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Long-Term Outcomes of Brugada Substrate Ablation: A Report from BRAVO (Brugada Ablation of VF Substrate Ongoing Multicenter Registry)

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BACKGROUND: Treatment options for high-risk Brugada syndrome (BrS) with recurrent ventricular fibrillation (VF) are limited. Catheter ablation is increasingly performed but a large study with long-term outcome data is lacking. We report the results of the multicenter, international BRAVO (Brugada Ablation of VF Substrate Ongoing Registry) for treatment of high-risk symptomatic BrS.

METHODS: We enrolled 159 patients (median age 42 years; 156 male) with BrS and spontaneous VF in BRAVO; 43 (27%) of them had BrS and early repolarization pattern. All but 5 had an implantable cardioverter-defibrillator for cardiac arrest (n=125) or syncope (n=34). A total of 140 (88%) had experienced numerous implantable cardioverter-defibrillator shocks for spontaneous VF before ablation. All patients underwent a percutaneous epicardial substrate ablation with electroanatomical mapping except for 8 who underwent open-thoracotomy ablation.

RESULTS: In all patients, VF/BrS substrates were recorded in the epicardial surface of the right ventricular outflow tract; 45 (29%) patients also had an arrhythmic substrate in the inferior right ventricular epicardium and 3 in the posterior left ventricular epicardium. After a single ablation procedure, 128 of 159 (81%) patients remained free of VF recurrence; this number increased to 153 (96%) after a repeated procedure (mean 1.2±0.5 procedures; median=1), with a mean follow-up period of 48±29 months from the last ablation. VF burden and frequency of shocks decreased significantly from 1.1±2.1 per month before ablation to 0.003±0.14 per month after the last ablation ($P<0.0001$). The Kaplan-Meier VF-free survival beyond 5 years after the last ablation was 95%. The only variable associated with a VF-free outcome in multivariable analysis was normalization of the type 1 Brugada ECG, both with and without sodium-channel blockade, after the ablation (hazard ratio, 0.078 [95% CI, 0.008 to 0.753]; $P=0.0274$). There were no arrhythmic or cardiac deaths. Complications included hemopericardium in 4 (2.5%) patients.

CONCLUSIONS: Ablation treatment is safe and highly effective in preventing VF recurrence in high-risk BrS. Prospective studies are needed to determine whether it can be an alternative treatment to implantable cardioverter-defibrillator implantation for selected patients with BrS.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04420078.

Key Words: Brugada syndrome ■ channelopathies ■ death, sudden ■ defibrillators, implantable ■ ventricular fibrillation

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Clinical Perspective

What Is New?

- In a large cohort of highly symptomatic patients with Brugada syndrome, epicardial substrate ablation treatment is safe and effective in preventing ventricular fibrillation recurrence during a long-term follow-up period.
- Normalization of type 1 Brugada ECG after ablation, both with and without sodium channel blockade, suggests elimination of ventricular fibrillation substrates and is associated with excellent outcomes, resulting in patients with no overlapping early repolarization ECG pattern and free of ventricular fibrillation recurrence.

What Are the Clinical Implications?

- Catheter ablation of Brugada syndrome epicardial substrates is an important therapeutic addition for symptomatic Brugada syndrome.
- Patients with Brugada syndrome who do not have concomitant early repolarization whose ECG is normalized after ablation will likely be free from ventricular fibrillation recurrence and may not need implantable cardioverter-defibrillator treatment.

Nonstandard Abbreviations and Acronyms

BRAVO	Brugada Ablation of VF Substrate Ongoing Multicenter Registry
BrS	Brugada syndrome
CT	computed tomography
ICD	implantable cardioverter-defibrillator
ICS	intercostal space
LV	left ventricular
MRI	magnetic resonance imaging
PVC	premature ventricular contraction
RV	right ventricular
RVOT	right ventricular outflow tract
VF	ventricular fibrillation
VT	ventricular tachycardia

Treatment of Brugada syndrome (BrS) is a challenge and curative options remain elusive. During the 2 decades since BrS was first described, the implantable cardioverter-defibrillator (ICD) has been the only established treatment option for high-risk patients with BrS (ie, those with a history of cardiac arrest or recurrent ventricular fibrillation [VF]).[1–4] Whereas an ICD is effective at reverting VF episodes to sinus rhythm, thus preventing arrhythmic death, it does not prevent VF occurrences and results in painful ICD shocks, with profound unwanted effects in young patients with BrS.[5] Quinidine is the only oral antiarrhythmic drug documented to be effective at preventing recurrent VF episodes, but the drug has shortcomings: it frequently causes intolerable side effects during long-term treatment and is unavailable in most countries.[6] Moreover, when patients with BrS present with arrhythmic storm, necessitating frequent ICD discharges for recurrent VF, physicians face the daunting task of suppressing such VF episodes.[7]

A decade ago, we reported that catheter ablation of arrhythmic substrate areas located on the right anterior right ventricular outflow tract (RVOT) epicardium prevented recurrent ventricular tachycardia (VT)/VF in selected patients with BrS with high arrhythmic burden.[8] This report raised the hope that this procedure could be an effective therapeutic addition to ICD and quinidine. Since then, there has been an increase in use of epicardial substrate ablation to treat patients with symptomatic BrS.[9–13] However, a large study of patients with symptomatic BrS with long-term follow-up is lacking. We therefore conducted the international BRAVO study (Brugada Ablation of VF Substrate Ongoing Multicenter Registry) of catheter ablation (URL: https://www.clinicaltrials.gov; Unique identifier: NCT04420078) for treatment of patients with symptomatic BrS.

METHODS

All supporting data are available within the article.

