Sodium Channel Blockers Enhance the Temporal QT Interval Variability in the Right Precordial Leads in Brugada Syndrome

Tetsuzou Kanemori, M.D.,* Hiroki Shimizu, M.D.,* Katsumi Oka, M.D.,* Yoshio Furukawa, M.D.,* Kenji Hiromoto, M.D.,‡ Takanao Mine, M.D.,§ Tohru Masuyama, M.D., Ph.D.,† and Mitsumasa Ohyanagi, M.D., Ph.D.*

From the *Department of Internal Medicine, Division of Coronary Heart Disease and †Cardiovascular Division, Hyogo College of Medicine, Nishinomiya, Japan; ‡Division of Cardiology, Takarazuka Municipal Hospital, Takarazuka, Japan; and §Division of Cardiology, Osaka General Medical Center, Osaka, Japan

Background: Temporal QT interval variability is associated with sudden cardiac death. The purpose of this study was to evaluate temporal QT interval variability in Brugada syndrome (BS).

Methods: We measured QT and RR intervals in precordial leads (V_1 – V_6) based on 12-beat resting ECG recordings from 16 BS patients (B group) with spontaneous ST elevation in right precordial leads (V_1 – V_2) and from 10 patients with normal hearts (C group). We measured the response in B group before and after administration of pilsicainide (1 mg/kg). The standard deviation (QT-SD, RR-SD) of the time domain and total frequency power (QT-TP, RR-TP) were calculated for all precordial leads, and the latter was to analyze the frequency domain.

Results: The right precordial leads in BS exhibited an additional and prominent ST elevation (coved-type) after pilsicainide administration. Both QT-SD and QT-TP values were significantly more increased in B, than in C (5.1 ± 1.2 vs 3.6 ± 0.2 and 23.4 ± 2.9 vs 12.3 ± 1.7 msec², $P < 0.01$, respectively) and after pilsicainide administration in B. (5.1 ± 0.4 vs 3.9 ± 0.3 , 25.8 ± 3.4 vs 16.3 ± 2.6 msec², $P < 0.01$, respectively) However, QT-SD and QT-TP did not significantly change in any of other leads (V_3 – V_6) and RR-SD and RR-TP were similar for both groups, as well as after intravenous pilsicainide administration in B.

Conclusions: The temporal QT interval variability was identified in BS. Moreover, sodium channel blocker induced temporal fluctuation in QT interval and it may possibly provide a substrate for ventricular arrhythmia in BS patients.

A.N.E. 2008;13(1):74–80

QT interval variability; T-wave alternans; pilsicainide; Brugada syndrome; ventricular arrhythmia

Brugada syndrome (BS) is characterized by a right bundle branch block morphology with ST segment elevation in the right precordial leads of the 12-lead surface electrocardiogram (ECG).¹ The Brugada type ECG can be unmasked by antiarrhythmic drugs.^{2,3} Moreover, T-wave alternans (TWA) and ventricular arrhythmias can be induced by sodium channel blockers in patients with BS.⁴ Sodium channel blockers induce changes in the cardiac ion channel function and alter the morphology of the action potentials in the epicardium but not in the endocardium, and create a transmural voltage gradient, phase 2 reentry (P2R) in the right ventricular

free wall and ventricular arrhythmias in patients with BS.^{5–7} However, the precise mechanism of the ventricular arrhythmias in BS remains unclear. Other studies have suggested that ventricular repolarization is abnormal in patients with BS. An increased temporal QT interval variability, which reflects repolarization abnormalities, is associated with sudden cardiac death in patients with organic heart disease.^{8–10} No evidence indicates that the temporal QT dispersion is associated with BS. This study evaluated the temporal QT interval dispersion in patients with BS before and after the administration of a sodium channel blocker.

Address for reprints: Tetsuzou Kanemori, M.D., Hyogo College of Medicine, Department of Internal Medicine, Division of Coronary Heart Disease, 1-1 Mukogawa-cho, Nishinomiya, Japan. Fax: +81-798-45-6551; E-mail: kinchan@hyo-med.ac.jp

©2008, Copyright the Authors
Journal compilation ©2008, Blackwell Publishing, Inc.

