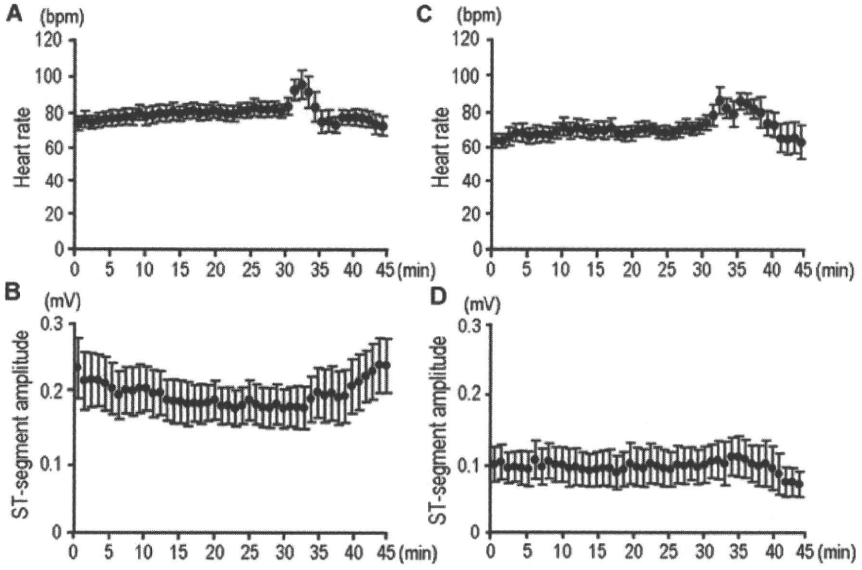

Figure 2. *Response of the heart rate and ST-segment amplitude during the head-up tilt (HUT) test in 16 HUT-positive patients with Brugada electrocardiogram (ECG) (A, B) and in 10 HUT-positive patients with suspected neurally mediated syncope (NMS) (C, D). At first, the passive tilt (Control-Tilt) was performed for 30 minutes (0–30 minutes). When Control-Tilt was negative, nitroglycerin tilt was continued for 15 minutes (30–45 minutes). The responses of heart rate during positive responses to the HUT test were similar in patients with Brugada ECG (A) to those in patients with suspected NMS (C). In patients with Brugada ECG, ST-segment in lead V2 was augmented before and after positive responses to the HUT test (B), but not in those with suspected NMS (D).*

