Risk stratification of ventricular fibrillation in Brugada syndrome using noninvasive scoring methods

Hiroshi Kawazoe, MD,* Yukiko Nakano, MD, PhD,* Hidenori Ochi, MD, PhD,† Masahiko Takagi, MD, PhD,‡ Yusuke Hayashi, MD, PhD,‡ Yuko Uchimura, MD, PhD,* Takehito Tokuyama, MD, PhD,* Yoshikazu Watanabe, MD, PhD,* Hiroya Matsumura, MD,* Shunsuke Tomomori, MD,* Akinori Sairaku, MD,* Kazuyoshi Suenari, MD, PhD,* Akinori Awazu, PhD,§ Yosuke Miwa, MD, PhD,¶ Kyoko Soejima, MD, PhD,¶ Kazuaki Chayama, MD, PhD,† Yasuki Kihara, MD, PhD*

*From the *Department of Cardiovascular Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan, †Department of Gastroenterology and Metabolism, Applied Life Sciences, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan, ‡Department of Internal Medicine and Cardiology, Osaka City University Graduate School of Medicine, Osaka, Japan, §Department of Mathematical and Life Sciences, Hiroshima University, Hiroshima, Japan, and ¶Department of Cardiology, Kyorin University Hospital, Tokyo, Japan.*

BACKGROUND Risk stratification for ventricular fibrillation (VF) in patients with Brugada syndrome (BrS) remains controversial.

OBJECTIVE The purpose of this study was to construct a novel prediction model for VF risk in BrS patients using noninvasive parameters.

METHODS A total of 143 Japanese BrS patients with VF (n = 35) and without VF (n = 108) were retrospectively enrolled. We built a logistic regression model predicting VF occurrence and evaluated it by cross-validation.

RESULTS Frequencies of history of syncope and spontaneous type 1 ECG, r–J interval in V_1, QRS duration in V_6, and LAS_{40}, Tpeak–Tend dispersion, and max T-wave alternans were significantly associated with VF occurrence in univariate analyses. The history of syncope, r–J interval in V_1, QRS duration in V_6, and Tpeak–Tend dispersion were identified as independent predictors by multivariate logistic regression analysis. The predictive model was constructed using all these parameters with good discrimination of VF occurrence (area under the curve 0.869 with 97.1% sensitivity and 65.7% specificity). The area under the curve based on leave-one-out cross-validation was 0.845, with 97.1% sensitivity and 63.0% specificity suggesting good performance of the model. Retrospective survival analysis revealed that the cumulative VF event rate was significantly higher in patients at high risk than in those with low risk using the log rank test ($P = 2.97 \times 10^{-8}$). Notably, no BrS patient below the cutoff value developed a subsequent VF event.

CONCLUSION This novel prediction method may effectively assesses VF risk in BrS patients, especially when determining implantable cardioverter-defibrillator placement for asymptomatic BrS patients.

KEYWORDS Brugada syndrome; Risk stratification; Ventricular fibrillation; Scoring method; T-wave alternans

(Heart Rhythm 2016;13:1947–1954)

Introduction

Brugada syndrome (BrS) is an inherited arrhythmogenic disorder characterized by a typical Brugada-type ECG pattern of ST-segment elevation in the right precordial leads and a high risk of ventricular fibrillation (VF) or sudden cardiac death (SCD).[1] Primary prevention of SCD in BrS patients has been recognized as important; however, VF risk stratification in BrS remains challenging and controversial.

Address reprint requests and correspondence: Dr. Yukiko Nakano, Department of Cardiovascular Medicine, Hiroshima University, Graduate School of Biomedical Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. E-mail address: nakanoy@hiroshima-u.ac.jp.

Several studies on VF occurrence prediction in BrS patients have been reported.[2–8] Spontaneous type 1 ECG (Sp1), history of syncope probably caused by ventricular arrhythmia, family history of SCD, positive late potential, Tpeak–Tend (Tp-e) dispersion in leads V_1–V_6,[9] QRS duration in lead V_6,[5] r–J interval in lead V_2,[5] fragmented QRS,[10] ventricular tachycardia/VF inducibility by programmed electrical stimulation (PES), and ventricular effective refractory period <200 ms on electrophysiologic study (EPS)[8] have been reported to be useful in identifying high-risk patients. However, individual prediction performances of these parameters were limited in discriminating BrS patients with VF high risk.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2016.07.009

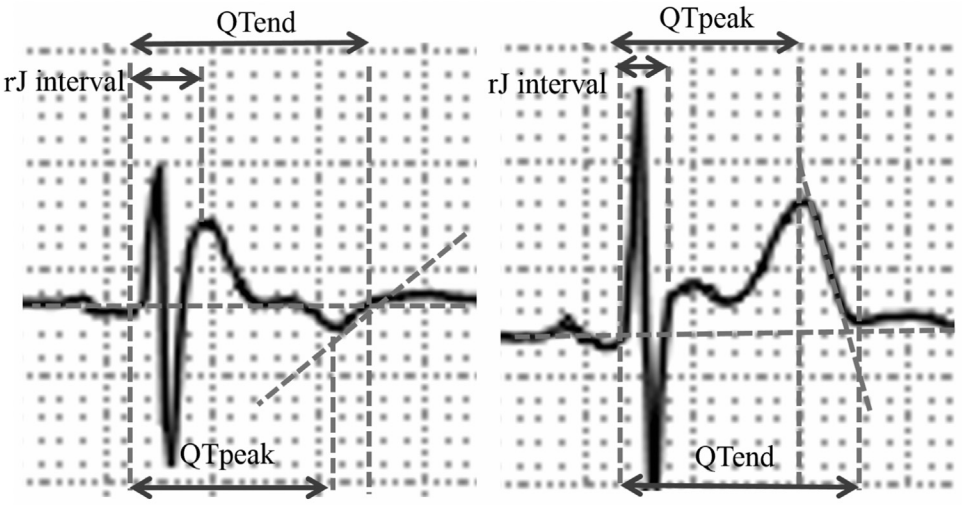

Figure 1 Sample measurements of QTend, QTpeak, and r–J interval in type 1 and non–type 1 Brugada ECG. Tp-e was measured in each precordial lead and obtained from the difference between QT interval and QT peak interval. r–J interval was defined as the time between the earliest deflection of the QRS complex and J wave.