MATERIALS AND METHODS

Study Population and ECG Recording

Fourteen male and two female patients with Brugada syndrome (BS, B group; 3 symptomatic and 13 asymptomatic) and 10 patients with normal heart findings (C group) were enrolled in this study. BS was diagnosed in accordance with current diagnosis criteria.¹¹ BS patients included spontaneous or sodium channel blocker-induced coved-type ST elevation in right precordial leads (V_1 – V_2) with or without some degree of right bundle branch block. None of all patients showed obvious structural heart disease on chest radiography and echocardiography. The mean age of group B was 53 ± 12 years old, and that of group C was 54 ± 19 . The symptomatic patients had recurrent syncopal episodes of unknown origin (two patients) or were resuscitated from VF (one patient). The patients were excluded if atrial fibrillation, sick sinus syndrome, or atrioventricular block were evident, or if they were undergoing treatment with any antiarrhythmic medications.

All the study patients underwent a 12-lead ECG (FDX-6531 Fukuda Denshi, Tokoyo, Japan), while supine and awake for 512 beats during sinus rhythm during the day (09.00–16.00 h) in a quiet and light-attenuated room for subsequent QT and RR interval variability analysis as follows. The patients were excluded if their ECG rhythms indicated anything other than normal sinus. The presence of atrial or ventricular ectopy was accepted unless such beats represented $> 5\%$ of all 512 beats.

Pharmacological Test

Pilsicainide was administered in 10 of the BS patients. We evaluated the following parameters in the precordial leads before and 5 minutes after the administration of pilsicainide: ST level, QT interval variability, heart rate variability, macroscopic TWA, and ventricular arrhythmias defined as polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).

Electrophysiological Study

All participants provided written informed consent and an electrophysiological study (EPS) was performed in 13 of the 16 group B patients. Three of those patients were symptomatic and the remaining 10 were asymptomatic. Programmed extrastim-

ulation was performed from both the right ventricular apex (RVA) and right ventricular outflow tract (RVOT). The protocol of the ventricular stimuli included up to three extrastimuli at two basic cycle lengths of 600 and 400 ms. The extrastimuli were decreased to a coupling interval of no less than 180 ms. If ventricular arrhythmias were not induced by extrastimulation from the RVA, the extrastimulation was performed from the RVOT. The EPS was ended when it induced either sustained VT/VF or completed the programmed extrastimulation. Patients with inducible VT/VF (defined as ventricular arrhythmia lasting more than 30 seconds or requiring emergency interventions) were classified as inducible.

ECG Analysis

The 12-lead ECG results were continuously recorded and analyzed offline. The QT intervals were measured in the precordial leads by use of a newly developed software (QTD-1; Fukuda Denshi Co Ltd) that detects the onset of the QRS and the end of the T wave. The differential threshold technique was used by this software and it has been described elsewhere.^{12,13} The 512-beat data were analyzed for the heart rate variability as described.¹⁴ The standard deviation of the RR and QT intervals (RR-SD, QT-SD), respectively, were computed from the respective beat series for each 512-beat epoch for time domain measurements.

In addition, the fast Fourier transformation (FFT) was calculated from the 512-beat RR and QT interval data. The power density spectrum was estimated by summing the squares of the magnitude of the FFT for the 512 beats. We computed the power spectral densities of the 512 usable beats and calculated four frequency domains as follows: the low-frequency power of the RR interval (RR-LF, 0.04–0.15 Hz), high-frequency power of the RR interval (RR-HF, 0.15–0.40 Hz), total-frequency power of the RR and QT intervals (RR-TP and QT-TP, 0.01–0.40 Hz) and ratio of the low- to high-frequency powers of the RR intervals (RR-LF/HF).

