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CLINICAL RESEARCH
Electrocardiography and risk stratification

The β-angle can help guide clinical decisions in the diagnostic work-up of patients suspected of Brugada syndrome: a validation study of the β-angle in determining the outcome of a sodium channel provocation test

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Aims In patients with Brugada syndrome (BrS) but without spontaneous Type-1 electrocardiogram, several electrocardiographic characteristics have been studied, including the β-angle. Previous studies suggested that the β-angle might be useful in distinguishing BrS-patients from patients with only suggestive repolarization patterns *without* performing sodium channel blocker provocation testing. In this study, we aimed to determine the diagnostic value of the β-angle in patients suspected of BrS.

Methods and results A large cohort ($n = 1430$) of consecutive patients who underwent provocation testing was evaluated. β-angles were measured in leads V1, V2, and their corresponding positions over the second and third intercostal space. Receiver-operating characteristic curves were constructed and the diagnostic accuracy of previously reported β-angle cut-offs were calculated and evaluated. The importance of the β-angle for predicting the provocation test outcome was determined using a prediction model constructed with logistic regression. The optimum β-angle cut-off in our cohort for ruling out a positive provocation test was 15°; sensitivities were 80–98% and negative predictive values were 79–96% among the right precordial leads. Previously reported β-angle cut-offs performed less well, indicated by lower Youden indices. In the optimism-corrected prediction model [*C*-statistic: 0.78 (95% CI: 0.75–0.81)], the β-angle had large value (*Z*-score: 2.1–10.3) and aided construction of a nomogram to predict test outcome.

Conclusion To predict the outcome of provocation testing for BrS, the β-angle alone does not demonstrate strong diagnostic characteristics. However, the β-angle is an important variable to predict provocation test outcome and thus has added value.

Keywords Brugada syndrome • Electrocardiographic characteristics • β-angle • Diagnostic characteristics

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What's new?

- This study evaluated the value of the β-angle in a large cohort of 1430 patients suspected of Brugada syndrome.
- The diagnostic accuracy of previously reported β-angle cut-off values is not reproducible in our cohort.
- The diagnostic accuracy of the β-angle does not demonstrate strong enough diagnostic characteristics to serve as a stand-alone diagnostic tool but is of value in the context of a prediction model.
- The duration at the base of the triangle could be of more clinical use as it is easier to measure and appears to have better individual diagnostic characteristics.
- We present a nomogram, as visual representation of the prediction model, which after external validation could help guide clinical decisions in the diagnostic work-up of patients of Brugada syndrome and prevent unnecessary sodium channel blocker testing.

Introduction

A Brugada syndrome (BrS) diagnosis is made upon documenting the characteristic Type-1 electrocardiogram (ECG) abnormalities, spontaneously, or after a sodium channel blocker provocation test (Class 1 anti-arrhythmic drugs, such as ajmaline) in combination with previously proposed criteria.[1] Reasons for sodium channel provocation testing—in the absence of a diagnostic ECG—include symptoms (e.g. syncope, cardiac arrest), suggestive ECG features (e.g. a Type-2 or Type-3 ECG) or family history for BrS or sudden cardiac death. If we would be able to determine the a priori probability of a positive sodium channel provocation test, this could guide physicians in the decision whether or not to perform such a test. This could result in the prevention of unnecessary provocation testing, which is desirable as provocation testing requires hospital admission and is not without risks.[2]

Several electrocardiographic characteristics of individuals with suspected BrS and their baseline ECGs have been studied for diagnostic purposes.[3–6] Among others, two characteristics have been described: (i) the β-angle (i.e. the angle in degrees between the right precordial S-upslope and the r'- or J-ST-downslope)[3–6] and (ii) the duration at the base of the triangle (DBT) 5 mm from the r' spike at the intersection of the right precordial S-upslope and the r'- or J-ST-downslope.[6] These characteristics may be useful in distinguishing persons with a Type-2/3 Brugada ECG at baseline and a positive provocation test, from those with a negative provocation test without the necessity of performing a sodium channel provocation test. Using these characteristics, in previous studies sensitivities of 60–100% and specificities of 44–95% have been achieved. A limitation of these studies was their small size (19–108 patients).[3–6]

The present study was conducted in a large consecutive cohort of patients who underwent a provocation test for BrS. The goal of this study was to (i) determine the optimum β-angle for ruling out a positive provocation test, (ii) evaluate the performance of several previously reported β-angles cut-off values in our cohort, and (iii) determine the importance of measuring the β-angle in predicting the outcome of the provocation test.

