QRS Vector Magnitude as Predictor of Ventricular Arrhythmia in Patients With Brugada Syndrome

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Risk stratification is the most challenging part in management of patients with Brugada syndrome (BrS). Conduction delay in the right ventricular outflow tract (RVOT) is the major mechanism underlying ventricular tachyarrhythmia (VTA) in BrS. However, QRS duration was not useful in stratifying high-risk patients in large registries. Reconstructing the traditional 12-lead electrocardiogram into QRS vector magnitude can be used to quantify depolarization dispersion and identify high-risk BrS patients. The aim of the study is to test the significance of the QRSvm as a predictor for VTA in patients with BrS. In this retrospective cohort, we included 136 patients (47 ± 15 years, 66% male) who visited outpatient clinic for cardiogenetic screening. All medical records were examined, all 12- lead electrocardiograms were reconstructed into QRSvm using Kors' quasiorthogonal method and were assessed for the presence of electrocardiographic signs indicative of RVOT conduction delay including R wave sign, deep SI, SII >SIII pattern, and Tzou criteria. QRSvm was significantly lower in patients who either presented with VTA or developed VTA during follow-up (1.24 ± 0.35 vs 1.78 ± 0.42 mV, $p < 0.001$). Positive RVOT conduction delay signs occurred more frequently in symptomatic patients (20% vs 7%, $p < 0.001$).The area under receiver operator characteristic curve for QRSvm was 0.85 (95% confidence interval [CI] 0.77 to 0.92). Using QRSvm cutoff of 1.55 mV, sensitivity and specificity were 89% and 71%, respectively. Multivariate regression analysis showed that QRSvm and RVOT signs are independent predictors for VTA in BrS patients (QRS vector magnitude: odds ratio 3.68, 95% CI 2.4 to 6.2, p = 0.001; RVOT: odds ratio 2.6, 95% CI 1.4 to 4.9, p = 0.001). In conclusion, not only electrocardiographic signs indicative of RVOT conduction delay but also QRSvm can be used as a predictor for VTA events in BrS patients. **(Am J Cardiol 2019;123:1962−1966)**

Brugada syndrome (BrS) is an autosomal dominant channelopathy characterized by an increased risk of sudden cardiac death in young subjects without structural anomalies.[1] This channelopathy has an incidence of 0.05% to 0.6% in the general population and can be diagnosed by ST-segment elevation in the right precordial leads either spontaneously or after provocation test using sodium channel blockers.[2] Stratifying the high-risk patients is the most challenging part of BrS management. Many investigators reported on testing different electrocardiographic parameters to quantify the risk of ventricular tachyarrhythmia (VTA) especially in asymptomatic patients. The controversial outcomes make this task unfortunately very challenging.[3−5] However, there is a strong evidence that conduction delay in right ventricular outflow tract (RVOT) is the main mechanism underlying VTA in BrS yet, time parameters such as QRS duration did not have strong prognostic value in large registries.[6,7] Voltage-dependent vectorcardiographic parameters have proved to add diagnostic and prognostic value to the 12-lead surface electrocardiogram (ECG).[8−10] Voltage-dependent QRS 3-dimensional vector magnitude (QRSvm) is a promising parameter for predicting VTA in patients with tetralogy of Fallot (TOF).[11,12] Lower QRSvm indicates scattering of slowly propagating electrical waves, resulting in dispersion of depolarization vectors. As a consequence, the QRS magnitude decreases. In this study, we tested if QRSvm can be a useful predictor for VTA including VT and VF during long-term follow-up.

Methods

This blinded retrospective study is part of the "EvaluatioN of CardiOgenetic Disease and Effectiveness of scReening" (ENCODER) project, which was approved by the local ethics committee in the Erasmus Medical Center Rotterdam, the Netherlands (MEC-2014-313). Informed consent was not required. All data, including clinical characteristics and tests outcomes, were collected from digital medical records. During the follow-up period, all patients visited the cardiology outpatient clinic at least once a year and implantable cardioverter defibrillator (ICD) were checked twice a year. ECGs, Holter recordings signal-averaged electrocardiograms (SAECG) and ICD print outs were reviewed for the occurrence of VTA or ICD shocks. Patients were excluded when data regarding the diagnostic process (i.e., test outcomes and patient or family history) were missing.

