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Assessing the Malignant Ventricular Arrhythmic Substrate in Patients With Brugada Syndrome

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ABSTRACT

BACKGROUND Guidelines recommend the use of implanted cardioverter-defibrillators in patients with Brugada syndrome and induced ventricular tachyarrhythmias, but there is no evidence supporting it.

OBJECTIVES This prospective registry study was designed to explore clinical and electrophysiological predictors of malignant ventricular tachyarrhythmia inducibility in Brugada syndrome.

METHODS A total of 191 consecutive selected patients with (group 1; n = 88) and without (group 2; n = 103) Brugada syndrome–related symptoms were prospectively enrolled in the registry. Patients underwent electrophysiological study and substrate mapping or ablation before and after ajmaline testing (1 mg/kg/5 min).

RESULTS Overall, before ajmaline testing, 53.4% of patients had ventricular tachyarrhythmia inducibility, which was more frequent in group 1 (65.9%) than in group 2 (42.7%; $p < 0.001$). Regardless of clinical presentation, larger substrates with more fragmented long-duration ventricular potentials were found in patients with inducible arrhythmias than in patients without inducible arrhythmias ($p < 0.001$). One extrastimulus was used in more extensive substrates (median 13 cm^2; $p < 0.001$), and ventricular fibrillation was the more frequently induced rhythm ($p < 0.001$). After ajmaline, patients without arrhythmia inducibility had arrhythmia inducibility without a difference in substrate characteristics between the 2 groups. The substrate size was the only independent predictor of inducibility (odds ratio: 4.51; 95% confidence interval: 2.51 to 8.09; $p < 0.001$). A substrate size of 4 cm^2 best identified patients with inducible arrhythmias (area under the curve: 0.98; $p < 0.001$). Substrate ablation prevented ventricular tachyarrhythmia reinducibility.

CONCLUSIONS In Brugada syndrome dynamic substrate variability represents the pathophysiological basis of lethal ventricular tachyarrhythmias. Substrate size is independently associated with arrhythmia inducibility, and its determination after ajmaline identifies high-risk patients missed by clinical criteria. Substrate ablation is associated with electrocardiogram normalization and not arrhythmia reinducibility. (Epicardial Ablation in Brugada Syndrome [BRUGADA_I]; NCT02641431; Epicardial Ablation in Brugada Syndrome: An Extension Study of 200 BrS Patients; NCT03106701) (J Am Coll Cardiol 2018;71:1631–46) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In the span of 16 years, the Brugada syndrome (BrS) has rapidly generated increasing interest and gained recognition as a major cause of sudden cardiac death in patients with structurally normal hearts (1–10). Syncope and cardiac arrest are the most common clinical manifestations, and they have been consistently identified as risk factors for further recurrent arrhythmic events (1). However, in many

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ABBREVIATIONS AND ACRONYMS

BrS = Brugada syndrome

ECG = electrocardiogram

EGM = electrogram

ICD = implantable cardioverter-defibrillator

RF = radiofrequency

RV = right ventricular

RVOT = right ventricular outflow tract

VA = ventricular arrhythmias

VF = ventricular fibrillation

VT = ventricular tachycardia

patients the disease may be less symptomatic or may remain even asymptomatic, and BrS frequently is diagnosed only after Class 1c antiarrhythmic drugs are administered. Current guidelines neither encourage nor discourage the use of programmed ventricular stimulation for risk stratification, and they state that a defibrillator may be considered for patients with induced ventricular arrhythmias (VAs) during electrophysiological study (1). Although the pathophysiology of VA remains unclear (11), recent pioneering studies in selected patients with BrS have described complex arrhythmic substrates in the right ventricular (RV) outflow tract (RVOT) or the anterior RV wall, thereby potentially leading to initiation of malignant VA (12–16). We hypothesized that in BrS the presence of an arrhythmic substrate may have a central role in clinical presentation and VA inducibility. Therefore, the objective of our study was to explore and systematically evaluate, in a large series of patients BrS, whether there are clinical and electrophysiological characteristics that are linked to, or predictive of, VA inducibility.

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METHODS

STUDY POPULATION AND PROCEDURES. Full details of the rationale and design of the BrS Registry study have been published previously (14). All consecutive selected patients with BrS who had an implantable cardioverter-defibrillator (ICD) and who were referred at the Policlinico University Hospital San Donato, in San Donato, Italy, for electrophysiological study and substrate mapping or ablation were enrolled (14). Patients were diagnosed with a type 1 BrS electrocardiogram (ECG) pattern either spontaneously or after ajmaline administration. None of the patients had prior mapping or ablation procedures. The study started in November 2015 as Epicardial Ablation in Brugada Syndrome (NCT02641431), enrolling the first 135 patients (13); the last patient was enrolled in November 2017 in an extension study (NCT03106701). The protocol was reviewed and approved by the local Institutional Review Board, and all participants gave written informed consent.

ELECTROPHYSIOLOGICAL PROCEDURE. Electrophysiological study was systematically performed with patients in a drug-free state by using standard technique, as previously described (13,14). Programmed electrical stimulation was achieved during sinus rhythm at twice the diastolic threshold and was randomly performed at the RV apex or RVOT by using up to 3 basic drive cycle lengths (from 600 to 350 ms) and up to 3 extrastimuli (S2 to S4) delivered from the apex and outflow tract of the right ventricle. The coupling interval of extrastimuli was reduced in decrements of 10 ms until 200 ms was reached for S1 to S2 or S2 to S3. For S3 to S4, the coupling interval of extrastimuli was until 180 ms. If sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) lasting >30 s or requiring electrical cardioversion was induced, the patient was categorized as having inducible arrhythmia, and the electrophysiological study was terminated regardless of completion of the stimulation protocol. In the absence of inducible sustained VT or VF, the stimulation protocol was repeated after ajmaline administration (1 mg/kg in 5 min). In patients with a type 1 ECG pattern and without inducible arrhythmias, ajmaline was administered with repeated single boluses of the drug up to a 30% increase of coved-type ST-segment elevation from baseline.

MAPPING AND ABLATION PROCEDURE. None of the patients had prior mapping or ablation procedures. After the electrophysiological study, patients underwent a combined epicardial-endocardial mapping procedure, as previously described (13,14). After pericardial access was obtained, a dedicated decapolar catheter (Decanav catheter, 1-mm electrodes with 2-8-2 interelectrode spacing, Biosense Webster, Diamond Bar, California) was introduced into the pericardial sac to map the epicardium. Three-dimensional RV endocardial (mean acquired points 452.7 ± 72.9) and epicardial mapping (521.6 ± 87.3 and 582.5 ± 94.1 points before and after ajmaline, respectively) was performed using CARTO 3 (Biosense Webster) in all patients during stable sinus rhythm.

Epicardial mapping was systematically performed after endocardial mapping, for adequate delimitation of the RV boundaries when mapping the epicardium. BrS epicardial substrate identification consisted of mapping the entire RV epicardial surface under baseline conditions and after ajmaline infusion (1 mg/kg in 5 min). Areas of low voltage were identified using a <0.5 mV cutoff value. All the potential duration maps were obtained by collecting the duration of each bipolar electrogram (EGM). Abnormal EGMs were identified if they met at least 1 of the following characteristics: 1) a wide duration (>110 ms) with fragmented component (>3 distinct peaks); 2) late component of low-voltage amplitude ranging from 0.05 to 1.5 mV; 3) distinct and delayed component exceeding the end of the QRS complex; or 4) discrete double activity. Bipolar EGMs were filtered

from 16 to 500 Hz with 0.32- to 0.39-mV gain, displayed at 200 mm/s speed.

EGMs were acquired only from the electrode pairs of the decapolar catheter (all electrodes have a 1-mm dimension, except for the tip, which is 2 mm), with the smallest interelectrode distance (2 mm) limiting the possibility to consider noise as late activity. The gain used to evaluate the EGMs was 0.32 or 0.39 mV in all patients.