Methods

Patients and sodium channel provocation testing

Patients who underwent provocation testing in the period 2009–15 in our tertiary referral centre were included in this study. None of the patients had exhibited a spontaneous Brugada Type-1 ECG before and they all underwent provocation testing because of symptoms (e.g. unexplained syncope or documented ventricular arrhythmias), a baseline ECG suggestive of BrS, family screening for BrS, or family screening in the context of sudden cardiac death or sudden unexplained death. Baseline ECGs included leads V1 and V2, and corresponding right precordial leads over the third and second intercostal spaces (V1ic3, V2ic3, V1ic2, and V2ic2). Ajmaline was used as sodium channel blocker and was infused intravenously in boluses of 10 mg/min until a maximum of 1 mg/kg body weight was reached. After each bolus, ECG recordings were made. The test was prematurely terminated in case of a positive result, defined as the occurrence of a Type-1 ECG.[1] The test was also prematurely terminated in case of an abnormal result—which was defined as the occurrence of arrhythmias or excessive QRS-widening of ≥40%. Only patients with a positive or negative test result were included in this study.

Electrocardiogram analysis

Electrocardiogram recordings were extracted from the ECG-file-system MUSE (version 8.0, GE Healthcare, USA), and analysed with MEANS.[7] MEANS' marker settings (e.g. P-onset, P-offset, QRS-onset, etc.) were manually inspected for accuracy and adjusted when necessary. Patients with atrial fibrillation or atrial flutter ($n = 37$) were excluded from analysis of all P-wave related values. Defined parameters were P, PR, QRS, S, JT, QT, and QTc duration (all in ms), J-amplitude and S-amplitude (both in μV), and the P-, QRS-, and T-axis (all in °).

β-angle and duration at the base of the triangle measurements

The β-angle and DBT were measured in ECGs from leads V1, V2, V1ic3, V2ic3, V1ic2, and V2ic2 that met the following criteria: (i) presence of an r' wave with an amplitude of >100 μV (=1 mm) above baseline and (ii) a descending part of the r' wave of >100 μV. To decrease the influence of baseline drift and/or noise, signal-averaged QRS-T plots were used for the measurements, and these plots were magnified four times. The β-angle and DBT measurements start at the highest take-off of the r', in which a vertical 5 mm line was placed. A horizontal line perpendicular to the vertical 5 mm line was made in Adobe Illustrator (CS6, Adobe Systems Incorporated, USA), creating the 'inverted T', as seen in red in *Figure 1*. Subsequently, the β-angle, the angle between the upslope of the S-wave (the intersection from the horizontal line and the upsloping S-wave) and the downslope of the r'-wave, was measured using ImageJ (version 1.50, National Institute of Health, Bethesda, MD, USA).[8] In addition, the duration at the base of the triangle 5 mm from the r' spike (=DBT) was measured as the length between the intersection of the horizontal line and the upslope of the S-wave, and the intersection of the horizontal line and the downslope of the r'-wave (*Figure 1*). In patients with no intersection between the horizontal line and the downslope of the r'-wave, the DBT could not be determined. Measurements were performed by one

