Original Article

Electrical Substrate Elimination in 135 Consecutive Patients With Brugada Syndrome

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Background—There is emerging evidence that localization and elimination of abnormal electric activity in the epicardial right ventricular outflow tract may be beneficial in patients with Brugada syndrome.

Methods and Results—A total of 135 symptomatic Brugada syndrome patients having implantable cardiac defibrillator were enrolled: 63 (group 1) having documented ventricular tachycardia (VT)/ventricular fibrillation (VF) and Brugada syndrome–related symptoms, and 72 (group 2) having inducible VT/VF without ECG documentation at the time of symptoms. About 27 patients of group 1 experienced multiple implantable cardiac defibrillator shocks for recurrent VT/VF episodes. Three-dimensional maps before and after ajmaline determined the arrhythmogenic electrophysiological substrate (AES) as characterized by prolonged fragmented ventricular potentials. Primary end point was identification and elimination of AES leading to ECG pattern normalization and VT/VF noninducibility. Extensive areas of AES were found in the right ventricle epicardium, which were wider in group 1 (P=0.007). AES increased after ajmaline in both groups (P<0.001) and was larger in men (P=0.008). The increase of type-1 ST-segment elevation correlated with AES expansion (r=0.682, P<0.001). Radiofrequency ablation eliminated AES leading to ECG normalization and VT/VF noninducibility in all patients. During a median follow-up of 10 months, the ECG remained normal even after ajmaline in all except 2 patients who underwent a repeated effective procedure for recurrent VF.

Conclusions—In Brugada syndrome, AES is commonly located in the right ventricle epicardium and ajmaline exposes its extent and distribution, which is correlated with the degree of coved ST-elevation. AES elimination by radiofrequency ablation results in ECG normalization and VT/VF noninducibility. Substrate-based ablation is effective in potentially eliminating the arrhythmic consequences of this genetic disease.

Clinical Trial Registration—URL: https://clinicaltrials.gov. Unique identifier: NCT02641431.

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Key Words: ajmaline ■ Brugada syndrome ■ catheter ablation ■ documentation ■ sudden cardiac death

Brugada syndrome (BrS) is a genetically determined disease that predisposes to cardiac arrest or sudden cardiac death due to ventricular malignant tachyarrhythmia.[1–3] Therefore, the use of an implantable cardiac defibrillator (ICD) was an evident option since the first description of the syndrome for patients with BrS who usually are young and otherwise healthy individuals.[2] Symptomatic BrS patients can experience recurrent ICD shocks and impaired quality of life, with significant psychological sequelae. Recently, the epicardium of the right ventricle has been reported to be a potential area where the imbalance between eventually abnormal inward/outward currents would manifest. More recently, substrate-based epicardial ablation has been proposed as a promising adjunct in symptomatic BrS patients with recurrent episodes of ventricular fibrillation (VF),[4–6] but the small sample size precluded any firm conclusion on its actual role.[7] The purpose of this prospective study was to investigate the methodology and results of substrate-based mapping/ablation in a large series of consecutive BrS patients with various clinical presentations and to verify if radiofrequency ablation (RFA) could normalize the consequences of a genetic disease.

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WHAT IS KNOWN

- Data on epicardial mapping and ablation to control ventricular arrhythmias in patients with Brugada syndrome is limited to selected high-risk patients.
- Ablation of the abnormal substrate, that is characterized by low-voltage prolonged fragmented epicardial right ventricular electrograms, can normalize the ECG.

WHAT THE STUDY ADDS

- This is the largest study on epicardial mapping/ablation in symptomatic patients with Brugada syndrome.
- Ajmaline increased the identifiable area of epicardial substrate defined by 3-dimensional maps of electrogram duration that was targeted for ablation.
- The results support efficacy of this substrate-based ablation approach in eliminating the Brugada syndrome–ECG pattern and preventing recurrent ventricular arrhythmias.

Methods

Patient Population

Consecutive selected symptomatic patients diagnosed with type 1 BrS-ECG pattern either spontaneously or after ajmaline who had an ICD implanted were enrolled. Ajmaline administration (1 mg/kg in 5 minutes) was considered positive if the typical coved-type ECG pattern appeared in more than one right precordial lead (V1–V3). We terminated the ajmaline administration before reaching the target dose only if QRS prolongation exceeded 30% compared with baseline interval or premature ventricular beats occurred. This prospective study started in 2015 and the last patient was enrolled in September 2016 to allow a minimum follow-up of 3 months. Patients were asked to participate after providing signed written informed consent. The local Ethics Committee approved the study protocol. Further details on eligibility criteria are provided in the Methods section in the online-only Data Supplement. All authors had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Substrate Mapping

Patients underwent a combined epi–endocardial mapping procedure as previously described.[5] Under general anesthesia, an invasive arterial pressure line was obtained through radial artery access. The ECG was continuously recorded during the procedure. After femoral venous access, a multipolar diagnostic catheter was positioned at the right ventricle (RV) apex. The epicardial access was gained by a percutaneous subxyphoid access to the pericardial space as described by Sosa et al.[8] Three-dimensional (3D) RV endocardial and epicardial mapping (CARTO 3, Biosense Webster, Diamond Bar, CA) was performed in all patients during stable sinus rhythm and presence of type I BrS-ECG pattern. Epicardial mapping was systematically performed after endocardial mapping, in order to have adequate delimitation of the RV boundaries when mapping the epicardium. Epicardial RV mapping and ablation catheter manipulation were assisted by a steerable sheath (Agilis EPI St Jude Medical, St. Paul, MN). BrS epicardial substrate identification consisted in mapping the entire RV epicardial surface under baseline conditions and after ajmaline infusion (1 mg/kg in 5 minutes). We obtained 3 groups of RV epicardial electrograms properties using CARTO3 mapping system: (1) bipolar/unipolar voltage map, (2) local activation time map, and (3) potential duration map, in which abnormal long-duration bipolar electrograms were defined as low-frequency (up to 100 Hz) prolonged duration (>200 ms) bipolar signals with delayed activity extending beyond the end of the QRS complex (Figures 1–3).

Three-Dimensional Mapping

Bipolar electrograms were filtered from 16 to 500 Hz, displayed at 200 mm/s speed and were recorded between the distal electrode pair. Electrograms were excluded if their technical quality was insufficient or if catheter-induced extrasystoles occurred.

Voltage Mapping

Color-coded electroanatomical voltage, activation and duration maps were performed and superimposed to cardiac anatomy. Red color indicated low-voltage dense scar, which arbitrarily was defined as bipolar signal amplitude <0.5 mV, whereas purple color indicated voltage areas >1.5 mV. Areas of low voltage were identified using standard voltage cut-off values for dense scar (<0.5 mV) and border zone (<1.5 mV). Electrograms below the 0.05 mV threshold were not considered for analysis.

Local Activation Mapping

To study activation, we assessed the local activation time, defined as the interval (ms) from the onset of QRS in lead II to the steepest negative dV/dt of the intrinsic deflection in the epicardial unipolar electrogram corresponding with a positive or negative deflection in the bipolar electrogram. Activation duration was defined as the interval (ms) between the earliest activation time of any electrogram (activation-start) and the latest activation time of any electrogram (activation-end).

Potential Duration Mapping

The maximum electrogram duration was the longest electrogram with continuous deflections without an intervening isoelectric line as recorded within a 0.45 s window of interest. Fractionation of electrograms was defined as the presence of >2 intrinsic deflections and expressed as number of intrinsic deflections per electrogram. Electrogram duration was measured before and after ajmaline in the bipolar signal as the interval between the onset of the first and the offset of the last component of the electrogram, measured at the time scale of 200 mm/s, and expressed as mean bipolar electrogram duration (ms). A cut-off range from 110 ms to 200, 250, and 280 ms was used for defining color-coded duration maps. As a result, a color-code map was obtained showing the regions displaying the shortest (<110 ms cut-off, red color) and the longest duration (>200 ms cut-off, purple color), respectively. The degree of duration of the potentials was displayed from the longest (purple) to the shortest potential (red) using different duration cut-off values (Figures 1–5). According to the selected cutoffs, 3 different concentric circles were drawn around purple areas (Figure 2). The potential duration map was performed by collecting the duration of each bipolar electrogram. Measurements were undertaken online by 2 observers with electronic and manual calipers using the CARTO3 system.