Measurements were interpreted and validated online by 2 expert electrophysiologists using CARTO3 system electronic calipers. EGM acquisition was performed only if the multipolar catheter was stable in each epicardial position and if the EGM morphology, evaluated by the operators, was consistent and repetitive for at least 3 consecutive beats, thus avoiding artifacts. Acquisition was excluded if the technical quality was insufficient or if catheter-induced extrasystoles occurred. Total signal duration was measured for each potential before and after drug challenge. As a result, a color-coded map was obtained showing the regions displaying the shortest (<110 ms cutoff, red) and longest (>200 ms cutoff, purple) durations.

Radiofrequency (RF) ablation was performed during sinus rhythm 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 with an irrigation rate of 17 ml/min during ablation. RF applications were delivered by a dragging strategy up to complete elimination of all long-duration and delayed EGMs by covering the entire region exhibiting abnormal activities. The first ablation site always corresponded with the region showing the longest activity, subsequently moving toward areas with less delayed and fragmented potentials, according to a stepwise strategy. The immediate ablation endpoint was the elimination of all abnormally prolonged activity with normalization of the BrS ECG pattern.

REPEATED AJMALINE CHALLENGE AND REMAP AFTER ABLATION. At the end of ablation, ajmaline was systematically reinfused to ensure abolition of all abnormal ventricular potentials while confirming elimination of the BrS ECG pattern. When a BrS ECG pattern reappeared during infusion, epicardial duration maps were repeated to identify any residual or additional abnormal signals for further RF applications to normalize the ECG pattern definitively. Only when the final ajmaline challenge proved either abnormal epicardial activity abolition or BrS ECG pattern elimination (Online Figures 1 to 3) was VT or VF inducibility assessed.

TABLE 1 Characteristics of 191 Patients With BrS Stratified by Clinical Presentation

	Group 1 (n = 88)		Group 2 (n = 103)	p Value
	VF (n = 51)	VT (n = 37)		
Male	38 (74.5)	29 (78.4)	83 (80.6)	0.688
Age, yrs				0.196
Mean ± SD	42.1 ± 11.9	40.3 ± 9.6	38.6 ± 12.2	
Min-max	22–67	21–59	18–71	
BrS ECG pattern				0.277
Type 1	9 (17.6)	13 (36.1)	19 (18.4)	
Type 2	16 (31.4)	9 (24.3)	32 (31.1)	
Type 3	26 (51.0)	15 (40.5)	52 (50.5)	
Family history of sudden death	9 (17.6)	10 (27.0)	28 (27.2)	0.403
Probands	12 (23.5)	8 (21.6)	16 (15.5)	0.437
Relatives	9 (17.6)	2 (5.4)	23 (22.3)	0.070
Positive *SCN5A* test result	13 (25.5)	7 (18.9)	15 (14.6)	0.255
Inducibility before ajmaline	36 (70.6)	22 (59.5)	44 (42.7)	0.003
Inducibility site				0.430
Apex	21 (58.3)	9 (40.9)	22 (50.0)	
RVOT	15 (41.7)	13 (59.1)	22 (50.0)	
Extrastimuli number				0.861
1	16 (44.4)	8 (36.4)	17 (38.6)	
2	14 (38.9)	10 (45.5)	16 (36.4)	
3	6 (16.7)	4 (18.2)	11 (25.5)	
Configuration				0.592
Monomorphic VT	0 (0)	1 (4.5)	2 (4.5)	
Polymorphic VT	20 (55.6)	14 (63.6)	28 (63.6)	
VF	16 (44.4)	7 (31.8)	14 (31.8)	
Inducibility after ajmaline	15 (29.4)	15 (40.5)	59 (57.3)	0.003
Inducibility site				0.861
Apex	7 (46.7)	8 (53.3)	27 (45.8)	
RVOT	8 (53.3)	7 (46.7)	32 (54.2)	
Extrastimuli number				0.651
1	4 (26.7)	2 (13.3)	7 (11.9)	
2	4 (26.7)	3 (20.0)	14 (23.3)	
3	7 (46.7)	10 (66.7)	38 (64.4)	
Configuration				0.497
Monomorphic VT	4 (26.7)	2 (13.3)	7 (11.9)	
Polymorphic VT	9 (60.0)	11 (73.3)	48 (81.4)	
VF	2 (13.3)	2 (13.3)	4 (6.8)	

Values are n (%), unless otherwise indicated.

BrS = Brugada syndrome; ECG = electrocardiogram; Min-max = minimum-maximum; RVOT = right ventricular outflow tract; VF = ventricular fibrillation; VT = ventricular tachycardia.

DEFINITIONS. Details on definitions are reported in the Definitions section of the Online Appendix.

STATISTICAL ANALYSIS. Descriptive variables are summarized by means of frequency distributions, means, and SD or by medians and interquartile ranges and were tested with the use of chi-square tests, unpaired Student's *t*-test, Mann-Whitney *U* test, 1-way analysis of variance, or the Kruskal-Wallis *H* test with Dunn's test for multiple comparisons, as appropriate. A receiver-operating characteristic curve for substrate size and VT or VF inducibility was generated, and the area under the curve was calculated. Substrate size threshold was selected as that

TABLE 2 Electrophysiological Characteristics of 191 Patients With BrS Stratified by Clinical Presentation

	Group 1 (n = 88)		Group 2	
	VF (n = 51)	VT (n = 37)	(n = 103)	p Value
Baseline substrate size, cm^2				0.013
Median	7.0	5.7	3.2	
IQR	2.4–12.0	1.4–9.4	1.1–7.2	
Min-max	0–56.6	0.2–23.9	0–17.4	
Substrate size after ajmaline, cm^2				
>200 ms				<0.001
Median	18.9	16.0	15.1	
IQR	15.4–22.4	13.0–22.4	11.0–18.5	
Min-max	5.8–64.2	7.6–36.6	3.2–51	
>250 ms				0.003
Median	10.0	8.0	6.9	
IQR	7.1–11.6	4.7–10.7	4.1–9.1	
Min-max	0.2–35.0	1.3–16.0	0.4–23.5	
>280 ms				<0.001
Median	6.0	4.7	3.0	
IQR	3.6–7.2	1.2–7.0	1.0–5.2	
Min-max	0–22.1	0–12.3	0–12.5	
Baseline potential duration, ms				<0.001
Median	230	190	167	
IQR	192–233	156–221	150–222	
Min-max	129–310	124–310	123–325	
Potential duration after ajmaline, ms				<0.001
Median	330	315	300	
IQR	310–333	295–330	260–320	
Min-max	219–423	226–405	219–480	
Baseline local activation time, ms				0.006
Median	71	65	75	
IQR	64–76	62–76	66–81	
Min-max	59–84	53–83	53–89	
Local activation time after ajmaline, ms				0.003
Median	82	78	85	
IQR	78–87	73–89	78–94	
Min-max	70–96	68–95	68–103	
Baseline low-voltage area, cm^2				<0.001
Median	1	0	0	
IQR	0–5	0–0	0–0	
Min-max	0–13	0–1	0–2	
Low-voltage area after ajmaline, cm^2				<0.001
Median	2	0	0	
IQR	0–8	0–0	0–0	
Min-max	0–21	0–2	0–4	

IQR = interquartile range; other abbreviations as in Table 1.

