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Increased Tpeak-Tend interval is highly and independently related to arrhythmic events in Brugada syndrome

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BACKGROUND Risk stratification in Brugada syndrome (BS) remains controversial. The time interval between the peak and the end of the T wave (Tpe interval), a marker of transmural dispersion of repolarization, has been linked to malignant ventricular arrhythmias in various settings but leads to discordant results in BS.

OBJECTIVE We study the correlation of the Tpe interval with arrhythmic events in a large cohort of patients with BS.

METHODS A total of 325 consecutive patients with BS (mean age 47 ± 13 years, 259 men-80%) with spontaneous (n = 143, 44%) or drug-induced (n = 182, 56%) type 1 electrocardiogram were retrospectively included. 235 were asymptomatic (70%), 80 presented with unexplained syncope (22%), and 10 presented with sudden death (SD) or appropriate implantable cardioverter-defibrillator therapy (AT) (8%) at diagnosis or over a mean follow-up of 48 ± 34 months. The Tpe interval was calculated as the difference between the QT interval and the QT peak interval as measured in each of the precordial leads.

RESULTS The Tpe interval from lead V_1 to lead V_4, maximum value of the Tpe interval (max Tpe), and Tpe dispersion in all precordial leads were significantly higher in patients with SD/AT or in patients with syncope than in asymptomatic patients ($P < .001$). A max Tpe of ≥100 ms was present in 47 of 226 asymptomatic patients (21%), in 48 of 73 patients with syncope (66%), and in 22 of 26 patients with SD/AT (85%) ($P < .0001$). In multivariate analysis, a max Tpe of ≥100 ms was independently related to arrhythmic events (odds ratio 9.61; 95% confidence interval 3.13–29.41; $P < .0001$).

CONCLUSION The Tpe interval in the precordial leads is highly related to malignant ventricular arrhythmias in this large cohort of patients with BS. This simple electrocardiographic parameter could be used to refine risk stratification.

KEYWORDS Brugada syndrome; Transmural dispersion of repolarization; Sudden death; QT interval

ABBREVIATIONS **AT** = appropriate therapy; **BS** = Brugada syndrome; **CI** = confidence interval; **ECG** = electrocardiogram/electrocardiographic; **ICD** = implantable cardioverter-defibrillator; **Max Tpe** = maximum value of the time interval between the peak and the end of the T wave; **OR** = odds ratio; **ROC** = receiver operating characteristic; **RVOT** = right ventricular outflow tract; **SD** = sudden death; **Tpe interval** = time interval between the peak and the end of the T wave

Introduction

Brugada syndrome (BS) is defined as ≥2 mV coved ST segment elevation with negative T waves in the right precordial leads in patients without structural heart disease carrying the risk of sudden cardiac death (SD) due to malignant ventricular arrhythmias.[1] To date, the implantable cardioverter-defibrillator (ICD) is the only validated therapy for patients with BS, which are proposed to symptomatic patients, while risk stratification in asymptomatic patients remains largely debated. The annual rate of cardiac events in asymptomatic patients with BS is however not negligible,[2] and thus there is an urgent need for new reliable markers for SD in asymptomatic patients with BS.

The time interval between the peak and the end of the T wave (Tpe interval) has been proposed as a marker of transmural dispersion of repolarization[3] and has been shown to identify patients at higher risk of malignant arrhythmic events in various settings.[4–10] A few studies[11–14] have also addressed this issue in BS but have led to discordant results.

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The aim of this study was to investigate the feasibility of the evaluation of the Tpe interval, the correlation of the Tpe interval with the clinical or electrophysiological parameters and with the occurrence of arrhythmic events in a large cohort of patients with BS.

Methods

We performed a retrospective multicenter study, including consecutive patients with BS recruited at the French university hospitals of Nantes, Bordeaux, Toulouse, and Montpellier from 1996 to 2010. BS diagnosis was made according to the currently accepted criteria in the case of spontaneous or drug-induced type 1 ST elevation in the right precordial leads.[1] This study was approved by the institutional committee on human research at the authors' institution. Written informed consent was obtained for all the subjects who participated in the study.

For each patient, the 12-lead surface electrocardiogram (ECG) recorded at the time of diagnosis and showing the highest type 1 ST elevation was used for the analysis, either spontaneously or after provocative drug test (ajmaline 1 mg/kg over 5 minutes or flecainide 2 mg/kg over 10 minutes; paper speed 25 mm/s; amplification 1 cm/mV). The QT interval duration was measured between the QRS onset and the end of T wave,[15] and the QT peak interval was measured between the QRS onset and the peak of the T wave. Leads with T-wave amplitude < 0.1 mV or without discernible T wave (fully included in ST elevation) were not analyzed. The Tpe interval in each lead was then calculated by the difference between the QT interval and the QT peak interval (Figure 1A). Maximal Tpe interval (max Tpe) was defined as the maximum value of the Tpe interval in the precordial leads. We also calculated the Tpe/QT ratio and Tpe dispersion (defined as the difference between the maximum and the minimum value of the Tpe interval in the precordial leads). Peripheral ECG leads did not give any supplementary information through the intermediate analysis of the first 80 patients (data not shown), and therefore measurements were performed in the precordial leads only for the remaining patients.