Substrate-Based Ablation

Epicardial ablation was performed during sinus rhythm using a stepwise strategy in a descending order of abnormal potential duration as displayed on the map and beginning from the longest potentials. The longest duration potential area was displayed in purple by setting the color-bar upper limit (300 ms) in the 3D duration map, as created simultaneously during voltage and local activation time mapping. Afterward, RFA was performed sequentially by gradually moving at substrate sites toward areas with less prolonged late (250 and 200 ms) potentials according to the stepwise strategy. Radiofrequency was delivered with an externally irrigated 3.5-mm tip ablation catheter (ThermoCool SF, Navistar, Biosense Webster). A 35 W up to 45 W power control mode was used. The irrigation rate was 17 mL/min for RF applications, which were delivered by a dragging strategy up to complete elimination of all long duration, delayed activity. BrS-ECG pattern changes during epicardial RFA were analyzed by continuous ECG monitoring (Figure 6; Figure I in the online-only Data Supplement). The ST-segment modifications were evaluated using a correlation software (PASO module, Biosense Webster). Immediate ablation end point was the elimination of all abnormally prolonged late activity with normalization of

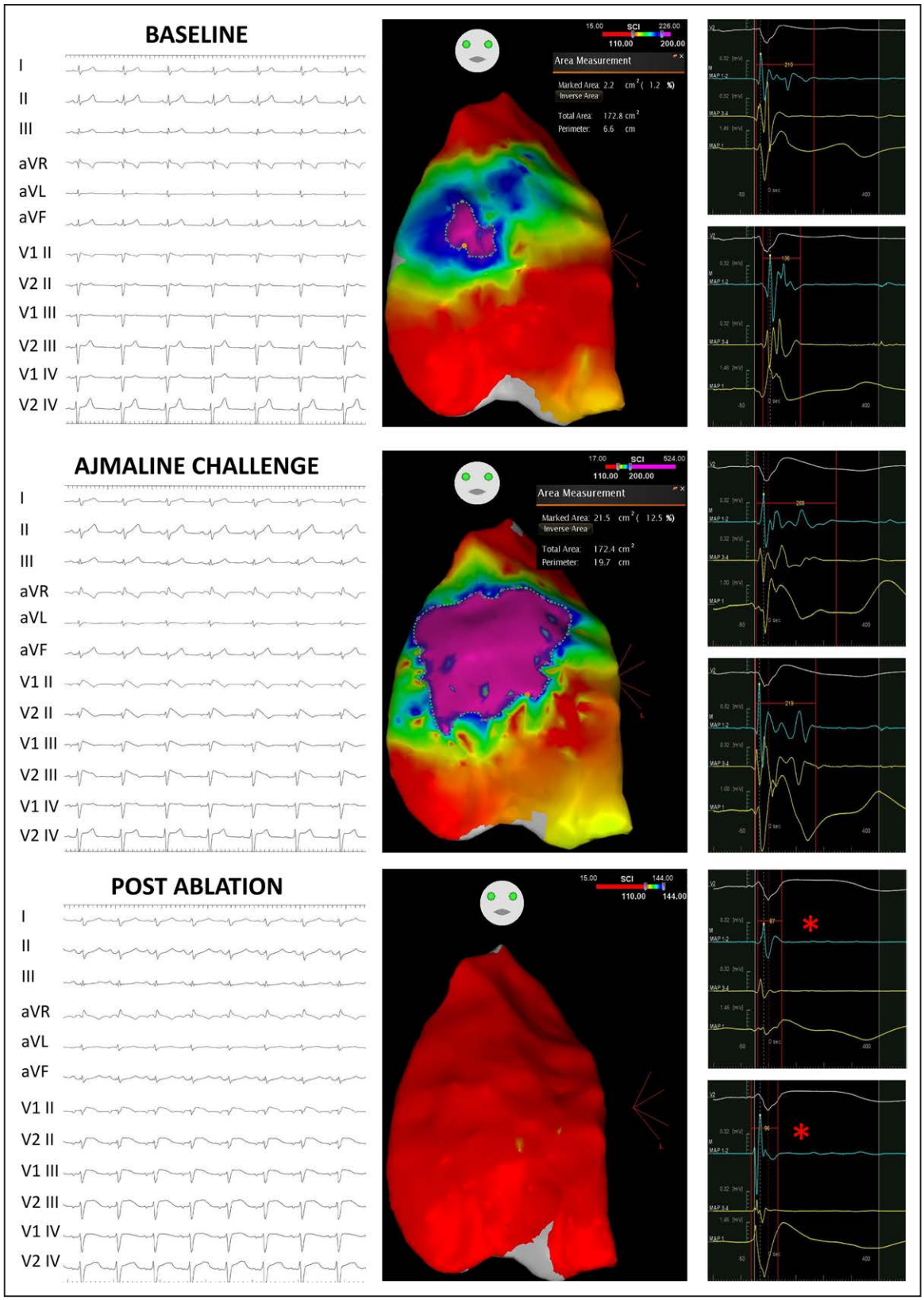

Figure 1. Phenotype abolition by epicardial substrate ablation. A 39-year-old patient with Brugada syndrome (BrS), presenting with a family history of BrS and syncope, had an implantable cardiac defibrillator implantation. The patient had positive ajmaline test and ventricular tachycardia/ventricular fibrillation inducibility during an electrophysiological study. **Top**, Baseline BrS-ECG pattern and epicardial color-coded duration CARTO maps. A saddle-back pattern is evident in V2 (II intercostal space) with a corresponding small (2.2 cm^2) purple area of abnormally prolonged potentials (210 ms in the example). The border-zone area (green/blue area >110 and <200 ms) shows potentials with relatively shorter duration (136 ms). **Middle**, BrS-ECG pattern and color-coded duration maps after ajmaline. After type 1 ajmaline-induced (*Continued*)

Figure 1 Continued. ECG pattern, the abnormal purple area significantly increased to 21.5 cm^2. Examples of abnormal and prolonged electrograms found in the purple area after ajmaline test are shown beside the map (289 and 219 ms). **Bottom**, BrS-ECG pattern and color-coded duration maps after radiofrequency ablation of epicardial substrate. After ajmaline rechallenge at the end of the procedure, the ECG showed a horizontal and ascendant ST-segment elevation, with minimal intraventricular conduction delay characterized by slight QRS broadening with a more pronounced S wave in leads I and II and qR morphology in aVR. Abnormally prolonged fragmented and delayed electrograms disappeared (87 and 96 ms, light blue color). The 2 examples of ventricular electrograms were recorded from the previously abnormal area, and the red asterisks indicate disappearance of the late components. Electrogram panels are from the CARTO3 system and show V2 ECG lead (white), distal (light blue) and proximal bipolar (yellow) and unipolar signals (yellow) at 200 mm/s speed, from top to bottom, respectively. Of note, in the **middle**, V2 lead shows a typical coved-type pattern, which after ablation was modified into a horizontal and flat ST-segment elevation.

BrS-ECG pattern (Figure 6). Examples and details of the mapping and ablation procedure are provided in Figures I–IX in the online-only Data Supplement).

Repeated Ajmaline Challenge and Remap After Ablation

Ajmaline was systematically reinfused after RFA to ensure abolition of all abnormal ventricular potentials while confirming the BrS-ECG pattern elimination. In patients in whom the BrS-ECG pattern reappeared during infusion, epicardial duration maps were repeated to identify any residual or additional abnormal signals for further RF applications to definitively normalize the ECG pattern. Once a stable BrS-ECG pattern elimination was obtained, ventricular tachycardia (VT)/VF inducibility was assessed. Intrapericardial liquid was permanently withdrawn through the deflectable sheet during the procedure to avoid serum accumulation.