BRAVO Registry and Study Population

Patients with BrS who underwent substrate ablations for prevention of VF recurrences/ICD discharges attributable to VF in tertiary centers in 3 continents (Asia, Europe, and North America) were registered in the BRAVO registry database. To be included in the registry, the patient must have had coved type ST-segment elevation >2 mm (type 1) pattern over the right precordial leads (leads V1, V2, or V3, as shown in Figure S1), either spontaneously or after sodium channel blocker administration, and must have had an epicardial Brugada-substrate ablation for symptomatic BrS. Symptomatic BrS was defined as a history of cardiac arrest or a history of arrhythmic syncope with subsequently documented spontaneous VF episodes. None of the patients had overt structural heart disease on the basis of cardiac imaging studies, including computed tomography (CT) study of the heart or magnetic resonance imaging (MRI) and echocardiography. The study was approved by the respective institutional review boards and all patients signed an informed consent. The number of patients enrolled at each center is listed in the Appendix.

Electrophysiologic Studies and Mapping of VF Substrates

All patients underwent comprehensive electrophysiologic studies. If the patient had premature ventricular contractions (PVCs) that were VF triggers (defined as PVC that initiated VF), we

attempted to identify the site of earliest activation relative to the onset of the QRS complex of PVC that had the same QRS morphology as the one that triggered VF; if there was a Purkinje potential preceding a spontaneous ventricular activation, it was interpreted as an indication of a Purkinje origin of that premature beat. This was only possible when these PVCs were frequent enough to map. For substrate mapping, electroanatomic mapping was carried out with either CARTO (Biosense Webster) or Ensite Precision (Abbott). The endocardial and epicardial mapping of the arrhythmogenic substrates of the right ventricular (RV) and left ventricular (LV) epicardium was performed during sinus rhythm. Abnormal electrograms were defined as electrograms with all the following characteristics: low voltage (≤1 mV); split electrograms or fractionated electrograms with multiple potentials with ≥2 distinct components, with >20 ms isoelectric segments between the peaks of individual components; and long-duration (>80 ms) or late potentials.

During the ablation procedure, programmed stimulation was first performed for VT/VF induction at baseline (2 to 3 cycle lengths [600, 500, and 400 ms] up to triple stimuli by a quadripolar catheter in the RV apex or RVOT with the shortest coupling interval of 200 msec). Programmed stimulation was then repeated at the end of the ablation procedure (see the following section).

Ablation Protocol and Ablation End Points

Ablation procedures were initially performed with irrigated-tip catheters, but contact force catheters became the main catheter used, when available, from 2013 onward. We used a contact force >5 g at all target sites; radiofrequency power was titrated between 20 and 50 W depending on the contact force, guided by close continuous observation of the voltage reduction of the late fractionated electrogram, including the disappearance of mid and late components of fractionated potentials during ablation, as described previously.[9] Intravenous or intrapericardial infusion of corticosteroids was given at the end of the procedure.

The ablation targets were VF trigger, as defined previously; VF substrates, defined as areas that harbor abnormal ventricular electrograms solely on the basis of electroanatomic mapping; or both. The ablation end point for VF triggers was the elimination of PVC-VF triggers; for VF substrates, it was the elimination of all abnormal late fractionated electrograms. Intravenous sodium channel blockers ajmaline, procainamide, flecainide, or pilsicainide were used to aid mapping and unmasking arrhythmogenic substrates; if the remapping time after ajmaline was protracted >10 minutes, an additional bolus dose was administered. In the Taipei site, warm saline technique was used to identify and unmask the substrates.[11] Noninducibility of sustained ventricular arrhythmias was not our ablation end point, although it was carried out at the discretion of the operators in most patients. If sustained VT/VF (lasting ≥10 seconds) remained inducible, it was also at the discretion of the operators as to whether they would continue to provide additional ablation.

Clinical End Points

All patients were followed within 1 month after the ablation session and every 3 months thereafter or by remote monitoring. Study end points were death or spontaneous VF episodes.

Statistical Analysis

The primary analysis was comparison of VF recurrent rates; patient VF-free survival probabilities and standard error were estimated using the Kaplan-Meier method and were tested by log-rank test. Student *t* test and Wilcoxon rank-sum test for continuous variables and Pearson χ^2 or Fisher exact tests for categorical variables were used for comparisons between groups. Wilcoxon rank-sum test was also used to compare the number of episodes before and after ablation (the number of VF episodes before ablation was counted from the time of the first VF to the time of the ablation). All data were analyzed with the SAS version 9.2 statistical package.

Secondary analyses were conducted to compare the results among different subgroups and to adjust covariates, including (1) spontaneous type 1 BrS ECG with high intercostal space (ICS) lead positioning (ICS-3 and ICS-4); for those patients who needed sodium channel blockers to unmask the Brugada ECG pattern, repeat sodium channel blockade was also required to determine the absence of the Brugada ECG pattern after ablation at ≥3 months after the ablation; (2) early repolarization ECG (an example ECG is provided in Figure S2); (3) family history of BrS or unexpected sudden death or cardiac arrest; (4) frequency of ICD shocks/VF before ablation; (5) genetics (*SCN5A* mutation); (6) VT/VF-inducible after radiofrequency ablation; and (7) persistent type 1 BrS ECG after the last radiofrequency ablation. Covariates were selected on the basis of available data and previous clinical knowledge. Cox proportional hazards survival model was used to evaluate the effect of these covariates. Significant covariates were then used to adjust the primary treatment comparison.