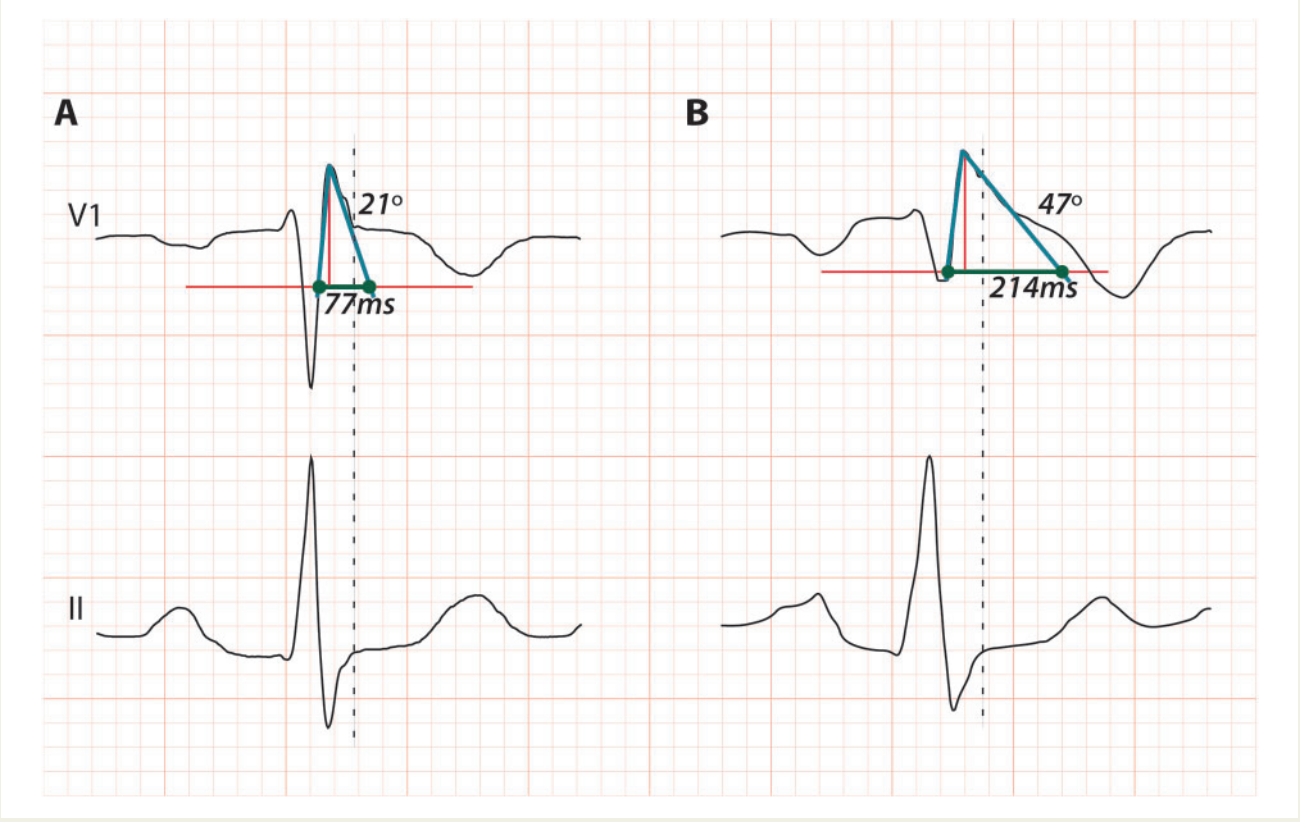

Figure 1 Examples of measuring the β-angle and DBT in baseline ECGs. The β-angle and DBT measurements started at the highest take-off of the r′, in which a vertical 5 mm line was placed. A horizontal line perpendicular to the vertical 5 mm line was made creating the 'inverted T', as seen in red. Subsequently, the β-angle, the angle between the upslope of the S-wave and the downslope of the r′-wave, as indicated with the blue lines, was measured. The duration at the base of the triangle 5 mm from the r′ spike (=DBT) was measured as the length between the intersection of the horizontal line and the upslope of the S-wave, and the intersection of the horizontal line and the downslope of the r′-wave as indicated by the green dots and line. The dotted black line indicates the J-point. (*A*) A 44-year-old man with positive FH of SCD, sodium channel provocation test negative. (*B*) A 53-year-old woman with positive FH of BrS, sodium channel provocation test positive. BrS, Brugada syndrome; DBT, duration at the base of the triangle; ECG, electrocardiogram.

reviewer, difficult cases were discussed with a second reviewer until consensus was reached ($n = 139$). Although the DBT might be slightly easier to measure in clinical practice, for this study we focused particularly on the value of the β-angle as this value has most often been investigated.

Statistical analysis

Statistical analysis was performed with SPSS Statistics (version 25.0, IBM Corporation, Armonk, NY, USA) and Rstudio (version 1.2.1335, RStudio, Inc., Boston, MA, USA). Categorical variables are presented as frequencies (%) and compared using the Fisher's exact test. Continuous data were evaluated for normal distribution using histograms and the Kolmogorov–Smirnov test; they are expressed as mean ± standard deviation, or median (inter-quartile range) in case of non-normal distribution. Comparisons were performed using an unpaired two-tailed *t*-test in case of normal distribution; otherwise, the Mann–Whitney *U* test was used. Receiver-operating characteristic (ROC) curves were constructed and area under the curves (AUCs) were calculated. The optimum cut-off value for all leads to rule out the occurrence of a positive test was determined based on scatterplots, coordinates of the ROC curves and by discussion as every lead has its own optimum cut-off and an appropriate cut-off that is the same for all leads was preferred. For our optimum cut-off value, and previously described optimum cut-off values, the diagnostic accuracy was determined and compared with the previously reported values. Diagnostic accuracy analysis consisted of calculating the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). The Youden index was used [(sensitivity + specificity) − 1] to compare the performance of several previously reported β-angle cut-off values.[9] For this comparison, the largest β-angle in V1 and/or V2 was used, similar to previous studies. In Supplementary material online, *Table S1*, an overview of the previously reported cut-off values and study details is presented. Multiple testing correction was performed with a Bonferroni corrected *P*-value ≤0.003 as the level of statistical significance.