Study End Point

End point of the study was elimination of all abnormal electric ventricular potentials before and after ajmaline leading to ECG normalization and noninducibility of VT/VF.

Definitions

BrS was diagnosed in the presence of a coved-type ST elevation of >2 mm as documented in >1 lead from V1 to V3 positioned in the second, third, or fourth intercostal space. Because of the variable nature of the BrS-ECG pattern, patients with BrS were classified according to their ECG at the time of the presentation and defined as spontaneous ECG pattern. Three BrS patient groups (BrS-1 to BrS-3) were defined as coved-type (BrS-1), saddleback ST configuration (BrS-2) or either type 1 or type 2 but with <2 mm of ST-segment elevation (BrS-3). BrS patients with typical BrS-related symptoms included those with documented ventricular fibrillation or polymorphic ventricular

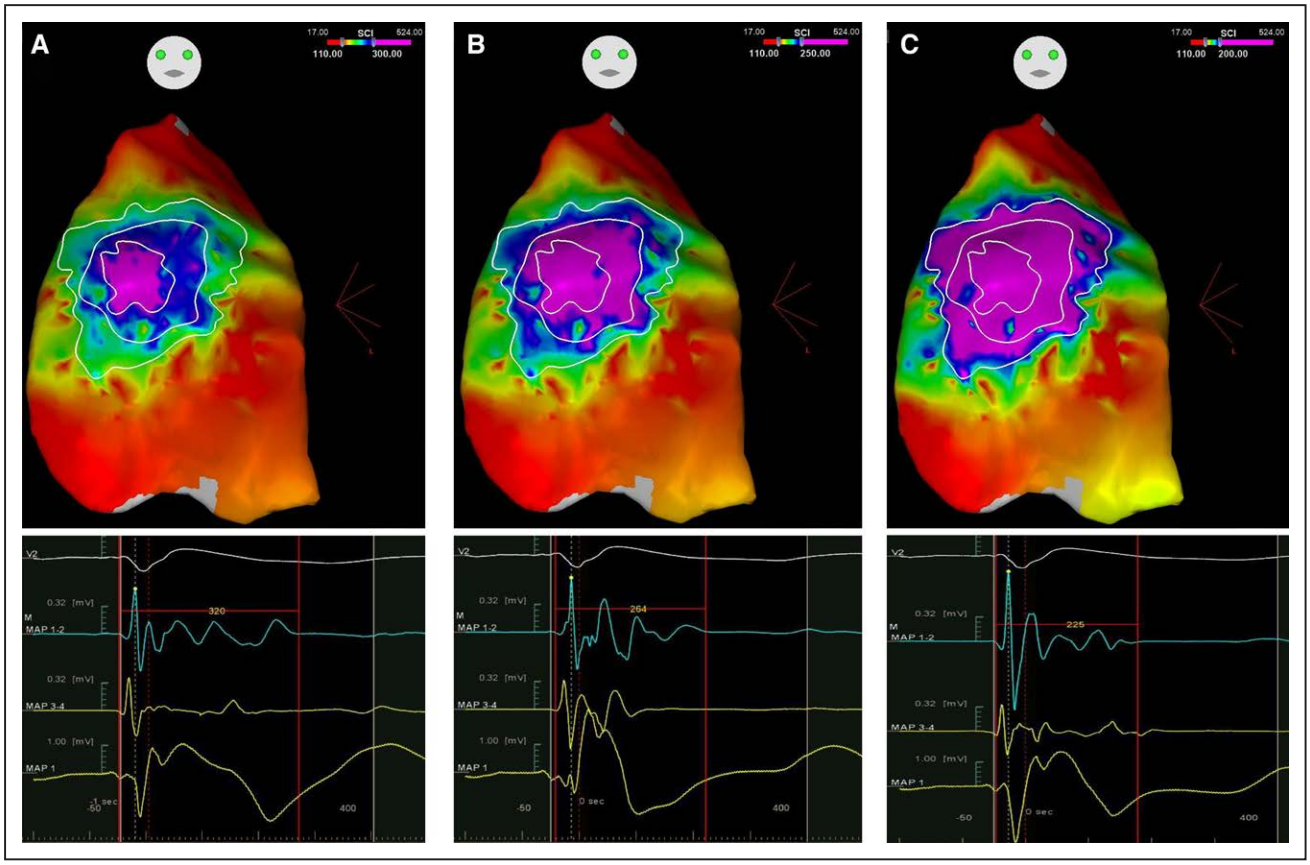

Figure 2. Potential duration map and concentric "onion-like" substrate. A 39-year-old patient with Brugada Syndrome (BrS), presenting with a family history of BrS and syncope, had an implantable cardiac defibrillator implantation. The epicardial map shows a concentric onion-like" substrate distribution after ajmaline. White lines delimitate multiple areas exhibiting electrograms with different duration (**A**, ≥300 ms; **B**, ≥250 ms; and **C**, ≥200 ms). Areas with the longest potential duration (≥300 ms) are in the inner circle (**A**), whereas relatively shorter areas (≥250 and ≥200 ms) are in the outer circle (**B** and **C**). Red regions represent areas with electrogram potential duration of ≤110 ms. Below each map, there is an example of the electrogram recorded in the purple area (320 ms duration in **A**, 264 ms in **B**, and 225 ms in **C**, respectively). Each electrogram panel from CARTO system shows V2 ECG lead (white), distal (light blue) and proximal bipolar (yellow) and unipolar (light blue) signals at 200 mm/s speed, from top to bottom, respectively.

Figure 3. Spontaneous type 1 Brugada pattern. The figure refers to a 32-year-old patient with spontaneous type 1 Brugada pattern implanted with an implantable cardiac defibrillator due to a history of frank syncope without prodromes and an electrophysiological study positive for ventricular tachycardia/ventricular fibrillation induction. **Left**, The 12-lead ECG with precordial leads placed in V1 and V2 at higher intercostal spaces (II, III, and IV ICS) shows typical type 1 Brugada pattern particularly evident in V1 and V2 II ICS and in V1 III ICS. Besides the ECG, **middle**, the epicardial potential duration map (CARTO3) shown in purple color, the area exhibiting long duration potentials (≥200 ms; dimensions 21.5 cm^2). **Right**, Two examples of electrograms found in the most fragmented and prolonged region (purple area). Of note, typical electrogram of wide duration with low voltage and fragmented delayed components are shown in the distal bipolar (light blue signal, 320 and 280 ms duration, respectively). In each electrograms panel, V1 and V2 II ICS ECG lead (white), distal (light blue) and proximal bipolar and unipolar (yellow) signals are shown at 200 mm/s speed, from top to bottom, respectively. AP indicates antero-posterior; INF, inferior; LAO, left anterior oblique; LL, latero-lateral; PA, postero-anterior; RAO, right anterior oblique; RL, right lateral; and SUP, superior.

tachyarrhythmia at the time of symptoms. BrS patients without typical BrS-related symptoms were considered as patients with different symptoms (from dizziness to palpitations) without ECG documentation at the time of events but all with inducible VT/VF. Patients with worst clinical presentation were defined as those who experienced cardiac arrest or syncope because of documented ventricular fibrillation. A proband was defined as the first patient diagnosed with BrS in a family on the basis of a type 1 Brugada ECG pattern. Major complications were defined as those who required prolonged hospitalization.