Statistical Analysis

The patient characteristics are expressed as the mean $\pm$ SD. All HRV and QT parameters are expressed as the mean $\pm$ standard error of the mean. An unpaired *t*-test was used for the univariate analysis. A P value of < 0.05 was considered statistically significant.

Table 1. Patient Characteristics

	B Group	C Group	P Value
n	16	12	-
Sex (M/F)	14/2	10/2	N.S.
Age	53 ± 15	54 ± 19	N.S.
FH. +.	3	-	-
Symptomatic	3	-	-
Asymptomatic	13	-	-
Induced VF by EPS	9/13	-	-

BS = Brugada syndrome; C = normal heart; M = male; F = female; FH = family history; EPS = electrophysiological study.

RESULTS

Patient Characteristics

Table 1 shows the characteristics of groups B and C. Three of the 16 patients with BS had a history of syncope, and 3 had a family history of sudden cardiac death. Pilsicainide was administered in 10 of the 16 patients with BS. The presentation of the BS in 7 of 10 patients changed from a saddle-back to coved-type ECG morphology, and it went unchanged in 3 patients (coved pattern). However, the ST level was prominently elevated (more than 0.2 mV) in the right precordial leads (V_1 or V_2).

Macroscopic TWA developed in 3 patients (one symptomatic and 2 asymptomatic) in group B after the pilsicainide administration. Figure 1 shows the data from 1 asymptomatic patient. TWA devel-

oped and the QT interval fluctuation increased after the pilsicainide administration, but ventricular arrhythmias were not evident. Thirteen patients underwent an EPS and VF was induced in 9 patients (2 symptomatic and 7 asymptomatic).

RR and QT Interval Analysis

Both the mean and SD of the RR intervals did not significantly differ between groups B and C (983 ± 68 vs 926 ± 38 and 35 ± 8 vs 29 ± 3 ms, respectively) or before and after the pilsicainide administration in group B (906 ± 41 vs 889 ± 57 , 27 ± 5 vs 22 ± 4 ms, respectively) (Table 2). The SD of the QT interval significantly varied in the precordial leads among the group B patients, but did not significantly change in group C. This value significantly increased in the right precordial leads in group B, rather than in group C (V_1 , 5.1 ± 0.3 vs 3.7 ± 0.1 ms, $P < 0.01$; V_2 , 4.2 ± 0.3 vs 3.5 ± 0.2 ms, $P < 0.05$), but not in any other leads (Fig. 2). Moreover, the SD of the QT interval significantly increased after the intravenous administration of pilsicainide in group B in the right precordial lead (V_2) (5.3 ± 0.4 vs 3.9 ± 0.3 ms, $P < 0.05$), but not in any other leads (Fig. 3). Figure 4 shows the QT interval changes in the precordial leads (V_2 , V_5) in one asymptomatic BS patient before and after the administration of pilsicainide. The QT interval fluctuated in lead V_2 , but not in lead V_5 , and increased after the pilsicainide administration.

Figure 1. The QT interval in lead V_2 before and after the administration of pilsicainide.

Table 2. Data of the RR Interval Parameters

	B Group	C Group	P Value	Before	After	P Value
RR mean (ms)	983 ± 68	926 ± 38	N.S.	906 ± 41	889 ± 57	N.S.
RR SD (ms)	35 ± 8	29 ± 3	N.S.	27 ± 5	22 ± 4	N.S.
RR TP (ms ²)	860 ± 675	880 ± 756	N.S.	1147 ± 424	614 ± 196	N.S.
RR LF (ms ²)	397 ± 338	218 ± 74	N.S.	216 ± 103	134 ± 51	N.S.
RR HF (ms ²)	237 ± 110	104 ± 27	N.S.	116 ± 40	77 ± 27	N.S.
RR LF/HF	0.9 ± 0.4	3.2 ± 1.5	N.S.	2.2 ± 1.4	2.3 ± 1.1	N.S.