RESULTS

There were 171 patients eligible for the study, but 12 were excluded from enrollment into the registry: 7 did not fulfill diagnostic criteria for type 1 Brugada ECG pattern and 5 never came to a follow-up visit after the ablation (they are alive, as informed by the local contact). Thus, 159 patients (156 male; mean age 41.8±12.8 years; median age 42 years), all with symptomatic BrS (125 cardiac arrest survivors and 34 with arrhythmogenic syncope and subsequent documentation of spontaneous VF), were included in the BRAVO registry (Table). Of these patients, 122 (77%) had a spontaneous type 1 Brugada ECG pattern and 43 (27%) had a combined Brugada and early repolarization ECG patterns. Of the 159 patients, all except 5 (who declined) had an implanted ICD; 140 (91%) of the 154 patients who had an ICD had experienced (often multiple) ICD shocks because of recurrent VF episodes (ranging from 1 to >100 episodes per patient within 6 months before the procedure); 36 patients (23%) had experienced arrhythmic storms, defined as ≥3 episodes of VF within 24 hours as recorded by their ICD or documented during hospitalization in intensive care units. The mean time from the first VF to ablation was 30±37 months. Of those patients whose time of implantation to first ICD shock is known (n=108), 81

Table. Clinical Characteristics of the Study Patients

Characteristics	Values (total n=159)
Age, y	42.8±12.8 (42)
Sex, M/F	156/3
Symptoms	
Aborted cardiac arrests/VF	125 (79)
Arrhythmogenic syncope/VF	34 (21)
Family history	
Positive	32 (20)
Negative	113 (71)
Unknown	14 (9)
Type I Brugada ECG	
Spontaneous	122 (77)
With Na channel blockade	37 (23)
Concomitant early repolarization ECG (n=43)	
Inferior wall only	31 (72)
Inferolateral	10 (23)
Lateral wall only	2 (5)
Distribution of patients according to number of VF episodes on ICD* (n=154)	
No episode	14 (9)
1–4 episodes	59 (38)
5-9 5–9 episodes	26 (17)
≥10 episodes	55 (36)
Quinidine treatment	
Failed or not tolerated	48 (30)
SCN5A mutation (n=116)	
SCN5A tested positive	22 (19)
Racial distribution	
Southeast Asian	63 (40)
Japanese	21 (13)
Chinese	45 (28)
White	27 (17)
Hispanic	2 (1.3)
Black	1 (7)

Values are mean±SD (median) or n (%). ICD indicates implantable cardioverter-defibrillator; and VF, ventricular fibrillation.

*5 of 159 patients had no ICD.

(75%) had their first ICD shock for VF within the 2 years after ICD implantation (Figure 1A). Patients who experienced ICD shocks for VF shortly after ICD implantation were also at high risk for subsequent frequent recurrent VF (Figure 1B).

Distribution of VF Substrates

Almost all patients (151 of 159) underwent percutaneous epicardial mapping and ablations by the subxiphoid approach; the remaining 8 patients underwent open thoracotomy because of inaccessible percutaneous pericardial space (n=7) or during thoracotomy surgery for infected ICD lead removal (n=1). All patients had arrhythmic substrates in the RVOT/RV epicardium; 45 patients (29%) also had an arrhythmic substrate in the inferior RV epicardium and 3 patients had it in the posterolateral LV epicardium (all 3 had concomitant early repolarization ECG abnormality; Figure 2).

Effects of Ablation on Brugada ECG Pattern and VF Inducibility

Of the 159 patients, 136 underwent programmed ventricular stimulation before the ablation procedure: 119 (87.5%) of them had inducible sustained polymorphic VT/VF and 17 (12.5%) were noninducible at baseline. Of the patients who were inducible at baseline, 96 (81%) had a second attempt at VT/VF induction after completion of the ablation procedure; a repeated induction was not attempted in 23 patients (19%) at the discretion of the operator. Additional radiofrequency application was delivered at the substrate sites to the patients whose VF remained inducible if the operators believed there were remaining substrate areas. Only 20 of the 96 patients (21%) remained VF-inducible.

After the first ablation (≥3 months), 133 patients (83%) demonstrated normalization of their type 1 ECG pattern, whereas 26 (17%) continued to demonstrate a type 1 Brugada ECG. Ten of the 26 patients who continued to exhibit a type 1 Brugada pattern and recurrent VF underwent a repeat ablation at a later date, resulting in a total of 150 patients (94%) who had their ECGs normalized.

Clinical Outcomes and Complications

The radiofrequency duration time, available for 117 patients, was 25±16 minutes (median, 22 minutes). There were no cases of in-hospital mortality. A serious periprocedural complication occurred in 4 patients, who developed hemopericardium. None of them had recurrent pericardial bleeding over the ensuing 48 hours after the procedure; 1 patient had severe pericarditis, which resolved completely after 2 weeks. One patient developed sustained monomorphic VT within 24 hours after the initial epicardial ablation and underwent mapping and ablation of the monomorphic VT; the tachycardia focus was on the endocardial RVOT not near the epicardial RVOT ablation site and was successfully ablated.

Effects of Catheter Ablation on VF Recurrences

There were no arrhythmic or cardiac deaths during follow-up. There were 2 noncardiac deaths: 1 from a gunshot wound and the other from a car accident (with no evidence of spontaneous arrhythmias on postmortem ICD interrogation).