Some reports that combined clinical parameters may be helpful in risk stratification of BrS patients without a history of cardiac arrest. Delise et al[11,12] reported that each single risk factor (Sp1 pattern, familial juvenile sudden death, and positive EPS) displayed limited specificity and positive predictive value for predicting VF, and presence of a basal type 1 ECG is able to identify subjects at higher risk in combination with other clinical risk factors including syncope, family history of SCD, and positive EPS increased risk.[11,12] Okamura et al[13] reported that combined assessment of history of syncope, Sp1, and VF induction by PES are important for stratifying VF risk in BrS patients. More recently, we reported that elevated time–domain T-wave alternans (TWA) on ambulatory ECG is a high-risk marker of VF occurrence in BrS patients.[14]

The purpose of this study was to develop a logistic regression model for VF risk stratification in BrS patients based on noninvasive examination.

Method

Study protocol of risk stratification of BrS patients using noninvasive scoring method

A total of 143 patients diagnosed with BrS (140 men, mean age 46 ± 12 years) between January 2001 and December 2014 were retrospectively enrolled from 3 different institutions in Japan: 58 patients at Hiroshima University Hospital (56 male, mean age 45 ± 13 years, VF history in 15), 83 patients at Osaka City University Hospital (82 male, mean age 47 ± 13 years, VF history in 19), and 2 patients at Kyorin University Hospital (2 male, age 37 and 43 years, VF history in 1). BrS was definitively diagnosed based on the 2014 HRS/EHRA/APHRS consensus statement.[15]

All subjects were classified into 2 groups: the VF group, which included patients with documented VF (n = 35), and the non-VF group, which comprised patients without prior documented VF (n = 108). We compared clinical characteristics, type of Brugada ECG and other 12-lead ECG parameters, signal-averaged ECG parameters, and time–domain TWA between the VF and non-VF groups, and all possible risk factors were screened by univariate analysis. Thereafter, multivariate analysis was performed in all subjects, followed by assessment of the performance of the prediction model for VF risk by cross-validation.

The study was approved by the ethics review committee of the hospital. We prospectively followed the 143 BrS patients after their diagnosis of BrS and investigated the relationships between the subsequent VF events (appropriate shocks/VF recordings on implantable cardioverter-defibrillator [ICD]) during follow-up periods and the score of our logistic model.

Twelve-lead ECG findings

The 12-lead ECG was recorded at a paper speed of 25 mm/s and amplification of 1 cm/mV. The following parameters were measured for the 143 patients (Figure 1): (1) r–J interval, defined as the time between the earliest deflection of the QRS complex and J wave [5]; (2) Tp-e, measured in each precordial lead and obtained from the difference between QT interval and QT peak interval, using the tangent method to define the end of the T wave[16]; (3) QT dispersion, defined as the difference between the maximum and minimum QT interval of the precordial leads; and (4) fragmented QRS complex, defined as >2 notches or multiple notches of the R wave or in the nadir of the S wave in at least 2 consecutive leads.[17]

Because the ST configurations in the right precordial leads showed day-to-day variation, >5 ECGs were recorded on different days in each BrS patient. When an SP1 pattern was recorded at least once in the recorded ECGs of a BrS patient, that person was defined as having an SP1 pattern. We determined SP1 only in the right precordial leads, with V_1 and V_2 positioned in the 4th intercostal space.

Signal-averaged ECG

A signal-averaged ECG was recorded and analyzed using the EP-705LP system (Fukuda Denshi, Tokyo, Japan). Three parameters were assessed using a computer algorithm: (1) total filtered QRS duration (f-QRS); (2) root mean square voltage of the terminal 40 ms of the f-QRS complexes (RMS_{40}); and (3) duration of low-amplitude signals <40 μV of the f-QRS complexes (LAS_{40}). Late potential was identified when 2 of the following criteria were satisfied: f-QRS $\geq$114 ms, RMS_{40} <20 μV, or LAS_{40} $\geq$38 ms.[18] We lacked late potential data for 8 patients (VF group: n = 34; non-VF group: n = 101).

Measurement of time–domain TWA

ECGs were recorded using a 24-hour ambulatory ECG device. Time–domain TWA in leads V_5 and V_2 was assessed via the modified moving average method using the MARS PC system (GE Healthcare, Milwaukee, WI) as previously described.[19] In brief, the modified moving average algorithm separates odd and even beats into separate bins and creates median templates for both the odd and even complexes every 15 seconds. These templates then are superimposed, and the entire JT segment is analyzed for alternans. The difference between the odd and even median complexes at any point is defined as the TWA value. We used max TWA during 24-hour ambulatory ECG in lead V_5 or V_2.

Statistical analysis

Data are given as mean ± SD. The χ^2 test or Student *t* test was conducted to determine statistically significant differences. Multivariate analysis based on the factors significant by univariate analysis was performed using logistic regression with stepwise forward selection method in a total of 143 Japanese BrS subjects. The predictive value of VF risk was assessed, and the performance of the univariate and logistic model was analyzed by receiver operating characteristic (ROC) analysis. We evaluated cross-validation of the logistic model using the leave-one-out method[20] and internal validation of our logistic model using 2000 bootstrapped samples to form a bias-corrected concordance statistic area under the curve (AUC). Predicted probabilities were compared with observed probabilities using a bias-corrected calibration plot to judge the performance of the model with respect to over- or underestimating the occurrence of VF. Based on logistic regression analysis, we developed a nomogram to estimate the probability of VF occurrence in BrS patients using the rms package in R program.[21]

For all tests, $P<.05$ was considered significant. Statistical analyses were conducted using R and the JMP statistical package (version 8.0J, SAS Institute, Cary, NC).