The goal of the prediction model was to determine the importance of measuring the β-angle in predicting the outcome of the provocation test. In order to use all patients, also those without any measurable β-angle, the β-angles were categorized: not measurable in any of the leads V1–V2ic2, 0–15°, 15–27°, 27–39°, and ≥39°. The prediction model was constructed with logistic regression to predict a positive provocation test. Final predictors in the multivariable model were selected from the candidate predictors (Supplementary material online 'Candidate predictors') using backward stepwise selection, based on Akaike's information criterion. Discriminative ability was described with Harrell's *C*-statistic, and corrected for over-optimism using bootstrapping based internal

Table 1 Baseline characteristics

Characteristic	Ajmaline test positive ($n = 345$)	Ajmaline test negative ($n = 1047$)	*P*-value
Age (years)	45 (35–55)	42 (30–54)	0.003
Male	175 (51)	563 (54)	0.325
Length (cm)	174 ± 11	177 ± 10	<0.001
Weight (kg)	77 ± 15	78 ± 15	0.120
BMI (kg/m^2)	25 ± 4	25 ± 4	0.513
History of SVT	6 (2)	29 (3)	0.329
History of VT/VF	12 (4)	51 (5)	0.370
History of syncope	63 (18)	154 (15)	0.124
Family history of SCD/SUD	170 (49)	582 (56)	0.040
Family history of BrS	171 (50)	389 (37)	<0.001
Genetic testing	209 (61)	95 (9)	<0.001
(Likely) pathogenic SCN5A variant	29 (14[a]–8[b])	8 (8[a]–1[b])	0.192[a]; <0.001[b]
Likely pathogenic	14 (48[c])	7 (88[c])	0.104
Pathogenic	15 (52[c])	1 (13[c])	0.104
Indication for test			
Suspicious ECG	73 (21)	130 (12)	<0.001
Symptoms (syncope, VT/VF or AF)	26 (8)	79 (8)	1.000
Family screening BrS	173 (50)	393 (38)	<0.001
Family screening SCD/SUD	73 (21)	444 (42)	<0.001
Ajmaline administered (mg)	73 ± 24	81 ± 16	<0.001
Percentage of target dose (%)	95 ± 28	104 ± 10	<0.001

Data are presented as mean ± SD, median (IQR), or *n* (%).
BMI, body mass index; BrS, Brugada syndrome; SCD, sudden cardiac death; SVT, supraventricular tachycardia; SUD, sudden unexplained death; VT, ventricular tachycardia; VF, ventricular fibrillation.
[a]Patients who underwent genetic testing.
[b]Total group.
[c]Patients with a (likely) pathogenic mutation.

validation (1000 bootstraps). To evaluate agreement between predicted and observed risk, calibration plots were visually inspected. Linearity between continuous predictors and the log odds of the outcome was inspected. The variable importance within the final model was expressed with the *Z*-score—the regression coefficient divided by its standard error. The higher the *Z*-score, the higher the variable importance. A nomogram was constructed for visual representation of the model. R package rms was used.[10]

Results

Baseline characteristics and electrocardiogram analysis

Baseline characteristics

Of 1430 patients who underwent ajmaline testing, 345 (24%) patients tested positive, 1047 (73%) tested negative, and 38 (3%) patients had an abnormal test. *Table 1* gives an overview of the baseline characteristics. Patients with a positive test were slightly older [45 (35–55) vs. 42 (30–54) years, $P = 0.003$] but sex distribution was similar. In patients with a positive test, the indication for ajmaline testing was more often a suspicious ECG (21% vs. 12%, $P < 0.001$) or family screening for BrS (50% vs. 38%, $P < 0.001$). Since testing was prematurely terminated when a Type-1 ECG occurred, significantly less ajmaline was given in patients with a positive test (95 ± 28% vs. 104 ± 10% of target dose, $P < 0.001$). Patients with a positive test more frequently underwent genetic testing (61% vs. 9%, $P < 0.001$). Of the patients who underwent genetic testing, a Class 4 (likely pathogenic) or 5 (pathogenic) *SCN5A* variant was found in 14% of patients with a positive ajmaline test, and in 8% of patients with a negative test ($P = 0.192$).

Electrocardiogram analysis

Electrocardiogram parameters are summarized in *Table 2*. Patients with a positive test showed more depolarization abnormalities at baseline compared with patients with a negative test, as evidenced by slightly longer durations of the P-wave (116 ± 14 vs. 114 ± 15 ms, $P = 0.005$), PR-interval (168 ± 29 vs. 160 ± 27 ms, $P < 0.001$), and QRS-interval (104 ± 15 vs. 99 ± 13 ms, $P < 0.001$). In patients with a positive test, the baseline JT-duration (301 ± 28 vs. 312 ± 31 ms, $P < 0.001$) and the QT-interval (405 ± 29 vs. 411 ± 31 ms, $P = 0.001$) were significantly shorter. For the heart rate corrected QT-interval (QTc), no between-group difference was found. In patients with a positive test, the baseline maximum right precordial J-amplitude in lead V1–V2ic3 was higher (106 ± 85 vs. 85 ± 65 μV, $P < 0.001$), and the S-wave duration in lead I was longer [38 ms (32–50) vs. 34 ms

