Right Ventricular Outflow Tract Electroanatomical Abnormalities Predict Ventricular Fibrillation Inducibility in Brugada Syndrome

Konstantinos P. Letsas, MD
Michael Efremidis, MD
Dimitrios Asvestas, MD
Konstantinos Vlachos, MD
Stamatis Georgopoulos, MD
Gary Tse, MBBS, PhD
Tong Liu, MD, PhD
George Bazoukis, MD
Antonios Sideris, MD
Adrian Baranchuk, MD, PhD
Joachim R. Ehrlich, MD
Pedro Brugada, MD

Electroanatomical mapping has demonstrated abnormal bipolar electrograms at the anterior aspect of the right ventricular outflow tract (RVOT) epicardium along with histopathologic evidence of fibrosis in patients with Brugada syndrome (BrS).[1,2] These epicardial abnormalities are believed to serve as the electric substrate for ventricular fibrillation (VF) initiation and maintenance in BrS.[1,2] We have recently demonstrated that patients with BrS display wide areas of endocardial unipolar voltage abnormalities that possibly reflect epicardial structural abnormalities at the free wall of the RVOT.[3] We hypothesized that electroanatomical abnormalities detected by high-density endocardial unipolar voltage mapping at the RVOT predict VF inducibility during programmed ventricular stimulation (PVS).

The study population consisted of 17 asymptomatic probands (15 males, 37.3±10.8 years) with spontaneous type 1 BrS ECG pattern referred for risk stratification with PVS. A comprehensive evaluation including late gadolinium enhancement cardiac magnetic resonance imaging ruled out structural heart disease in all patients. The study was approved by the Hospital Ethics Committee and written informed consent was obtained from all patients.

High-density electroanatomical mapping of the RVOT during sinus rhythm was performed as described previously (Methods in the Data Supplement).[3] In brief, a minimum of 800 points were sampled to build the RVOT geometry (CARTO 3, Biosense-Webster, CA). An electroanatomical mapping was considered abnormal in the presence of low-voltage areas >1.5 cm^2 including ≥3 adjacent points with a bipolar signal amplitude <1 mV and an unipolar signal amplitude <4 mV (Figure [A] and [B]).[3] PVS was performed from the right ventricular apex and RVOT sites at 3 drive trains (600, 500, and 400 ms) inserting up to 3 extrastimuli (no <200 ms), and considered positive if VF (lasting ≥30 s or requiring termination because of rapid hemodynamic deterioration) was induced.

Continuous data are presented as mean±SD. Continuous variables with and without normal distribution were compared using Student *t* test and Mann–Whitney *U* test, respectively. The association between abnormal bipolar and unipolar electroanatomical mapping and VF induction during PVS was determined by means of univariate analysis. A receiver operating characteristics curve analysis was performed to determine the optimal cutoff value of the abnormal area size, defined as the value maximizing the sum of sensitivity and specificity, that predict VF inducibility. A probability of <0.05 was considered significant.

The clinical and electrophysiological data of the study cohort are depicted in Table I in the Data Supplement. PVS induced VF in 6 patients (35%) with the use of 2 extrastimuli in 3 patients and 3 in the rest of them. All 6 patients received an implantable cardioverter defibrillator. The mean number of right ventricular sites sampled for high-density electroanatomical mapping was 1007.2±176.0. The mean RVOT area presenting low-voltage bipolar signals was 3.2±1.6 cm^2 (range, 1.5–7 cm^2; Figure [A]). A significantly greater area of low-amplitude unipolar sig-

Correspondence to:
Konstantinos P. Letsas, MD, Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, Evangelismos General Hospital of Athens, Athens 10676, Greece. E-mail k.letsas@gmail.com

Key Words: Brugada syndrome ■ gadolinium ■ magnetic resonance imaging ■ ventricular fibrillation ■ voltage mapping