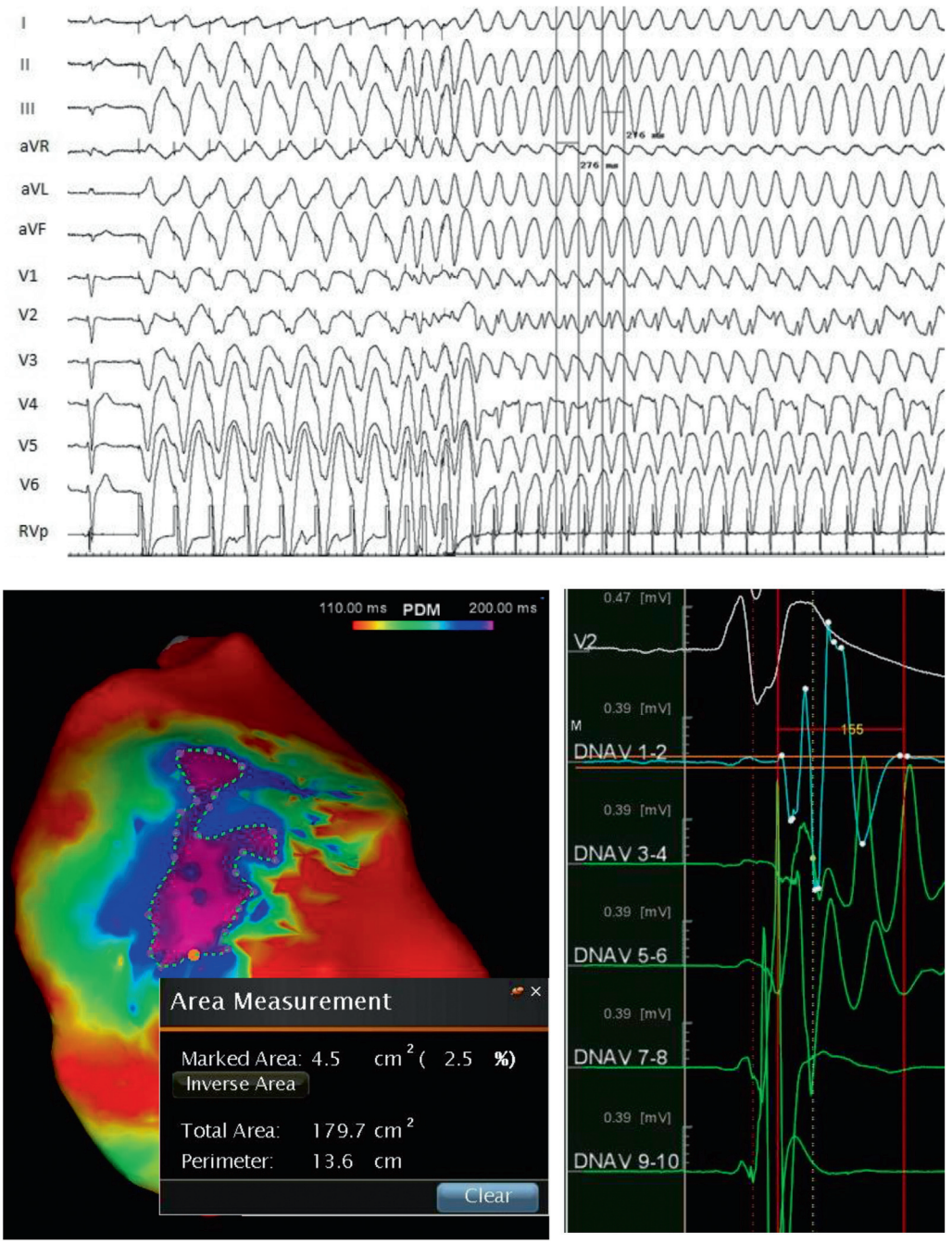
displaying optimal sensitivity and specificity for VT or VF discrimination. The receiver-operating characteristic curve was obtained with StatsDirect statistical software (release 3.1.4, StatsDirect, Ltd., Altrincham, United Kingdom). Logistic regression analysis was used in univariate and multivariate models to predict the presence or absence of inducibility on the basis of values of a set of predictor variables. Significant risk factors from univariate analysis were entered in a multivariate model using the block entry method. Logistic regression coefficients were also used to estimate odds ratios for each of the independent variables in the model. Values of $p < 0.05$ (2-tailed) were taken as statistically significant. SPSS Statistics for Windows version 23.0 software (IBM Corp., Armonk, New York) was used for statistical analysis.

RESULTS

STUDY GROUP. Among 690 screened patients with BrS who had an ICD, 191 were selected and underwent electrophysiological study and epicardial mapping or ablation. Device implantation was done at our institution in 169 patients at 12 ± 3 months before enrollment. Of the 191 subjects, 88 had cardiac arrest or syncope secondary to VF or VT (group 1), whereas 103 patients did not (group 2). The second group of patients experienced a variety of other symptoms attributable to VAs and a history of multiple documented spontaneous episodes of self-terminating ventricular tachyarrhythmias on Holter recordings. No patients were receiving antiarrhythmic drugs before the procedure. In group 1, 51 patients had the worst clinical presentation, with documented VF at the time of symptoms. The median procedure and RF application times were 166 min (interquartile range [IQR]: 142 to 196 min, minimum 102 min and maximum 266 min), and 18 min (IQR: 16 to 20 min, minimum 4 min and maximum 31 min), respectively.

CLINICAL AND ELECTROPHYSIOLOGICAL CHARACTERISTICS IN PATIENTS STRATIFIED BY CLINICAL PRESENTATION. Clinical and electrophysiological characteristics of the study group were compared according to clinical presentation (Tables 1 and 2). There were no differences between the 2 groups in clinical characteristics. Arrhythmia inducibility was prevalent in group 1, but the site of inducibility, the number of extrastimuli, and VA configuration did not differ between the 2 groups. Three different configurations of VA were induced, and polymorphic VT was the prevalent induced rhythm (Figures 1 to 6). Overall, monomorphic VT (mean cycle length 280 ± 15 ms) was inducible in 16 patients, in 3 patients before ajmaline administration (Figure 1) and in 13 after ajmaline. At baseline, polymorphic VT (mean cycle length 205 ± 16 ms) was induced in 62 patients (34 in group 1 and 28 in group 2), and it rapidly degenerated to VF in 47 patients (26 patients in group 1 and 21 in group 2) (Figures 2 and 3). After ajmaline, fast, irregular polymorphic VT (mean cycle length 215 ± 10 ms) was induced in 68 patients (20 in group 1 and 48 in group 2) (Figures 4 to

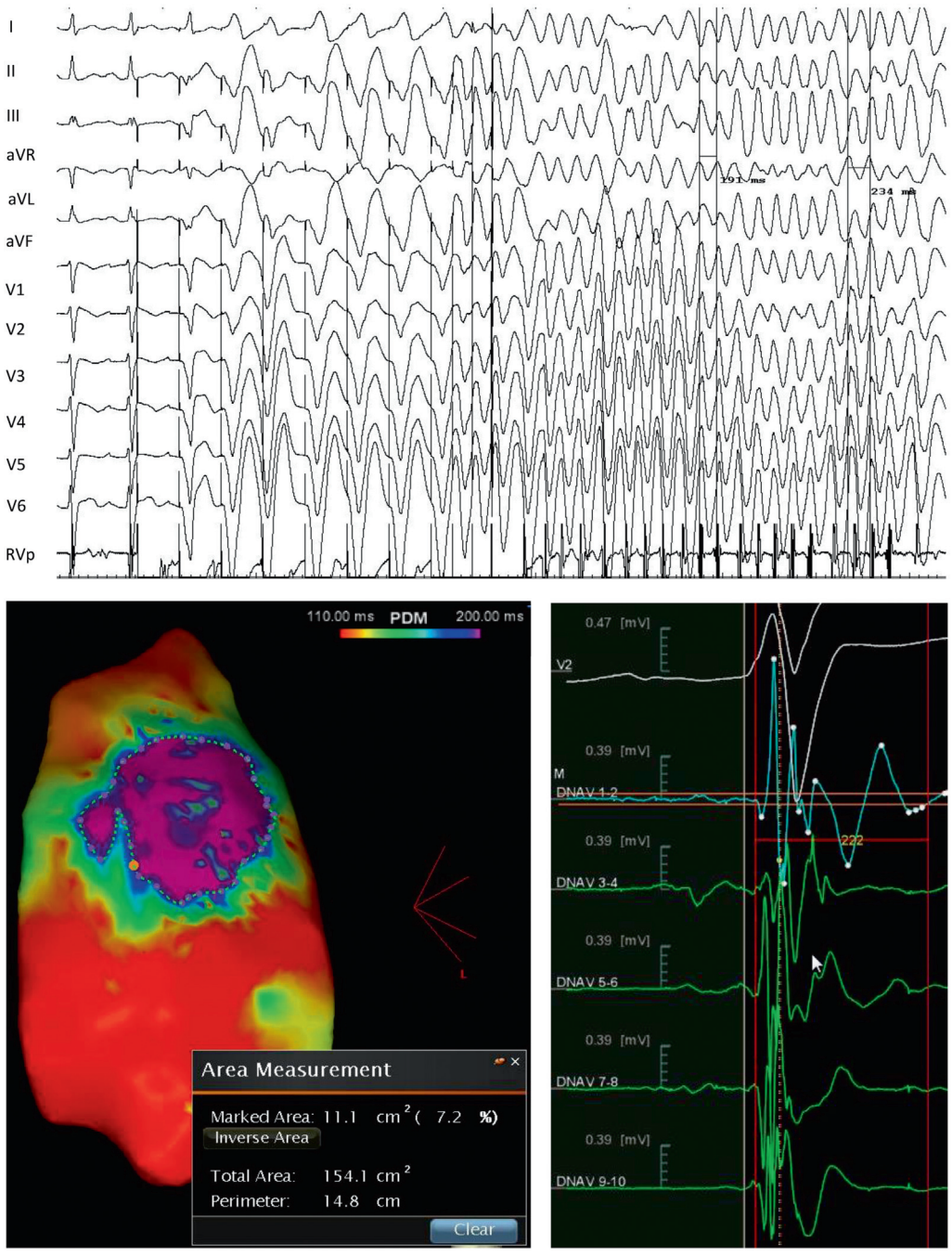
FIGURE 1 **Before Ajmaline, Monomorphic VT Was Induced With Triple Extrastimulation in a Patient With BrS-Related Symptoms**