Results

Comparison of clinical characteristics and noninvasive parameters between VF and non-VF groups in all subjects

Clinical characteristics, 12-leads ECG parameters, signal-averaged ECG parameters, and TWA findings are listed in Table 1. Age, sex, and family history of SCD were similar in both groups. The prevalences of Sp1 and syncope were higher in the VF group than in the non-VF group (80% vs 51%, $P = .004$; and 34.3% vs 11.1%, $P = .002$, respectively).

The following ECG parameters were significantly higher in the VF group than in the non-VF group: r–J interval in lead V_1/V_2 (V_1: 95.6 ± 16.8 ms vs 82.0 ± 16.1 ms, $P = .0001$; V_2: 99.7 ± 18.2 ms vs 86.0 ± 17.0 ms, $P = .0003$); QRS duration in lead V_6 (99.9 ± 22.3 ms vs 85.8 ± 15.7 ms, $P = .0003$), max QTc time (400.7 ± 32.1 ms vs 385.5 ± 36.7 ms, $P = .033$), Tp-e interval (124.4 ± 33.2 ms vs 104.4 ± 21.7 ms, $P = .001$), and Tp-e dispersion (58.8 ± 29.3 vs 35.0 ± 23.4, $P = .0001$).

Filtered QRS was longer and LAS_{40} was higher in the VF group than in the non-VF group (filtered QRS: 140.1 ± 33.9 ms vs 126.9 ± 30.8 ms, $P = .041$; LAS_{40}: 52.5 ± 15.0 vs 44.2 ± 12.1, $P = .003$). The max TWA and frequency of positive TWA were higher in the VF group than in the non-VF group (70.1 ± 19.3 vs 61.8 ± 18.5, $P = .026$; and 68.6% vs 43.5%, $P = .011$, respectively).

Construction of the prediction model

Multivariate logistic regression analysis and the logistic model are given in Table 2. The history of syncope, QRS duration in V_6, r–J interval in V_1, and Tp-e dispersion remained as independent predictors for VF occurrence with an AUC in ROC curve of 0.869, sensitivity of 97.1%, and specificity of 65.7% (Figure 2A). The AUCs of the univariate logistic models are shown in Online Supplemental Figure 1.

Validation of the prediction model

Internal validation was performed by the leave-one-out cross-validation technique. The AUC based on cross-validation was 0.845, with sensitivity of 97.1% and specificity of 63.0% (Figure 2B). The bias-corrected AUC for predicting probability of the VF events in our subjects was good (0.8533). The calibration plot demonstrated that the model was well calibrated as a whole, with slight underestimation and overestimation of risk probability (Figure 3).

Based on the logistic equation including the coefficients in Table 2, predicted risk probability plots were generated over a range of Tp-e dispersion, QRS duration in V_6, and r–J interval in V_1 (Figure 4). For example, a patient without a history of syncope and Tp-e dispersion = 75 has a probability of VF occurrence of 0.375, whereas the probability increases to 0.75 for a patient without history of syncope and Tp-e dispersion = 110.

We further developed a nomogram that can be used to predict individual risk probabilities for VF occurrence based on the logistic model (Figure 5). A straight line must be drawn upward to the points to determine how many points a patient will receive for each parameter, and the sum of the points for each predictor must be located on the total point axis. By drawing a straight line downward, the patient's VF

Table 1 Comparison of clinical, 12-lead ECG, signal-averaged ECG, and TWA findings between VF group and non-VF groups of Brugada syndrome patients

	VF group (n = 35)	Non-VF group (n = 108)	*P* value (univariate analysis)
Clinical findings			
Age (years)	43.3 ± 10.9	47.1 ± 13.1	.126
Male	35 (100)	105 (97.2)	1
History of syncope	12 (34.3)	12 (11.1)	.002
Family history of SCD	12 (34.2)	24 (22.2)	.156
Sp1	28 (80.0)	56 (51.0)	.004
ICD placement	35 (100)	45 (41.7)	.988
Twelve-lead ECG findings			
V_1			
r–J interval (ms)	95.6 ± 16.8	82.0 ± 16.1	.0001
ST level at J point (mV)	0.18 ± 0.16	0.16 ± 0.18	.712
ST level 0.08 s from J point (mV)	0.09 ± 0.15	0.07 ± 0.06	.253
V_2			
r–J interval (ms)	99.7 ± 18.2	86.0 ± 17.0	.0003
ST level at J point (mV)	0.30 ± 0.20	0.30 ± 0.17	.954
ST level 0.08 s from J point (mV)	0.23 ± 0.17	0.20 ± 0.11	.353
V_6			
QRS duration (ms)	99.9 ± 22.3	85.8 ± 15.7	.0003
II			
P-wave duration (ms)	94.7 ± 17.3	90.0 ± 14.5	.120
PQ (ms)	175.3 ± 32.5	168.4 ± 24.0	.177
RR (ms)	924.5 ± 97.0	951.8 ± 115.0	.208
V_1–V_3			
Fragmented QRS	9 (26.5)	21 (19.4)	.383
Precordial			
Max QT (ms)	388.5 ± 39.6	374.6 ± 34.5	.052
Max QTc (ms)	400.7 ± 32.1	385.5 ± 36.7	.033
Tp-e interval (ms)	124.4 ± 33.2	104.4 ± 21.7	.001
Tp-e dispersion (ms)	58.8 ± 29.3	35.0 ± 23.4	.0001
Presence of ER	2 (5.7)	6 (5.5)	.971
Signal-averaged ECG findings (lacked data from 8 patients)	(n = 34)	(n = 101)	
Positive late potentials	30 (85.7)	78 (72.2)	.113
Filtered QRS (ms)	140.1 ± 33.9	126.9 ± 30.8	.041
LAS_{40} (ms)	52.5 ± 15.0	44.2 ± 12.1	.003
RMS_{40} (μV)	13.4 ± 17.6	16.7 ± 12.0	.215
TWA findings			
Positive TWA	24 (68.6)	47 (43.5)	.011
Max TWA (μV)	70.1 ± 19.3	61.8 ± 18.5	.026