Table 2 Electrocardiogram parameters at baseline

	Ajmaline test positive ($n = 345$)	Ajmaline test negative ($n = 1047$)	*P*-value
Heart rate (b.p.m.)	67 ± 13	65 ± 12	0.003
P-wave duration (ms)	116 ± 14	114 ± 15	0.005
PR-interval (ms)	168 ± 29	160 ± 27	<0.001
QRS-duration (ms)	104 ± 15	99 ± 13	<0.001
S-duration in *I* > 40 ms	55 (17)	97 (10)	0.001
S-amplitude in *I* > 100 μV	144 (43)	405 (41)	0.441
JT-duration (ms)	301 ± 28	312 ± 31	<0.001
Max. J-amplitude in V1-V2ic3 (μV)	106 ± 87	85 ± 65	<0.001
QT-interval (ms)	405 ± 29	411 ± 31	0.001
QTc-interval (ms)	424 ± 27	423 ± 27	0.627
P-axis (°)	55 (37–67)	52 (35–64)	0.050
QRS-axis (°)	31 ± 41	40 ± 38	<0.001
T-axis (°)	40 ± 20	38 ± 23	0.193

Data are presented as mean ± SD, median (IQR), or *n* (%).

Table 3 β-angle and duration at base of 5 mm triangle compared between patients with a positive test and with a negative test.

	Measurable number of patients and % of cohort	Ajmaline test positive ($n = 345$)	Ajmaline test negative ($n = 1047$)	*P*-Value
β-angle				
β-angle in V1 (°)	52 (4%)	28 (20–47) ($n = 17$)	18 (12–24) ($n = 35$)	0.004
β-angle in V2 (°)	35 (3%)	33 (15–64) ($n = 10$)	19 (13–25) ($n = 25$)	0.103
β-angle in V1ic3 (°)	133 (10%)	36 (27–58) ($n = 45$)	23 (17–30) ($n = 88$)	<0.001
β-angle in V2ic3 (°)	134 (10%)	31 (21–46) ($n = 52$)	21 (14–28) ($n = 82$)	<0.001
β-angle in V1ic2 (°)	517 (37%)	29 (21–37) ($n = 180$)	22 (15–28) ($n = 337$)	<0.001
β-angle in V2ic2 (°)	469 (34%)	25 (18–33) ($n = 169$)	18 (14–25) ($n = 300$)	<0.001
DBT				
DBT in V1 (ms)	51 (4%)	130 (89–214) ($n = 17$)	65 (42–92) ($n = 34$)	0.002
DBT in V2 (ms)	32 (2%)	187 (56–463) ($n = 9$)	69 (43–89) ($n = 23$)	0.048
DBT in V1ic3 (ms)	127 (9%)	148 (106–317) ($n = 44$)	85 (61–115) ($n = 83$)	<0.001
DBT in V2ic3 (ms)	107 (8%)	120 (77–214) ($n = 51$)	77 (47–110) ($n = 56$)	<0.001
DBT in V1ic2 (ms)	506 (36%)	109 (77–151) ($n = 180$)	77 (54–102) ($n = 326$)	<0.001
DBT in V2ic2 (ms)	461 (33%)	93 (65–128) ($n = 169$)	65 (50–93) ($n = 292$)	<0.001

Data are presented as median (IQR).
DBT, duration at the base of the triangle.

(28–43), $P < 0.001$]. No between-group differences in S-amplitude were observed.

β-angle and duration at the base of the triangle

Data on the β-angle and the DBT are shown in *Table 3*. In patients with a positive test, the β-angle and DBT were larger in all right precordial leads compared with patients with a negative test. Of note, the β-angle and DBT were only measurable in the minority of patients although in the third or second intercostal spaces, angles could more often be defined. In 584 (42%) patients, it was possible to measure a β-angle in at least one of the right precordial leads in the 4th to the 2nd intercostal space. In male patients, the β-angle was more often measurable [346 (45.7%) vs. 253 (37.6%), $P = 0.002$].

Diagnostic characteristics

Receiver-operating characteristic curve

In order to determine the optimum β-angle for ruling out a positive test in our cohort, ROC curves and scatter plots were constructed (note that patients without measurable β-angle cannot be included in this analysis). Supplementary material online, *Figure S1* shows the ROC curves for the β-angle in each lead separately. The AUC ranged

Table 4 Diagnostic characteristics of the previously reported β-angle cut-off values for the largest angle in V1 and/or V2.