The patient had a normal electrocardiogram pattern and a substrate size of 2.1 cm^2, which after ajmaline increased to 4.5 cm^2. The duration of fragmented potentials increased after ajmaline from 145 ms to 155 ms. BrS = Brugada syndrome; PDM = potential duration map; VT = ventricular tachycardia.

6), and in 45 of these patients the arrhythmia rapidly degenerated to VF (15 in group 1 and 30 in group 2). Overall, VF was induced in 37 patients (23 in group 1 and 14 in group 2) and after ajmaline in 8 patients (4 in group 1 and 4 in group 2). According to clinical presentation, the substrate characteristics were significantly different between the 2 groups (Table 2). Before and after ajmaline administration,

FIGURE 2 Before Ajmaline, Sustained Polymorphic VT Was Induced With Triple Extrastimulation in a Patient Without BrS-Related Symptoms

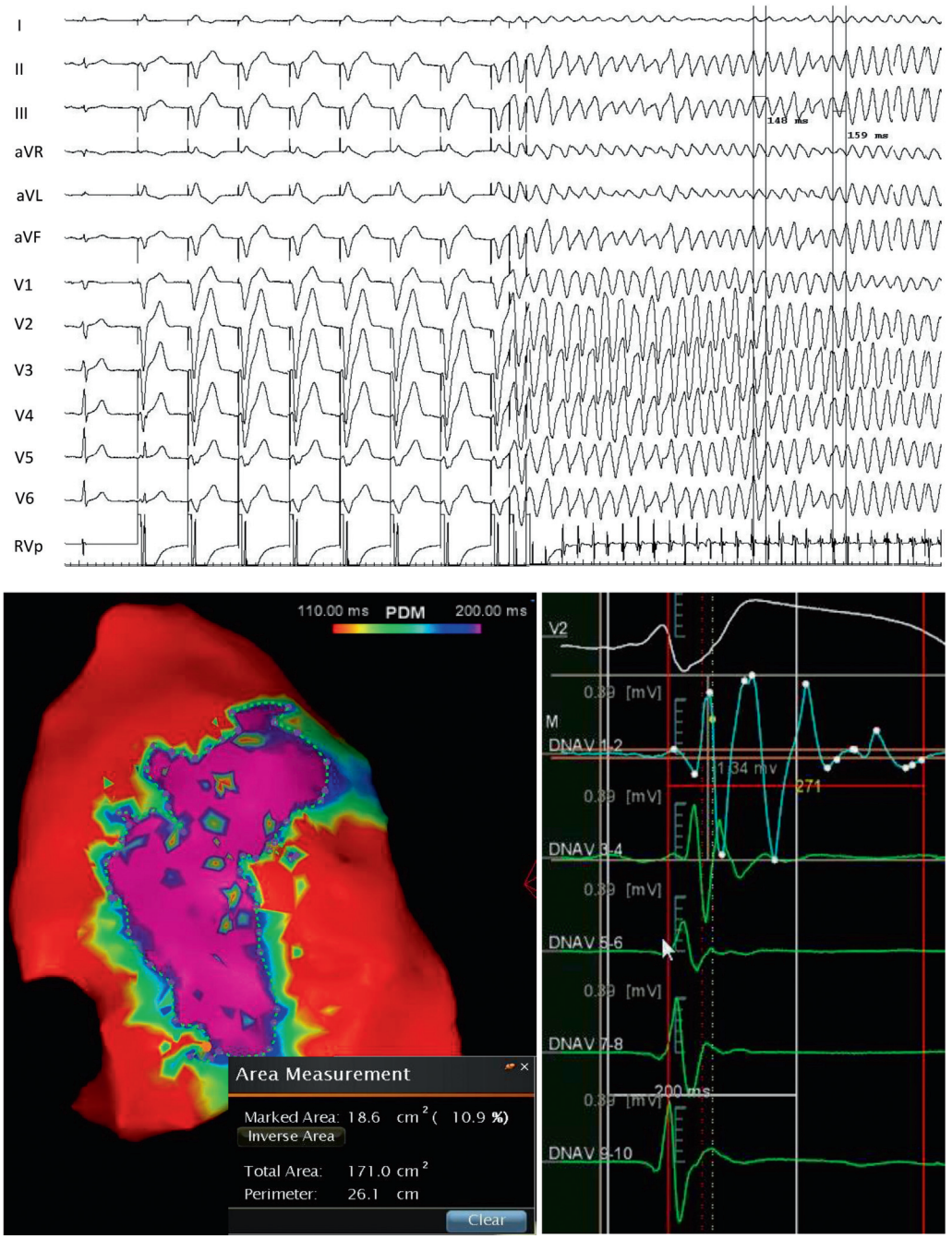


The patient had a type 1 electrocardiogram pattern and substrate size of 8 cm^2, which after ajmaline increased to 11.1 cm^2. The duration of abnormal potentials increased from 148 to 222 ms. VF = ventricular fibrillation; other abbreviations as in Figure 1.

group 1 showed a larger substrate with more prolonged fragmented potentials than group 2, but the low-voltage area was larger only in patients with VF (Table 2).

CLINICAL AND ELECTROPHYSIOLOGICAL CHARACTERISTICS IN PATIENTS STRATIFIED BY INDUCIBILITY. Table 3 shows the clinical and electrophysiological characteristics of the 191 patients after stratification by inducibility.