Follow-Up

Patients were monitored for at least 3 days after the procedure. Before hospital discharge, both 12-lead ECG and echocardiography were systematically performed. After discharge, patients were followed up at 3-, 6-, and 12-month intervals and every 6 months thereafter. Each visit included 12-lead ECG, ajmaline test, 24-hour ambulatory ECG monitoring, ICD interrogation, and VT/VF inducibility. At each visit, patients were questioned about the presence of any potential arrhythmic symptoms, including syncope or device discharges and their ICD interrogated. No patients were lost to follow-up.

Statistical Analysis

Descriptive variables are summarized by means of frequency distributions, means, and SDs, or medians and interquartile ranges (IQR) and tested with the use of χ^2 tests, unpaired *t* test, Mann–Whitney test, 1-way ANOVA, or Kruskal–Wallis H test with Dunn test for multiple comparisons, as appropriate. The relationship between the ST elevation and the abnormal area after ajmaline infusion was investigated by means of Spearman rank correlation coefficient (ρ). Values of $P<0.05$ (2-tailed) were taken as statistically significant. IBM SPSS Statistics for Windows, Version 23.0. (IBM Corp, Armonk, NY) was used for the statistical analysis.

Results

Patients

Among 375 screened patients with BrS, 226 were eligible and 135 patients accepted to be included completing the study protocol (Table 1). According to guidelines recommendations, the indication for ICD implantation was typical Brugada–related symptoms (group 1, n=63 patients including 39 patients with cardiac arrest or syncope and documented arrhythmia [severe clinical presentation]) or VT/VF inducibility with symptoms without documented arrhythmia (group 2, n=72). Group 2 includes 18 first-degree relatives of a proband who was also included in the study who were diagnosed during family member screening (Table I in the online-only Data Supplement). Among the 39 patients with a severe clinical presentation, 27 experienced multiple (median 4 episodes) ICD shocks for recurrent VT/VF during the month before ablation procedure (Table 1). Diagnosis, study, and ICD implant were done at San Donato University-Hospital in 111 patients and in another Institution in 24 patients. Before ablation, in group 2, frequent monomorphic premature ventricular complexes with a right ventricular outflow tract (RVOT) morphology (28 patients) and at least one episode of sustained (7 patients) or nonsustained (37 patients) VT were recorded on ECG, Holter, or ICD. All patients were inducible, and VF was the induced rhythm in 111 patients, whereas in 24 patients, it was polymorphic VT. Structural heart disease was excluded by clinical history, physical examination, and extensive noninvasive methods, including 2D echocardiography, ergometric testing. Cardiac magnetic resonance imaging whenever possible (111 patients at San Donato University-Hospital) did not show criteria for arrhythmogenic ventricular cardiomyopathy displasia diagnosis. One patient had a suspected arrhythmogenic ventricular cardiomyopathy on echocardiography, but magnetic resonance imaging was not performed because the patient had ICD implantation. Five patients had episodes of atrial fibrillation and 2 patients had paroxysmal supraventricular tachycardia due to concealed accessory pathways and atrioventricular nodal tachycardia. Quinidine had failed in 2 patients.

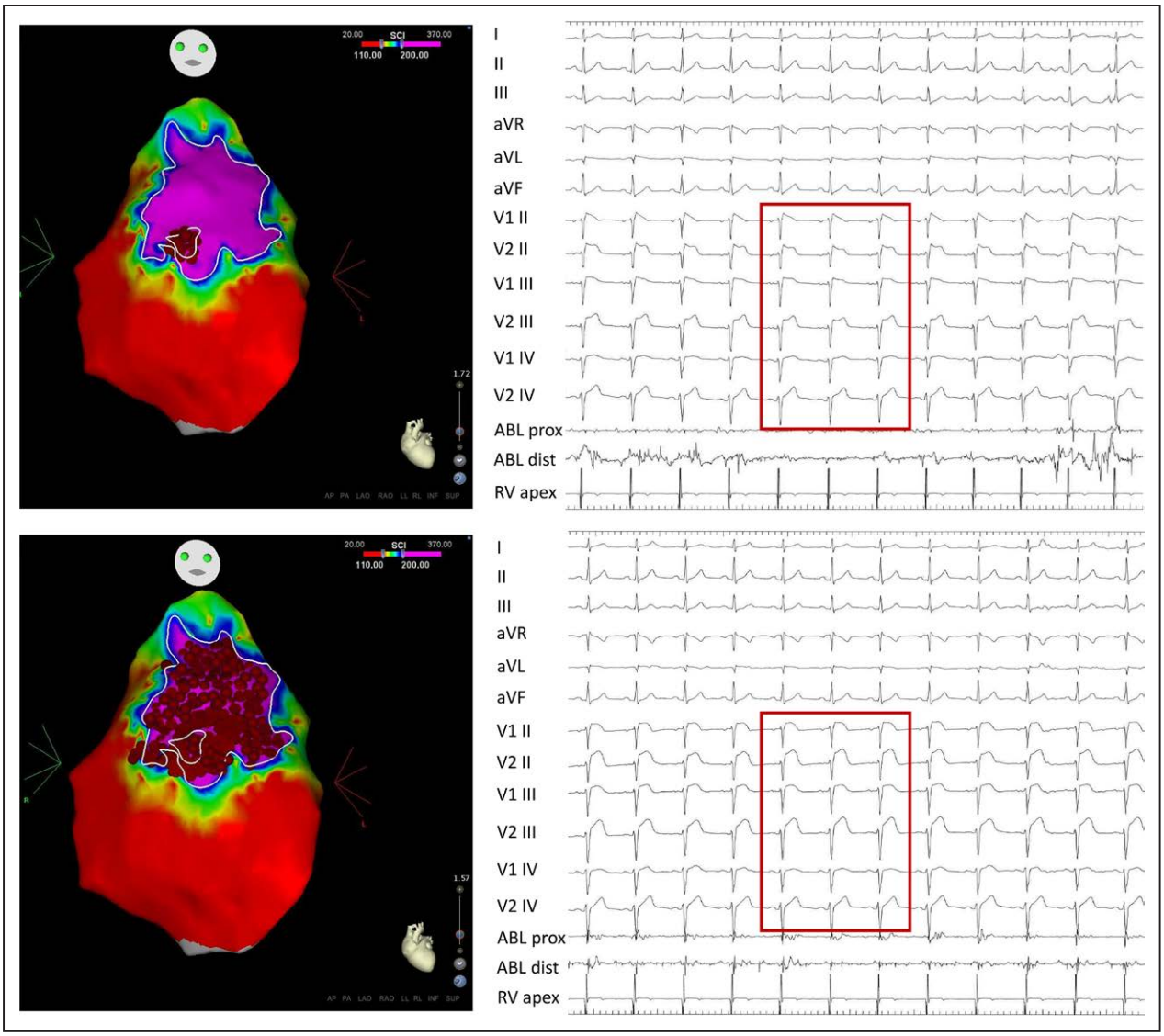

Figure 4. Radiofrequency ablation in spontaneous type 1 Brugada pattern. The figure refers to a 32-year-old patient with spontaneous type 1 Brugada pattern implanted with an implantable cardiac defibrillator due to a history of frank syncope without prodromes and an electrophysiological study positive for ventricular tachycardia/ventricular fibrillation induction. **Top**, The potential duration map with white circles delimitating the areas exhibiting potentials duration of ≥300 ms (inner circle) and ≥200 ms (outer circle). Radiofrequency ablation in the inner circle (red dots) determined initial ascending and horizontal ST-segment elevation in the high right precordial leads (**top** on the right, red box). **Bottom**, The complete set of lesions has been delivered in the whole area ≥200 ms resulting in persistent horizontal and flat ST elevation in the right precordial leads, which are not showing the Brugada type 1 pattern at the end of ablation (**bottom** on the right, red box). ABL indicates ablation; AP, antero-posterior; INF, inferior; LAO, left anterior oblique; LL, latero-lateral; PA, postero-anterior; RAO, right anterior oblique; RL, right lateral; and SUP, superior.

