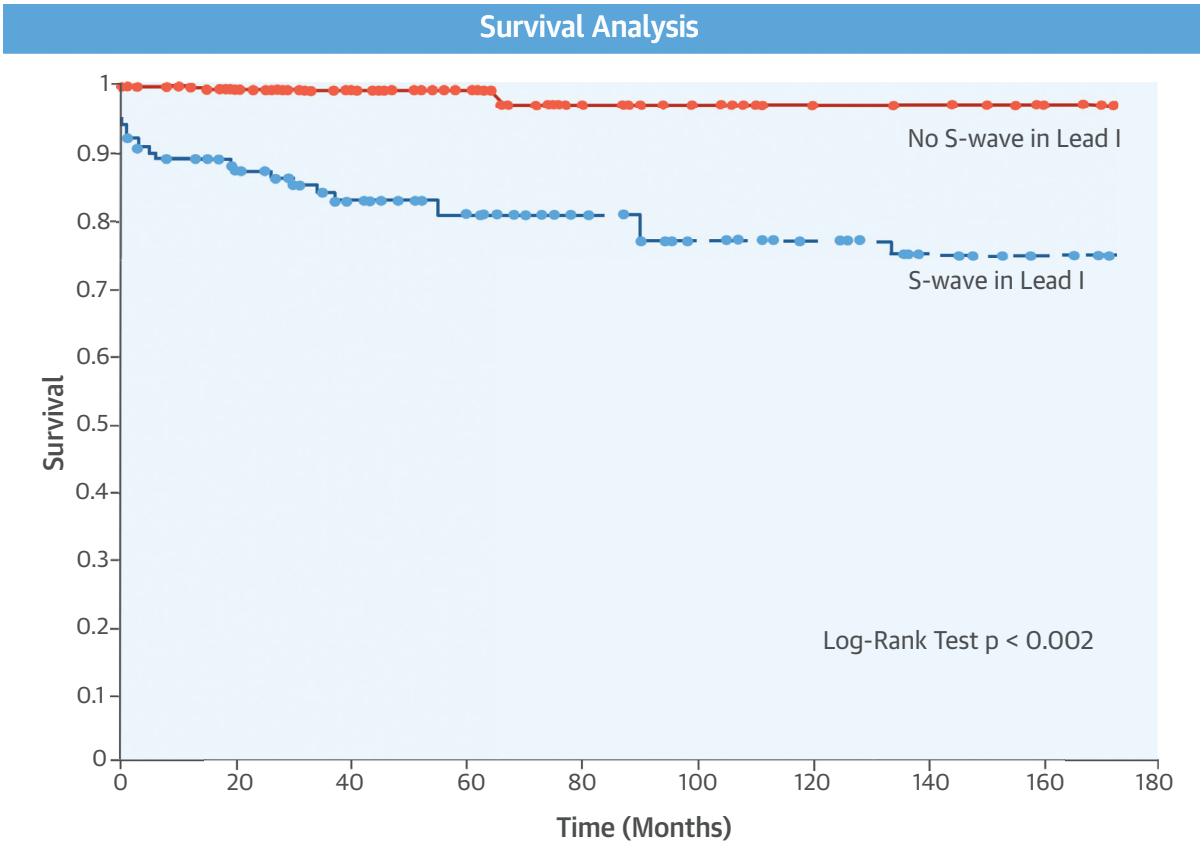
STUDY LIMITATIONS. First, we analyzed cardiac magnetic resonance imaging results in only 22 of 346 patients (6.3%) and endocardial electroanatomic mapping in only 12 of 346 patients (3.5%). Some investigations (14,16,18) reported endocardial abnormal electrograms, whereas others (5,15,19,21,35) found areas of slow conduction only over the RVOT epicardium. In future studies, it could be very important to obtain cardiac magnetic resonance imaging with a more detailed characterization of fibrosis, such as T_1 mapping, and to perform high-density epicardial and endocardial electroanatomic mapping with the aim of gaining a better understanding of the substrate in BrS, the role of RV conduction delay, and the relationship with ECG findings.

Second, over the years, several prognostic parameters (including markers of conduction delay) have been proposed in BrS. However, none proved useful in larger studies. Such could also be the case for the S-wave in lead I. Therefore, an independent confirmation cohort is necessary to confirm the value of the current study. Notably, because the cutpoints of the S-wave in lead I were identified and evaluated on the same dataset, they will require validation in a separate sample of healthy subjects.

Third, a potential limitation is that the ECG analysis could be influenced by the orientation of the RVOT because it could change the terminal vector of the QRS interval, particularly in some patients with significant deviation.

Another limitation is that our centers are institutions that treat cardiac arrhythmias. Therefore,

CENTRAL ILLUSTRATION **Brugada Syndrome: A New Marker of Sudden Death**



Calò, L. et al. J Am Coll Cardiol. 2016; 67(12):1427–40.

Kaplan-Meier analysis of freedom from ventricular fibrillation/sudden cardiac death events during follow-up in patients with S waves in lead I versus those without S waves in lead I.

we cannot exclude some form of selection bias, such as referral of patients with higher risk at baseline to our centers.

Finally, EPSs and genetic screening were performed in only 54% and 31% of the included patients, respectively. The group with VF/SCD had a lower prevalence of *SCN5A* mutation (17%) and more EPS inducibility (65%). In patients with BrS who had aborted SCD, Eckardt et al. (4) reported a 12% prevalence of *SCN5A* mutation and a 62% prevalence of VF induction. However, only 25% to 30% of patients with BrS have a known genotype, a finding implying that additional, as yet unidentified genes may be linked to this disease. BrS is probably a disease of the connexome (35,38), and the genes involved may include those encoding components of structures such as desmosomes, gap junctions, and the sodium channel complex. Therefore, the relationships among ECG characteristics, genes, and EPS inducibility should be revisited in the near future.

CONCLUSIONS

In the last decade, several markers have been proposed for risk stratification of BrS. The depolarization theory has been reinforced by our observations that highlight the role of RV conduction delay in this syndrome. The presence of a wide and/or large S wave in lead I, resulting from delayed activation in the RVOT, was demonstrated to be a powerful predictor of life-threatening ventricular arrhythmias. This substrate could favor re-entrant ventricular tachyarrhythmias and can be used as a potential novel marker of SCD risk stratification in patients

with BrS. However, the prognostic value of a significant S wave in lead I should be confirmed by larger studies and by an independent confirmation cohort of healthy subjects.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A wide and/or deep S-wave in lead I of the surface ECG study, reflecting delayed activation of the RVOT, is a simple but powerful predictor of life-threatening ventricular arrhythmias in patients with the BrS.

TRANSLATIONAL OUTLOOK: Further studies should examine the relative predictive value of the various ECG markers of ventricular depolarization and repolarization that have been reported to identify high-risk patients with BrS.

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KEY WORDS arrhythmia, electrocardiography, prognosis

APPENDIX For supplemental tables, please see the online version of this article.