ECG analysis and measurements were performed by a single observer blinded to the symptoms (A.R.). Measurements were independently performed by a second observer (P.M.) in a randomly selected subgroup of ECG (1 of 5 patients) in order to define the interobserver correlations.

Patients were divided into 3 groups depending on their symptoms and/or documented spontaneous ventricular arrhythmias: asymptomatic, unexplained syncope (supposed to be caused by malignant ventricular arrhythmia after exclusion of other causes such as neurocardiogenic syncope), and malignant ventricular arrhythmias: SD or

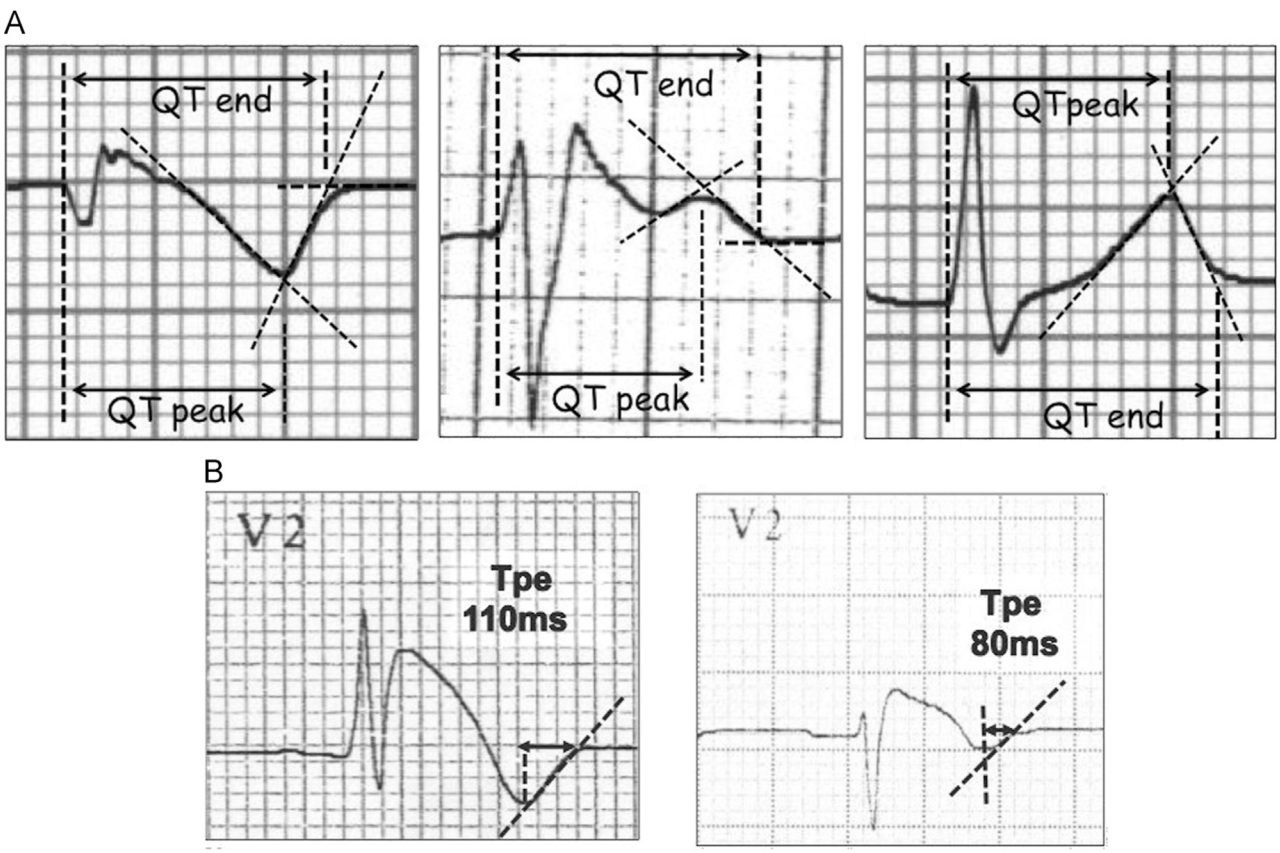

Figure 1 A: Methods for calculating the time interval between the peak and the end of the T wave (Tpe interval) in the presence of various types of ST elevation (left, coved ST-segment elevation with negative T wave; middle, saddle-back type ST elevation with positive T wave; right, no ST elevation and positive T waves). B: Examples of the Tpe interval in a patient who presented with sudden death (left) and in an asymptomatic patient (right).

appropriate implantable cardioverter-defibrillator therapy (AT). The Tpe interval was correlated with the usual clinical and electrophysiological parameters and with the occurrence of syncope and malignant ventricular arrhythmias (SD and/or AT).