We selected patients' definitive BrS diagnosis from the database of patients with suspicion of cardiac channelopathies visiting the outpatient clinic for cardiogenetic evaluation in

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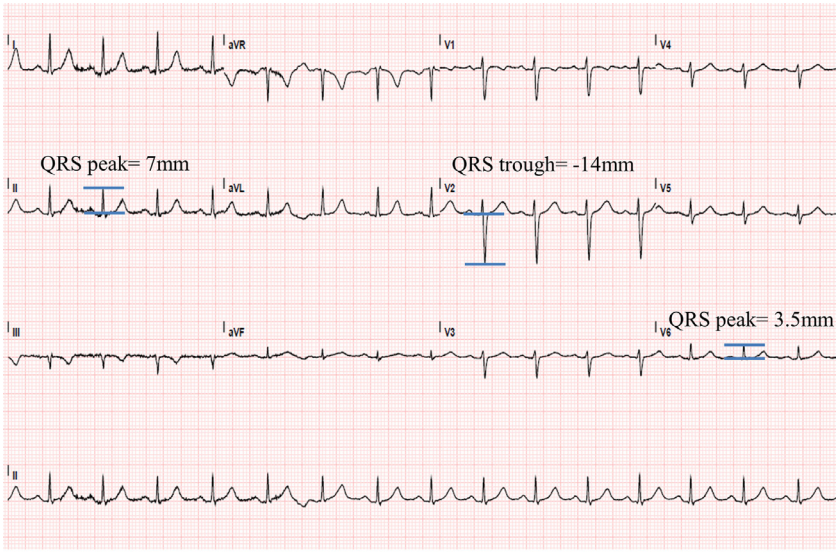

QRSVm = SQRT[QRSII² + QRSV6² + (-0.5*-QRSv2)²]

Figure 1. Baseline electrocardiogram of an Ajmaline-induced BrS patient demonstrating measurement of QRSvm.

the Erasmus Medical Center Rotterdam, the Netherlands. According to the criteria defined in the latest consensus report, diagnosis of type I BrS was based on the presence of either spontaneous or sodium channel blockers induced type I morphology (coved pattern) ST segment elevation ≥2 mm in 1 or more of the right precordial leads V1 to V3. Type II diagnosis was defined as conversion of type II morphology ST segment elevation into type I morphology after drug challenge test in 1 or more lead among the right precordial leads V1 to V3.[2] Patients with obesity (body mass index >29.9), Chronic Obstructive Pulmonary Disease (COPD), or BrS patients who developed ischemic heart disease were excluded.

RVOT conduction delay signs were tested, including the R wave sign, deep SI, SII >SIII pattern, Tzou criteria (V1R >0.15 mV, V6S >0.15 mV; and V6S:R >0.2).[13–15] Patients with 3 or more positive signs were considered as positive for RVOT conduction delay; QRS durations were measured in lead aVR.

Figure 1 demonstrated determination of the QRS vector magnitude (QRSvm). This parameter was tested in all ECGs using the regression-related Frank-lead technique of Kors.[16] The following formula was used for QRSvm estimation:

$$\sqrt{\{(\text{QRS peak lead II})^2+(\text{QRS peak lead V6})^2+(-0.5*-\text{QRS trough lead V2})^2\}}$$

All peaks were measured manually from digital ECGs (25 mm/s; 10 mm/mV).

Continuous normally distributed variables were expressed as mean ± standard deviation. Continuous not normally distributed variables were expressed as median and interquartile range. Independent samples *t* test were used to compare patient groups. Categorical data were denoted by percentages and compared with continuity correction chi-squared test. Receiver operator characteristic curves were used to estimate the optimal cutoff and to evaluate sensitivity and specificity of tested parameters. The multivariable regression model was used to assess the relation between development of VTA and independent variables including the different electrocardiographic parameters (R wave sign, deep SI, SII >SIII pattern, Tzou criteria; V1R >0.15 mV, V6S >0.15 mV, and V6S:R >0.2) A p value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 21 (IBM, Armonk, New York).

Results

The study population consists of 136 BrS patients (90 male, 66%); characteristics are summarized in Table 1. Mean age at the time of diagnosis was 47 ± 15 years. The median duration of the follow-up period was 57 (interquartile range 39 to 75) months and mean age at the time of the last follow-up was 47 ± 15 years. Whole genome sequencing was done in 43 patients (32%) and 8 (6%) of them had SCN5A mutation. An ICD was implanted in 34 patients (25%) either for primary (n = 14, 14 of 136, 10%) or secondary prevention (n = 20, 20 of 136, 15%).

