Europace (2010) **12**, 271–274
doi:10.1093/europace/eup357

T_{peak}–T_{end} interval and T_{peak}–T_{end}/QT ratio as markers of ventricular tachycardia inducibility in subjects with Brugada ECG phenotype

Konstantinos P. Letsas*, Reinhold Weber, Klaus Astheimer, Dietrich Kalusche, and Thomas Arentz

Abteilung Rhythmologie, Herz-Zentrum, Südring 15, 79189 Bad Krozingen, Germany

Received 12 August 2009; accepted after revision 15 October 2009; online publish-ahead-of-print 6 November 2009

Aims The present study investigated whether several ECG markers of ventricular repolarization are associated with ventricular tachycardia/fibrillation (VT/VF) inducibility in subjects with type 1 ECG pattern of Brugada syndrome (BS).

Methods and results The clinical data of 23 individuals (19 males, age 42.69 ± 14.63) with spontaneous ($n = 10$) or drug-induced ($n = 13$) type 1 ECG pattern of BS who underwent programmed ventricular stimulation were analysed. Sustained VT/VF was induced in 17 subjects (74%) and was significantly associated with the presence of spontaneous type 1 ECG of BS ($P = 0.012$). Among the studied ECG repolarization markers, subjects with inducible VT/VF displayed an increased T_{peak}–T_{end} interval in leads V_2 (88.82 ± 15.70 vs. 78.33 ± 4.08 ms, $P = 0.02$) and V_6 (76.33 ± 10.08 vs. 66.66 ± 5.16 ms, $P = 0.04$) and a greater T_{peak}–T_{end}/QT ratio in lead V_6 (0.214 ± 0.028 vs. 0.180 ± 0.014, $P = 0.009$) compared with those without arrhythmias. Ventricular tachycardia/fibrillation inducibility was not associated with arrhythmic events during a mean follow-up period of 4.61 ± 2.14 years ($P = 0.739$).

Conclusion The T_{peak}–T_{end} interval and T_{peak}–T_{end}/QT ratio were associated with VT/VF inducibility in BS. The utility of T_{peak}–T_{end}/QT ratio as a new marker of arrhythmogenesis in BS requires further studies, including a large number of patients.

Keywords T_{peak}–T_{end} interval • T_{peak}–T_{end}/QT ratio • Brugada syndrome • Ventricular arrhythmias • Electrophysiological study

Introduction

The Brugada syndrome (BS) is an arrhythmogenic entity characterized by the presence of ST-segment elevation in leads V_1 through V_3 on surface ECG, the absence of structural heart disease, and a high risk of ventricular tachycardia/fibrillation (VT/VF) and sudden cardiac death (SCD).[1–3] Transmural dispersion of repolarization (TDR) within the ventricular myocardium has been suggested to underlie arrhythmogenesis in BS.[4] A number of ECG markers of ventricular repolarization have been reported to identify high-risk patients with BS.[5] The present study investigated whether several new and old ECG markers of ventricular repolarization are associated with VT/VF inducibility in subjects with BS.

Methods

Data on 23 consecutive individuals (19 males, mean age 42.69 ± 14.63 years) with spontaneous ($n = 10$) or drug-induced (ajmaline 1 mg/kg or flecainide 2 mg/kg) ($n = 13$) type 1 BS ECG phenotype were retrospectively analysed. Thirteen individuals were symptomatic exhibiting a history of syncope, and 10 subjects were asymptomatic. None of the participants suffered aborted SCD. Eight displayed a positive family history of BS and/or SCD. The ECG diagnosis of BS was strictly based on the recommendations of the Second Consensus Conference on BS.[3] The presence of structural heart disease was excluded in all subjects. Subjects with a previous history of syncope, documented sustained ventricular arrhythmia, or aborted SCD were considered as symptomatic. Baseline electrophysiological study (EPS) was performed

* Corresponding author. Tel: +49 302106843854, Fax: +49 76334022429, Email: k.letsas@mail.gr

in all participants. Programmed right ventricular apex stimulation was performed at three running cycle length (600, 500, and 430 ms) with up to triple extrastimuli (minimum coupled extrastimuli of 180 ms). Inducible ventricular arrhythmia was defined as any ventricular arrhythmia (VT/VF) lasting >30 s, causing syncope/circulatory collapse, or requiring intervention to be terminated. During follow-up, patients were considered to have had an arrhythmic event in the case of SCD, VT/VF, or appropriate shock from the implantable cardioverter defibrillator (ICD).