Testing of the results on a new group of patients with BS

The Tpe interval was measured in ECG leads V_1–V_4 in 55 other symptomatic or asymptomatic patients with BS with type 1 ECG by 4 independents observers (P.M., A.R., J.B.G., and V.P.) in order to test the correlations on a new group of patients.

Statistical analysis

Continuous data are expressed as mean ± standard deviation. Continuous variables were compared using nonparametric Mann-Whitney test, except in the case of normal distribution showing homoscedasticity in which an unpaired *t* test was used. Categorical variables were compared using the χ^2 test.

The intraclass correlation coefficient was used to evaluate the interobserver correlation. To define the discriminant power from the Tpe interval, Tpe/QT ratio, and max Tpe for the occurrence of arrhythmic events, we constructed receiver operating characteristic (ROC) curves. The curve point with a specificity of $>80\%$ was labeled as the optimized cutoff point and used in the analysis of odds ratio (OR), sensitivity, and specificity.

Logistic regression was used to investigate the association between variables and arrhythmic events and to determine OR and 95% confidence interval (CI) for univariate and multivariate analysis. Multivariate analysis was performed using the variables significantly associated with univariate analysis (with $P < .1$), and the number of variables allowed to be included in the model was dictated by the number of arrhythmic events. Since a few events occurred during follow-up, and for a more simple presentation of the results, cardiac events both at the initial presentation and during follow-up were combined for statistical analysis. Analysis and calculations were performed using the StatView program (1992–1996, version 5.0, Abacus Concepts, Inc., Berkeley, CA,). A P value of $<.05$ was considered statistically significant for each analysis.

Results

Three hundred twenty-five consecutive patients with BS were included. With a few exceptions, the studied population has already been described in our previous reports.[16,17] Hundred seventeen patients were included in the FINGER (France, Italy, The Netherlands, and Germany) Brugada Syndrome Registry,[2] with 36 of them and 30 additional patients being also included in a previous study.[18] Most patients were index cases (only 35 related cases from 14 families). The characteristics of the patient population are listed in Table 1. An ICD had been implanted in 136 patients (42%): because of resuscitated SD in 10, unexplained syncope in 33, inducibility at electrophysiology study in 77, family history of SD in 12, and physician's choice in 4.

At the initial presentation, 235 patients were asymptomatic while 80 patients complained of unexplained syncope and 10 patients had been resuscitated from SD. During a mean follow-up of 48 ± 34 months, 2 and 7 of the initially asymptomatic patients experienced SD and presented with AT, respectively, while 0 and 7 patients initially presenting with unexplained syncope experienced SD and AT, respectively. Including cardiac events and symptoms at diagnosis and during follow-up, 226 patients (70%) were asymptomatic and 99 patients (30%) have presented with a cardiac event: unexplained syncope in 73 (22%) and documented ventricular arrhythmias in 26 (8%) (12 with SD and 14 with AT).

Measurements of QT and QT peak intervals were feasible in 94% of the cases (74 measurements could not be performed mainly because of not discernible T wave). The intraclass correlation coefficients were between .71 and .82 for the Tpe measurement.

There was no significant difference in Tpe intervals, and except in lead V_1, there were only a few borderline differences in the Tpe/QT ratio between patients with baseline type 1 ST elevation and patients in whom ST elevation was elicited by drugs (Table 2). The QT interval was larger in patients with a Tpe interval of ≥ 100 ms, but there was no difference in QRS duration or QT peak values according to the presence of a Tpe interval $<$ 100 ms or $\geq$ 100 ms (Table 3).

The corrected QT intervals in any lead were not significantly correlated with the occurrence of SD/AT or syncope. The Tpe interval and Tpe/QT ratio in leads V_1, V_2, V_3, V_4 as well as max Tpe and Tpe dispersion were longer in patients with malignant ventricular arrhythmias (SD and/or AT) than in patients with syncope, who displayed longer values than did asymptomatic patients (Table 4). Differences were highly significant between patients with SD/AT and asymptomatic patients or between patients with syncope and asymptomatic patients, while differences between patients

Table 1 Characteristics of the patient population

Age (y)	47 ± 13
Sex: male	259/325 (80)
Spontaneous type 1 ST elevation	143/325 (44)
ST elevation after drug challenge	182/325 (56)
Fragmented QRS complex	8/325 (2.5)
Family history of SD	94/325 (29)
History of atrial fibrillation	26/325 (8)
Genetic testing	190/325 (58)
SCN5A gene mutations	43/190 (23)
ST elevation in the peripheral ECG leads	30/325 (9)
First-degree atrioventricular block	114/325 (35)
Electrophysiology study	218/325 (67)
Inducible at electrophysiology study	92/218 (42)

Values are presented as mean ± standard deviation or as n/N (%).
ECG = electrocardiographic; SD = sudden death.