B = Brugada syndrome; C = normal heart; Before = before the administration of pilsicainide; After = after the administration of pilsicainide; RR mean = mean RR interval; RR SD = standard deviation of the RR interval; RR TP = total-power of the RR interval; RR LF = low-frequency of the RR interval; RR HF = high frequency of the RR interval; RR LF/HF = the ratio of the low-frequency to high-frequency power of the RR interval. All frequencydomain variables were calculated from 512-beats.

Spectral Analysis of the QT and RR Interval

The TP, HF, and LF/HF of the RR interval did not differ between the two groups, or between that observed after the pilsicainide administration in group B (Table 2). However, the TP of the QT interval significantly increased in the right precordial leads (V₁, V₂) in group B, as compared to group C (25.8 ± 2.5 vs 13.0 ± 1.3 msec², $P < 0.01$ and 17.8 ± 1.7 vs 11.6 ± 1.4 msec², $P < 0.05$, respectively), but not in any other leads (Fig. 2). Moreover, this value significantly increased in the right precordial lead (V₂) after intravenous pilsicainide was administered in group B (25.8 ± 3.4 vs 16.3 ± 2.6 msec², $P < 0.05$), but not significantly in any other leads (Fig. 3).

DISCUSSION

This study showed that the temporal QT interval variability increased significantly in the BS patients as compared to the controls in the right precordial leads, and moreover, it increased more significantly in lead V₂ after the intravenous administration of pilsicainide in those patients. However, the spectral analysis of the RR interval did not differ between the two groups.

QT Interval Variability

The beat-to-beat repolarization lability is associated with an increased risk for ventricular arrhythmias with organic heart disease.^{9,15} Berger et al.⁸ reported that dilated cardiomyopathy is associated

Figure 2. The distribution of the QT interval variability among the BS and C groups. † $P < 0.05$. ‡ $P < 0.01$.

Figure 3. The distribution of the QT interval variability before and after the administration of pilscainide. †P < 0.05.

with increased beat-to-beat fluctuations in the QT interval as compared with normal hearts and that the increase causes a temporal lability in the ventricular repolarization. Increased QT interval variability has been also demonstrated in patients with congenital long QT syndrome, another inherited arrhythmia syndrome.¹⁶ However, QT interval variability in the patients with BS has not been described. This study discovered that the QT interval variability in only the right precordial leads was increased in the patients with BS as compared

with those whose hearts were normal. We suggest that BS patients have a temporal lability of the ventricular repolarization around the right ventricular outflow tract.

Mechanism of the Ventricular Arrhythmias in Brugada Syndrome

Several studies suggest that a conduction abnormality is important for arrhythmogenesis in patients with BS.¹⁷⁻²⁰ Eckardt et al.¹⁷ showed that

Figure 4. The serial changes in the QT interval in the precordial leads (V₂ and V₅) before and after the administration of pilscainide.

late potentials in the signal-averaged ECG, which reflect ventricular conduction abnormalities, is a good marker for the inducibility of malignant ventricular arrhythmias in patients with BS. Furushima et al.²⁰ indicated that the dominant prolongation of the filtered QRS duration in the right precordial leads is related to the risk of arrhythmic events in BS.

On the other hand, several studies support the notion that the mechanism of malignant ventricular arrhythmias in BS is caused by repolarization abnormalities.^{5-7,21} Phase 2 reentry in the epicardium at the right ventricular outflow tract might be associated with the initiation of ventricular arrhythmias in BS. The presence of an I_{to} -mediated spike-and-dome morphology or a notch in the right ventricular epicardium but not the endocardium creates a transmural voltage gradient, and sodium channel blockers, but not I_{to} , promote the loss of the action potential duration dome in the right ventricular epicardium. This results in the development of an obvious transmural dispersion of the repolarization and leads to phase 2 reentry in a model of BS in vitro.^{5,7,21} Kurita et al.²² showed that an abnormal spike-and-dome of the monophasic action potentials in the RV epicardium, but not in the endocardium, would induce a transmural current in the BS patients. This study showed that the temporal QT interval dispersion, which reflects ventricular repolarization abnormalities, was increased only in the right precordial leads and that it increased in lead V_2 but not in any other leads after the pilsicainide administration. These findings indicate that the repolarization around the right ventricular outflow tract in BS patients is abnormal.