Procedural Data

The median procedure, fluoroscopy, and RF application times were 169 (IQR, 160–214, min–max 105–266), 8 (IQR, 7–9, min–max 6–14), and 18 (IQR, 17–21, min–max 12–31) minutes, respectively. During the procedure, the activation, voltage, and duration maps were successfully acquired during sinus rhythm and after ajmaline-induced type 1 BrS-ECG pattern in all patients. At baseline, epicardial activation started in the lower septum/apex and subsequently diverged toward the tricuspid annulus and RVOT (Figure II in the online-only Data Supplement). The red areas indicate short activation times, whereas the blue areas indicate longer activation times. No apparent conduction block was observed in any patient. After ajmaline infusion, the epicardial activation time was slightly longer without change in the sequence activation pattern, but this difference was not statistically significant (Table 2). Overall, electro-anatomic voltage maps showed small low-voltage areas in the RVOT, which were larger in group 1, particularly in patients with worst clinical presentation than in group 2 ($P<0.001$, Table 2). Before and after ajmaline, 3D epicardial duration maps displayed in the RVOT large areas of variable size with abnormally prolonged potentials, which contrasted with normal signals in the surrounding areas.

Electrophysiological Substrate Characteristics According to Clinical Presentation

Baseline clinical and ECG characteristics did not differ between the 2 groups including patients with worst clinical presentation;

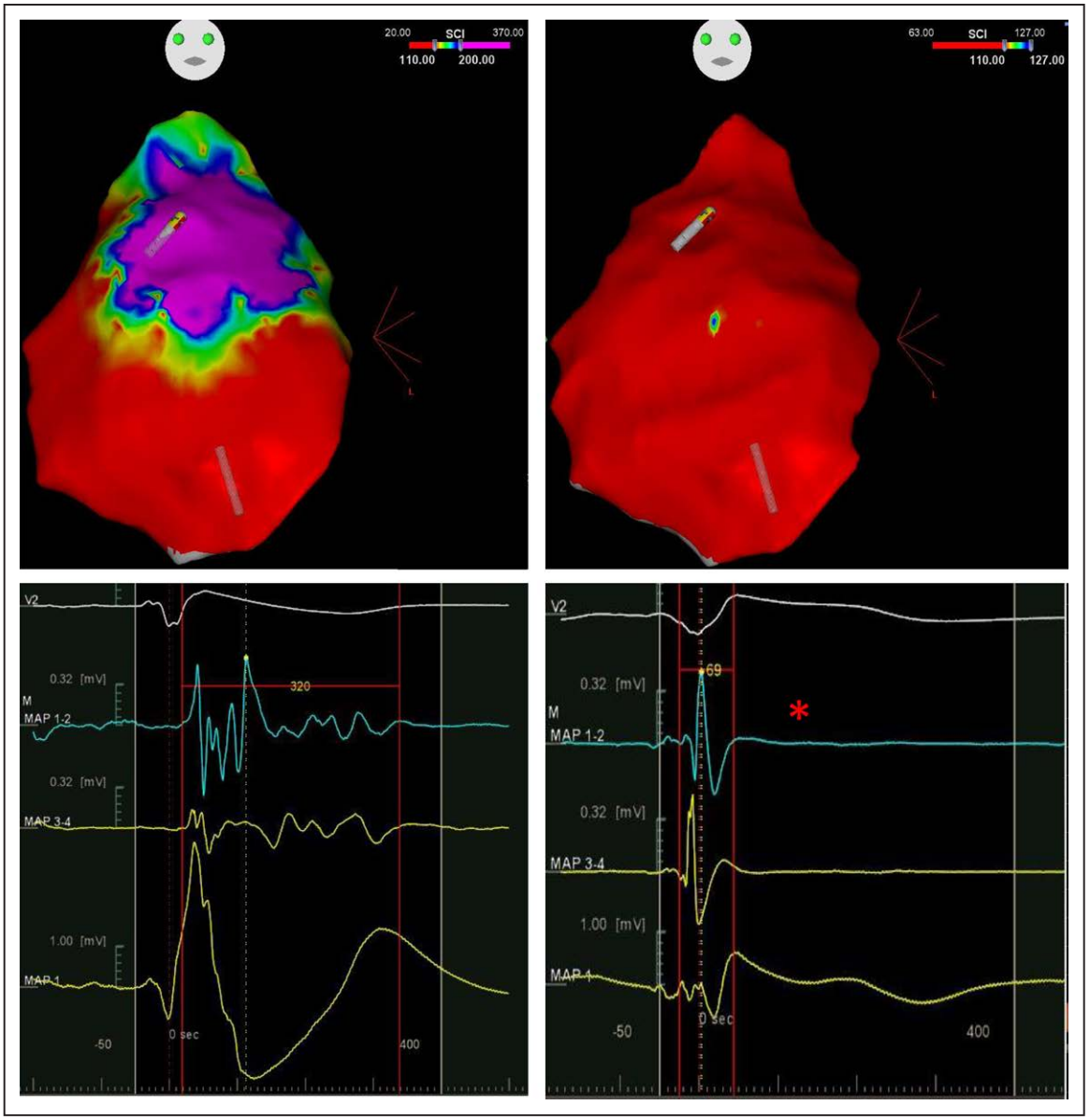

Figure 5. Potential duration map (PDM) before and after radiofrequency ablation. The figure refers to a 32-year-old patient with spontaneous type 1 Brugada pattern implanted with an implantable cardiac defibrillator due to a history of frank syncope without prodromes and an electrophysiological study positive for ventricular tachycardia/ventricular fibrillation induction. **Left**, The PDM (**left top**) before ablation. Below (**left-bottom**), example of a wide and fragmented potential discovered in the purple area (distal bipolar electrogram 320 ms duration [light blue color]). After ablation, the PDM (**right top**) shows the disappearance of abnormally prolonged electrograms, highlighting that the late component has been abolished by ablation (electrogram duration of 69 ms, light blue color; **right-bottom**, red asterisk). The electrogram showed in the **right-bottom** has been recorded in the same region which was previously exhibiting the prolonged and fragmented potential illustrated in the **left** panel on bottom. The ablation catheter shadow in both CARTO maps indicates the location where such potentials have been recorded. In each electrogram panel, V2 II ICS ECG lead (white), distal (light blue), and proximal bipolar (yellow) and unipolar (yellow) signals are shown at 200 mm/s speed, from top to bottom, respectively. Of note, in the **left-bottom** panel, the V2 lead is showing typical coved-type pattern, whereas in the **right-bottom** panel, the same ECG lead is demonstrating that the Brugada pattern has been modified, showing a horizontal and flat ST-segment elevation after ablation (**left** and **right** panels on bottom, respectively).

spontaneous type 1 BrS-ECG pattern was less frequently found regardless of clinical presentation (Table 1). CARTO maps identified epicardial areas of abnormal prolonged electric signals over the RVOT (>75%) extending after ajmaline to RV free wall (Figures 1–5; Figures VI–X in the online-only Data Supplement). The area of electric substrate significantly increased in size after ajmaline in both groups (Table 2). Before and after ajmaline, group 1 showed wider areas and more prolonged and abnormal potentials than group 2, although the increase in group 2 was 3× higher when compared with baseline values (Table 2). Of note, regardless of clinical presentation, before and after ajmaline the epicardial electric substrate was larger in men than in women (Table II in the online-only Data Supplement). Areas with the longest abnormal potentials (>280 ms) in different RV regions appeared on color-coded maps to be smaller displaying a characteristic onion-like substrate of concentric circles showing in the center the area with the widest electrograms (Figure 2; Figure Vb in the online-only Data Supplement).