Cut-off	23°		36.8°		38.6°		58°		
Publication	van der Ree	Ohkubo *et al.*[5]	van der Ree	Serra *et al.*[6]	van der Ree	Serra *et al.*[6]	van der Ree	Chevallier *et al.*[3]	Gottschalk *et al.*[4]
PPV (%)	45	76	88	94	100	94	100	73	75
NPV (%)	87	100	80	89	81	88	75	87	64
Sensitivity (%)	77	100	41	86	41	85	17	79	60
Specificity (%)	62	54	98	95	100	96	100	83	78
Youden index[a]	0.38	0.54	0.39	0.81	0.41	0.81	0.18	0.62	0.38

NPV, negative predictive value; PPV, positive predictive value.
[a]Youden index: (sensitivity + specificity) − 1.

from 0.67 in lead V2ic2 to 0.79 in lead V1ic3. Based on these ROC-curves and the scatter plots (Supplementary material online, *Figure S2*), an optimal β-angle cut-off point for our cohort in any of the leads V1–V2ic2 of 15° was determined in order to optimize the sensitivity and negative predicting value for ruling out a positive test and still have sufficient patients meeting the cut-off. Supplementary material online, *Figure S3* shows the result for the ROC curves of the DBT (AUC: 0.67–0.80)

Diagnostic accuracy

With our proposed optimal β-angle cut-off value of 15°, sensitivities of 80–98% and NPVs of 79–96% were achieved in leads V1–V2ic2. The results of the individual leads are shown in Supplementary material online, *Table S2*.

To establish the diagnostic accuracy of previously reported cut-off values, we calculated the sensitivity, specificity, PPV, and NPV for the largest β-angle in V1 and/or V2 (similar to the other studies). In these leads, the β-angle could only be determined in 60 patients (4%). *Table 4* shows the diagnostic accuracy of several previously reported cut-off values in our cohort, compared with previously reported results. The performance of previously reported β-angle cut-offs is less good in our cohort than in the original cohorts, as indicated by the lower Youden index values.

Prediction model

To determine the importance of measuring the β-angle in predicting the sodium channel provocation test outcome, univariable and multivariable logistic regression was performed.

Supplementary material online, *Table S3* shows the results for the univariable analysis. For the multivariable analysis, the following variables were selected: gender, indication for sodium channel provocation test, P-wave duration, S duration of >40 ms, JT-duration, the maximum right precordial J-amplitude, and the β-angle. Multivariable analysis results are presented in Supplementary material online, *Table S4* and show that the higher the β-angle, the higher the odds ratio for a positive sodium channel provocation test. The odds ratio ranges from 0.32 (95% CI: −0.11–0.95) in the 0–15° group to 56.1 (95% CI: 26.1–120.6) in the >39° group. With this model, a *C*-statistic of 0.80 (95% CI: 0.77–0.93) was achieved. After bootstrapping, we found an optimism corrected *C*-statistic of 0.78 (95% CI: 0.75–0.81) suggesting a good prediction model. The calibration plot is presented in Supplementary material online, *Figure S4*.

Importance of the β-angle in the prediction model

For the categorical β-angle variables in the model, the variable importance—as expressed by the Z-score—ranges from 2.0 to 10.3. The *Z*-score progressively increases with higher β-angle cut-off values (Supplementary material online, *Table S4*). To visualize the importance of the β-angle in predicting the sodium channel provocation test outcome, a nomogram is presented in *Figure 2*. In Supplementary material online, *Figures S5–S7*, we demonstrate the risk prediction of three patient cases using this nomogram.

Discussion

Main findings

In this study, we show that (i) in our cohort of patients suspected of BrS, the optimum β-angle cut-off value for ruling out a positive sodium channel blocker test in lead V1–V2ic2 at a baseline ECG is 15°, (ii) the performance of the previously reported β-angle cut-off values is less good in our cohort as indicated by lower diagnostic Youden indices, and (iii) the β-angle is an important variable in predicting the outcome of a sodium channel blocker test for BrS.

In our cohort of 1430 patients who consecutively underwent sodium channel blocker testing, we show that the baseline β-angle in patients with a positive test is significantly larger than in patients with a negative test. These findings are in accordance with previous studies.[3–6] This larger β-angle at baseline in patients with a positive test may be explained by the fact that BrS-patients show excessive terminal delayed conduction in the right ventricular outflow tract (RVOT). As a consequence, the electrical vector towards the right precordial leads progresses more gradually resulting in a less steep upslope of the S-wave and, similarly, the terminal part of right ventricular depolarization is slower resulting in a slower decay from the r′ to the J-point.[1,11–13] The J-point elevation itself is believed to rely on excitation failure in the RVOT.[14] In patients with for example a right bundle branch block, more proximal conduction slowing occurs. The electrocardiographic effects of earlier conduction slowing are thus different from patients with later conduction slowing in the RVOT.