Recent studies have demonstrated that some patients with BS who receive sodium channel blockers develop not only ST-elevation but also ventricular arrhythmias and macroscopic TWA.^{4,23-25} Nishizaki et al.²⁶ demonstrated that macroscopic TWA occurred and the QT interval changed alternately after the administration of a sodium channel blocker. Macroscopic TWA was induced in only the right precordial leads in 3 patients with BS after the pilsicainide administration. These findings indicate that the repolarization was destabilized in the right ventricular outflow tract in the BS patients. Moreover, sodium channel blockers might cause an increase in the repolarization fluctuations in the right ventricular outflow tract, but not at any other sites in such patients.

A preparation study has shown that the TWA value reflects the temporal and spatial dispersion of the ventricular repolarization.^{27,28} However, Kirchhof et al.²⁹ indicated that microvolt TWA is not an appropriate means of detecting the arrhythmic risk in patients with BS. Ikeda et al.³⁰ suggested that neither the microvolt TWA nor spatial QT interval dispersion are independent predictors of life-threatening events associated with BS. Microvolt TWA might not be associated with the development of ventricular arrhythmias in patients with BS.

STUDY LIMITATIONS

The study population was small because it excluded the patients with poor recordings in order to minimize the measurement errors. In addition, the controls after the pilsicainide administration were lacking. After the pilsicainide administration, TWA developed whereas ventricular arrhythmias were not induced. However, Morita et al.⁴ found that a macroscopic TWA developed in 6 (60%) of 10 BS patients during pilsicainide-induced ventricular arrhythmias. Thus, further investigation is required to elucidate the mechanism of the ventricular arrhythmias in the patients with BS.

CONCLUSIONS

The temporal QT interval variability identified in BS. Moreover, sodium channel blocker induced temporal fluctuation in QT interval and it may possibly provide a substrate for ventricular arrhythmia in patients with BS.

REFERENCES

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;20:1391-1396.
2. Miyazaki T, Mitamura H, Miyoshi S, et al. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Coll Cardiol* 1996;27:1061-1070.
3. Fujiki A, Usui M, Nagasawa H, et al. ST segment elevation in the right precordial leads induced with class IC antiarrhythmic drugs: Insight into the mechanism of Brugada syndrome. *J Cardiovasc Electrophysiol* 1999;10:214-218.
4. Morita H, Morita ST, Nagase S, et al. Ventricular arrhythmia induced by sodium channel blocker in patients with Brugada syndrome. *J Am Coll Cardiol* 2003;42:1624-1631.
5. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation* 1996;93:372-379.
6. Gussak I, Antzelevitch C, Bjerregaard P, et al. The Brugada syndrome: Clinical, electrophysiologic and genetic aspects. *J Am Coll Cardiol* 1999;33:5-15.