Quantitative data are given as mean ± SD or n (%). Binary variables were compared by χ^2 test, and quantitative traits were tested using the Mann–Whitney U test.

ER = early repolarization; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; Sp1 = spontaneous type 1 Brugada ECG; Tp-e = Tpeak–Tend; TWA = T-wave alternans; VF = ventricular fibrillation.

probability is found. For example, using this nomogram, a 22-year-old male case with a family history of SCD and Sp1 but without a history of syncope (0 points), r–J interval in V_1 = 84 (35 points), and QRS duration in V_6 = 100 ms (20 points) and Tp-e dispersion = 19 (10 points) receives a total points value = 65. Using the lower scales of the figure, this score corresponds to a probability of VF occurrence of about 0.08 (Figure 5A). No VF events were documented in this patient during 105-month follow-up. The other 36-year-old male case with Sp1, without a family history of SCD, with a history of syncope (23 points), r–J interval in V_1 = 103 (45 points), and QRS duration in V_6 = 109 ms (23 points) and Tp-e dispersion = 34 (18 points) receives a total points value = 109. His probability of VF occurrence is about 0.69 (Figure 5B). This patient suffered VF 23 months after ICD placement.

BrS risk score and subsequent VF events in BrS cases

An ICD was inserted in all patients of the VF group as secondary prevention and in 47 BrS patients without a history of VF as primary prevention because of (1) Sp1, a family history of SCD, syncope, and VF induction during EPS (n = 4); (2) Sp1, syncope, and VF induction during EPS (n = 7); or (3) Sp1, a family history of SCD, and VF induction during EPS (n = 14), in accordance with the Japanese guidelines.[22,23] Twenty-two cases with Sp1 desired ICD placement because of VF induction by PES.

During mean follow-up of 82.8 ± 49.0 months (range 6–164 months) after the diagnosis of BrS, VF occurred in 25 of 143 patients. Fifteen of them also had VF history. The Kaplan–Meier event-free survival curves revealed that the rate of VF events was significantly lower in the cases under the cutoff value than over the cutoff value of this logistic

Table 2 Stepwise logistic analysis of VF group and non-VF groups of Brugada syndrome patients

			Univariate analysis	Multivariate analysis				
	VF group (n = 35)	Non-VF group (n = 108)	*P* value	Odds ratio	95% CI	*P* value	Coefficient	Standard error
Age (years)	43.3 ± 10.9	47.1 ± 13.1	0.126					
Male	32 (97.0)	105 (97.2)	1					
History of syncope	12 (34.3)	12 (11.1)	0.002	4.909	1.40–17.1	.013	1.591	0.638
Sp1	28 (80.0)	56 (51.0)	0.004					
r–J interval in V_1 (ms)	95.6 ± 16.8	82.0 ± 16.1	0.0001	1.040	1.04–1.08	.028	0.040	0.018
Tp-e dispersion (ms)	58.8 ± 29.3	35.0 ± 23.4	0.0001	1.069	1.03–1.10	.001	0.036	0.011
QRS duration in V_6 (ms)	99.9 ± 22.3	85.8 ± 15.7	0.0003	1.043	1.01–1.08	.021	0.042	0.018
LAS_{40} (ms)	52.5 ± 15.0	44.2 ± 12.1	0.003					
Max TWA (μV)	70.1 ± 19.3	61.8 ± 18.5	0.026					
Institute (Hiroshima University) (%)	17 (48.6)	41 (38.0)	0.750					

Quantitative data are given as mean ± SD or n (%). Binary variables were compared by $\chi 2$ test, and quantitative traits were tested using the Mann–Whitney U test for univariate analysis. Stepwise logistic analysis was used for multivariate analysis.

CI = confidence interval; Sp1 = spontaneous type 1 Brugada ECG; Tp-e = Tpeak–Tend; TWA = T-wave alternans; VF = ventricular fibrillation.

model using the log-rank test ($P = 2.97 \times 10^{-8}$; Figure 6). In particular, no BrS patient under the cutoff value of this model developed subsequent VF event.

No complications occurred upon ICD placement, and 3 BrS patients suffered inappropriate shocks because of the rapid AF.

Discussion

The major finding of this study was that we established a logistic model consisting of noninvasive parameters to discriminate high-risk and low-risk BrS patients for developing VF. This is an important finding because such discrimination in asymptomatic BrS patients may help to determine the requirements for ICD placement.

History of syncope, Sp1, LAS_{40}, max TWA, r–J interval in V_1, QRS duration in V_6, and Tp-e dispersion showed significant differences between VF and non-VF group. The logistic regression model constructed by the combination of history of syncope, r–J interval in V_1, QRS duration in V_6, and Tp-e dispersion obtained a satisfactory AUC in ROC analysis.