Table 2 Tpe interval and Tpe/QT ratio according to the presence of spontaneous or drug-induced ST elevation

Variable	Spontaneous type 1 ECG (n = 143)	Class 1 drug-induced type 1 ECG (n = 182)	*P*
Tpe interval in lead V_1 (ms)	69 ± 21	65 ± 19	.08
Tpe V_2 (ms)	71 ± 22	73 ± 24	.5
Tpe V_3 (ms)	76 ± 23	76 ± 23	.9
Tpe V_4 (ms)	75 ± 18	73 ± 22	.6
Tpe V_5 (ms)	68 ± 16	70 ± 17	.5
Tpe V_6 (ms)	67 ± 17	67 ± 19	.6
Max Tpe (ms)	89 ± 21	86 ± 22	.2
Tpe dispersion	35 ± 20	34 ± 20	.7
Tpe/QT ratio in lead V_1	0.18 ± 0.04	0.17 ± 0.04	.01
Tpe/QT V_2	0.18 ± 0.05	0.18 ± 0.06	.8
Tpe/QT V_3	0.20 ± 0,06	0.19 ± 0.06	.5
Tpe/QT V_4	0.20 ± 0,04	0.19 ± 0.05	.04
Tpe/QT V_5	0.18 ± 0,04	0.18 ± 0.05	.6
Tpe/QT V_6	0.18 ± 0.04	0.17 ± 0.05	.08
Heart rate (beats/min)	69 ± 19	68 ± 20	.6

Values are presented as mean ± standard deviation.

ECG = electrocardiogram; Max Tpe = maximum value of the time interval between the peak and the end of the T wave; Tpe interval = time interval between the peak and the end of the T wave.

with SD/AT and patients with syncope were nonsignificant (borderline value for max Tpe). Box plots for max Tpe according to the 3 groups of patients are shown in Figure 2.

In order to test whether these results were linked to the presence of type 1 ST elevation and whether an increased Tpe interval may be simply due to a deeper negative T wave (Figure 1B), we compared the presence of type 1 ST elevation in ECG leads V1-V4 to the distribution of max Tpe over the precordial leads. Type 1 ST elevation was mostly present in lead V_1 (292 of 325) and lead V_2 (235 of 325), more rarely in lead V_3 (24 of 325), and exceptionally in lead V_4 (4 of 325), while max Tpe was equally distributed from lead V_1 to lead V_4 (lead V_1: 103 of 325; lead V_2: 152 of 325; lead V_3: 150 of 325; lead V_4: 139 of 325), regardless of the spontaneous or drug-induced ST elevation and regardless of whether patients were symptomatic or not.

Table 3 QRS duration, QT interval duration, and QT peak values according to the presence of a Tpe interval <100 ms or ≥100 ms

Variable	Tpe interval < 100 ms	Tpe interval ≥ 100 ms	*P*
QRS duration (ms)	108 ± 19	110 ± 19	.4
QT interval in lead V_1 (ms)	394 ± 67	445 ± 75	.0001
QT peak V_1 (ms)	332 ± 66	339 ± 74	.6
QT V_2 (ms)	416 ± 77	456 ± 86	.0008
QT peak V_2 (ms)	352 ± 76	347 ± 85	.6
QT V_3 (ms)	399 ± 69	440 ± 78	<.0001
QT peak V_3 (ms)	332 ± 70	330 ± 79	.8
QT V_4 (ms)	398 ± 69	431 ± 79	.004
QT peak V_4 (ms)	330 ± 68	323 ± 78	.5
QT V_5 (ms)	389 ± 66	438 ± 71	.001
QT peak V_5 (ms)	323 ± 67	332 ± 67	.5
QT V_6 (ms)	391 ± 66	461 ± 107	<.0001
QT peak V_6 (ms)	326 ± 66	356 ± 102	.06

Values are presented as mean ± standard deviation.

Tpe interval = time interval between the peak and the end of the T wave.

The area under ROC curves for the Tpe interval in leads V_1–V_4, Tpe dispersion, and max Tpe was 0.7 (for each lead V_1, V_2, V_3, and V_4), 0.62, and 0.79, respectively. No additional information was given by the ROC curves for Tpe/QT ratios. According to this observation, the best performing variable was max Tpe (Figure 3). An optimized cutoff point was determined from the ROC curve for this variable with respect to SD/AT: a max Tpe of ≥100 ms in any precordial lead has a sensitivity of 84%, a specificity of 68%, a positive predictive value of 19%, and a negative predictive value of 98% for the occurrence of any ventricular arrhythmic event. A max Tpe of ≥100 ms was present in 47 of 226 asymptomatic patients (21%), in 48 of 73 patients with syncope (66%), and in 22 of 26 patients with SD/AT (85%) (relative risk 3.4; $P < .0001$).