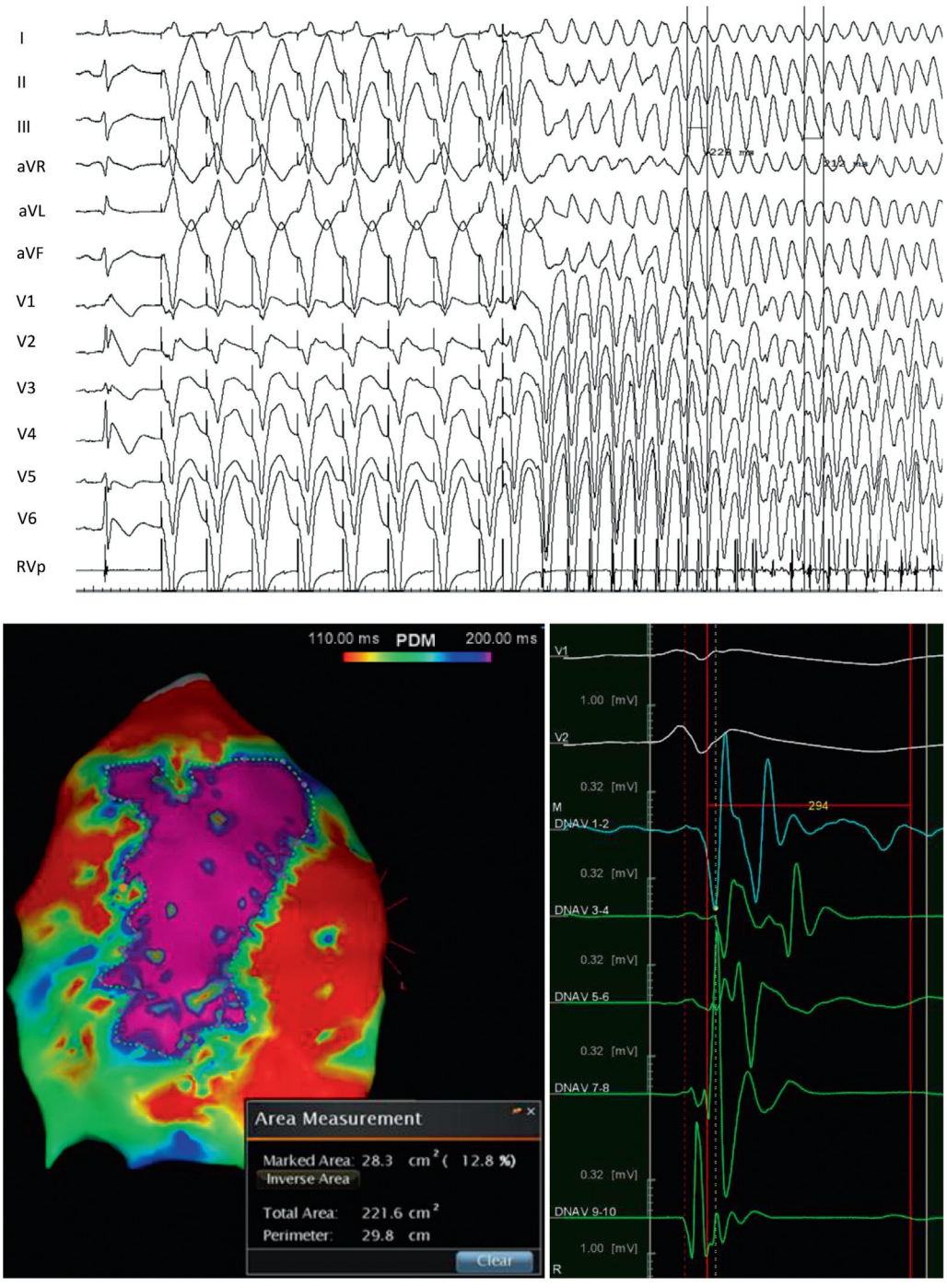
FIGURE 3 At Baseline, an Episode of Sustained Polymorphic VT Was Induced With Double Extrastimulation in a Patient With BrS-Related Symptoms



The patient had a normal baseline electrocardiogram pattern and a substrate size of 12.3 cm^2, which after ajmaline increased to 18.6 cm^2. The duration of fragmented potentials also increased after ajmaline from 230 to 271 ms. Abbreviations as in Figures 1 and 2.

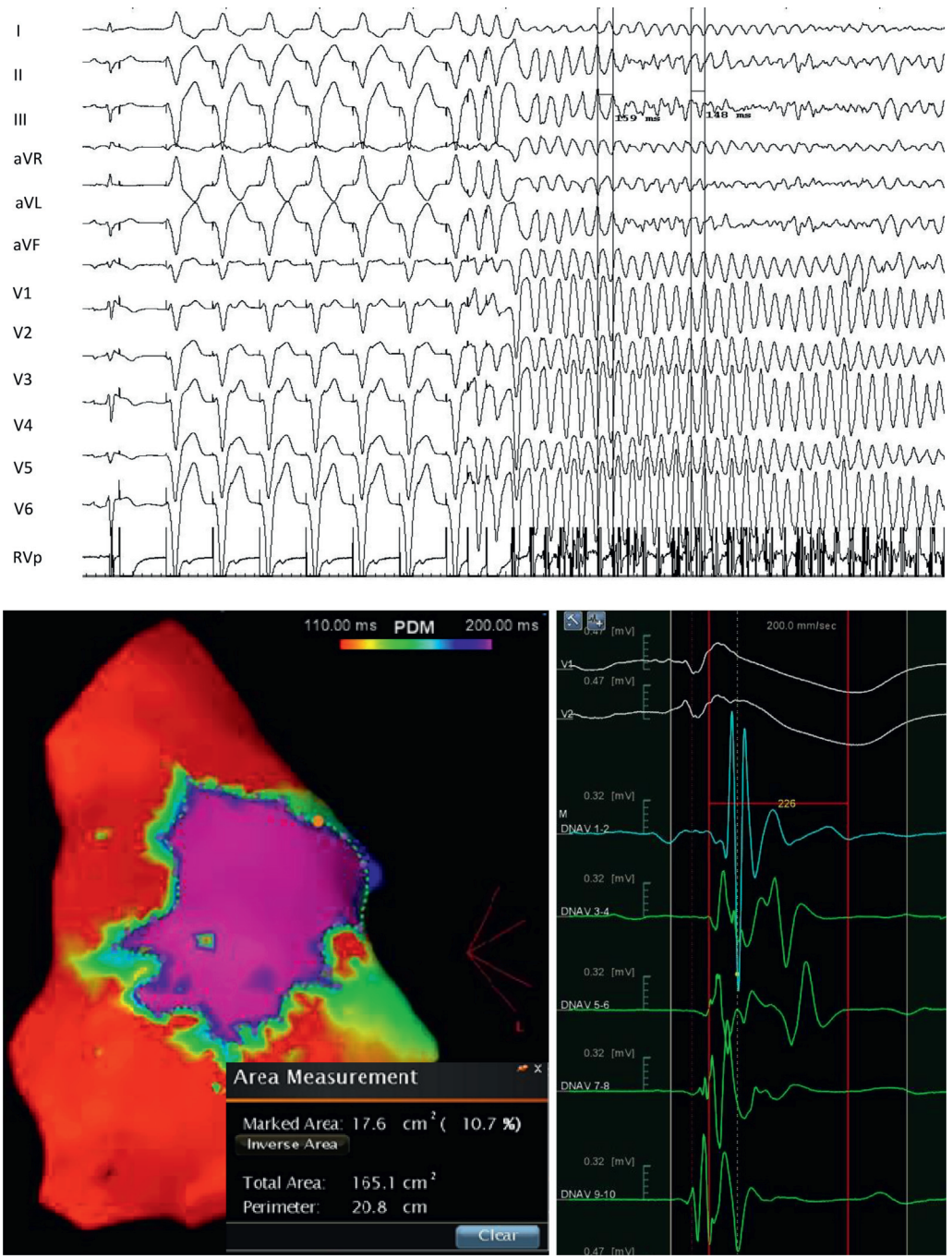
Overall, 102 of 191 patients (53.4%) had inducible VT or VF, which was more frequent in group 1 (65.9%) than in group 2 (43.1%; $p < 0.001$). The remaining 89 patients did not have inducible VT or VF (30 in group 1 and 59 in group 2; $p < 0.001$) (Table 3), but after ajmaline all patients had inducible sustained VT or VF without difference between the 2 groups in the site of inducibility, the number of extrastimuli, and VT

FIGURE 4 After Ajmaline, Polymorphic VT Was Inducible Using Single Extrastimulation in a Patient Without BrS-Related Symptoms