There are no clear standards with regard to appropriate management of BrS patients because the prognosis and high-risk factors of VF occurrence vary based on currently available reports.[2–4,24,25] The management of BrS patients differs slightly in Europe, the United States, and Japan. In Europe and the United States, history of syncope is emphasized as an indication for ICD placement. In Japan, the indication for ICD placement for primary prevention of

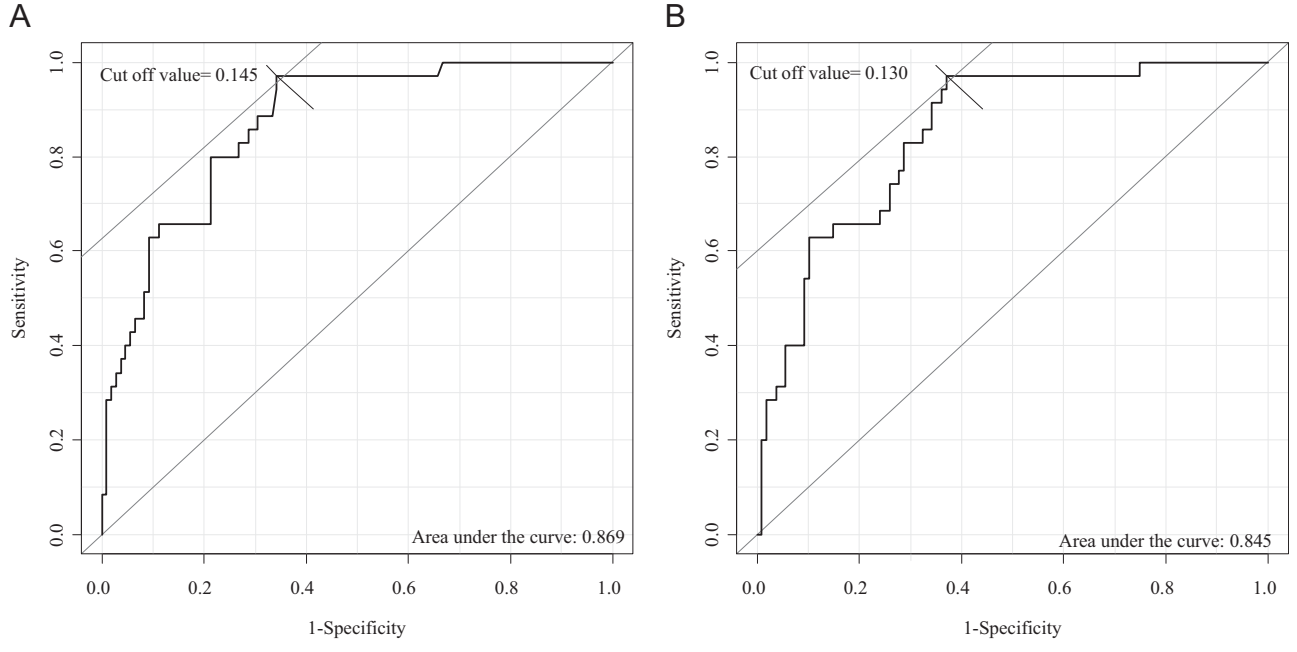

Figure 2 **A:** Receiver operating characteristic (ROC) analysis of the logistic model for the prediction of ventricular fibrillation occurrence. Area under the ROC curve was 0.869. **B:** Cross-validation using the leave-one-out technique. Area under the ROC curve was 0.845.

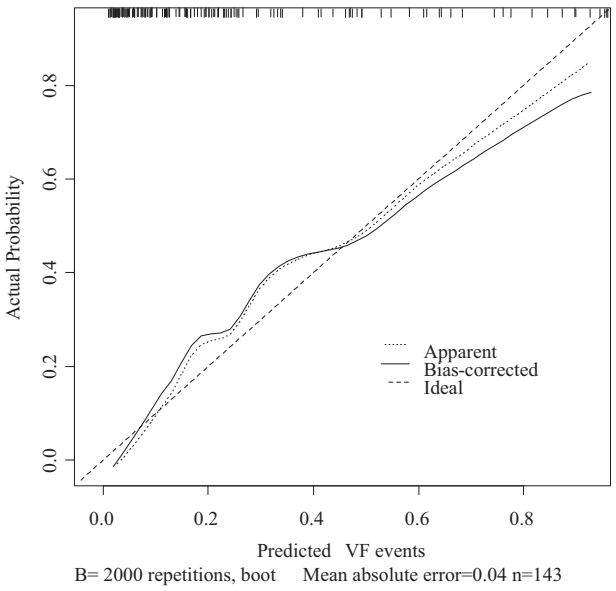

Figure 3 Bootstrap calibration plot showing actual vs predicted probability of ventricular fibrillation (VF) events (B = 2000).

SCD in BrS patients is determined by 3 risk factors (syncope, family history, and PES) according to the 2011 guidelines (2012 focused update). ICD indication is categorized as class IIa in patients with 2 or 3 risk factors. However, in 2 large European BrS registries (FINGER and PRELUDE), VF induction had a small role.[7,8] In our study, not family history of SCD but history of syncope was significantly associated with VF events. The multi-institutional research study by Eckardt et al[4] and the report by Giustetto et al[25] demonstrated that the incidence of cardiovascular events in patients with a history of syncope was significantly higher (8.6%) compared with asymptomatic cases (6.2%). Sacher et al[26] reported that each single risk factor (SP1, family history of SCD, and VF induction by PES) displayed limited clinical value. More importantly, they also demonstrated the difficulty of event estimation in BrS patients because in BrS patients without ICD placement we cannot determine and evaluate event occurrence perfectly.