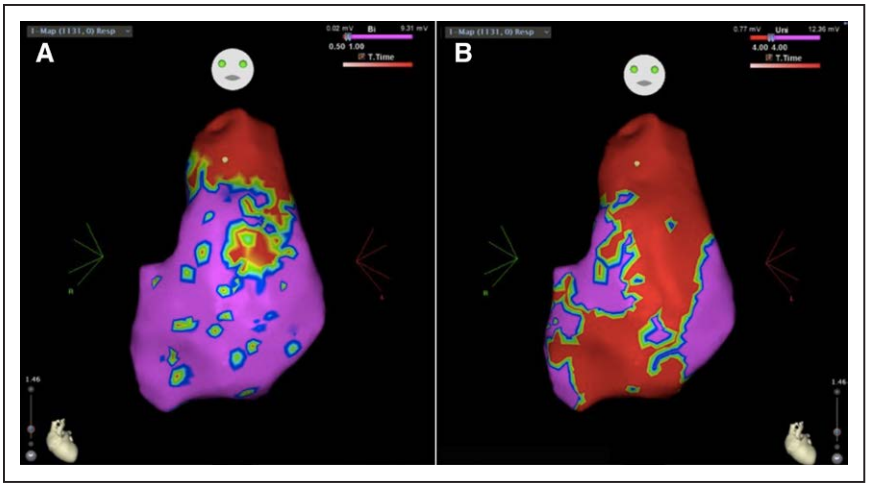

Figure. Right ventricular outflow tract electroanatomical mapping in Brugada syndrome.
A, High-density endocardial mapping showing small areas of low-voltage bipolar signals (<1 mV) at the free wall of the right ventricular outflow tract in a patient with Brugada syndrome and inducible ventricular fibrillation during programmed ventricular stimulation; (**B**) a broad area of abnormal unipolar signals (< 4 mV) was recorded at the same region, possibly reflecting epicardial lesions.

nals was recorded (10.9±5.4 cm^2 [range, 1.5–22 cm^2]; *P*=0.001; Figure [B]). Both bipolar and unipolar electroanatomical abnormalities were mainly located at the free wall of the RVOT and less commonly at the inflow tract. Of note, 4 patients with no or minimal bipolar lesions (≤2 cm^2) depicted broad areas of abnormal unipolar lesions (7–12 cm^2). Two subjects exhibited normal bipolar and unipolar electroanatomical maps (≤1.5 cm^2). Patients with VF inducibility demonstrated greater areas of abnormal unipolar (16.0±3.8 versus 8.1±4.0 cm^2; *P*=0.010) and bipolar (4.2±0.7 versus 2.6±1.6 cm^2; *P*=0.016) signals compared with those without arrhythmia induction. In univariate analysis, both unipolar (*P*=0.001) and bipolar (*P*=0.016) electroanatomical abnormalities were significantly associated with VF inducibility. Receiver operating characteristics curve analysis demonstrated that the presence of an area size >11 cm^2 for low-amplitude unipolar signals (area under the curve, 0.939; sensitivity, 100%; specificity, 73%; *P*=0.004) and >3.5 cm^2 for low-amplitude bipolar signals (area under the curve, 0.856; sensitivity, 83%; specificity, 82%; *P*=0.018) predict VF inducibility during PVS. None of the BrS subjects displaying normal electroanatomical findings were inducible for VF during PVS. During a mean follow-up period of 8.4±3.9 months, 1 patient received an appropriate implantable cardioverter defibrillator shock.

High-density endocardial unipolar voltage mapping may prove a valuable tool for the diagnosis and risk stratification of BrS. Using an endocardial unipolar voltage threshold of 4 mV, we showed that patients with BrS, even with no or minimal bipolar voltage lesions, display large areas of abnormal unipolar voltage mapping at the free wall of the RVOT. In a recent study, a similar endocardial unipolar voltage cutoff value for the identification of epicardial bipolar voltage abnormalities in the right ventricle has been proposed (3.9 mV).[4] Low-unipolar endocardial area indicates epicardial involvement in patients with no or minimal bipolar endocardial changes.[4,5] The identification of large abnormal endocardial unipolar areas that possibly reflect a diseased epicardium may strengthen the diagnosis of BrS. The later may add important information for distinguishing true BrS patients from those with Brugada phenocopies, based on the presence of abnormal and normal maps, respectively.

Electroanatomical mapping may additionally improve the prognostic accuracy of PVS in patients with BrS. We demonstrated that BrS patients with broad endocardial unipolar voltage abnormalities are more vulnerable to VF induction during PVS. On the contrary, subjects with normal electroanatomical maps were noninducible. Previous epicardial studies support the present findings.[1,2] After epicardial substrate elimination, patients with BrS become noninducible during PVS and the ECG normalizes.[1,2] The prognostic significance of this novel electroanatomical marker in asymptomatic individuals with BrS remains to be prospectively validated in the setting of multiparametric risk stratification models.

DISCLOSURES

None.

AFFILIATIONS

From the Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, Evangelismos General Hospital of Athens, Greece (K.P.L., M.E., D.A., K.V., S.G., G.B., A.S.); Department of Medicine and Therapeutics and Li Ka Shing Institute of Health Sciences, Chinese University of Hong Kong, SAR, P.R. China (G.T.); Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, P.R. China (T.L.); Division of Cardiology, Queen's University, Kingston General Hospital, Ontario, Canada (A.B.); Electrophysiology Section, St. Josefs-Hospital, Wiesbaden, Germany (J.R.E.); and Heart Rhythm Management Centre, UZ Brussel-VUB, Belgium (P.B.).