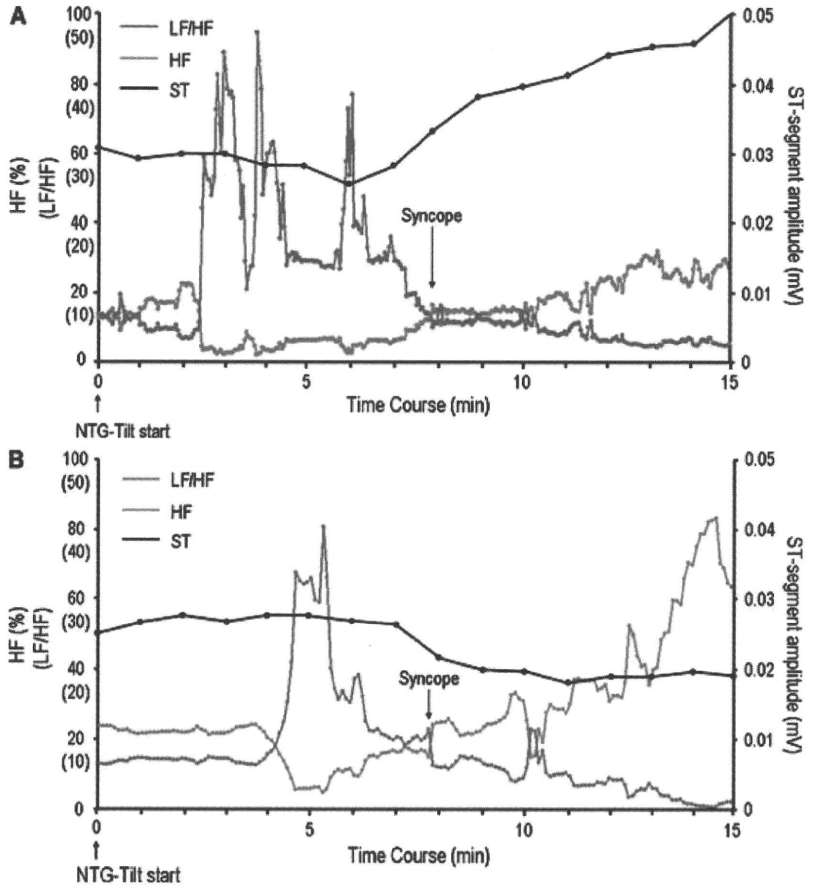

Figure 3. *Autonomic responses during head-up tilt (HUT) test. The autonomic activities in a representative nitroglycerin (NTG)-Tilt-positive patient with type 1 Brugada electrocardiogram (ECG) (A) and those in a representative NTG-Tilt-positive patient with suspected NMS (B). Before tilt-induced syncope, sympathetic activity (LF/HF ratio) dramatically increased; and then, sympathetic withdrawal occurred immediately. Thereafter, parasympathetic nerve activity (the normalized unit of the HF components) gradually increased. In the HUT-positive patient with Brugada ECG, ST-segment augmentation in lead V2 was observed just before and after positive responses, and the LF/HF ratio decreased and the HF component increased gradually toward the maximum ST-segment elevation (A). In contrast, in the HUT-positive patient with suspected NMS, ST-segment amplitude in lead V2 was decreased gradually after positive responses (B).*

It is well known that the autonomic nervous system plays an important role on the arrhythmogenesis of Brugada syndrome. Previous studies showed that the withdrawal of sympathetic activity and the sudden rise in vagal activity was an important triggering factor of ventricular fibrillation.[13-15] Similarly, it has been presumed that parasympathetic tone increase during NMS events in patients with Brugada ECG. Recent basic study showed that *SCN5A*, a major responsible gene in Brugada patients, is expressed not only in the myocardial cells but also in intracardiac ganglia.[16] Makita *et al.* also demonstrated a novel nonsense mutation in *SCN5A* gene in a patient with Brugada syndrome who had been diagnosed as NMS.[17] These results suggested that the abnormal regulation or imbalance of autonomic nervous system may exist regardless of the presence or absence of cardiac events in patients with Brugada ECG.

ST-Segment Elevation in the Precordial Leads During the HUT Test in Patients with Brugada ECG

In Brugada syndrome, spontaneous augmentation of ST-segment elevation occurred along with an increase in vagal activity, especially just before and after the occurrence of ventricular fibrillation.[14] The ST-segment elevation is also known to be modulated by exercise,[18] pharmacological interventions that interact with automatic nervous activities,[19] or taking meals associated with glucose-induced insulin levels.[20] In this study, ST-segment augmentation in the right precordial leads was observed just before and after positive responses to the HUT test in two-thirds (69%) of the HUT-positive patients with Brugada ECG but only in 7% of the HUT-negative patients. In patients with Brugada ECG, the preceding increase of sympathetic nerve activity during the HUT test may cause augmentation of ICa-L, resulting in attenuation of ST-segment elevation.[19] Subsequent augmentation of parasympathetic nerve activity during the HUT test may decrease of ICa-L, and increase Ito, thus augmenting ST-segment amplitude.

Clinical Implication

The second consensus report suggested that symptomatic patients displaying type 1 Brugada ECG (either spontaneous or after class Ic drugs) who present with aborted sudden death should undergo ICD implantation.[3] ICD implantation is also recommended in patients with syncope, seizure, or nocturnal agonal respiration, after noncardiac causes of these symptoms have been carefully ruled out.[3] Needless to say, the ECG recording during syncope is the only convincing way to rule in or out VT during syncope, and only clinical judgment can be used to guide diagnostic and therapeutic decisions. However, in patients with Brugada syndrome, there is an abnormal regulatory imbalance of the autonomic nervous system that may be a common denominator to both syncope and ventricular fibrillation.

Limitations

The control subjects were significantly younger than patients with Brugada ECG or those with suspected NMS. However, it is reported that the positive rate of NTG-Tilt in the elderly was comparable to that seen in younger subjects.[21] Therefore, lower incidence of positive rate of the HUT test in the control subjects than that in the other 2 groups was not due to the relevant difference of age. The incidence of spontaneous type 1 ECG and the positive rate of the HUT test are smaller in Brugada patients with syncope episodes only than in those with documented VT or asymptomatic patients; however, statistical significance was not observed between the 3 groups.