Time–domain TWA can be analyzed from routine 24-hour ambulatory ECG recordings without the requirement for a provocative stimulus and has been reported to be a useful predictor of SCD.[24,25,27] Uchimura et al[14] reported that elevated time–domain TWA on ambulatory ECG confirms VF risk with sensitivity of 82% and specificity of 88% in BrS patients. Time–domain TWA has an advantage in BrS patients whose VF frequently occurs during bradycardia or sleep, during periods of parasympathetic nerve predominance.[27–29]

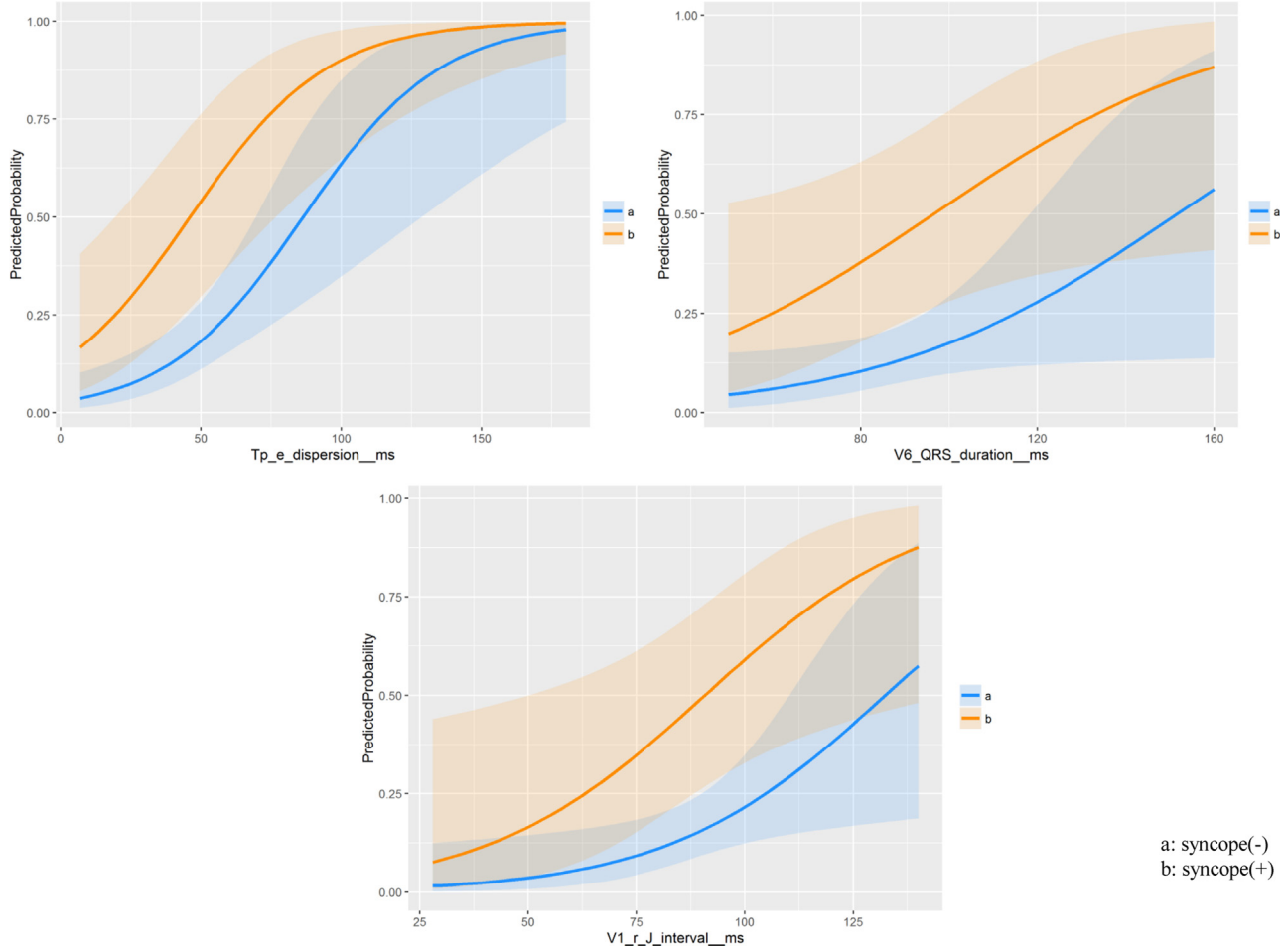

Figure 4 Predicted risk probability plots generated over a range of Tp-e dispersion, QRS duration in V_6, and r–J interval in V_1.