7. Antzelevitch C. The Brugada syndrome: Ionic basis and arrhythmia mechanism. *J Cardiovasc Electrophysiol* 2001;12:268–272.
8. Berger RD, Kasper EK, Baughman KL, et al. Beat-to-beat QT interval variability: Novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. *Circulation* 1997;96:1557–1565.
9. Atiga WL, Calkins H, Lawrence JH, et al. Beat-to-beat repolarization lability identifies patients at risk for sudden cardiac death. *J Cardiovasc Electrophysiol* 1998;9:899–908.
10. Haigney MC, Zareba W, Gentlesk PJ, et al. Multicenter Automatic Defibrillator Implantation Trial II investigators. QT interval variability and spontaneous ventricular tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. *J Am Coll Cardiol* 2004;44:1481–1487.
11. Wilde AA, Antzelevitch C, Borggrefe M, et al. Proposed diagnostic criteria for the Brugada syndrome: Consensus report. *Circulation* 2002;106:2514–2519.
12. McLaughlin NB, Campbell RW, Murray A. Accuracy of four automatic QT measurement techniques in cardiac patients and healthy subjects. *Heart* 1996;76:422–426.
13. Xue Q, Reddy S. Algorithms for computerized QT analysis. *J Electrocardiol* 1998;30(Suppl):181–186.
14. Tsuji H, Venditti FJ Jr, Manders ES, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation* 1994;90:878–883.
15. Galeano EJ, Yoshida A, Ohnishi Y, et al. Comparative usefulness of beat-to-beat QT dispersion and QT interval fluctuations for identifying patients with organic heart disease at risk for ventricular arrhythmias. *Circ J* 2003;67:125–128.
16. Satomi K, Shimizu W, Takaki H, et al. Response of beat-by-beat QT variability to sympathetic stimulation in LQT1 form of congenital long QT syndrome. *Heart Rhythm* 2005;2:149–154.
17. Eckardt L, Bruns HJ, Paul M, et al. Body surface area of ST elevation and the presence of late potentials correlate to the inducibility of ventricular tachyarrhythmia in Brugada syndrome. *J Cardiovasc Electrophysiol* 2002;13:742–749.
18. Masaki R, Watanabe I, Nakai T, et al. Role of signal-averaged electrocardiograms for predicting the inducibility of ventricular fibrillation in the syndrome consisting of right bundle branch block and ST segment elevation in leads V1–V3. *Jpn Heart J* 2002;43:367–378.
19. Morita H, Takenaka-Morita S, Fukushima-Kusano K, et al. Risk stratification for asymptomatic patients with Brugada syndrome. *Circ J* 2003;67:312–316.
20. Furushima H, Chinushi M, Hirono T, et al. Relationship between dominant prolongation of the filtered QRS duration in the right precordial leads and clinical characteristics in Brugada syndrome. *J Cardiovasc Electrophysiol* 2005;16:1311–1317.
21. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. *Circulation* 1999;100:1660–1666.
22. Kurita T, Shimizu W, Inagaki M, et al. The electrophysiologic mechanism of ST-segment elevation in Brugada syndrome. *J Am Coll Cardiol* 2002;40:330–334.
23. Ohkubo K, Watanabe I, Okumura Y, et al. Intravenous administration of class I antiarrhythmic drug induced T wave alternans in an asymptomatic Brugada syndrome patient. *Pacing Clin Electrophysiol* 2003;26:1900–1903.
24. Takagi M, Doi A, Takeuchi K, et al. Pilsicainide-induced marked T wave alternans and ventricular fibrillation in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 2002;13:837.
25. Tada H, Nogami A, Shimizu W, et al. ST segment and T wave alternans in a patient with Brugada syndrome. *Pacing Clin Electrophysiol* 2000;23:413–415.
26. Nishizaki M, Fujii H, Sakurada H, et al. Spontaneous T wave alternans in a patient with Brugada syndrome—responses to intravenous administration of class I antiarrhythmic drug, glucose tolerance test, and atrial pacing. *J Cardiovasc Electrophysiol* 2005;16:217–220.
27. Chinushi M, Restivo M, Caref EB, et al. Electrophysiological basis of arrhythmogenicity of QT/T alternans in the long-QT syndrome: Tridimensional analysis of the kinetics of cardiac repolarization. *Circ Res* 1998;83:614–628.
28. Pastore JM, Girouard SD, Laurita KR, et al. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. *Circulation* 1999;99:1385–1394.
29. Kirchhof P, Eckardt L, Rolf S, et al. T wave alternans does not assess arrhythmic risk in patients with Brugada syndrome. *Ann Noninvasive Electrocardiol* 2004;9:162–165.
30. Ikeda T, Sakurada H, Sakabe K, et al. Assessment of noninvasive markers in identifying patients at risk in the Brugada syndrome: Insight into risk stratification. *J Am Coll Cardiol* 2001;37:1628–1634.