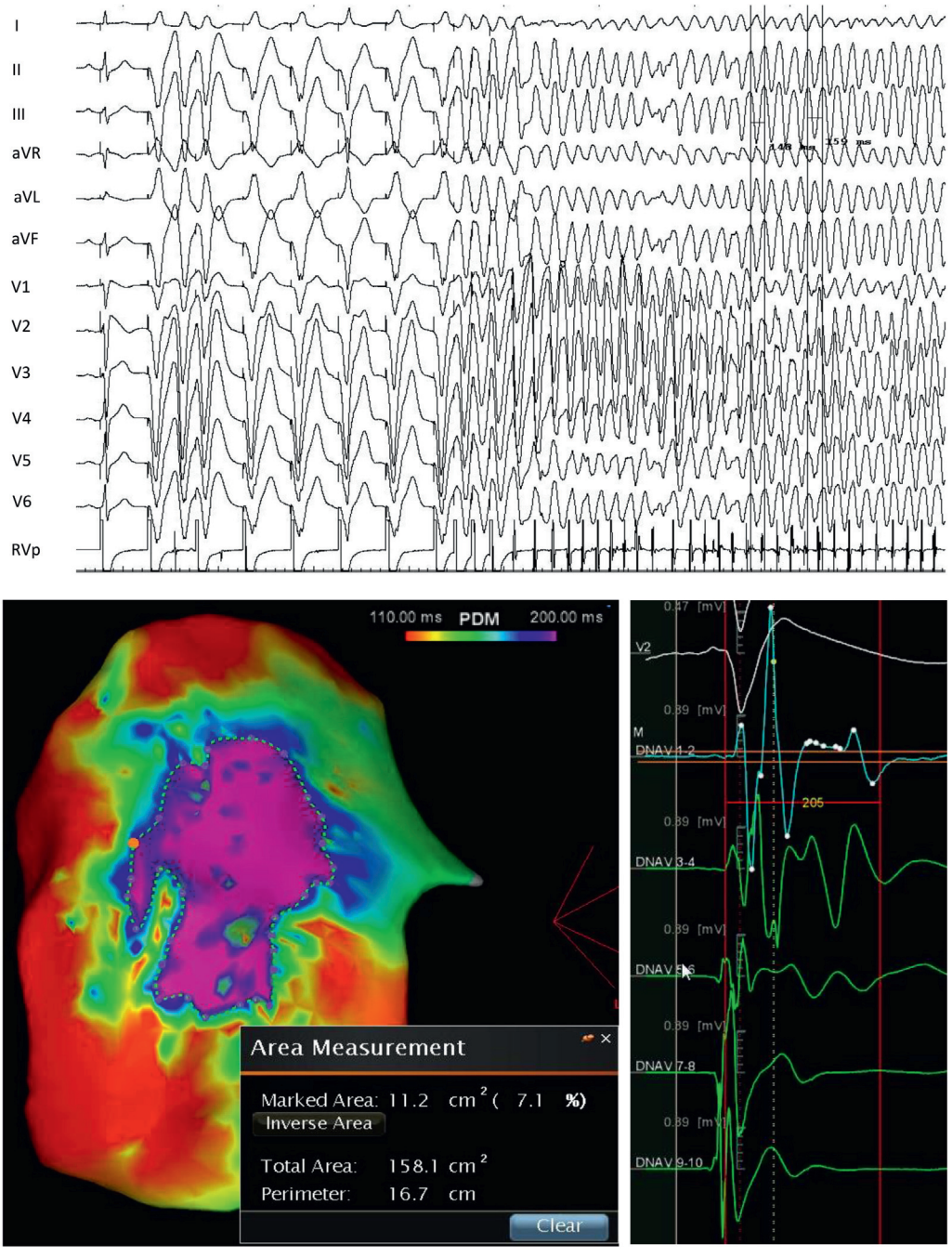
The drug induced a type 1 electrocardiogram pattern and an impressive substrate increase from 7 to 28.3 cm^2. The duration of abnormal fragmented potentials significantly increased after ajmaline from 130 to 294 ms. Abbreviations as in Figure 1.

FIGURE 5 After Ajmaline, Polymorphic VT Degenerating to VF Was Inducible Using Double Extrastimulation in a Patient Without BrS-Related Symptoms



This was associated with appearance of a type 1 Brugada syndrome (BrS) electrocardiogram pattern and a concomitant substrate increase from 5.2 cm^2 at baseline to 17.6 cm^2 after ajmaline. The duration of fragmented potentials also increased from 145 to 226 ms. Abbreviations as in Figures 1 and 2.

FIGURE 6 After Ajmaline, Sustained Polymorphic VT Degenerating to VF Was Induced Using Triple Extrastimulation in a Patient With BrS-Related Symptoms Who Did Not Have Inducible Arrhythmia at Baseline



Inducibility of ventricular tachycardia (VT) or ventricular fibrillation (VF) was associated with appearance of type 1 Brugada syndrome (BrS) electrocardiogram pattern and an impressive expansion of the substrate size from 0.5 cm^2 at baseline to 11.2 cm^2 after ajmaline. The duration of fragmented potentials also increased from 123 to 205 ms. Abbreviations as in Figure 1.

TABLE 3 Characteristics of 191 Patients With BrS Stratified by Inducibility

	Inducibility		
	Yes (n = 102)	No (n = 89)	p Value
Male	82 (80.4)	68 (76.4)	0.503
Age, yrs			0.875
Mean ± SD	40 ± 10.7	39.7 ± 12.8	
Min-max	18–63	20–71	
Spontaneous BrS ECG pattern			<0.001
Type 1	36 (35.5)	5 (5.6)	
Type 2	27 (26.5)	30 (33.7)	
Type 3	39 (38.2)	54 (60.7)	
Family history of sudden death	23 (22.5)	24 (27.0)	0.480
Probands	22 (21.6)	14 (15.7)	0.303
Relatives	17 (16.7)	17 (19.1)	0.661
Positive *SCN5A* test result	25 (24.5)	10 (11.2)	0.018
Baseline substrate, cm^2			<0.001
Median	8	1	
IQR	6.1–12.2	0.3–2.5	
Min-max	2–56.6	0–7	
Baseline potential duration, ms			<0.001
Median	220	160	
IQR	170–234	150–210	
Min-max	124–325	123–280	
Group			<0.001
VF	36 (35.3)	15 (16.9)	
VT	22 (21.6)	15 (16.9)	
Group 2	44 (43.1)	59 (66.3)	

Values are n (%), unless otherwise indicated.
Abbreviations as in Tables 1 and 2.

TABLE 4 Substrate Size and Inducibility Findings in 102 Patients With BrS With Pre-Ajmaline Inducible Arrhythmias as Stratified by Clinical Presentation

	Group 1 (n = 58)			
	VF (n = 36)	VT (n = 22)	Group 2 (n = 44)	p Value
Baseline substrate size, cm^2				0.523
Median	9.1	7.5	8	
IQR	6.0–13.5	6.1–12.3	5.8–11.5	
Min-max	3.1–56.6	2.1–23.9	2–17.4	
Extrastimuli number				
1				0.321
Median	13.8	12.9	11.9	
IQR	12.1–17.8	12–16.5	11.1–14.7	
Min-max	9.9–56.6	10–23.9	10–17.4	
2				0.646
Median	7.5	7	7.4	
IQR	6.6–8.3	6.6–8.0	7–8.5	
Min-max	6–9.8	6–9.8	6–9.6	
3				0.475
Median	5.1	4.5	5	
IQR	3.9–5.4	2.6–5	4.2–5.5	
Min-max	31–5.4	2.1–5	2–5.7	
Configuration				
Polymorphic VT				0.858
Median	7.2	7.0	7.1	
IQR	6–8.6	5.8–8.0	5.5–8.5	
Min-max	3.1–14	4–10	2–17.4	
VF				0.398
Median	13.3	13	12.5	
IQR	11.6–17.8	12.1–16.9	10.9–14.6	
Min-max	5.1–56.6	11.9–23.9	10–17.2	
Inducibility site				
Apex				0.043
Median	12.3	10	7.8	
IQR	8.0–15.7	6.5–14.5	5.5–10.3	
Min-max	3.1–56.6	4–23.9	2–16.9	
RVOT				0.384
Median	7.1	7.2	9.0	
IQR	6.0–9.0	5.6–11.3	5.9–13.0	
Min-max	5.1–12.4	2.1–15.2	4.2–17.4	

Abbreviations as in Tables 1 and 2.

configuration. Patients with inducible arrhythmia more often had a spontaneous type 1 ECG pattern (35.5%), a larger substrate, and more prolonged fragmented potentials than patients without inducible arrhythmia, but there were no differences in sex and age (Table 3). Positive results of genetic testing for *SCN5A* were more frequently found in patients who had inducible arrhythmia than in patients without inducible arrhythmia (Table 3). Overall, of the 102 patients with inducible arrhythmia, 40.2% had the arrhythmia induced with 1 premature beat, 39.2% with 2 premature beats, and 20.6% with 3 premature beats (Table 1). However, regardless of clinical presentation, after ajmaline the number of patients with inducible arrhythmia was higher when more aggressive protocols were used (Table 1).