The 12-lead ECGs were recorded at a paper speed of 50 mm/s with an amplification of 10 mm/mV. The following markers of ventricular repolarization were evaluated: (i) the corrected QT (QTc) interval calculated by Bazett's method ($\times 1/\sqrt{}$RR interval) in leads II, V_2, and V_6; (ii) the corrected JT (JTc) interval calculated by subtracting the QRS duration from the QTc interval in leads II, V_2, and V_6; (iii) the QTc dispersion defined as the difference between the maximum and the minimum QTc interval of the 12 leads; (iv) the JTc dispersion defined as the difference between the maximum and the minimum JTc interval of the 12 leads; (v) the T_{peak}–T_{end} interval in leads V_2 and V_6 defined as the interval from the peak of a positive T-wave or the nadir of a negative T-wave to the end of T-wave; (vi) the T_{peak}–T_{end} dispersion defined as the difference between the maximum and the minimum T_{peak}–T_{end} duration of the precordial leads (V_1–V_6); and (vii) the T_{peak}–T_{end}/QT ratio in leads V_2 and V_6. The T_{peak}–T_{end} interval was measured in precordial leads that are considered to reflect the transmural axis of the left ventricle, and therefore to provide an index of TDR.[6] All ECG measurements were performed by two independent cardiologists who were blinded to other patient information. When measurements were not identical, the mean of the values was calculated. The study was approved by the medical ethical review committees of the participating hospitals. Informed consent was obtained from all subjects.

The SPSS software package (Version 13.0 for Windows, Inc., Chicago, IL, USA) was used for statistical analysis. Data are expressed as mean values ± standard deviation. Categorical data were analysed by the Pearson χ^2 test. The mean differences between the study groups were evaluated by calculating Student's *t*-test after controlling for equality of variances with the Levene's statistic. A *P*-value of <0.05 was considered to be statistically significant.

Results

The study population consisted of 23 individuals with spontaneous or drug-induced type 1 ECG pattern of BS who underwent programmed ventricular stimulation. Sustained VT/VF was induced in 17 subjects (74%). Ventricular arrhythmias were induced with double extrastimuli in 5 subjects and with triple extrastimuli in 12 subjects. There were no significant differences among the studied ECG repolarization markers with regard to induction mode. An ICD was implanted in 14 cases. During a mean follow-up period of 4.61 ± 2.14 years, one symptomatic patient suffered an appropriate ICD discharge due to sustained polymorphic VT. There were no inappropriate ICD therapies in our cohort.

As shown in *Table 1*, subjects with VT/VF inducibility tended to be older compared with those without arrhythmias (47.05 ± 12.52 vs. 30.33 ± 12.38 years, $P = 0.01$). The presence of spontaneous type 1 ECG of BS was significantly associated with VT/VF inducibility during EPS ($P = 0.012$). There were no significant correlations between symptoms or family history of BS and/or SCD and VT/VF inducibility. Among the studied ECG repolarization markers, subjects with inducible VT/VF displayed an increased T_{peak}–T_{end} interval in leads V_2 (88.82 ± 15.70 vs. 78.33 ± 4.08 ms, $P = 0.02$)

Table 1 Baseline clinical and electrocardiographic data of patients with and without inducible VT/VF at EPS