Correlations between max Tpe ≥ 100 ms and other clinical and electrophysiological variables are listed in Table 5. A max Tpe of ≥ 100 ms was significantly correlated with male sex, the presence of an ICD, the presence of fascicular block, and type 1 ST elevation in the peripheral leads.

Correlations between clinical and electrophysiological factors and the occurrence of any ventricular arrhythmic event (SD/AT) in univariate or multivariate analysis are listed in Table 6. A max Tpe of ≥100 ms was the most powerful parameter associated with outcome in multivariate analysis (OR 9.61; 95% CI 3.13–29.41; $P < .0001$). This was also the case in the subgroups of patients with spontaneous ST elevation (OR 8.40; 95% CI 2.21–32.26; $P = .002$) and patients without spontaneous ST elevation (OR 14.08; 95% CI 1.65–125; $P = .01$).

This remained significant in the subgroup of ICD-implanted patients (n = 136; OR 6.09; 95% CI 1.9–19.6; $P = .002$). In the nonimplanted patients (n = 189), there was no significant association between max Tpe ≥100 ms and SD in logistic regression, but there was only 2 SDs in this population: both SDs occurred in patients with a max Tpe of ≥100 ms (2 of 51) vs none in other patients (0 of 138) ($P = .02$).

For the subgroup of initially asymptomatic patients (n = 235), a max Tpe of ≥100 ms remained associated with the occurrence of SD/AT (OR 13.3; 95% CI 2.68–66.6; $P = .001$), but this was significant only for patients with spontaneous type 1 ST elevation (OR 15.87; 95% CI 2.75–90.9; $P = .002$) (7 of these initially asymptomatic patients with spontaneous type 1 will present with AT, and 5 of them had a max Tpe of ≥100 ms). In patients without baseline type 1 ECG, there was no significant association between max Tpe ≥ 100 ms and SD/AT in logistic regression, but there was only 2 SDs in this population: both SDs occurred in patients with a max Tpe of ≥100 ms (2 of 37) vs none in other patients (0 of 103) ($P = .02$).

Testing of the correlations on a new group of patients with BS

Of the 55 patients with BS with type 1 ECG (18 SDs, 17 patients presenting with syncope, and 20 asymptomatic

Table 4 Tpe interval and Tpe/QT ratio values in asymptomatic patients, patients with syncope, and patients with SD and/or AT

Variable	Asymptomatic (n = 226)	Syncope (n = 73)	SD/AT (n = 26)	*P* Asymptomatic vs SD/AT	*P* Asymptomatic vs syncope	*P* Syncope vs SD/AT
Tpe V_1 (ms)	63 ± 18	73 ± 18	84 ± 27	<.0001	<.0001	.17
Tpe V_2 (ms)	67 ± 22	83 ± 24	85 ± 18	<.0001	<.0001	.6
Tpe V_3 (ms)	72 ± 21	83 ± 25	92 ± 22	<.0001	.0002	.2
Tpe V_4 (ms)	70 ± 18	79 ± 21	90 ± 24	<.0001	.002	.06
Tpe V_5 (ms)	68 ± 18	69 ± 17	74 ± 21	.11	.48	.28
Tpe V_6 (ms)	66 ± 18	68 ± 17	75 ± 21	.02	.3	.14
Max Tpe (ms)	81 ± 18	101 ± 18	110 ± 23	<.0001	<.0001	.07
Tpe dispersion (ms)	30 ± 17	44 ± 21	47 ± 27	.005	<.0001	.98
Tpe/QT V_1	0.17 ± 0.04	0.19 ± 0.04	0.21 ± 0.06	.001	<.0001	.42
Tpe/QT V_2	0.17 ± 0.05	0.21 ± 0.06	0.21 ± 0.04	<.0001	<.0001	.76
Tpe/QT V_3	0.19 ± 0.05	0.22 ± 0.07	0.24 ± 0.06	.002	.0003	.44
Tpe/QT V_4	0.19 ± 0.05	0.21 ± 0.05	0.23 ± 0.05	.0003	.001	.2
Tpe/QT V_5	0.18 ± 0.04	0.19 ± 0.04	0.19 ± 0.04	.36	.31	.83
Tpe/QT V_6	0.18 ± 0.04	0.19 ± 0.05	0.19 ± 0.04	.11	.32	.5
Heart rate (beats/min)	69 ± 18	66 ± 18	69 ± 33	.9	.64	.24

Values are presented as mean ± standard deviation.