Most patients (n = 101, 74%) remained asymptomatic during the follow-up period. Thirty-five patients developed VTA either before diagnosis (n = 22, 16%) or de novo

Table 1
Baseline characteristics of study population

	Overall population (n = 136)
Age (years)	47±15
Males	90 (66%)
Age of diagnosis (years)	42 ± 14
Symptoms at the moment of diagnosis	22 (16%)
De novo VTA events during follow-up	13 (10%)
SCN5A mutation	8/43
Implantable cardioverter defibrillator	34 (25)
VT/VF ICD shocks	8 (5%)
Inappropriate ICD shocks	10 (7%)
Positive late potentials	56 (41%)

events during follow-up (n = 13, 10%). During the follow-up period, 8 patients (5%) received appropriate ICD shocks and 10 patients (7%) received inappropriate ICD shocks caused by supraventricular arrhythmia. Six patients used Quinidine and none of them developed VTA (Table 1). Fifty-one patients (38%) underwent electrophysiological study and VT/VF was inducible in 7 patients (5%). The SA-ECG was positive for late potentials in 56 patients (41%).

There were no differences between symptomatic and asymptomatic patients with respect to age, gender, or age of diagnosis. Also, mean QRS duration in lead aVR and late potentials did not differ between symptomatic and asymptomatic patients (respectively, 113 ± 17 vs 117 ± 17 ms, p = 0.26 and 10 of 35, 29% vs 46 of 101, 46%, p = 0.07).

Positive RVOT signs (3 or more) appeared in 25 patients (18%), RVOT signs were more frequently observed among symptomatic patients (54% vs 6%, p < 0.001).

By comparing QRS peak in lead II, QRS peak in lead V6 and QRS trough in lead V2, symptomatic patients showed smaller QRS peak or trough than asymptomatic patients (QRS II: 8 ± 3 vs 12 ± 4 mm, p < 0.001; QRS V6: 8 ± 3 vs 11 ± 3 mm, p < 0.001; QRS V2: 9 ± 4 vs 12 ± 4 mm, p < 0.001; Table 2). As demonstrated in Figure 2, QRSvm was significantly lower in patients who developed VTA (at the time of presentation or de novo) than patients who did not (1.24 ± 0.35 vs 1.78 ± 0.42 mV, p < 0.001).

Area under receiver operator characteristic curve for QRSvm was 0.85 (95% confidence interval [CI] 0.77 to 0.92; Figure 3). Using QRSvm cutoff of 1.55 mV, sensitivity and specificity were, respectively, 89% and 71%. Area under receiver operator characteristic for RVOT was 0.74 (95% CI 0.633 to 0.85) with a sensitivity of 54% and specificity of 94%.

In multivariable regression analysis, both QRSvm and positive RVOT signs are independent predictors for VTA events in BrS. Patients with lower QRSmv had fourfold higher risk to develop VTA (odds ratio [OR] 3.68, 95% CI 2.4 to 6.2, p = 0.001), whereas patients with positive RVOT signs had threefold higher risk (OR 2.6, 95% CI 1.4 to 4.9, p = 0.001).

Table 2
Differences in electrocardiographic parameters between symptomatic and asymptomatic BrS patients

	Symptomatic cases (n = 35)	Asymptomatic cases (n = 101)	p value
Age (years)	48 ± 15	46 ± 15	0.53
Male	23 (66%)	67 (66%)	0.23
Age of diagnosis (years)	42 ± 13	42 ± 15	0.86
QRS duration (ms)	113 ± 17	117 ± 17	0.26
QRS peak lead II (mm)	8 ± 3	12 ± 4	<0.001
QRS peak lead V6 (mm)	8 ± 3	11 ± 3	<0.001
QRS trough lead V2 (mm)	9 ± 4	12 ± 4	0.001
QRS vector magnitude (mV)	1.24 ± 0.35	1.78 ± 0.42	<0.001
Positive RVOT signs	19 (54%)	6 (6%)	<0.001
Positive late potentials	10 (29%)	46 (46%)	0.07

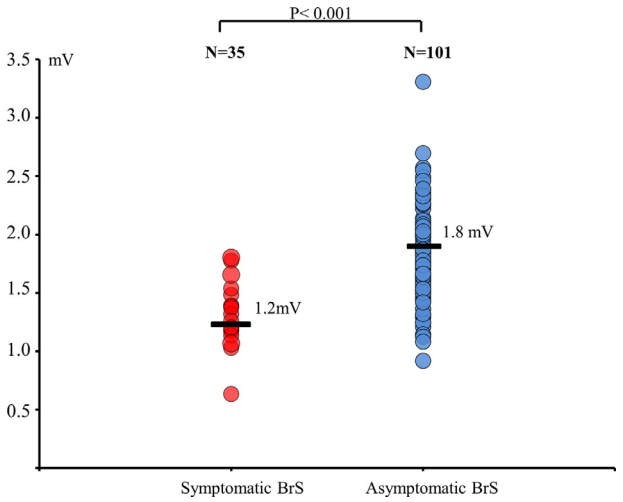

Figure 2. Scatterplot demonstrating the QRSvm of symptomatic and asymptomatic BrS patients.