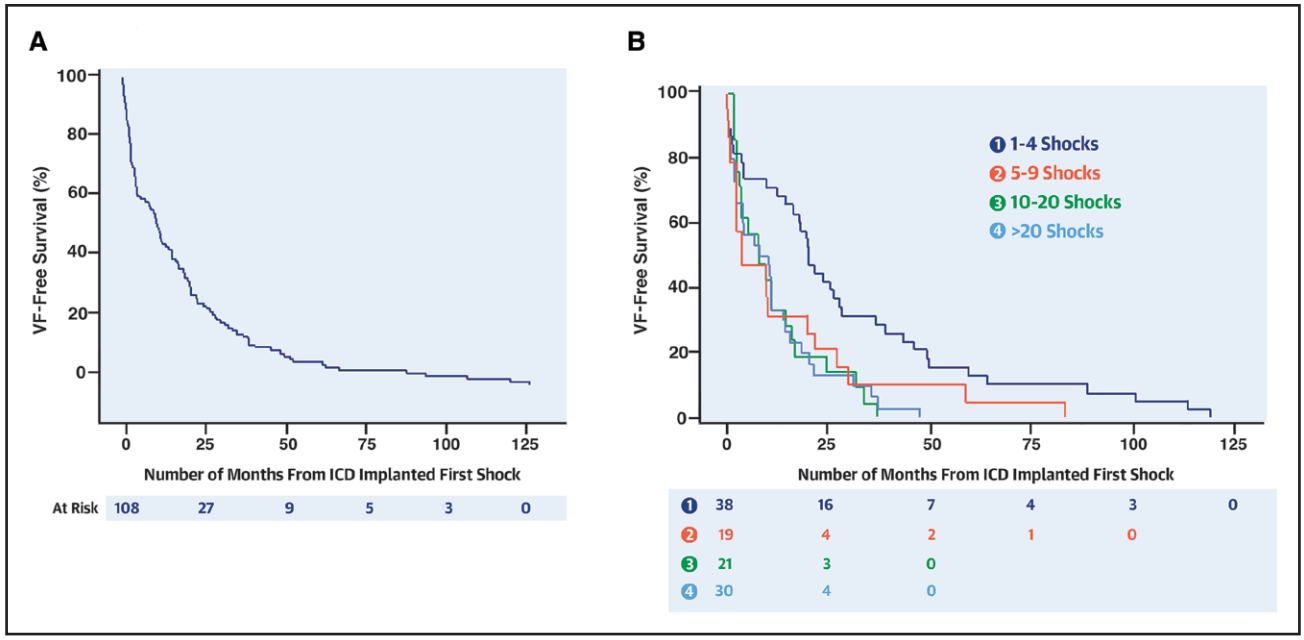

Figure 1. Kaplan-Meier plots of cumulative survival from ICD implantation to the first shock for VF before catheter ablation and association between number of months from ICD implanted to first shock and frequency of shocks for VF before ablation.
A, Kaplan-Meier plot of cumulative survival from implantable cardioverter-defibrillator (ICD) implantation to the first ICD shock for ventricular fibrillation (VF) before catheter ablation for the 108 patients for whom the time since ICD implantation to first ICD shock was known. **B**, Kaplan-Meier plot showing association between number of months from ICD implanted to first shock and frequency of ICD shocks/VF before ablation by the following groups: group 1 (dark blue), 1 to 4 shocks; group 2 (red), 5 to 9 shocks; group 3 (green), 10 to 20 shocks; group 4 (light blue), >20 shocks. Hazard ratio (95% CI) for grade 1 vs grade 2, 1.945 (1.105, 3.421), *P*=0.0211; for grade 3 vs grade 1, 2.286 (1.296, 4.034), *P*=0.0043; for grade 4 vs grade 1, 2.347 (1.406, 3.920), *P*=0.0011.

The 159 patients had a total of 15.4±21 VF events during a preablation period (from the first VF event to the ablation procedure) of 49±48.7 months, for an average number of 1.1±2.1 VF events per month. The same cohort had a total of 0.18±0.19 VF events during the postablation follow-up period of 48±29 months, for an average of 0.003±0.014 VF episodes per month (*P*<0.0001).

After a single procedure, 128 of 159 (81%) patients remained free of VF recurrences. The number of patients who became free of VF recurrences increased to 153 (96%) after an additional procedure (mean, 1.2±0.5 procedures; median, 1 procedure), with a mean follow-up period of 48±29 months from the last ablation (Figure 3). The remaining 6 patients, who had VF recurrence after ablation, declined a second procedure on the basis of a drastic reduction in the number of VF episodes. Five had only 1 shock for VF recurrence and the remaining patient had 2 shocks during sleep. None of the patients were on antiarrhythmic drugs after the last ablation except 3 patients who continued taking quinidine. The 3 patients on quinidine include 2 who had combined early repolarization

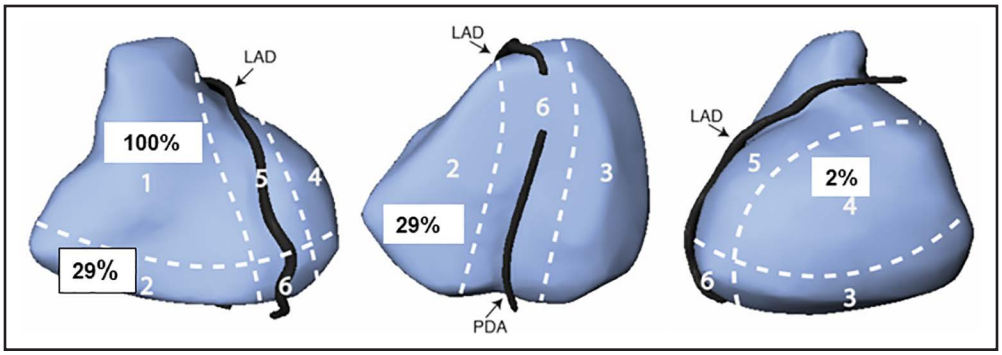

Figure 2. Distribution of epicardial Brugada substrates where ablations were performed.
The epicardial surface of both ventricles was divided into 6 regions: (1) anterior right ventricular outflow tract/right ventricle; (2) inferior right ventricle; (3) inferior left ventricle; (4) posterolateral left ventricle; (5) interventricular septum; and (6) interventricular groove. LAD indicates left anterior descending artery; and PDA, posterior descending artery.