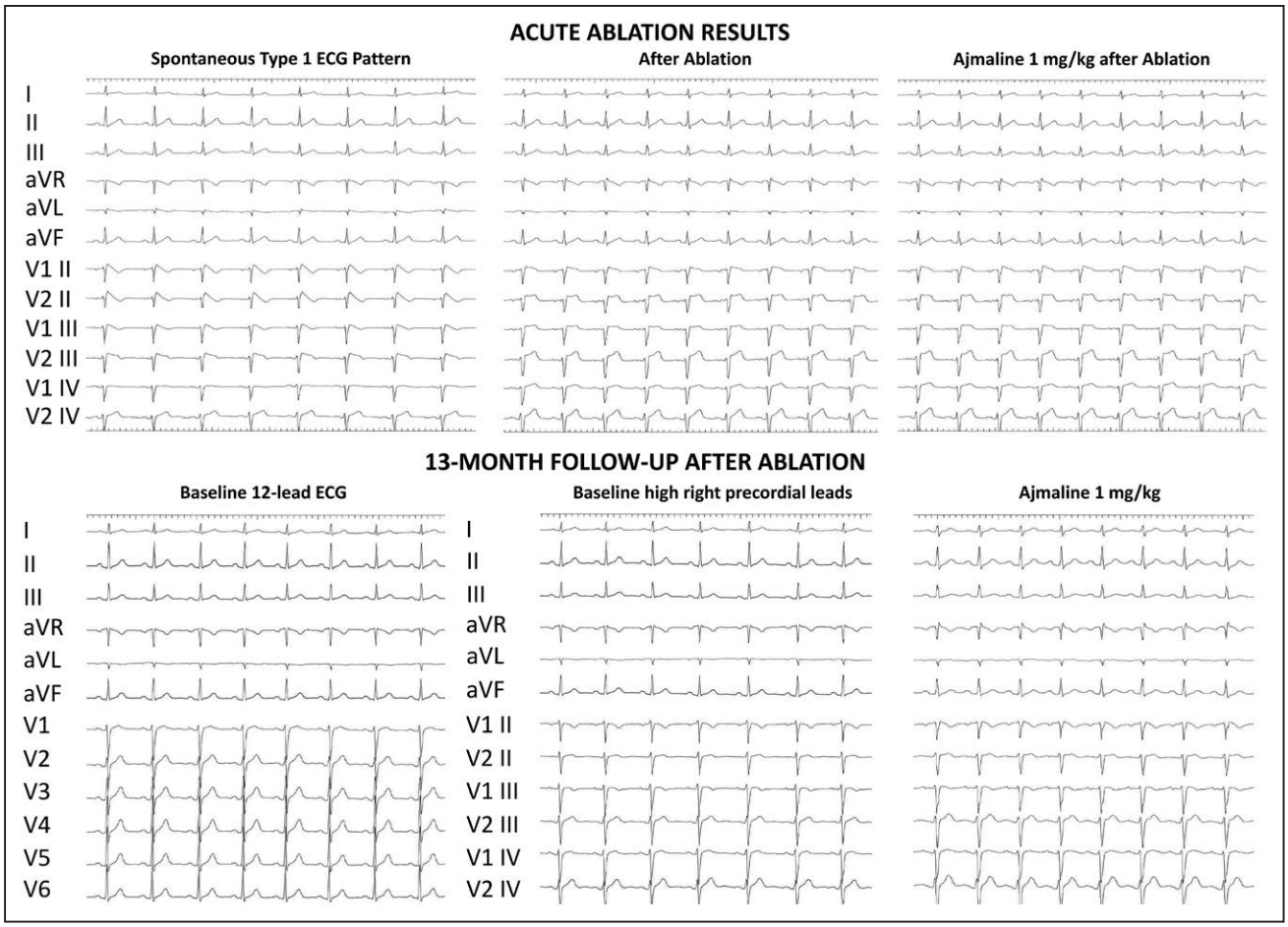

Figure 6. ECG changes immediately after ablation and 13 months after the procedure. The figure refers to a 32-year-old patient with spontaneous type 1 Brugada pattern implanted with an implantable cardiac defibrillator due to a history of frank syncope without prodromes and an electrophysiological study positive for ventricular tachycardia/ventricular fibrillation induction. **Top**, The acute disappearance of the type 1 pattern after radiofrequency ablation of the area showing fragmented and prolonged potentials. **Left**, The baseline Brugada ECG is followed by the disappearance of the type 1 pattern immediately after ablation (**top-middle**), proved by the final ajmaline challenge repeated at the end of the procedure (**top-right**). The high right precordial leads show horizontal and flat ST-segment elevation which disappears during the follow-up (**bottom**). **Bottom**, The persistent disappearance of Brugada type 1 pattern, proved by ajmaline challenge 13 months after ablation. Ajmaline infusion determines PR interval prolongation with QRS broadening and slight ST-segment horizontal elevation without the morphological characteristics of the coved-type ECG. From left to right, baseline 12-leads ECG, ECG with high right precordial leads at baseline and after ajmaline administration are shown.

Electrophysiological Substrate Characteristics According to Spontaneous ECG Pattern

There was no difference in clinical characteristics between patients with and without spontaneous type 1 ECG pattern, including age, sex, or family history of sudden death <45 years of age (Table III in the online-only Data Supplement). Larger abnormal areas and wider abnormal electrograms were found in patients with type 1 ECG pattern than in patients without (Table IV in the online-only Data Supplement). The localization of abnormal areas did not differ between patients with and without type 1 ECG pattern. Baseline ST-segment elevation did not differ between group 1 and group 2 (Table V in the online-only Data Supplement), but after ajmaline, the increase was significantly higher in group 1 (Table V in the online-only Data Supplement). Overall, after ajmaline, the degree of type 1 ST-segment elevation correlated with the magnitude of the wider area (r=0.682, P<0.001).

Substrate-Based Epicardial Ablation

Once the areas targeted for ablation were established on the map of electrogram duration, RF started beginning on areas with the widest electric potentials, which during ablation disappeared without significant change in voltage-amplitude after RF was turned off (Figures III–X in the online-only Data Supplement). Elimination of abnormal signals was confirmed by remap and ajmaline reinfusion. Seventy-eight patients after ajmaline reinfusion showed reappearance of suspicious coved ECG pattern requiring further RFA to eliminate any residual abnormal potentials. Ablation at these sites eliminated the type 1 ECG pattern with successful suppression of VT/VF. Characteristically, during initial delivery of RF energy on the longest potential duration areas, the type 1 ECG pattern increased for some seconds to progressively invert the ST-segment slope from descending to ascending (Figures 3; Figures III–X in the online-only Data Supplement), and the increase was higher in group 1 (Table V in the online-only

Table 1. Clinical Characteristics of the Study Patients According to Clinical Presentation

Characteristics	Group 1		Group 2 (N=72)	*P* Value
	Worst (N=39)	Not worst (N=24)		
Male sex, n (%)	29 (74.4)	18 (75.0)	59 (81.9)	0.584
Age, y				
Mean±SD	39.9±11.4	39.3±9.7	39.6±11.7	0.974*
Min–Max	22–63	21–59	18–71	
BrS-ECG pattern, n (%)				
Type 1	8 (20.5)	7 (29.2)	16 (22.2)	0.833
Type 2	15 (38.5)	7 (25.0)	26 (36.1)	
Type 3	16 (41.0)	11 (45.8)	30 (41.7)	
Family history of SD, n (%)	6 (15.4)	6 (25.0)	15 (20.8)	0.630
Probands,n (%)	9 (23.1)	5 (20.8)	8 (11.1)	0.213
Relatives, n (%)	4 (10.3)	2 (8.3)	12 (16.7)	0.465
Positive SCN5A, n (%)	12 (30.8)	7 (29.2)	13 (18.1)	0.254
Pre-RFA ICD therapy, n (%)	27 (69.2)	4 (16.7)	1 (1.4)	<0.001
Post-RFA ICD therapy, n (%)	2 (5.1)	0 (0)	0 (0)	0.112
Follow-up, mo				
Median	10	12	9	0.188†
IQR	7–12	8–12	7–11.8	
Min–Max	3–13	5–13	3–13	

BrS indicates Brugada syndrome; ICD, implantable cardiac defibrillator; IQR, interquartile range; and RFA, radiofrequency ablation.