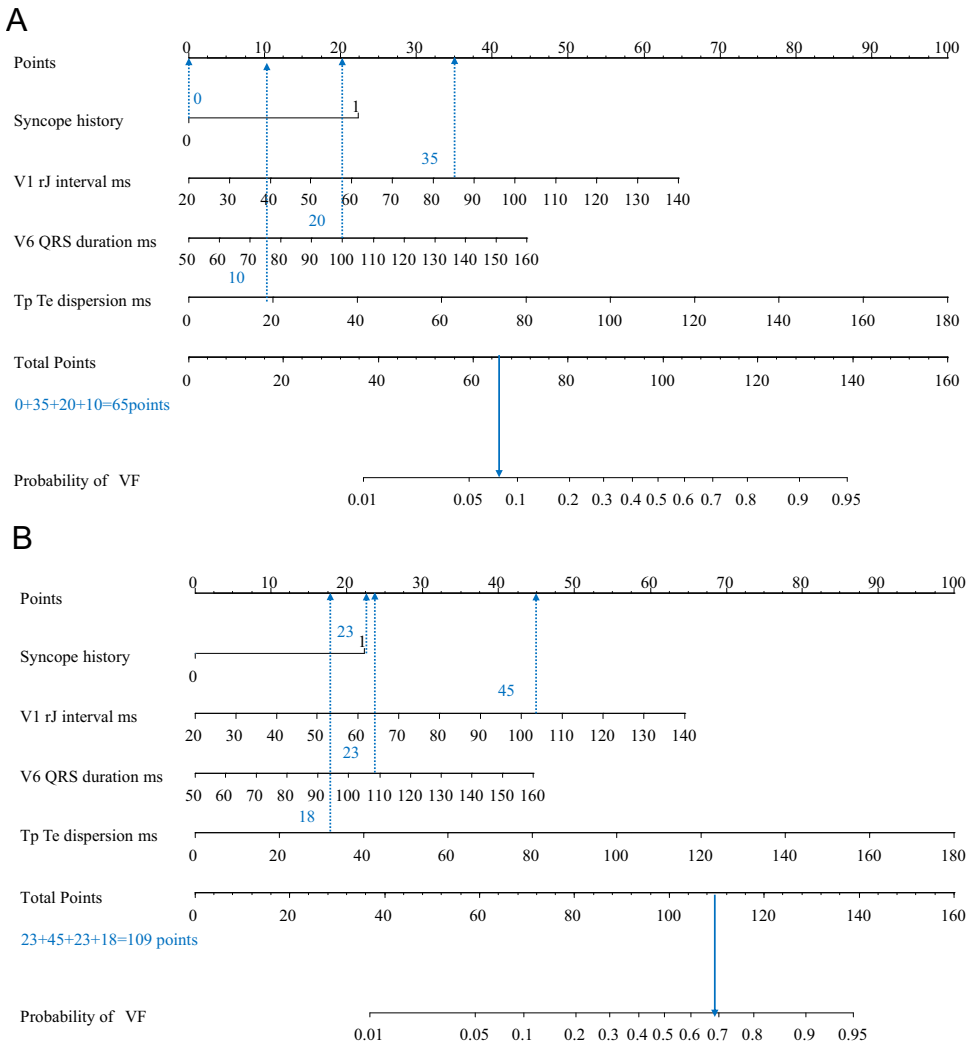

Figure 5 Nomograms of the representative 2 cases with **(A)** or without **(B)** subsequent ventricular fibrillation (VF) events.

Many ECG markers, including wide S in type 1 ECG,[30] r–J interval ≥90 ms, QRS duration in V_6 ≥90 ms,[5] QRS fragmentation,[8,10] Tp-e interval, Tp-e dispersion,[9] and aVR sign,[31] have been reported to contribute toward SCD risk stratification in BrS patients.

In this study, we first constructed a noninvasive logistic model combining history of syncope, r–J interval in V_1, QRS duration in V_6, and Tp-e dispersion for VF risk stratification in BrS patients and investigated the efficacy of the model. The AUC was 0.869 with sensitivity of 97.1% and specificity of 65.7%, suggesting a good performance of the logistic model constructed.

In addition, in our model none of the BrS patients under the cutoff value developed a subsequent VF event. Our model achieved high accuracy for predicting VF occurrence using only a subset of noninvasive markers. The nomogram may help clinicians to make appropriate treatment decisions for BrS patients, especially with regard to ICD placement.

The pathogenesis of BrS remains to be completely elucidated. There are many theories based on repolarization and depolarization abnormalities.[32] In our prediction model, both repolarization- and depolarization-related parameters mainly seem to contribute to VF risk.

Study limitation

The limitation of this study is the small number of cases analyzed. The sample size of 143 is too small for the predictive model. Although the adequacy of this scoring method must be validated in a larger prospective study with a longer follow-up period, it could be very useful and convenient for selecting the most appropriate therapeutic option in BrS patients.

Conclusion

Our novel logistic model using previously reported non-invasive risk factors of VF in BrS patients (a combination of history of syncope, r–J interval in V_1, QRS duration in V_6, and Tp-e dispersion) is useful for assessing risk stratification in routine clinical practice.

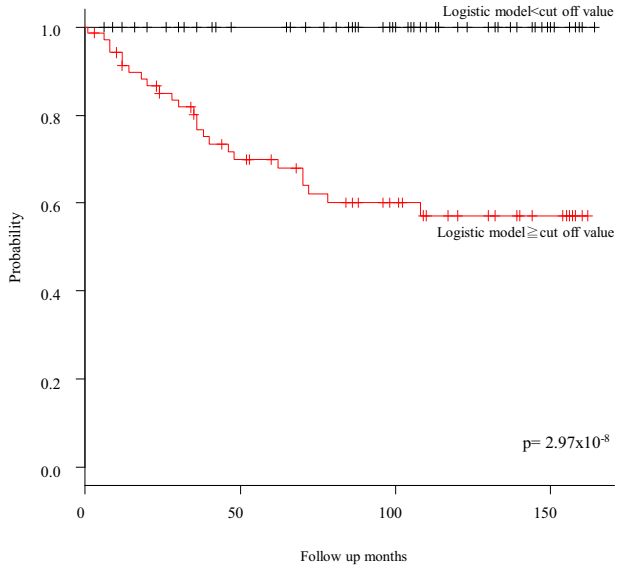

Figure 6 Kaplan–Meier curve of event-free survival of patients with Brugada syndrome (BrS) according to the cutoff value of logistic model. The rate of ventricular fibrillation (VF) events was significantly lower in the cases under the cutoff vale of this logistic model than in those over the cutoff value using the log-rank test ($P = 2.97 \times 10^{-8}$). No BrS patients under the cutoff value of this model developed a subsequent VF event.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2016.07.009.