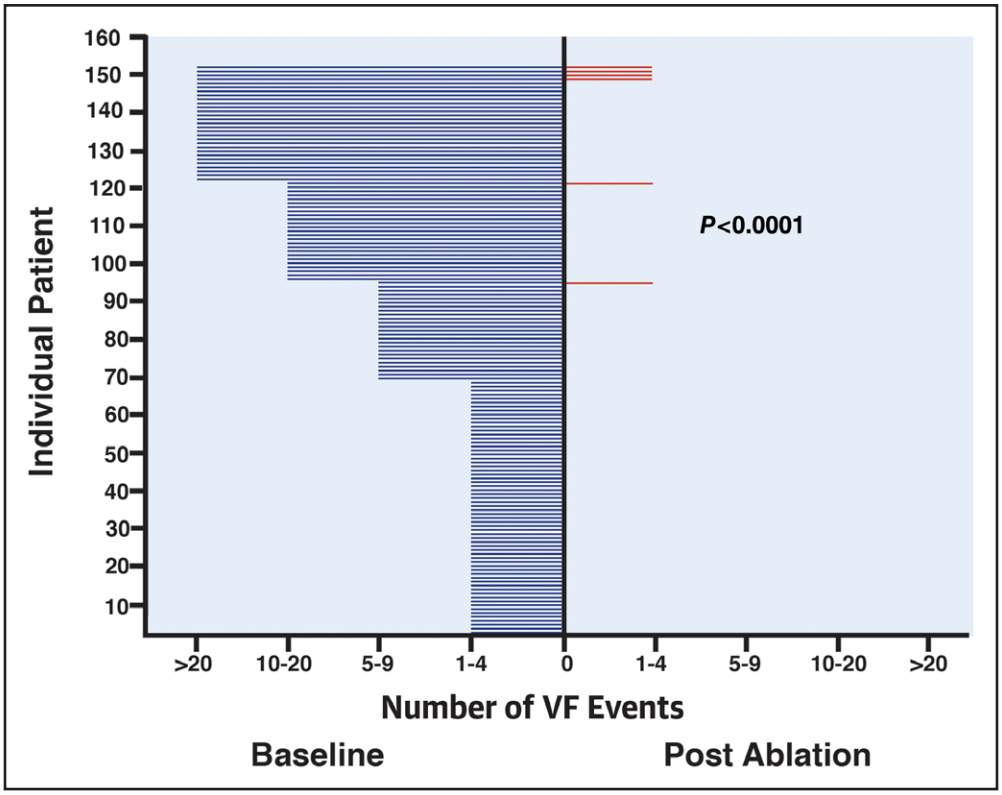

Figure 3. The number of ICD shocks before and after catheter ablation of VF substrates.
The number of implantable cardioverter-defibrillator (ICD) shocks before and after catheter ablation of ventricular fibrillation (VF) substrates for (154 patients). Each line on either side of the vertical line (time of ablation) represents 1 patient and the corresponding total number of shocks.

and Brugada ECG pattern with VF recurrence and one who preferred to continue quinidine despite the absence of VF recurrence. The Kaplan-Meier VF-free survival curve shows that after the last ablation, VF recurrence rate was low (Figure 4). Long-term VF-free survival beyond 5 years after the last ablation was 95%. Nine patients (6%) had inappropriate ICD discharges caused by supraventricular tachyarrhythmias.

Predictors of Successful Ablation

Univariate and multivariate analyses were conducted to determine whether the previously mentioned variables prevented VF recurrences after the last ablation. The only variable associated with a VF-free outcome was normalization of type 1 Brugada ECG pattern after the last catheter ablation, both with and without sodium channel blockade. Figures 5 and 6 show the Kaplan-Meier VF-free survival curve comparing patients whose type 1 Brugada ECG pattern normalized versus those remaining present after the ablations without and with sodium channel blockade, respectively; we included only patients who had ECGs with high ICS lead positioning at baseline and after ablation (n=110). Data were available for 74 patients who had sodium channel blockade challenge after ablation and high ICS lead positioning.

After ablation, patients without a Brugada ECG pattern had 95% 5-year VF-free survival, compared with only 65% of those who continued to have a type 1 Brugada ECG pattern after the ablation (hazard ratio, 0.120 [95% CI, 0.022, 0.65]; *P*=0.0142). Patients without type 1 Brugada ECG pattern even with sodium channel blockade after ablation had a >98% 5-year VF-free survival compared with 80% of those whose type 1 Brugada ECG pattern was induced after sodium channel blockade (negative versus positive; hazard ratio, 0.078 [95% CI, 0.008, 0.753]; *P*=0.0274). Of particular significance, only 1 patient in the group without a type 1 Brugada ECG absence after a single ablation had recurrent VF; however, he also had an early repolarization pattern. The patient declined to have a second ablation procedure. Thus, in our study, for patients with BrS without a concomitant early repolarization pattern, once their ECG normalized, especially after sodium channel provocative test, the risk of VF recurrences was nil.