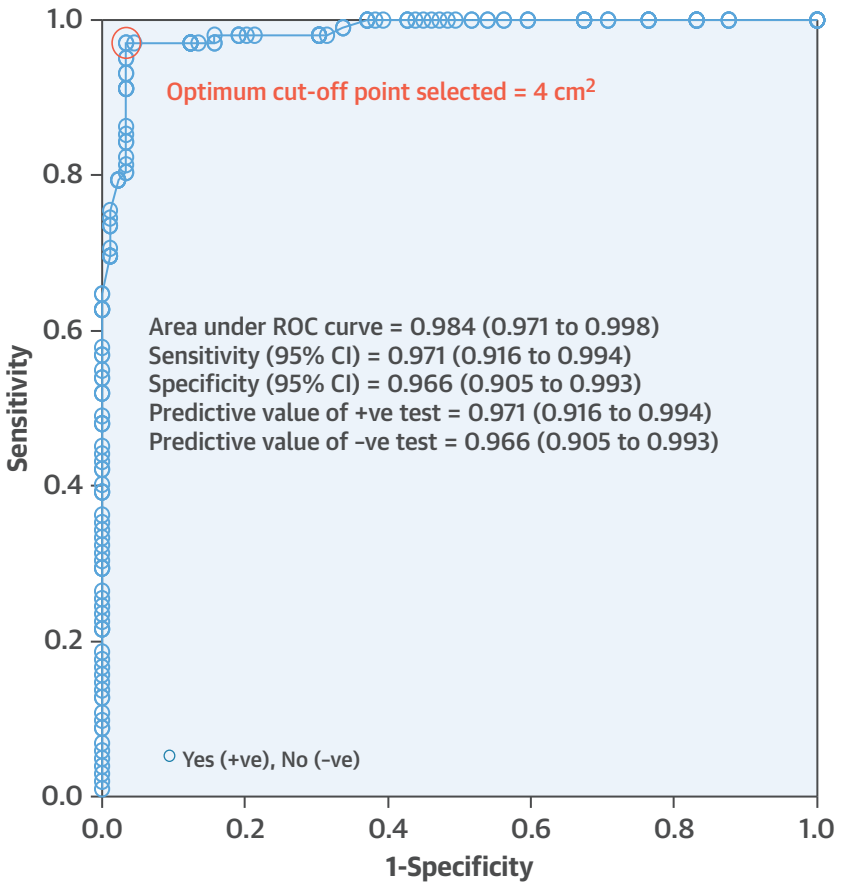
The site of arrhythmia inducibility was equally distributed between the RVOT (49%) and the RV apex (51%), without difference between the groups (Table 1). When patients with inducible arrhythmia were stratified by clinical presentation, there was no difference in substrate size between patients with (n = 58) and without (n = 44) BrS-related symptoms regardless of the number of extrastimuli or different VA configurations (Table 4). A larger substrate was found in group 1 when the site of inducibility was the apex (Table 4). According to substrate size and regardless of clinical presentation, fewer extrastimuli were required for VT or VF induction in patients with larger substrates, particularly after ajmaline administration (Figures 4 to 6), and VF rather than polymorphic VT was the more prevalent induced arrhythmia (Online Tables 1 and 2).

CENTRAL ILLUSTRATION **Predictors of VT or VF Inducibility in Patients With BrS**

A Clinical and Electrophysiological Variables Associated With Inducibility of VA in BrS Patients

	Regression coefficient	p Value	Adjusted OR	95% CI
Age	-0.014	0.616	0.986	0.932-1.042
Sex	0.610	0.472	1.841	0.349-9.698
Positive SCN5A	0.213	0.836	1.237	0.165-9.298
Clinical presentation	0.486	0.557	1.626	0.321-8.224
Substrate size, cm^2	1.506	< 0.001	4.511	2.515-8.090
Potential duration, ms	-0.011	0.372	0.989	0.966-1.013
Spontaneous type 1 ECG	0.040	0.971	0.961	0.109-8.431
Constant	-4.170			

B Optimal Substrate Cut-off Value Identifying Patients With Inducibility of VA in BrS



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BRUGADA SYNDROME ELECTROCARDIOGRAM PATTERN AND SUBSTRATE. Irrespective of the inducibility and clinical presentation, Online Table 3 shows the substrate characteristics according to spontaneous BrS ECG pattern. Overall, there were 41 patients with a type 1 ECG pattern, 57 with a type 2 ECG pattern, and 93 with a type 3 ECG pattern. Larger substrates and more fragmented prolonged ventricular potentials both before and after ajmaline administration were found in patients with a type 1 ECG pattern.

INDUCIBILITY AFTER SUBSTRATE ABLATION. Elimination of abnormal signals was confirmed by remapping and ajmaline reinfusion. A total of 109 patients after ajmaline reinfusion showed reappearance of a suspicious coved ECG pattern requiring additional RF applications to eliminate any residual abnormal potential. Ablation at these sites eliminated the type 1 ECG pattern while suppressing VT or VF inducibility.

UNIVARIATE AND MULTIVARIATE ANALYSIS. In univariate analysis, several variables were predictors of inducible VT or VF (Online Table 4). After multivariate analysis (**Central Illustration, A**), the substrate size was the only variable retained as an independent predictor of inducible ventricular tachyarrhythmias, and by receiver-operating characteristic analysis (**Central Illustration, B**), a substrate size of 4 cm^2 best differentiated patients with inducible arrhythmia from those without inducible arrhythmia (area under the curve: 0.98; $p < 0.001$).

COMPLICATIONS. No patients had serious complications resulting from both electrophysiological study and mapping. Two subjects experienced pericarditis, and 1 of them had a mild pericardial effusion, successfully treated with steroids. No spontaneous ventricular tachyarrhythmia developed before and during ajmaline administration.

DISCUSSION

This study systematically evaluated a correlation between VT or VF inducibility and the substrate size underlying BrS in a large cohort of patients with BrS who presented with various clinical manifestations.

CLINICAL PRESENTATION IN BRUGADA SYNDROME. Currently, the understanding of how BrS can manifest has expanded to include milder clinical forms as a result of better identification by pharmacological testing (8). In patients with BrS and structurally normal hearts, ventricular tachyarrhythmias may have less catastrophic presentations, including syncope, dizziness, or palpitations that are sometimes harbingers of a future fatal event. Although less symptomatic patients now represent the largest subgroup of patients encountered in clinical practice, at present there is a lack of evidence-based recommendations for patients without BrS-related symptoms, commonly defined as the "asymptomatic population," as in our study of group 2, which remained in the gray zone for ICD insertion (1).

INDUCIBILITY OF MALIGNANT ARRHYTHMIAS IN BRUGADA SYNDROME. Guidelines have proposed an extended and more liberal use of ICD insertion as Class IIb treatment for patients with inducible VT or VF during electrophysiological testing also in the absence of BrS-related symptoms (1). As a result, the clinical relevance of VT or VF inducibility in BrS has been gaining more attention in the last decade and now has been rehabilitated (1,7–10,17). The results of our study add to the understanding of a causative association between VT or VF inducibility and substrate size among patients with or without BrS-related symptoms (**Central Illustration, A and B**), thus providing new pathophysiological information to support existing guidelines.

ARRHYTHMIC SUBSTRATE AS A MECHANISM OF VENTRICULAR ARRHYTHMIAS IN BRUGADA SYNDROME. Traditionally, inducibility of VT is believed to be the result of interplay between a stable arrhythmogenic substrate and transient triggers leading to electrical instability and VT. Many patients undergo ICD insertion to teminate episodes of sustained VT acutely, but the device neither modifies the substrate nor prevents VT inducibility, whereas

CENTRAL ILLUSTRATION Continued

This study considered whether the arrhythmic substrate was an independent predictor of lethal ventricular tachyarrhythmias in patients with or without Brugada syndrome (BrS)-related symptoms. **(A)** Multivariate analysis demonstrates that unlike variables such as clinical presentation, type 1 Brugada syndrome electrocardiogram (ECG) pattern, and genetic test results, only substrate size was the variable retained as an independent predictor of inducibility. **(B)** By receiver-operating characteristic (ROC) analysis, a substrate size of 4 cm^2 best differentiated patients with inducible ventricular tachycardia (VT) or ventricular fibrillation (VF) from patients without inducible ventricular tachycardia or ventricular fibrillation (area under the curve: 0.98; $p < 0.001$). CI = confidence interval; OR = odds ratio; VA = ventricular arrhythmia.

elimination of the underlying arrhythmic substrate should prevent VA inducibility if the substrate behaved as a mechanism of the arrhythmia, as in our study in all patients who no longer had reinducible ventricular tachyarrhythmias after substrate ablation.