References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20:1391–1396.
2. Brugada J, Brugada R, Antzelevitch C. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. Circulation 2002;105:73–78.
3. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002;105:1342–1347.
4. Eckardt L, Probst V, Smits JP, et al. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. Circulation 2005;111:257–263.
5. Takagi M, Yokoyama Y, Aonuma K, Aihara N, Hiraoka M; Japan Idiopathic Ventricular Fibrillation Study (J-IVFS) Investigators. Clinical characteristics and risk stratification in symptomatic and asymptomatic patients with Brugada syndrome. J Cardiovasc Electrophysiol 2007;18:1244–1251.
6. Kamakura S, Ohe T, Nakazawa K, et al. Long-term prognosis of probands with Brugada-pattern ST elevation in V1-V3 leads. Circ Arrhythm Electrophysiol 2009;2:495–503.
7. Probst V, Veltmann C, Eckardt L, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada syndrome registry. Circulation 2010;121:635–643.
8. Priori SG, Gasparini M, Napolitano C, et al. Risk stratification in Brugada syndrome: results of the PRELUDE registry. J Am Coll Cardiol 2012;59:3745.
9. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, Dorantes Sánchez M, Dorticós Balea F, Zayas Molina R, Quiñones Pérez MA, Fayad Rodríguez Y. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol 2006;47:1828–1834.
10. Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, Ohe T, Zipes DP, Wu J. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. Circulation 2008;118:1697–1704.
11. Delise P, Allocca G, Sitta N, DiStefano P. Event rates and risk factors in patients with Brugada syndrome and no prior cardiac arrest: a cumulative analysis of the largest available studies distinguishing ICD-recorded fast ventricular arrhythmias and sudden death. Heart Rhythm 2014;11:252–258.
12. Delise P, Allocca G, Marras E, et al. Risk stratification in individuals with the Brugada type 1 ECG pattern without previous cardiac arrest: usefulness of a combined clinical and electrophysiologic approach. Eur Heart J 2011;32:169–176.
13. Okamura H, Kamakura T, Morita H, et al. Risk Stratification in patients with Brugada syndrome without previous cardiac arrest; Prognostic value of combined risk factors. Circ J 2015;79:310–317.
14. Uchimura-Makita Y, Nakano Y, Tokuyama T, et al. Time-domain t-wave alternans is strongly associated with a history of ventricular fibrillation in patients with Brugada syndrome. J Cardiovasc Electrophysiol 2014;25:1021–1027.
15. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Heart Rhythm 2013;10:1932–1963.
16. Postema PG, Wilde AA. The measurement of the QT interval. Curr Cardiol Rev 2014;10:287–294.
17. Brenyo A, Pietrasik G, Barsheshet A, Huang DT, Polonsky B, McNitt S, Moss AJ, Zareba WJ. QRS fragmentation and the risk of sudden cardiac death in MADIT II. J Cardiovasc Electrophysiol 2012;23:1343–1348.
18. Cain ME, Anderson JL, Ansdorf MF, Mason JW, Scheinman MM, Waldo AL. ACC expert consensus document: signal-averaged electrocardiography. J Am Coll Cardiol 1996;27:238–249.
19. Nearing BD, Verrier RL. Modified moving average analysis of Twave alternans to predict ventricular fibrillation with high accuracy. J Appl Physiol 2002;92:541–549.
20. Cawley GC, Talbot NLC. Efficient approximate leave-one-out cross-validation for kernel logistic regression. Machine Learning 2008;71:243–264.
21. Frank E, Harrell Jr. Rms. Regression modeling strategies. R package version 3.4-0. Available at: http://CRAN.Rproject.org/package_rms.
22. JCS Joint Working Group. Guidelines for non-pharmacotherapy of cardiac arrhythmias. Circ J 2001;65:1127–1160.
23. JCS Joint Working Group. Guidelines for non-pharmacotherapy of cardiac arrhythmias. Circ J 2013;77:249–274.
24. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation 2003;108:3092–3096.
25. Giustetto C, Drago S, Demarchi PG, Dalmasso P, Bianchi F, Masi AS, Carvalho P, Occhetta E, Rossetti G, Riccardi R, Bertona R, Gaita F. Italian Association of Arrhythmology and Cardiostimulation (AIAC)-Piedmont Section: risk stratification of the patients with Brugada type electrocardiogram: a community-based prospective study. Europace 2009;11:507–513.
26. Sacher F, Probst V, Maury P, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study-part 2. Circulation 2013;128:1739–1747.
27. Verrier RL, Nearing BD, La Rovere MT, Pinna GD, Mittleman MA, Bigger JT Jr, Schwartz PJ; ATRAMI Investigators. Ambulatory electrocardiogram-based tracking of T wave alternans in postmyocardial infarction patients to assess risk of cardiac arrest or arrhythmic death. J Cardiovasc Electrophysiol 2003;14:705–711.
28. Kirchhof P, Eckardt L, Rolf S, Esperer HD, Paul M, Wichter T, Klein HU, Breithardt G, Böcker D. T wave alternans does not assess arrhythmic risk in patients with Brugada syndrome. Ann Noninvasive Electrocardiol 2004;9:162–165.
29. Nishizaki M, Fujii H, Sakurada H, Kimura A, Hiraoka M. Spontaneous T-wave alternans in a patient with Brugada syndrome-responses to intravenous administration of class I antiarrhythmic drug, glucose tolerance test, and atrial pacing. J Cardiovasc Electrophysiol 2005;16:217–220.
30. Atarashi H, Ogawa S. Idiopathic Ventricular Fibrillation Investigators: new ECG criteria for high-risk Brugada syndrome. Circ J 2003;67:8–10.
31. Babaee Bigi MA, Aslani A, Shahrzad S. aVR sign as a risk factor for life-threatening arrhythmic events in patients with Brugada syndrome. Heart Rhythm 2007;4:1009–1012.
32. Wilde AA, Postema PG, Di Diego JM, Viskin S, Morita H, Fish JM, Antzelevitch C. The pathophysiological mechanism underlying Brugada syndrome; depolarization versus repolarization. J Mol Cell Cardiol 2010;49:543–553.