DISCUSSION

Our BRAVO registry data strongly suggest that catheter ablation of the epicardial arrhythmogenic substrates is safe and effectively prevents VF recurrences in high-risk

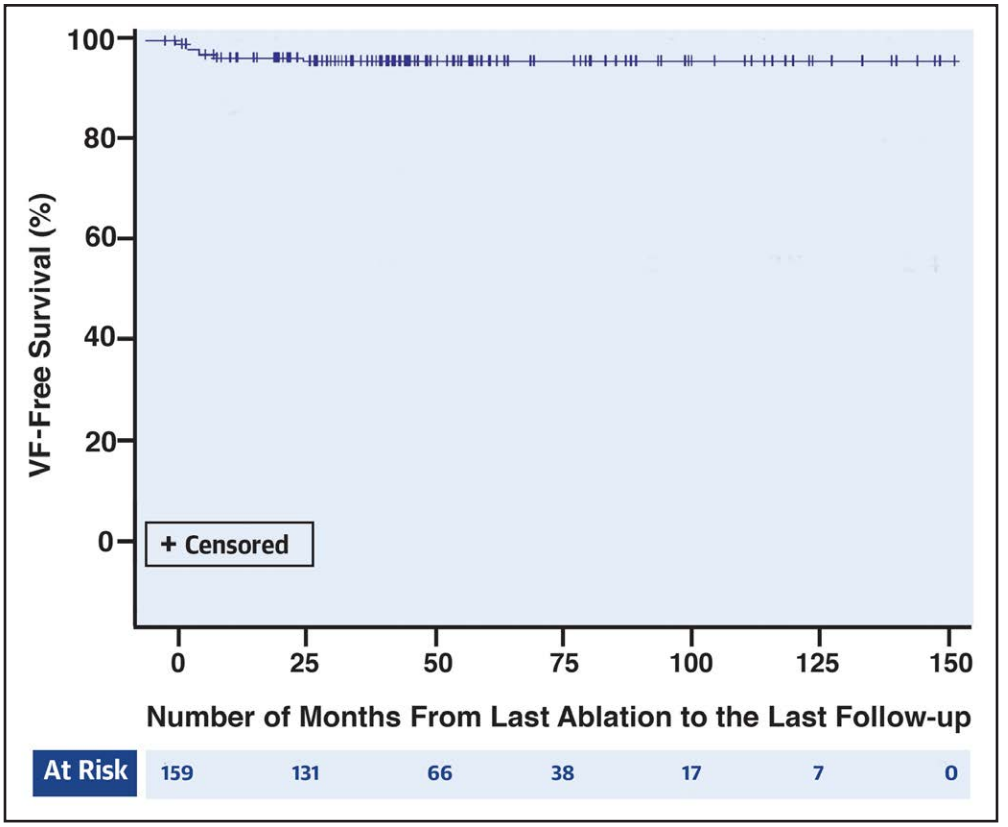

Figure 4. Kaplan-Meier plot of cumulative VF-free survival after the last ablation.
VF indicates ventricular fibrillation.

patients with BrS. Catheter ablation drastically reduced recurrent VF and rendered 5-year VF-free survival in >95% of these patients. Furthermore, in the small number of patients who still had VF recurrences, the VF episodes were infrequent and tolerable to the extent that these patients often declined additional ablation procedures. The only major complication in our study was pericardial effusion, which occurred in only 1% of patients and had no long-term consequences.

Our registry includes the largest number of patients with severely symptomatic BrS undergoing substrate ablation for the prevention of recurrent VF. Previous reports include only small series (recently reviewed),[12] also demonstrating the efficacy of substrate ablation. The only large series is the one by Pappone et al.,[10] reporting substrate ablation in 135 patients with BrS. Unlike our study population, only 39 of their patients (29%) had a history of cardiac arrest or syncope.[10] In any event, the ablation outcomes from their study were excellent, with 100% normalization of Brugada ECG pattern and noninducible VT/VF after ablation; only 2 patients in their study had recurrent VF triggering ICD discharges during follow-up. Thus, our registry data along with the aforementioned reports clearly establish that ablation is an important addition to the treatment for symptomatic BrS, especially for patients with frequent VF recurrences. Of note, our patient population had had mental trauma caused by numerous, painful ICD shocks and previously had no recourse except cardiac transplantation.[13] Some of our patients had reactive depression and had contemplated suicide because of their frequent ICD shocks. In our registry, patients who had ICD discharges for VF within 1 year of ICD implantation were very likely to have VF recurrences. This observation suggests that such patients should be considered for ablation therapy early on.

The lasting beneficial effects of catheter ablation enable our patients with symptomatic BrS to have VF-free lives, as evidenced by our data showing that for patients with BrS without concomitant early repolarization ECG, once their BrS substrate is eliminated (with normalization of the BrS pattern), they had no more VF episodes. Our findings contrast with the small study by Zhang et al.,[14] in which 11 patients with symptomatic BrS underwent substrate ablation. They concluded that despite normalization of the ECG (4th ICS lead placement) and noninducible VT/VF, the risk of VF recurrences remained, because 3 of 11 patients (27%) had major events: 2 had recurrent VF with ICD appropriately