Variables	Inducible VT/VF (*n* = 17)	No inducible VT/VF (*n* = 6)	*P*-value
Age	47.05 ± 12.52	30.33 ± 12.38	**0.010**
Males (*n*)	13 (76.5%)	6 (100%)	0.191
History of syncope (*n*)	10 (58.8%)	3 (50%)	0.708
Family history BS/SCD (*n*)	5 (29.4%)	3 (50%)	0.363
Spontaneous type 1 ECG pattern	10 (58.8%)	0 (0%)	**0.012**
QTc in lead II (ms)	406.76 ± 28.03	393.50 ± 37.86	0.373
QTc in lead V_2 (ms)	429.11 ± 43.44	397.33 ± 49.65	0.152
QTc in lead V_6 (ms)	388.86 ± 35.46	391.33 ± 41.39	0.892
QTc dispersion of the 12 leads (ms)	43.17 ± 33.76	27.16 ± 9.68	0.093
JTc in lead II (ms)	309.11 ± 36.30	290.33 ± 31.84	0.118
JTc in lead V_2 (ms)	319.64 ± 39.71	288.33 ± 42.57	0.275
JTc in lead V_6 (ms)	289.53 ± 41.41	289.66 ± 33.36	0.994
JTc dispersion of the 12 leads (ms)	37.20 ± 29.54	20.00 ± 9.05	0.057
T_{peak}–T_{end} in lead V_2 (ms)	88.82 ± 15.76	78.33 ± 4.08	**0.020**
T_{peak}–T_{end} in lead V_6 (ms)	76.33 ± 10.08	66.66 ± 5.16	**0.040**
T_{peak}–T_{end} dispersion of the precordial leads (ms)	15.11 ± 9.15	11.8 ± 7.22	0.437
T_{peak}–T_{end}/QT ratio in lead V_2	0.227 ± 0.034	0.206 ± 0.012	0.161
T_{peak}–T_{end}/QT ratio in lead V_6	0.214 ± 0.028	0.180 ± 0.014	**0.009**
Ventricular arrhythmic events during follow-up	1 (5.9%)	0 (0.0%)	0.544

Categorical data are presented as absolute and relative (column %) frequencies and continuous variables are presented as means ± standard deviations. Bold values represent statistically significant values.

and V_6 (76.33 ± 10.08 vs. 66.66 ± 5.16 ms, $P = 0.04$) and a greater $T_{peak}-T_{end}$/QT ratio in lead V_6 (0.214 ± 0.028 vs. 0.180 ± 0.014, $P = 0.009$) compared with those without arrhythmias. A trend towards an increased QTc dispersion (43.17 ± 33.76 vs. 27.16 ± 9.68 ms, $P = 0.093$) and JTc dispersion (37.20 ± 29.54 vs. 20.00 ± 9.05 ms, $P = 0.057$) was additionally observed in patients with inducible arrhythmias. As shown in *Table 1*, there were no significant differences regarding the QTc interval, JTc interval, or $T_{peak}-T_{end}$ dispersion of the precordial leads between the study groups. Ventricular tachycardia/fibrillation inducibility during EPS was not associated with arrhythmic events during follow-up ($P = 0.739$).

Discussion

This study investigated the utility of different ECG parameters of ventricular repolarization as markers of VT/VF inducibility in BS. We showed that the $T_{peak}-T_{end}$ interval and $T_{peak}-T_{end}$/QT ratio are associated with VT/VF inducibility in subjects with BS ECG phenotype.

In isolated ventricular wedge preparations, the peak of the T-wave was shown to coincide with epicardial repolarization and the end of the T-wave with repolarization of the M cells, so that the $T_{peak}-T_{end}$ interval provides a measure of TDR.[7,8] In other studies, the $T_{peak}-T_{end}$ interval was found to represent a measure of global and not of TDR.[9,10] Nevertheless, in previous reports, an increased $T_{peak}-T_{end}$ interval has been associated with VT/VF development and, therefore, may be considered as a non-invasive marker of arrhythmogenesis. The $T_{peak}-T_{end}$ interval has been found amplified in patients with congenital long QT syndrome (LQTS).[11] Epinephrine challenge significantly prolongs the $T_{peak}-T_{end}$ interval in subjects with congenital LQTS,[12] whereas propranolol suppresses these effects, particularly in those with LQTS1.[13] An exercise-induced accentuation of the $T_{peak}-T_{end}$ interval along with an increased propensity to develop Torsades de Pointes (TdP) has been additionally demonstrated in subjects with LQTS1.[14] In the setting of acquired bradyarrhythmias, the $T_{peak}-T_{end}$ interval was the best single predictor of TdP events.[15] Watanabe *et al.*[16] have demonstrated that a prolonged $T_{peak}-T_{end}$ interval is significantly associated with inducibility as well as spontaneous development of VT in high-risk patients with organic heart disease. There are limited data regarding the utility of $T_{peak}-T_{end}$ interval in BS. Castro Hevia *et al.*[5] have recently reported the efficacy of $T_{peak}-T_{end}$ interval and $T_{peak}-T_{end}$ dispersion in predicting recurrent ventricular arrhythmic events during follow-up in subjects with BS. Similar findings were reported by other investigators.[17,18] In this study, we showed that subjects with BS ECG phenotype and VT/VF inducibility at EPS display an increased $T_{peak}-T_{end}$ interval in leads V_2 and V_6 compared with those without inducible arrhythmias.