*By 1-way ANOVA.

†By Kruskal–Wallis *H* test.

Data Supplement). Immediately after there was a typical flat ST-segment elevation progressively becoming ascendant in V1 and V2, which was not further modified by ajmaline and isoproterenol infusion.

Acute Complications

No procedure-related complications occurred in any patient and no ventricular tachyarrhythmia developed during ajmaline administration.

Follow-Up

Immediately after the procedure and at discharge, all patients regardless of clinical presentation or spontaneous BrS-ECG pattern showed stable ECG normalization before and after ajmaline challenge and VT/VF noninducibility. The median follow-up duration was similar in both groups including patients with worst clinical presentation (Table 1). A follow-up longer or equal to 10 months was available for 70 (52%) patients, of whom 36 presented with BrS-related symptoms or previous appropriate ICD shocks for recurrent VT/VF (27 patients). Overall, after a median follow-up of 10 months (IQR, 8–12, min–max 3–13), all but 2 of the study patients (98.5%) showed persistent ECG pattern normalization before and after ajmaline challenge and ICD interrogation demonstrated no ventricular tachyarrhythmia and noninducibility of VT/VF. Only 2 patients (1.5%) with spontaneous type 1 ECG pattern, 3 months after ablation showed a drug-induced suspicious BrS-ECG pattern. Afterward, the first patient, a 34-year-old woman with previous electrical storm and multiple appropriate ICD therapies, had a new electrical storm with several episodes of VF successfully managed by her ICD. The second patient, a 46-year-old man with previous cardiac arrest, experienced an episode of nonsustained VT. In both patients, a repeat procedure demonstrated after ajmaline test residual abnormal areas smaller than at index mapping characterized by abnormal potentials of shorter duration (from 420 at index procedure to 210 ms and from 350 at index procedure to 200 ms, respectively). The first patient subsequently developed a new episode of VF terminated by the ICD 4 months after the second procedure. The patient was admitted and re-evaluated. The ECG was normal, and an ajmaline test at full dose was completely negative. The patient presented with severe hypokalemia (2.6 mEq/L), and abnormal values in chloride and calcium excretion. A diagnosis of tubular nephropathy was done by the nephrologists. After correction of ionic imbalance, no further arrhythmias occurred during a 9-month follow-up period. There were 5 patients who 4 months after the procedure developed a self-limiting epicardial effusion without acute hemodynamic compromise as detected by echocardiography. They received outpatient care with steroidal or nonsteroidal anti-inflammatory drugs without the use of pericardiocentesis.

Discussion

Main Findings

This large prospective study provides new insights on pathophysiology, mechanisms, and management of consecutive patients diagnosed with BrS. We have consistently demonstrated that symptomatic BrS patients regardless of the clinical presentation or spontaneous BrS-ECG pattern have a well-defined anatomic and electrophysiological substrate characterized by abnormal fragmented prolonged low-frequency ventricular electrograms. Combined endo–epicardial mapping localized the substrate exclusively on the anterior RVOT and RV anterior free wall of the pericardium, and ajmaline administration was able to delineate its extension and distribution as a suitable target for successful ablation. We also demonstrated an objective relationship between the degree of type 1 ECG pattern and the extent of the substrate: the wider the abnormal area, the higher the ST-segment elevation and coved-type appearance. Substrate ablation normalized the ECG pattern without complications resulting in VT/VF noninducibility in all patients. Ajmaline was systematically repeated during the follow-up and was negative in all but 2 patients requiring a repeated effective ablation procedure. During a median follow-up of 10 months among 135 symptomatic BrS patients only 2 (1.5%) with BrS-related symptoms and multiple recurrent VT/VF episodes before ablation, experienced just one episode of VT/VF after the procedure and in one of them electrolyte imbalance was the triggering mechanism. These findings are clinically important demonstrating for the first time an effective therapeutic role of epicardial ablation in preventing VF in a large series of high-risk BrS patients with recurrent VT/VF.

Table 2. Electrophysiological Characteristics of Study Population According to the Clinical Presentation

Characteristics	Group 1		Group 2	*P* Value*	
	[a]Worst (N=39)	[b]Not Worst (N=24)	[c]Group 2 (N=72)		
Baseline abnormal area, cm^2					
Median	8.0	7.0	4.6	0.013	a vs b *P*=0.234
IQR	5.4–12.3	3.6–11.4	2.5–9.4		a vs c *P*=0.004
Min–Max	0.5–56.6	0–23.9	0–17.4		b vs c *P*=0.229
Abnormal area after ajmaline, cm^2					
>200 ms				0.001	
Median	20.0	19.2	15.7		a vs b *P*=0.692
IQR	17.9–22.4	14.4–28.1	13.0–19.1		a vs c *P*<0.001
Min–Max	9.3–64.2	11.9–36.6	5–51		b vs c *P*=0.033
>250 ms				0.004	
Median	10.0	9.2	7.3		a vs b *P*=0.353
IQR	7.2–11.5	5.6–11.9	5.2–9.1		a vs c *P*=0.001
Min-Max	4.5–35.0	2.5–16.0	1–23.5		b vs c *P*=0.143
>280 ms				<0.001	
Median	6.5	5.2	4.8		a vs b *P*=0.357
IQR	4.7–7.3	4.3–7.2	2.9–5.6		a vs c *P*<0.001
Min–Max	1.9–22.1	0.6–12.3	0.4–12.5		b vs c *P*=0.028
Baseline potential duration, ms					
Median	230	185	177	0.003	a vs b *P*=0.031
IQR	192–234	157–227	150–226		a vs c *P*=0.001
Min–Max	129–310	124–310	123–325		b vs c *P*=0.408
Potential duration after ajmaline, ms					
Median	330	310	300	0.005	a vs b *P*=0.061
IQR	310–333	280–330	260–330		a vs c *P*=0.001
Min–Max	219–423	226–405	219–480		b vs c *P*=0.372
Baseline local activation time, ms					
Median	72	66	73	0.132	
IQR	64–76	62–76	64–81		
Min–Max	59–84	53–83	53–89		
Local activation time after ajmaline, ms					
Median	82	78	85	0.126	
IQR	78–89	74–89	77–94		
Min–Max	70–96	68–95	68–103		
Baseline low-voltage area, cm^2					
Median	1	0	0	<0.001	a vs b *P*<0.001
IQR	0–7	0–0	0–0		a vs c *P*<0.001
Min–Max	0–13	0–1	0–2		b vs c *P*=0.614
Low-voltage area after ajmaline, cm^2					
Median	2	0	0	<0.001	a vs b *P*<0.001
IQR	0–12	1–0	0–0		a vs c *P*<0.001
Min–Max	0–21	0–2	0–4		b vs c *P*=0.392

IQR indicates interquartile range.

*By Kruskal–Wallis *H* Test with Dunn test for multiple comparisons.