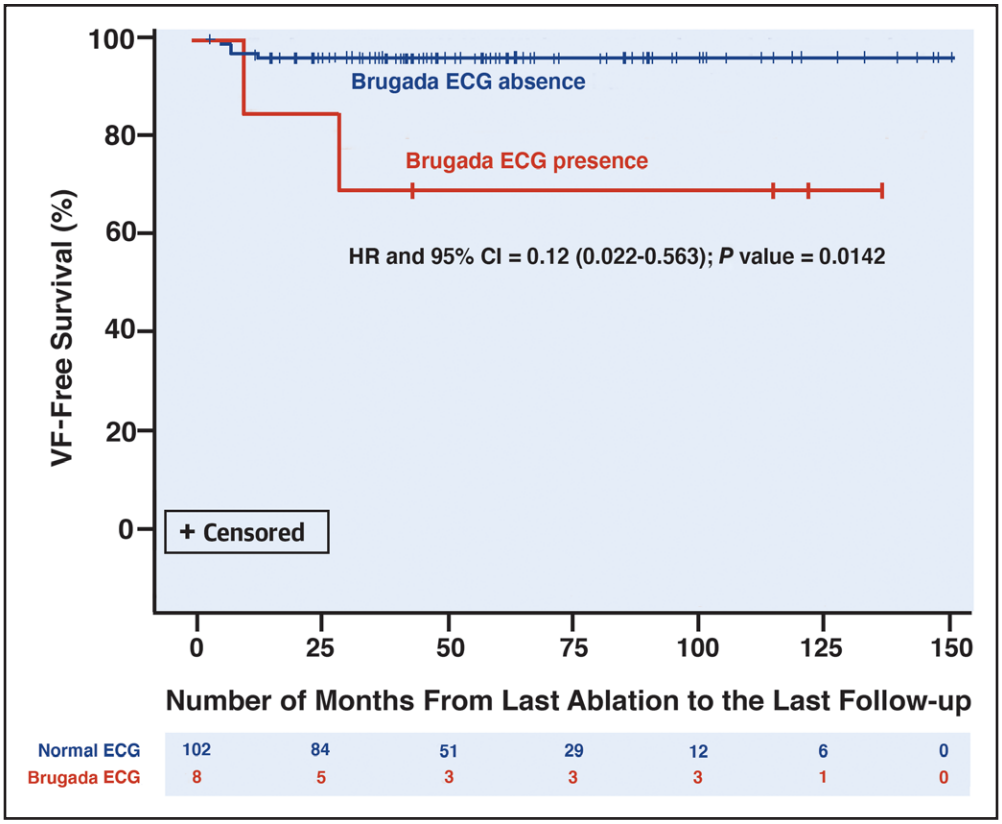

Figure 5. Kaplan-Meier curves comparing the VF-free survival curve after ablation between the 2 groups of patients.
Brugada ECG absence vs presence after the ablation procedure. HR indicates hazard ratio; and VF, ventricular fibrillation.

discharged and 1 patient without an ICD died suddenly. However, as pointed out in the accompanying editorial,[15] upon careful scrutiny, postablation ECG of study patients who had VF recurrences did not truly normalize. The ECG from the patient who died of VF still had 2-mm J-point elevation in lead V1 and type 2 BrS ECG pattern in lead V2, although the BrS ECG pattern and ST-segment elevation was much less impressive when compared with that of the preablation ECG. If the investigators performed higher ICS right precordial lead positioning with sodium channel blockade, it is highly likely that the BrS ECG pattern would have been manifested. This was shown in one of their patients who had ICD discharge for VF and a normal ECG with standard 4th ICS placement but had a coved-type BrS pattern in lead V1 and ST-segment elevation in lead V2 with the 3rd ICS lead placement.

More studies are needed to confirm our findings before we recommend substrate ablation as the sole treatment for patients with symptomatic BrS and to answer 2 key questions: Can epicardial substrate ablation offer a curative treatment for BrS? Can one treat a patient with symptomatic BrS only with catheter ablation without implanting an ICD? Randomized clinical trials, including our own multicenter randomized study (BRAVE [Ablation in Brugada Syndrome for the Prevention of VF]; URL: https://www.clinicaltrials.gov; Unique identifier: NCT02704416), may provide answers to these questions.

As shown by our findings, in addition to the RVOT epicardial substrate sites, approximately one third of patients also have substrate sites elsewhere in the RV epicardium, including the inferior aspect of the RV epicardium, and, in rare instances, over the LV epicardium. Patients who have J-wave syndrome that combines both Brugada and early repolarization ECG pattern may continue to have risk of VF recurrence even though the type 1 Brugada ECG pattern normalizes if some VF substrates outside the RVOT epicardium are not eliminated. One must recognize that in patients with combined syndromes, many of these sites can be unmasked only after using sodium channel blockade (ie, ajmaline). Thus, the ablation procedure must be done in centers that are well-equipped for complex ablation procedures and adroit in epicardial mapping alongside sodium channel blocker administration. Percutaneous epicardial mapping and ablation is an invasive procedure that could pose substantial risks to patients and requires experienced operators and electrophysiology team. Efficacy and safety of substrate ablation for treatment of BrS would be greatly dependent on the operator to ensure that all substrates are eliminated because one