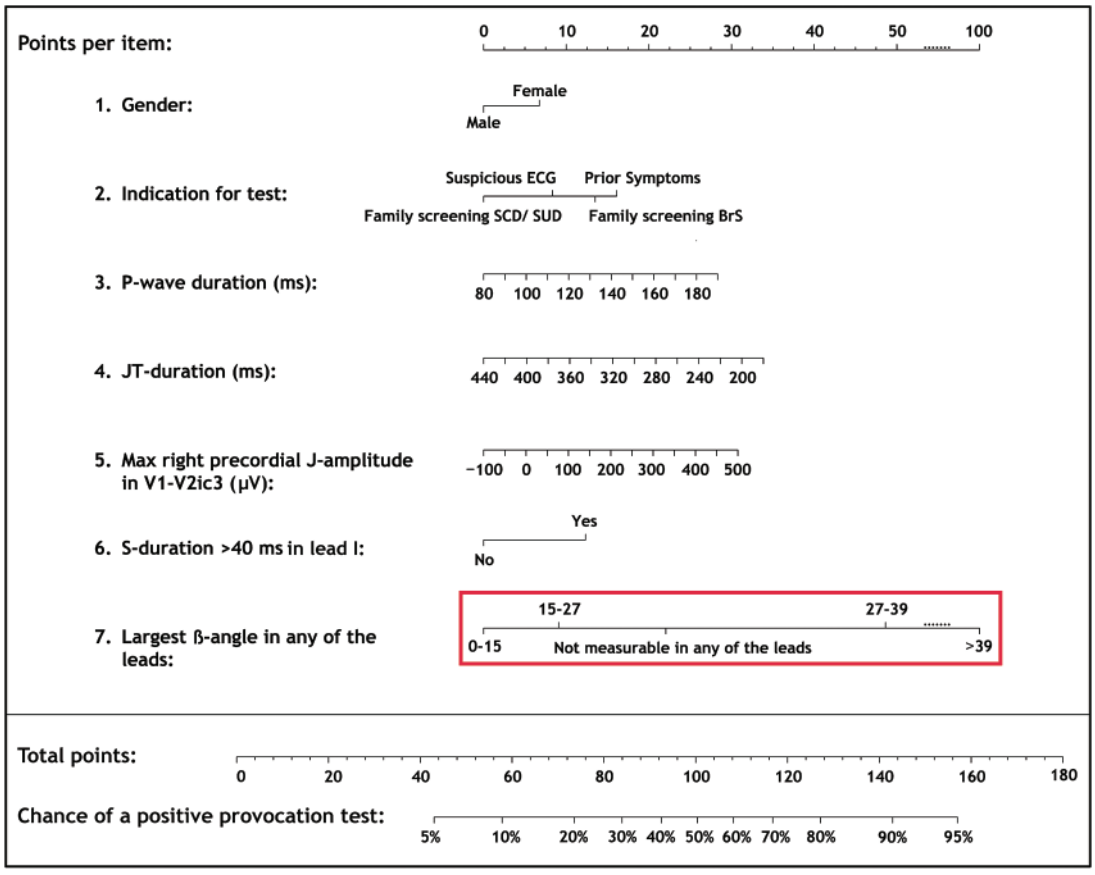

Figure 2 Nomogram for the risk prediction of a positive sodium channel provocation test. In red, the importance of the 'largest β-angle in any of the leads' in predicting the sodium channel provocation test outcome is emphasized. A β-angle of >39° is worth 100 points, already corresponding with a 50% chance of a positive test.

Interestingly, in our cohort, there was no statistical difference in *SCN5A* mutation status between patients with a positive and a negative provocation test. This closely relates to the issue that in fact there is no gold standard to define BrS. In addition to changing guidelines in the past years, the recently proposed Shanghai criteria (again) introduce BrS as a composition of several markers that make the diagnosis more certain.[1] This notwithstanding, one of the common denominators of BrS and its treatment, is the lack of sufficient depolarization reserve when challenged with sodium channel blocking drugs. In BrS-patients, this typically results in development (or worsening) of the Type-1 ECG, and an associated rise in the propensity for malignant arrhythmia. While *SCN5A* mutations may (importantly) contribute to a lack of depolarization reserve, and thus to the development of BrS, previous data already underscored that this actually is a complex matter.[15] It should, for example, be noted that a decreased depolarization reserve may result from much more than a single SCN5A mutation and that mutations can be counterbalanced by other variants.[16] The latter is indeed characterized by patients with the SCN5A mutation but without excessive or Type-1 ECG response to sodium channel blocker provocation. In addition, when in addition to right ventricular conduction delay, there is simultaneous left ventricular conduction delay, there can be a resultant electrical vector insufficient for the development of a Type-1 ECG, while this also does not preclude the presence of a RVOT substrate.[17,18]

Based on the ROC-curves, we determined the optimum β-angle cut-off for ruling out a positive test. In our view, ruling out a positive test is more useful in clinical practice so that patients with a very low a priori risk do not have to undergo unnecessary sodium channel blocker testing. However, we think that our β-angle cut-off of 15° does not show strong enough diagnostic characteristics to serve as a stand-alone 'ruling-out' tool. Using different previously reported β-angle cut-off values, sensitivity and NPV rose at the expense of specificity and PPV and vice versa. Overall, the diagnostic accuracy of those previously established β-angles in our cohort was slightly less good than in the original cohorts. It is also important to mention that these cut-offs are only useful if it is possible to measure a β-angle. The measurability of the β-angle was extremely low in the standard leads V1 ($n = 52$, 4%) and V2 ($n = 35$, 3%) and increased with higher placed leads V1ic2 ($n = 517$, 37%) and V2ic2 ($n = 469$, 34%). In only 42%, it was possible to measure a β-angle in at least one of the right precordial leads. Therefore, we consider the β-angle and its cut-off values alone of low clinical use.