AT = appropriate implantable cardioverter-defibrillator therapy; Max Tpe = maximum value of the time interval between the peak and the end of the T wave; SD = sudden death; Tpe interval = time interval between the peak and the end of the T wave.

patients), the Tpe interval in leads V_1–V_4 and max Tpe were consistently found larger in patients with SD than in other patients (max Tpe: 90 ± 41, 94 ± 64, 102 ± 52, 87 ± 41, and 109 ± 53 ms for leads V_1, V_2, V_3, V_4, respectively, in patients with SD vs 75 ± 21, 78 ± 22, 83 ± 23, 78 ± 21, and 98 ± 18 ms in other patients). Differences were significant for most of the comparisons and for every observer ($P \leq .05$ in 9 of 19 analysis, $P \leq .1$ in 6 of 19 analysis, and $P < .2$ in other analysis).

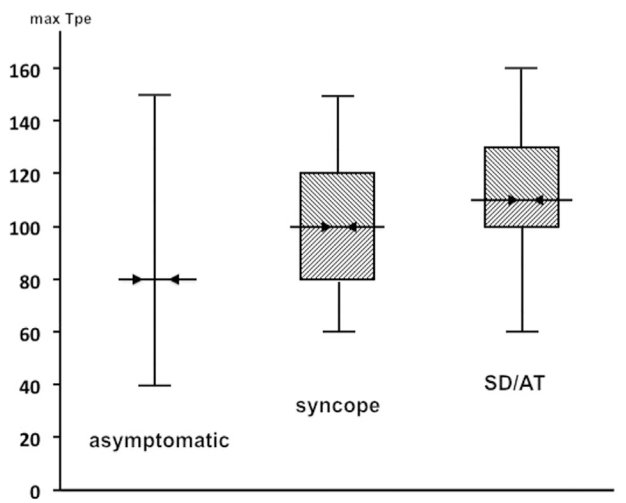

Figure 2 Box plots for the maximum value of the time interval between the peak and the end of the T wave (max Tpe) according to subgroups of asymptomatic patients, patients with syncope, and patients with sudden death (SD) and/or appropriate implantable cardioverter-defibrillator therapy (AT), showing for each group the interquartile range (ie, the range between the 25th and the 75th percentile; shaded boxes centered around the median) and the range of results (vertical bar between minimal and maximal values).

Discussion

In this large series of patients with BS, we found that the Tpe interval was significantly larger from lead V_1 to lead V_4 in patients with BS presenting with malignant ventricular arrhythmia or syncope than in asymptomatic patients. A max Tpe of ≥100 ms in the precordial leads was the stronger independent factor associated with SD and/or AT in our population (OR ~10; relative risk 3.4). Importantly, this parameter remains significantly correlated with the occurrence of malignant ventricular arrhythmias in asymptomatic patients with or without spontaneous ST elevation and in implanted or nonimplanted patients.

The Tpe interval is usually expected to represent the difference in repolarization times between subendocardial

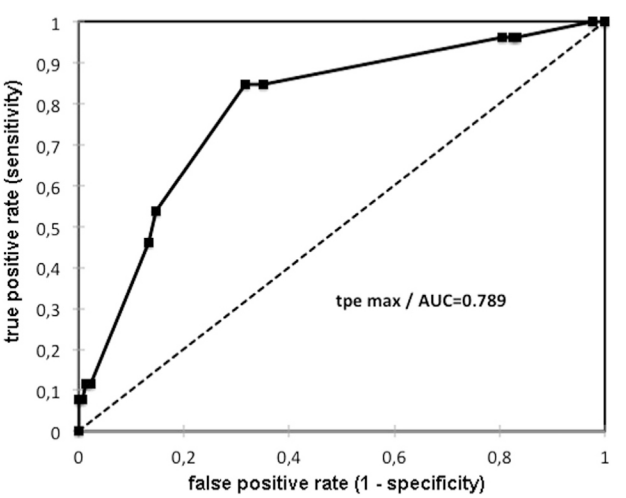

Figure 3 Receiver operating characteristic curve for the maximum value of the time interval between the peak and the end of the T wave (max Tpe). AUC = area under the curve.