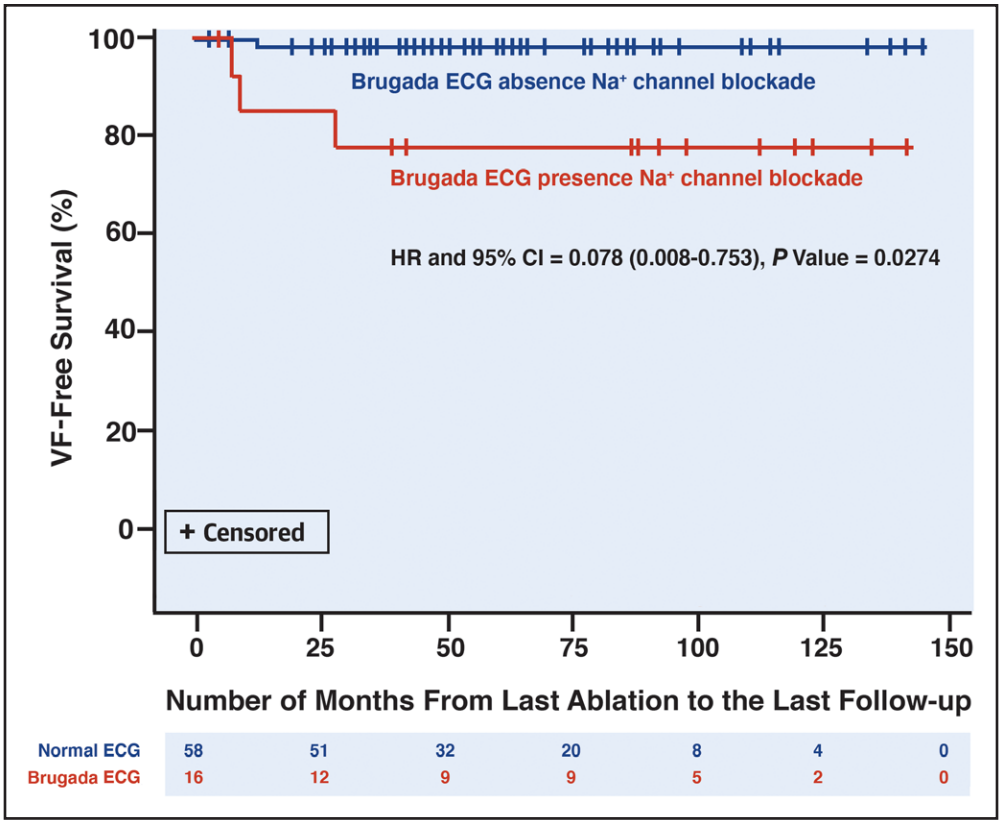

Figure 6. Kaplan-Meier curves comparing the VF-free survival curve after ablation for the 2 groups of patients.
Brugada ECG absence vs presence during the sodium-channel–blocking challenge after the ablation procedure. HR indicates hazard ratio; and VF, ventricular fibrillation.

cannot afford any VF recurrence in patients with BrS who have no ICD protection. One must also be aware that the scar caused by epicardial RV ablation may become an arrhythmogenic site for VT at a later date.[16] We have not observed late development of monomorphic VT during follow-up. The only patient who had sustained monomorphic VT within 24 hours of the initial epicardial ablation had the VT foci in the endocardial site near the epicardial RVOT ablation site. Thus, it is unlikely that this endocardial VT site, where ablation was successful in abolishing the VT, represents a proarrhythmic effect of the first epicardial ablation. In some patients with an existing conduction defect in addition to BrS, one may have difficulty discerning whether Brugada ECG pattern substrates are truly normalized using ECG criteria. Using sodium channel blockade to unmask BrS with concomitant conduction defect or true right bundle-branch block may not be helpful and may pose additional risks of severe conduction block.[17] Better tools for epicardial mapping and ablation are hoped to become readily available in the future, including lesion assessment, which will help operators carry out BrS substrate ablation with confidence that they have eliminated the risk of VF recurrences and in turn fully protected their patients.

STUDY LIMITATIONS

Our study did not include a control group. There was a much smaller number of patients from the European and US sites and some might not regard this as a true international registry. The main reasons that fewer patients from Europe and the United States participated in this study are most likely because the incidence of symptomatic BrS is much higher in Asia, especially in Southeast Asia and Japan, and quinidine is likely to be the first-line therapy in both Europe and the United States, potentially resulting in fewer symptomatic cases needing catheter ablation compared with those at the Asian sites. The ablation procedure was performed at different arrhythmia centers and involved slightly different protocols for electrophysiologic studies, mapping, and ablation. In particular, the procedure end point varied among centers (it did not include ajmaline test and verification of noninducibility at the end of the procedure in all centers). Nevertheless, given the high number of VF events before the ablation and taking into account that VF recurrences were almost abolished by ablations, our findings robustly support the value of catheter ablation of BrS, despite the heterogeneity of our registration data. Although we present the largest follow-up period after ablation of symptomatic BrS, one should bear in mind that a

mean follow-up period of 48±29 months represents a relatively short time frame for an inborn disease such as BrS.

CONCLUSIONS

Our study demonstrates the safety of substrate ablation of BrS. It also demonstrates efficacy in preventing recurrence during a mean 4-year follow-up period. Our study indicates that patients with BrS who have no overlapping early repolarization syndrome or other severe conduction diseases are expected to remain free of VF recurrences as long as the BrS substrates are eliminated as confirmed by a negative sodium channel blocker provocative test. This finding provides us with a hypothesis that such patients may one day be treated without an ICD. We await the results of ongoing clinical trials. If results confirm our observations, in a selected subset of patients with BrS, catheter ablation could be a curative treatment. Substrate ablation should be offered to treat patients with BrS who experience VF recurrence.

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Supplemental Material

Figures S1–S2

APPENDIX

Centers	Investigators	Enrolled patients, n
Chulalongkorn University and Pacific Rim EP Research Institute Center, Bangkok, Thailand; and Los Angeles, CA	Koonlawee Nademanee, MD Apichai Khongphatthanayothin, MD Gumpanart Veerakul, MD	74
Taipei Veterans General Hospital, Taiwan	Shih-Ann Chen, MD Fa-Po Chung, MD	30
LIRYC Institute, Bordeaux University Hospital, France	Michel Haissaguerre, MD Meleze Hocini, MD Frederic Sacher, MD	14
Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University, Hangzhou, China	Chen Yang Jiang, MD	12
Department of Cardiovascular Medicine, Cleveland Clinic, OH; Japanese Consortium	Hiroshi Nakagawa, MD Kohei Yamashiro, MD Yuichiro Sakamoto, MD Naomasa Makita, MD Masahiko Takagi, MD Kengo Kusano, MD Masatoshi Yamazaki, MD Taketsugu Tsuchiya, MD Kazuyoshi Suenari, MD Kentaro Nakamura, MD	10
Division of Cardiology, University of Tsukuba, Ibaraki, Japan	Akihiko Nogami, MD	9
Isala Clinic, Zwolle, the Netherlands	Jaap Jan Smit, MD, PhD	6
University of Amsterdam, Academic Medical Center, the Netherlands	Arthur Wilde, MD, PhD	2
Department of Cardiology, Ogaki Municipal Hospital, Japan	Itsuro Morishima, MD, PhD	1
St George's Hospital, University of London, UK	Elijah Behr, MD	1
Krannert Institute of Cardiology, University of Indiana, Indianapolis	Mithilesh K. Das, MD	1

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