The present study systematically determined and analyzed both inducibility and substrate characteristics among 191 consecutive patients diagnosed with BrS. Overall, at baseline 53.4% of patients had inducible sustained VT or VF; 65.9% of these patients presented with BrS-related symptoms, and 43.1% did not. Characteristically, arrhythmia inducibility increased in a linear fashion with the substrate size regardless of clinical presentation. We have found more extensive substrates in patients with inducible VT or VF (median 8 cm^2) than in patients who did not have inducible VT or VF (median 1 cm^2), independent of their initial clinical manifestation. The substrate was characterized by a high degree of electrical heterogeneity, largely because of extensive areas of fractionated abnormal ventricular EGMs, which were more prolonged in patients with inducible arrhythmias (median 220 ms) than in patients without inducible arrhythmias (median 160 ms).

Differences in the extent and heterogeneity of substrate among patients also influenced the number of extrastimuli for VA inducibility. In patients with larger and more fragmented substrates, induction of VT or VF became easier using a less aggressive protocol of single or double extrastimuli. Overall, patients with arrhythmias that were inducible with a single extrastimulus were found to have up to 3 times more extensive substrates (median size 13 cm^2) than patients with arrhythmias that were inducible with 3 extrastimuli (median size 5 cm^2). Of interest, 46.6% of patients who did not have inducible arrhythmias at baseline (34.1% in group 1 and 57.3% in group 2) did have inducible arrhythmias after ajmaline induced a significant expansion of the substrate; after ajmaline administration, the increase was 5 times larger in group 2, but the increase after ajmaline was less impressive in group 1, when compared with baseline values.

These findings are clinically relevant, suggesting that in BrS malignant arrhythmias are less likely to be induced in small substrates despite an aggressive protocol of stimulation, particularly localized in the RVOT, as in many patients in both groups before ajmaline. Independent of clinical presentation, in this study at baseline the arrhythmic substrate was highly variable in size among patients, and the use of ajmaline testing was able to unmask substrates at risk that were only minimally detectable or not detectable at baseline. These results strongly support the concept of a dynamic substrate in BrS, including that exposed by ajmaline, as the primary mechanism of VT or VF inducibility, unrelated to traditional "low-voltage" criteria for scar or fibrosis. This finding limits speculation and advocacy on the role of programmed electrical stimulation in the clinical selection of therapy for patients with BrS, as reported in a recent multicenter pooled analysis (7).

These findings are clinically significant and could readily explain why, in the large group of patients with BrS, the occurrence of cardiac arrest or sudden death appears to be relatively rare but not negligible, mostly depending on baseline substrate size and its potential expansion or activation in the presence of occasional transient triggers such as fever, drugs, vagal tone, as in many patients who only after ajmaline had arrhythmias inducible even by a single extrastimulus. Interestingly, in our study about 50% of the induction of arrhythmias was achieved from the RVOT, a site that has been previously reported to induce mainly false-positive test results (1,9). This is not surprising if one considers the RVOT area as the most common site of the arrhythmic substrate in BrS, as consistently demonstrated by 3D mapping in our study. After all, it is common practice during ablation of any supraventricular arrhythmia or VA first to localize the substrate, then induce it, for successful ablation and then check to ensure that the arrhythmia is not reinducible. The usefulness of performing pre- and post-ablation ajmaline testing and VT or VF inducibility is further justified by the finding that fragmented long-duration potentials often reappear after ablation under drug challenge, as in about 60% of our patients.

PREDICTORS OF INDUCIBILITY OF VENTRICULAR ARRHYTHMIAS IN BRUGADA SYNDROME. The striking feature of this study was the independent association between the extent of the substrate size and VT or VF inducibility, as well as the identification of an optimal cutoff for inducibility (**Central Illustration, A and B**). Other significant univariate clinical predictors, including a spontaneous type 1 ECG pattern, clinical presentation, and positive genetic test results, were all excluded from the next step in the multivariate analysis. In this study, some patients with the worst clinical presentation and minimal or no substrate at baseline, who had no inducible arrhythmias up to 3 extrastimuli, did have inducible arrhythmias with single or double extrastimulation

after substrate expansion induced by ajmaline. By contrast, other patients without BrS-related symptoms but with larger substrate at baseline had VT or VF inducibility without use of ajmaline. Interestingly, a recent study of >300 asymptomatic patients with BrS reported that only VT or VF inducibility was associated with events in the multivariate model (9).

In the present study, VF was the more prevalent induced rhythm (137 of 191 patients), but in 92 patients very fast polymorphic VT preceded VF. In BrS the endpoint of programmed ventricular stimulation has been generally considered VT or VF inducibility without distinguishing between fast, irregular polymorphic VT and VF (1–10,17). On the basis of their different ECG appearances, polymorphic unstable VT and VF have been traditionally thought of as resulting from 2 widely different mechanisms. Our data are consistent with observations made in animal models and in patients with structurally normal hearts, such as patients with BrS, whose frequent transition from very fast, irregular polymorphic VT to VF suggests a single arrhythmic mechanism underlying both VF and polymorphic unstable VT (18–24).

In agreement with our observations are the results of a recent study among 14 patients with BrS experiencing 21 episodes of VT or VF; polymorphic VT was recorded in 19 of the 21 episodes, whereas VF developed in 4 episodes, of which 2 episodes were triggered by polymorphic VT (22). We found that patients with inducible VF had 2 times larger substrates (median size 13 cm^2) than patients with inducible polymorphic VT (median size 7.1 cm^2) or inducible monomorphic VT (4.2 cm^2). These findings are of clinical relevance, suggesting that in patients with BrS the size, location, and transient varying extent with a high degree of electrical inhomogeneity over large areas of the right ventricle facilitate initiation of unstable VT or VF. We were able to demonstrate with high specificity and sensitivity that in patients with BrS a substrate size of 4 cm^2 best differentiated patients with inducible arrhythmias from patients without inducible arrhythmias (**Central Illustration, A and B**), a finding that supports a new substrate-based quantitative approach to management of BrS.

STUDY LIMITATIONS. These results were obtained in a high-volume, experienced center that has not reported any major procedure-related complications. Therefore, the results do not necessarily apply to other or less experienced centers. Bipolar EGMs were filtered from 16 to 500 Hz with 0.32 to 0.39 mV gain. Therefore, we cannot exclude that different settings could slightly affect the EGM measurement. However, the rigorous methodology applied in evaluating each signal acquired and the use of small electrodes with a short interelectrode distance represent strengths that help in the discrimination of late activity from noise or artifacts.

CONCLUSIONS

This study demonstrates that among patients with BrS the extent of substrate is the only independent predictor of inducibility of VT or VF and may serve as a new marker for risk stratification and therapy. Substrate elimination by RF catheter ablation is associated with no VT or VF inducibility. Understanding the site and electrophysiology of arrhythmic substrate can facilitate recognition of patients at higher risk for VT or VF, thus providing an understanding of therapeutic options and limitations and suggesting avenues for future investigations.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with BrS, the extent of arrhythmogenic substrate, including that exposed by ajmaline, is associated with inducible malignant ventricular tachyarrhythmias independent of clinical presentation or the presence of a BrS type 1 ECG pattern.

TRANSLATIONAL OUTLOOK: Additional studies are needed to explore such strategies as guiding RF ablation by 3-dimensional mapping of the arrhythmic substrate to reduce the risk of sudden death in patients with BrS.

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KEY WORDS Brugada syndrome, catheter ablation, mapping, programmed ventricular stimulation, sudden death, ventricular arrhythmias

APPENDIX For a Definitions section as well as a supplemental figure and tables, please see the online version of this paper.