Discussion

In this study, we demonstrate the significance of QRSvm and positive RVOT signs as predictors for VTA in BrS. Patients with QRSmv lower than 1.55 were 4 times more likely to develop VTA. Moreover, patients with 3 or more positive RVOT signs have a threefold higher risk of VTA.

BrS is an autosomal dominant channelopathy responsible for 4% to 12% of all sudden cardiac deaths. The highest prevalence of BrS is among Asians.[17] BrS is more prevalent among men and they also have worse prognosis compared with women.[18] BrS patients are either diagnosed incidentally or present with a wide range of symptoms such syncope, seizures, or VTA. Risk stratification of BrS patients is the most challenging part in the management of this channelopathy. Many investigators reported on to testing of electrocardiographic markers to identify high-risk BrS patients.[4,19–21] These markers include f-QRS and QRS duration in V2.[22] However, we still do not have clear noninvasive predictors for VTA, specifically for asymptomatic

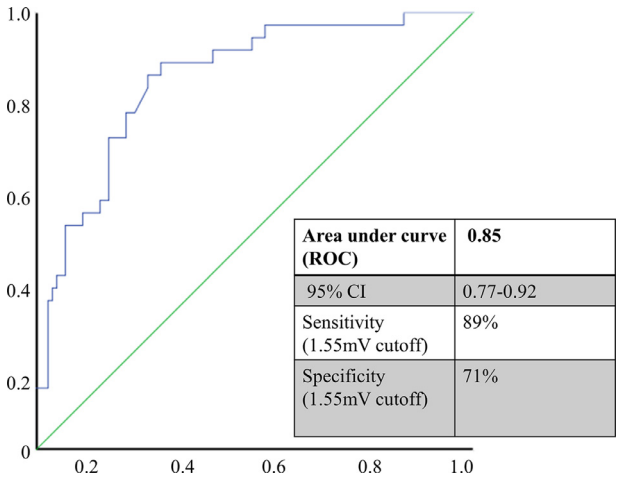

Figure 3. Receiver operator characteristic curve demonstrating the sensitivity and specificity of QRSmv parameter.

patients. QRS duration showed a promising prognostic value in some studies but it did not show value in large registries.[6,7] In addition, other diagnostic and prognostic parameters than QRS duration and ECG-derived vectorcardiographic parameters such as spatial QRS-T angle have been evaluated for stratifying high-risk patients in different populations. Borleffs et al[9] showed that a wide QRS-T angle is a strong predictor for appropriate ICD shocks in patients with ischemic heart disease. In another study, a wide spatial QRS-T angle is also associated with diabetes type 2, impaired glycemic control, and decreased left ventricular function.[8] Kardys et al[23] showed that spatial QRS-T angle is a strong predictor of cardiac mortality in the elderly.

Quantifying the scattering of electric waves by calculating the QRSvm showed a prognostic value in recent studies. Cortez et al[11] tested the significance of QRSvm as a predictor of VTA in TOF patients who underwent pulmonary valve replacement with a negative predictive value of 95% and OR of 34 (95% CI 3.9 to 293.3). They also showed that QRSvm can predict VTA inducibility in TOF patients with area under receiver operator characteristic curve of 0.75 and relative risk of 2.59 (95% CI 1.48 to 4.71).[12] Nagase et al[24] showed that low voltage type 1 ECG of BrS is highly and independently associated with VTA. The recent subxiphoid epicardial mapping approach revealed that the RVOT of symptomatic BrS patients showed areas of low voltage and delayed fragmented potentials and ablation of the anterior aspect of RVOT epicardium normalized BrS pattern in most of these patients.[25,26] In line with these results, our study not only supports that low voltage is associated with high risk of VTA in BrS, but also introduced a noninvasive ECG-derived parameter to identify these high-risk patients.

Positive RVOT conduction delay signs were tested by our group in 2 previous studies.[13,14] In this study, we combined all variables into 1 and still showed an independent predictor for VTA with odds ratio of 2.6 (95% CI 1.4 to 4.9, $p = 0.001$) and area under receiver operator characteristic of 0.74 (95% CI 0.633 to 0.85).

In conclusion, QRSvm and positive RVOT conduction delay signs can be beneficial noninvasive independent predictors of VTA in BrS patients. However, our observations need to be further evaluated in a multicenter study with larger number of BrS patients.

Disclosures

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