FOOTNOTES

Received October 2, 2017; accepted January 12, 2018.

The Data Supplement is available at http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.117.005928/-/DC1.

Circ Arrhythm Electrophysiol is available at http://circep.ahajournals.org.

REFERENCES

1. Nademanee K, Raju H, de Noronha SV, Papadakis M, Robinson L, Rothery S, Makita N, Kowase S, Boonmee N, Vitayakritsirikul V, Ratanarapee S, Sharma S, van der Wal AC, Christiansen M, Tan HL, Wilde AA, Nogami A, Sheppard MN, Veerakul G, Behr ER. Fibrosis, connexin-43, and conduction abnormalities in the Brugada syndrome. *J Am Coll Cardiol*. 2015;66:1976–1986. doi: 10.1016/j.jacc.2015.08.862.
2. Brugada J, Pappone C, Berruezo A, Vicedomini G, Manguso F, Ciconte G, Giannelli L, Santinelli V. Brugada syndrome phenotype elimination by epicardial substrate ablation. *Circ Arrhythm Electrophysiol*. 2015;8:1373–1381. doi: 10.1161/CIRCEP.115.003220.
3. Letsas KP, Efremidis M, Vlachos K, Georgopoulos S, Karamichalakis N, Asvestas D, Valkanas K, Korantzopoulos P, Liu T, Sideris A. Right ventricular outflow tract high-density endocardial unipolar voltage mapping in patients with Brugada syndrome: evidence for electroanatomical abnormalities [published online ahead of print May 2, 2017]. *Europace*. doi: 10.1093/europace/eux079. https://academic.oup.com/europace/advance-article-abstract/doi/10.1093/europace/eux079/3788900?redirectedFrom=fulltext.
4. Venlet J, Piers SRD, Kapel GFL, de Riva M, Pauli PFG, van der Geest RJ, Zeppenfeld K. Unipolar endocardial voltage mapping in the right ventricle: optimal cutoff values correcting for computed tomography-derived epicardial fat thickness and their clinical value for substrate delineation. *Circ Arrhythm Electrophysiol*. 2017;10:e005175. doi: 10.1161/CIRCEP.117.005175.
5. Hutchinson MD, Gerstenfeld EP, Desjardins B, Bala R, Riley MP, Garcia FC, Dixit S, Lin D, Tzou WS, Cooper JM, Verdino RJ, Callans DJ, Marchlinski FE. Endocardial unipolar voltage mapping to detect epicardial ventricular tachycardia substrate in patients with nonischemic left ventricular cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2011;4:49–55. doi: 10.1161/CIRCEP.110.959957.

Right Ventricular Outflow Tract Electroanatomical Abnormalities Predict Ventricular Fibrillation Inducibility in Brugada Syndrome

Konstantinos P. Letsas, Michael Efremidis, Dimitrios Asvestas, Konstantinos Vlachos, Stamatis Georgopoulos, Gary Tse, Tong Liu, George Bazoukis, Antonios Sideris, Adrian Baranchuk, Joachim R. Ehrlich and Pedro Brugada

Circ Arrhythm Electrophysiol. 2018;11:
doi: 10.1161/CIRCEP.117.005928
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3149. Online ISSN: 1941-3084

Supplemental material

Methods

Electroanatomical mapping

After written informed consent was obtained from all subjects, an electrophysiological study was performed with the patients in the fasting, non- sedated state. A high-density endocardial voltage mapping of the right ventricular outflow tract (RVOT) during sinus rhythm was performed using a three-dimensional non-fluoroscopic mapping system (CARTO 3, Biosense-Webster, Diamond Bar, CA, USA). All subjects displayed the characteristic type 1 ECG pattern of Brugada syndrome (BrS) during mapping. A minimum of 800 points was sampled throughout the right ventricle using a multipolar catheter (high-resolution multi-electrode mapping, DecaNav catheter, 2-8-2 interelectrode spacing, Biosense Webster). Areas displaying low-amplitude signals were mapped with greater point density to delineate the extent and borders of abnormal endocardial sites. A contact force sensing catheter (SmartTouch ™, Biosense Webster, Diamond Bar, CA, USA) was used for validation of bipolar and unipolar electrograms, particularly in low-voltage areas. The fill and the colour threshold for the electroanatomical mapping was set at 15 mm and 23 mm, respectively. Bipolar (filtered at 30–500 Hz) and unipolar signals (filtered at 1–240 Hz) were recorded and analysed simultaneously with regard to amplitude, duration, relation to the surface QRS, and the presence of multiple components.