In order to determine the importance of the β-angle in predicting the sodium channel blocker test outcome, we explored the variable

importance in a prediction model. In our prediction model, we were able to implement the non-measurability of the β-angle, which allowed us to use all available data. The β-angle turned out to be the most important variable—as demonstrated by the high *Z*-scores—to predict the test result with odds ratios of 0.32 (95% CI: 0.11–0.95) in the 0–15° β-angle group to 56.1 (95% CI: 26.1–120.6) in the >39° β-angle-group. For this reason, we believe that measuring the β-angle indeed has added value, especially when combined with other characteristics in the context of a risk prediction model. In our model, an optimism-corrected *C*-statistic of 0.78 was achieved indicating a good model. In previous work in which genetic data were also used, a slightly lower optimism-corrected *C*-statistic of 0.74 was achieved.[16] Our reasonable high *C*-statistic could indicate that electrocardiographic parameters are of more value in predicting the sodium channel blocker test outcome. Contradictory, based on our prediction model, female patients appear to have a higher chance of developing a positive sodium channel blocker test outcome. This can be explained by the higher proportion of male patients with a complete or incomplete right bundle branch block (27.9% vs. 12.5% in females, $P < 0.001$) in our cohort, while there is no gender difference in the outcome of the provocation test (positive: 23.7% males vs. 26.0% females, $P = 0.325$). Hence, an *r′* in the right precordial ECG leads in males is less suggestive of Brugada syndrome or a positive provocation test than an *r′* in females.

We feel that this model can help guide clinicians deciding whether to perform such a test and prevent the use of unnecessary sodium channel blocker testing in the future. However, before a model can be implemented in clinical care, it needs external validation. Also, to optimize the usability and performance of the prediction model, we believe it could be better to for example implement the DBT instead of the β-angle as the DBT is easier to measure for clinicians and appears to have at least comparable individual diagnostic characteristic.

Strengths and limitations

Our cohort differs from the other cohorts investigated by being much larger in size and by having less strict inclusion criteria.[3–6] Our cohort consisted of all patients who underwent a sodium channel blocker test in 2009–2015 in our centre, referred for any cause that raised the suspicion of BrS. Since we were aiming for a diagnostic tool which could be broadly used, we included all patients with a suspicion of BrS, and not only definite Type-2 Brugada ECGs or ECGs with a rSr′ morphology in leads V1 or V2 as in the previous studies.[3–6] In this study, we also used higher placed right precordial leads, as we anticipated that with these leads, more *r′* waves should be visible. This was indeed the case and therefore we were able to evaluate more β-angles and this made it possible to construct a prediction model. If only V1 and V2 were included in the conventional (fourth) intercostal space, as with the previous studies, the groups would have been too small to implement the β-angle. Still, in less than half of the patients, it was possible to measure the β-angle. Furthermore, in our study, we defined, for the first time, clear inclusion criteria for ECGs in which an angle could be defined. Furthermore, in this study, we propose a standardized manner of measuring the β-angle and determining the DBT. In earlier studies, these methods varied, which, in our opinion, could be more susceptible for inter-observer and intra-observer variability. Importantly, the prediction model was not validated in another cohort of patients who underwent provocation testing for BrS. Instead, our model was constructed in order to stratify the importance of the β-angle in predicting the chance of a positive sodium blocker test outcome. Hence, our model needs validation before wide spread use.

Future perspective

Future studies should explore whether this prediction model can be optimized and whether it remains a strong model when tested in other cohorts. Furthermore, it would be relevant to explore the prognostic value of the β-angle in the future. The current study was not designed for this purpose but it is conceivable that higher β-angles mirror more RV terminal conduction delay and subsequently associate with higher arrhythmogenic risk.

Conclusion

The diagnostic accuracy of the β-angle at several cut-off values did not demonstrate strong enough diagnostic characteristics to serve as a stand-alone diagnostic tool to rule out a positive outcome of a sodium channel blocker test for BrS. However, the β-angle is an important variable for the prediction of the outcome of such a test, with larger β-angles indicating higher chances of a positive test result, and thus has added value. If we are able to further optimize and validate our prediction model, this model can help guide diagnostic decision making in patients suspected of BrS and prevent unnecessary testing in the future.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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