The $T_{peak}-T_{end}$/QT ratio is a relatively new index of ventricular repolarization that remains constant, despite dynamic changes in heart rate.[19] The $T_{peak}-T_{end}$/QT ratio is considered a more sensitive index of arrhythmogenesis compared with $T_{peak}-T_{end}$ interval as it provides an estimate of dispersion of repolarization relative to total duration of repolarization.[19] Yamaguchi *et al.*[20] have demonstrated that the $T_{peak}-T_{end}$/QT ratio is a better predictor of TdP when compared with QTc interval and QT dispersion in patients with acquired LQTS. In a study including patients with hypertrophic cardiomyopathy, Shimizu *et al.*[21] have shown that the $T_{peak}-T_{end}$/QT ratio was significantly higher in patients who had an episode of SCD when compared with those without any symptoms. This is the first study addressing the utility of $T_{peak}-T_{end}$/QT ratio as an arrhythmogenic marker in subjects with BS ECG phenotype. We demonstrated that subjects with VT/VF inducibility during EPS display a greater $T_{peak}-T_{end}$/QT ratio in lead V_6 compared with those without arrhythmias.

In this study, we showed that VT/VF inducibility is high in patients with BS (74%). In a recent meta-analysis, the overall rate of VT/VF inducibility in BS was 53% (range 34–91%).[22] In accordance with previous data,[23] we showed that spontaneous type 1 BS ECG pattern is strongly associated with inducible ventricular arrhythmias during programmed ventricular stimulation. However, in a similar study, the 12-lead ECG pattern was not predictive of VT/VF inducibility.[24] We additionally demonstrated that older subjects (mean age 47.05 years) are more susceptible to VT/VF inducibility than younger individuals (mean age 30.33 years). An age-related enhanced electrical and/or structural right ventricular disease may explain this finding. A progressive cardiac conduction slowing with ageing was more prominent in BS probands with *SCN5A* mutation than in those without the mutation.[25] Catalano *et al.*[26] have recently demonstrated that patients with BS display a high prevalence of mild structural changes in the right ventricle. The role of EPS in the risk stratification of patients with BS still remains controversial.[2,3] In agreement with two previous meta-analyses,[22,27] we failed to demonstrate any association between VT/VF inducibility and arrhythmic events during follow-up.

Our study has the following limitations. First, a small number of subjects with BS ECG pattern were retrospectively studied, and hence our work is subject to the limitations inherent in any retrospective analysis. Secondly, keeping in mind the controversial role of EPS in BS population as well as the heterogeneous data derived using different stimulation protocols,[22,27] the prognostic significance of $T_{peak}-T_{end}$/QT ratio should also be investigated in relation to spontaneous long-term arrhythmic events. Finally, genetic analysis was not consistently performed. In conclusion, the $T_{peak}-T_{end}$ interval and $T_{peak}-T_{end}$/QT ratio were associated with VT/VF inducibility in subjects with BS ECG phenotype. The utility of $T_{peak}-T_{end}$/QT ratio as a new arrhythmogenic marker requires further studies.

Conflict of interest: none declared.

Funding

K.P.L. was supported by a Training Fellowship of the European Heart Rhythm Association (EHRA).

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