Table 5 Correlations between an increased Tpe interval (max Tpe > 100 ms) and other clinical and electrophysiological variables

Variable	Max Tpe interval ≥ 100 ms (n = 117 [36%])	Max Tpe interval < 100 ms (n = 208 [64%])	*P*
Age at diagnosis (y)	47 ± 14	46 ± 13	.7
Sex: male	100/117 (85)	159/208 (76)	.05
SCN5A mutation	19/74 (26)	24/116 (21)	.4
Spontaneous type 1 ST elevation	53/117 (45)	90/208 (43)	.7
Inducibility at electrophysiology testing	38/78 (48)	54/140 (39)	.15
Family history of sudden death	41/117 (35)	53/207 (25)	.07
Atrial fibrillation	13/117 (11)	13/208 (21)	.12
Implantable-cardioverter defibrillator*	66/117 (56)	70/208 (34)	<.0001
PR interval (ms)	184 ± 36	182 ± 35	.27
First-degree atrioventricular block (PR interval > 200 ms)	44/115 (38)	70/207 (34)	.4
Right bundle branch block	35/115 (30)	54/208 (26)	.4
Fascicular block	27/115 (23)	25/208 (12)	.007
QRS duration (ms)	110 ± 19	108 ± 19	.47
HV interval (ms)	52 ± 10	52 ± 10	.78
Fragmented QRS	1/115 (1)	7/208 (3.3)	.16
Max J-point elevation (mm)	3.7 ± 1.5	3.5 ± 1.4	.23
Type 1 ST elevation in peripheral leads	22/114 (19)	8/207 (4)	<.0001
Heart rate (beats/min)	66 ± 22	70 ± 18	.08

Values are presented as mean ± standard deviation or as n/N (%).

ICD = implantable cardioverter-defibrillator; Max Tpe = maximum value of the time interval between the peak and the end of the T wave; Tpe interval = time interval between the peak and the end of the T wave.

*The higher rate of ICD implantation in the subgroup of patients with max Tpe ≥ 100 ms suggests that max Tpe is correlated with malignant ventricular arrhythmias and that ICD had often been implanted in symptomatic patients (presence of an ICD was significantly correlated with the existence of sudden death or syncope; $P < .05$).

and subepicardial myocardial cells and has been proposed as an ECG marker of transmural dispersion of repolarization when measured in the precordial leads.[3,5,19] In humans, differences in endocardial and epicardial recovery intervals have been shown to correspond to the Tpe intervals on the surface ECG.[20] The Tpe interval may represent an interesting parameter for exploring the repolarization process in BS. An increased Tpe interval in the precordial leads may be the electrocardiographical representation of major transmural heterogeneity in the ventricular repolarization process according to one of the proposed mechanisms underlying ST elevation in BS[21] and thus possibly correlating with the arrhythmogenic risk.

Alternatively, on the basis of the "depolarization theory," ST elevation has been proposed to be linked to the conduction delays observed in the right ventricular outflow tract (RVOT) in patients with BS. During the time period corresponding to the QRS end and onset of repolarization,

Table 6 Correlations between clinical and electrophysiological factors and the occurrence of any ventricular arrhythmic event in univariate or multivariate analysis*

Variable	OR (95% CI)	*P*
Univariate analysis		
Max Tpe ≥ 100 ms	11.76 (3.95–35.71)	<.0001
Type 1 ST elevation in peripheral leads	6.89 (2.74–17.24)	<.0001
Syncope	3.09 (1.37–6.98)	.006
Spontaneous type 1 ST elevation	2.59 (1.12–6.00)	.02
SCN5A mutation	2.98 (1.04–8.55)	.04
First-degree atrioventricular block (PR interval ≥ 200 ms)	2.29 (1.02–5.13)	.045
Familial sudden death	2.25 (1.00–5.08)	.05
QRS duration	1.02 (1.00–1.04)	.05
Fragmented QRS	4.06 (0.78–21.28)	.09
Inducibility at electrophysiology study	2.43 (0.85–6.97)	.09
Sex: male	2.04 (0.59–7.03)	.25
Multivariate analysis		
Max Tpe ≥ 100 ms	9.61 (3.13–29.41)	<.0001
Type 1 ST elevation in peripheral leads	3.66 (1.37–9.8)	.009

Max Tpe = maximum value of the time interval between the peak and the end of the T wave; Tpe interval = time interval between the peak and the end of the T wave.

*Due to the low number of arrhythmic events, only the 2 variables showing the strongest association in univariate analysis were included in the multivariate model.

the membrane potential in the right ventricle is more positive than in the RVOT, leading to an extracellular current flowing from the right ventricle to the RVOT and a positive deflection in the right precordial leads (ST elevation) and the reverse occurs thereafter—that is, more positive membrane potentials at the RVOT than at the right ventricle—leading to a negative T wave.[22] Clinical arguments supporting the depolarization theory come from the high prevalence of late potentials or conduction disturbances on ECG in BS,[16] from the presence of delayed epicardial fragmented potentials at the RVOT whose ablation led to ECG normalization,[23] or from the simultaneous fragmentation and delay in epicardial RVOT electrograms and appearance of type 1 ST elevation during ajmaline perfusion.[24] The results of our study do not allow us to argue in favor of any mechanism, although changes in terminal repolarization may be involved (see Table 3).