Reference values for normal bipolar and unipolar electrograms were validated in 20 subjects without structural heart disease established by c-MRI. A minimum of 800 points was sampled. Pulmonary valve sites (defined as the abrupt appearance of very low signals during RVOT electroanatomical mapping) were excluded from the measurements. Normal bipolar electrograms were sharp with ≤ 3 rapid deflections and short duration (<70ms). The percentage of low-voltage areas (bipolar and unipolar electrograms) within the RVOT was calculated using a specific software included in the CARTO 3 version (Biosense-Webster, Diamond Bar, CA, USA). Abnormal bipolar and unipolar electrograms were defined as those exceeded by 95% of all electrograms.[1,2]

A mean of 1019.1±171.7 points was collected during high-density electronatomical mapping of the right ventricle in control population with idiopathic RVOT ventricular tachycardia. The mean bipolar amplitude within the RVOT aspects was 4.1 ± 0.4 mV (mean bipolar amplitude within the right ventricular body 4.6 ± 0.4 mV), with 95% of the recorded signals with normal configuration having an amplitude >1mV. The mean amplitude of unipolar electrograms within the RVOT segments was 7.9 ± 0.7 mV, (mean unipolar amplitude within the right ventricular body 8.8±0.8 mV) with 95% of the recorded unipolar signals having an amplitude >4mV. Based on these findings, an electroanatomical mapping was considered abnormal in the presence of low-voltage areas ≥1 cm^2 including ≥3 adjacent points with a bipolar signal amplitude < 1 mV and an unipolar

signal amplitude <4 mV.

Statistical analysis

Continuous data are presented as mean ± standard deviation. Continues variables were tested for normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables with and without normal distribution were compared using Student's t-test and Mann-Whitney U test, respectively. Categorical data are presented as frequency and percentage. The association between abnormal bipolar and unipolar electroanatomical mapping and VF induction during PVS was determined by means of univariate analysis. A receiver operating characteristics curve (ROC) analysis was performed to determine the optimal cut-off value of the abnormal area size, defined as the value maximizing the sum of sensitivity and specificity, that predict VF inducibility. A probability of less than 0.05 was considered significant. The IBM SPSS program (Statistics for Windows, Version 22.0. Armonk, NY, IBM Corp) was used for the statistical analysis.

Table 1. The clinical and electrophysiological characteristics of BrS patients.

	Age	Sex	Genetic testing	EAM (total points)	VF induction at PVS	Low voltage (<1 mV) bipolar area (cm^2)	Low voltage (<4 mV) unipolar area (cm^2)	Location of low voltage unipolar areas
1	22	M	NP	1150	Yes	4.5	18	RVOT: Free wall RV inflow tract: lateral sub-tricuspid regions
2	38	M	Negative	1080	No	7	12	RVOT: Free wall
3	30	M	NP	927	Yes	4	22	RVOT: Free wall RV inflow tract: lateral sub-tricuspid regions
4	21	M	Negative	886	No	1.5	7	RVOT: Free wall
5	45	M	NP	1494	No	4	14	RVOT: Free wall
6	34	M	NP	1248	Yes	3	12	RVOT: Free wall
7	27	M	Negative	883	No	2	8	RVOT: Free wall
8	29	F	NP	996	No	3	9	RVOT: Free wall
9	35	M	NP	1131	Yes	4	12	RVOT: Free wall RV inflow tract: lateral sub-tricuspid regions
10	60	F	NP	810	No	1.5	12	RVOT: Free wall
11	40	M	NP	1061	Yes	5	15	RVOT: Free wall
12	37	M	NP	933	No	1,5	6	RVOT: Free wall
13	30	M	NP	901	No	1,5	1,5	RVOT: Free wall
14	45	M	NP	1006	Yes	3	9	RVOT: Free wall
15	50	F	NP	843	No	3	10	RVOT: Free wall

16	54	M	Negative	953	Yes	5	17	RVOT: Free wall RV inflow tract: lateral sub-tricuspid regions
17	37	M	NP	821	No	1,5	1,5	RVOT: Free wall

EAM: electroanatomical mapping; NP: Not performed; PVS: programmed ventricular stimulation; RVOT: right ventricular outflow tract; RV: right ventricular; VF: ventricular fibrillation.

References

1. Polin GM, Haqqani H, Tzou W, Hutchinson MD, Garcia FC, Callans DJ, Zado ES, Marchlinski FE. Endocardial unipolar voltage mapping to identify epicardial substrate in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart Rhythm 2011;8:76–83.
2. Hutchinson MD, Gerstenfeld EP, Desjardins B, Bala R, Riley MP, Garcia FC, Dixit S, Lin D, Tzou WS, Cooper JM, Verdino RJ, Callans DJ, Marchlinski FE. Endocardial unipolar voltage mapping to detect epicardial ventricular tachycardia substrate in patients with nonischemic left ventricular cardiomyopathy. Circ Arrhythm Electrophysiol 2011;4:49–55.