Natural History of BrS

The natural history of the BrS, the arrhythmogenic mechanism of the clinical manifestations, and the management of the disease remain elusive, and no single causal factor seems to link all patients with BrS.[1–7,9–25] Indeed, in the past decade, with wider diagnosis of the syndrome, its clinical presentation has substantially changed ranging from an initially fatal disorder with documented VF, which may occur late and be the first manifestation of the disease, to several heterogeneous less symptomatic clinical presentations that are often without sudden death or cardiac arrest when initially diagnosed.[3] Because it is unclear whether BrS may aggravate over the time, repeated electrophysiology testing is commonly recommended in noninducible patients even after 10 years or before if the patients' cardiac status changes. In this study, we have prospectively enrolled 135 consecutive BrS patients with different clinical presentations ranging from highly symptomatic patients with documented VT/VT (63 patients) to less symptomatic patients with inducible VT/VF but without ECG documentation at the time of symptoms (72 patients). All enrolled patients were candidate for ICD implantation, according to guidelines recommendations.[2] Before enrollment, many high-symptomatic patients presenting with worst clinical presentation (about 70%) had frequent episodes of recurrent VT/VF requiring multiple appropriate ICD shocks discharges. However, despite different clinical manifestations of the study population, the baseline clinical and ECG pattern characteristics did not differ between the 2 groups of patients. Of interest, spontaneous type 1 ECG pattern was less frequently found in all patients including those with worst clinical presentation, which confirm that in BrS persistent type 1 BrS-ECG pattern is commonly transient.[3,20]

Substrate Characterization in BrS

Recent case reports and small size studies have reported preliminary data on the presence of an epicardial substrate in symptomatic BrS patients with recurrent VT/VF and implanted ICD, but anatomic and electrophysiological characteristics of the substrate remain undefined and not well established.[4–6,15,17,25–27] Because ablation of any arrhythmogenic substrate prevents the development of a later episode of an arrhythmia, the preventive ablation of a potential arrhythmic substrate in patients with BrS would be of benefit in modifying the natural history of the syndrome. In this study, which is the largest worldwide population of patients with BrS, we have systematically evaluated the effect of ajmaline to accurately identify, determine, and delineate the location and extension of any abnormal arrhythmogenic substrate by using 3D electroanatomic mapping. We administered ajmaline because it is an ideal drug because of its shorter duration of action and higher sensitivity than flecainide.[5] In our study, ajmaline was able to determine in all patients the substrate site and size, which consisted of large and variable epicardial areas identified on the basis of the presence of abnormally prolonged and fragmented ventricular electrograms, as accurately displayed on color-coded duration maps. These areas were commonly localized in the RVOT, but after ajmaline, they were extended toward the anterior right ventricular free wall in many patients, particularly in those with worst clinical presentation. Regardless of spontaneous BrS-ECG pattern, coved-type 1 ST-elevation became most prominent after ajmaline in the right precordial leads at second, third, and occasionally at fourth intercostal spaces characteristically overlying the corresponding anatomic abnormal areas displayed on the 3D maps. Of note, regardless of the clinical presentation, after ajmaline the substrate size significantly increased in all patients and the increase was larger in men than in women confirming previous studies on a sex difference in BrS.[24] The fact that in patients without BrS-related symptoms, the substrate increased more than 3× after ajmaline (with the longest duration of abnormal potential of about 500 ms after the drug) suggests that in less symptomatic patients without ECG documentation at the time of symptoms, the presence or persistence of aggravating triggers is required to activate the substrate to facilitate the development of malignant arrhythmias.[25,27,28] Regardless of clinical presentation, there was a correlation between the degree of coved-type ST-elevation and substrate magnitude. These findings are clinically important providing evidence that increases of coved-type ST-elevation in the right precordial leads V1–V3 really represent the corresponding electrophysiological changes of large abnormal RV epicardial substrates. Further evidence of a close relationship between the coved-type BrS-ECG pattern and the substrate size is the observation that in our study, the normalization of ECG pattern coincided with complete substrate elimination, frequently requiring repeated RF applications. Taken together, our data indicate that regardless of clinical presentation or spontaneous ECG pattern, the population with BrS has a well-defined potentially large epicardial substrate, which in many patients may be difficult to be activated in the absence of triggers. This may explain why in BrS the development of ventricular fibrillation is a rare and unpredictable event; why malignant tachyarrhythmias may be difficult to be rapidly managed, frequently requiring several electric cardioversions for termination;[2,26,29] and why EPT alone is not a good predictor of outcome, particularly in less symptomatic or asymptomatic patients frequently requiring multiple extrastimuli from different endocardial sites.

Substrate-Based Ablation in BrS

In 2011, Nademanee et al[4] initially reported on epicardial ablation in just 9 patients with type 1 BrS and a monthly median of 4 VT episodes requiring frequent ICD shocks. Ablation at epicardial sites rendered VT/VF noninducible in 7 of 9 patients with no clinical recurrence over a mean follow-up of 20 months. In that study, the ECG pattern normalized after ablation in 8 of 9 patients. In an editorial comment, Nademanee et al.[4] updated his preliminary results in >50 BrS patients with complete elimination of BrS-ECG pattern in all patients with no recurrent VF during a median follow-up of 3 years.[30] More recently, our group reported similar results in a series of 14 patients with symptomatic BrS (12 with ICD-documented VT/VF, in whom for the first time the substrate was determined by flecainide infusion. In this study, among 135 consecutive patients with BrS, the ECG pattern normalized in all patients after ablation of the arrhythmogenic substrate as determined by ajmaline administration and VT/VF was noninducible. These results while confirming the hypothesis that in BrS, there are extensive complex epicardial substrates,

also explain the ineffectiveness of endocardial ablation alone[15] and the lower success of less extensive epicardial ablation not systematically guided by Class Ic drug administration.[4,6] We have found that after ablation, ajmaline rechallenge in more than 60% of patients revealed additional abnormal potentials requiring further RF applications to persistently normalize the ECG pattern. In our study, RF was safely and effectively applied by a dragging technique, which did not significantly affect neither voltage amplitude nor local activation times, thus immediately "homogenizing" the entire abnormal area. Areas with low-voltage (<1 mV) fragmented potentials were found exclusively in patients with worst clinical presentation, which confirm previous studies among highly symptomatic BrS patients with recurrent VT/VF.[4–6] The mechanism of sudden ST-elevation after RF applications is unclear, and temperature sensitivity may be a potential explanation because fever commonly aggravates coved BrS pattern.[21,27] Our data suggest that the depolarization theory could be more appropriately applied to low-voltage (<1mV) fractionated substrates, as reported in patients with previous cardiac arrest or epicardial fibrosis.[4,5,17,23] These findings for the first time open the hypothesis that in most patients with BrS, the abnormal behavior of ion channels in the epicardium of the right ventricle is reversed by eliminating a layer of epicardial tissue creating what can qualify as an ionic epicardial scar.[31] Eliminating the influence of Ito in these areas might produce changes in the repolarization, normalizing the relationship in phase I of the action potential between INa and Ito, and thus avoiding electric gradients.[22]

Clinical Implications

The fact that extensive well-defined epicardial substrates are consistently present in patients with BrS regardless of clinical presentation or spontaneous BrS-ECG pattern have important clinical implications. Electrophysiological-guided epicardial ablation of the arrhythmogenic substrate can be safely and effectively achieved in an increasing number of high-volume centers, thus reducing the number of events in high-risk population, potentially limiting the number of implantable cardioverter defibrillators.[30] Our data suggest that epicardial ablation can be useful in symptomatic high-risk patients, offering a preventive therapy for VT/VF and suggesting future paths for investigation to further define the pathophysiology of the disease.

Study Limitations

These results were obtained from a high-volume center and do not automatically apply to other less experienced centers. Although among patients with BrS, who before ablation experienced frequent VT/VF recurrences and multiple ICD discharges, no further VT/VF recurrences were documented after epicardial ablation during a median follow-up of 10 months, longer follow-up are required before we can generalize or be conclusive on this point, particularly for less symptomatic patients without BrS-related symptoms.

Conclusions

In summary, the results of this prospective study in a large cohort of consecutive BrS patients with various clinical presentations, who represent the vast majority of patients currently diagnosed with BrS, have provided new information and insights into understanding of the pathophysiological substrate, mechanism, and management of the disease. We conclude that electro-physiologically and anatomically well-defined extensive abnormal epicardial areas, as exposed by ajmaline administration, are the primary site for BrS substrate and are responsible for type 1 BrS-ECG pattern and VT/VF inducibility. Persistent ECG pattern normalization without VF inducibility even after repeated ajmaline challenge suggests that substrate ablation can be considered as a potential therapy for preventing recurrent VT/VF.

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Disclosures

None.

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