An increased Tpe interval has been shown to identify patients at higher risk of malignant arrhythmic events in patients with or without structural heart diseases.[4–10] A few studies have also addressed this issue in BS. Castro Hevia et al[11] were the first to link increased Tpe interval as a risk factor in patients with BS: in 29 patients, max Tpe in the precordial leads was significantly prolonged in patients with BS with recurrences versus patients with BS without events or controls, with a best discriminant max Tpe cutoff value of $\geq$100 ms. The Tpe interval was found to be longer in symptomatic and/or inducible patients with BS vs patients with BS without events (who did not differ from controls) in a short series of 27 patients, with a Tpe interval of $\geq$ 120 ms being associated with higher cardiac events in patients with BS.[12] In another series of 23 patients with BS, inducible subjects displayed an increased Tpe interval in lead V_2 but no correlation with spontaneous events was made.[13] The largest series to date included 200 patients with BS, but failed to find any significant difference in the Tpe interval in leads II and V_2 between symptomatic and asymptomatic patients with BS.[14] Calculation of the Tpe interval in the 6 precordial leads and by 2 independent observers blinded to the symptoms may explain the diverging results of this study[14] and of the present study.

Some of these studies found increased Tpe interval to be associated with a poor prognosis but included only a limited number of patients, while other larger cohort studies failed in finding any prognosis role of the Tpe interval. Thus, our study is the first to demonstrate that an increased Tpe interval is highly and independently related to arrhythmic events in a large series of unselected patients with BS.

Risk stratification in BS remains an unsolved issue. Even if a lot of more or less accepted criteria have been proposed for selecting asymptomatic patients with BS prone to a significant risk of malignant ventricular arrhythmias and thus for suggesting primary ICD implantation, to date ICD in asymptomatic patients may only be considered in the case of spontaneous type 1 ECG and with inducible VF.[1] In our series, we found that an increased Tpe interval had a clearly higher correlation with malignant ventricular arrhythmias (OR $\sim$10) than did the usual parameters used in risk stratification. Large prospective trials are needed to confirm these results.

We speculated that an increased Tpe interval could only be the result of a larger or deeper negative T wave in the right precordial leads—the more deeper the T wave, the more longer the Tpe interval—which may have render ECG analysis easier. Moreover, deeper T waves would implicitly have the same meaning as increased Tpe interval in terms of electrophysiological mechanism underlying BS and higher arrhythmogenic risk. However, max Tpe was equally present in leads V_1 to V_4 while type 1 ST elevation was rare in lead V_3 and exceptional in lead V_4. Thus, the correlation between max Tpe with the presence of type 1 ECG or with leads exploring the RVOT, and an increased Tpe interval may be the manifestation of more subtle changes in the repolarization process in BS than the crude type 1 ECG pattern observed in the right precordial leads.

Study limitations

This was a retrospective study of a large series of patients with BS, and the value of an increased Tpe interval for risk stratification in BS should ideally now be confirmed in prospective trials.

Although interobserver variability was shown to be acceptable, measurements of the Tpe interval remain difficult and probably sometimes unreliable especially at a paper speed of 25 mm on the ECG. Achieving better reliability using a higher paper speed or automated ECG interpretation deserves further studies. However, our findings were confirmed by 4 independent Tpe interval measurements in an additional group of patients with BS.

A max Tpe of $\geq$100 ms was independently correlated with arrhythmic events in the subgroup of ICD-implanted patients only. This is probably due to the recording by the device of nonsustained ventricular arrhythmias destined to terminate spontaneously and those would have remained undetected/untreated in the absence of an ICD. However, this means that an increased Tpe interval is clearly related to arrhythmogenesis in patients with BS. The low number of SDs in nonimplanted patients possibly explains the lack of significant correlation between max Tpe $\geq$ 100 ms and symptomatic ventricular arrhythmias in logistic regression: actually, malignant ventricular arrhythmias in this subgroup occurred only in patients with a max Tpe of $\geq$100 ms ($P < .05$). The same occurred in asymptomatic patients without spontaneous type 1 ECG (not correlated with arrhythmic events in regression analysis, but the only 2 patients with SD/AT in this subgroup had a max Tpe of $\geq$100 ms; $P < .05$). Hence, an increased Tpe interval remained significantly associated with the occurrence of ventricular arrhythmia regardless of whether the patients were implanted with an ICD or not and regardless of whether type 1 ST elevation in asymptomatic patients was present at baseline or not.

Conclusion

Risk stratification in BS remains difficult and controversial. The transmural dispersion of repolarization may be

approached by the Tpe interval. A max Tpe of $\geq$100 ms in the precordial leads was highly related to malignant ventricular arrhythmias in this large series of patients with BS. Once prospectively evaluated, this simple ECG parameter could be proposed for refining risk stratification in BS in addition to accepted or other recently recognized markers.

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