Conclusions

Thirty-five percent of patients with Brugada ECG showed vasovagal responses during the HUT test. The HUT test was also positive in 41% among only Brugada patients with documented VT or no symptoms. During vasovagal response, ST-segment augmentation in the right precordial leads was observed in 69% of the HUT-positive Brugada patients, but no ventricular arrhythmias were induced. These data suggest that some Brugada patients have impaired balance of autonomic nervous system, which may relate to their syncopal episodes. Additional studies including a large number of subjects are needed to validate our findings and possibly evaluate the role of the HUT test in risk stratification of patients with Brugada ECG.

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QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia

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ABSTRACT

Many antipsychotic drugs cause QT prolongation, although the effect differs based on the particular drug. We sought to determine the potential for antipsychotic drugs to prolong the QTc interval (>470 ms in men and >480 ms in women) using the Bazett formula in a "real-world" setting by analyzing the electrocardiograms of 1017 patients suffering from schizophrenia. Using logistic regression analysis to calculate the adjusted relative risk (RR), we found that chlorpromazine (RR for 100 mg = 1.37, 95% confidence interval (CI) = 1.14 to 1.64; $p<.005$), intravenous haloperidol (RR for 2 mg = 1.29, 95% CI = 1.18 to 1.43; $p<.001$), and sultopride (RR for 200 mg = 1.45, 95% CI = 1.28 to 1.63; $p<.001$) were associated with an increased risk of QTc prolongation. Levomepromazine also significantly lengthened the QTc interval. The second-generation antipsychotic drugs (i.e., olanzapine, quetiapine, risperidone, and zotepine), mood stabilizers, benzodiazepines, and antiparkinsonian drugs did not prolong the QTc interval. Our results suggest that second-generation antipsychotic drugs are generally less likely than first-generation antipsychotic drugs to produce QTc interval prolongation, which may be of use in clinical decision making concerning the choice of antipsychotic medication.

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1. Introduction

QTc interval prolongation is associated with presyncope, syncope, polymorphic ventricular tachycardia, the subtype torsade de pointes, and sudden cardiac death (Faber et al., 1994). Previous studies have indicated an increased risk of sudden cardiac death in patients treated with antipsychotics (Hennessy et al., 2002; Ray et al., 2001; Straus et al., 2004). A retrospective cohort study of 481,744 Tennessee Medicaid enrollees, of whom 1487 died from sudden cardiac death, found that current moderate-dose antipsychotic use (>100 mg of thioridazine equivalents) increased the rate of sudden cardiac death (multivariate risk ratio of 2.39), when compared with the nonuse of antipsychotics (Ray et al., 2001). A cohort study of three U.S. medical programs found that patients with treated schizophrenia had higher rates of cardiac arrest and ventricular arrhythmia than did controls (patients with glaucoma and those with psoriasis), with risk ratios ranging from 1.7 to 3.2 (Hennessy et al., 2002). A study of 554 sudden cardiac death subjects reported that the current use of antipsychotics was associated with a three-fold increased risk of cardiac death (Straus et al., 2004).

Although torsade de pointes and sudden death are rare, rate-corrected QT (QTc) prolongation serves as a risk factor for these conditions. In a study of 495 psychiatric patients receiving various psychotropic drugs and 101 healthy reference individuals, 8% of patients showed QTc prolongation (>456 ms) (Reilly et al., 2000). Advanced age (>65 years), as well as the use of tricyclic antidepressants, thioridazine, and droperidol were indicated as robust predictors of QTc lengthening (Reilly et al., 2000). High antipsychotic doses were also associated with QTc prolongation (Reilly et al., 2000). In a sample of 111 psychiatric inpatients receiving a median daily dose of more than 600 mg [chlorpromazine (CP) equivalent] of antipsychotics, 90% had schizophrenia or related psychoses, and 23% showed QTc interval of >420 ms, whereas only 2% of unmedicated controls did (Warner et al., 1996). However, there is little clinical data to aid in assessing the

Abbreviations: QTc, rate-corrected QT; 95% CI, 95% confidence interval; HPD, haloperidol; HPDiv, intravenous injection of haloperidol; RR, relative risk; ECG, electrocardiogram; SGAs, second-generation antipsychotics; FGAs, first-generation antipsychotics; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; CP, chlorpromazine; LP, levomepromazine; OR, odds ratio.

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risk of QTc prolongation for an individual antipsychotic in a dose-dependent manner, particularly for second-generation antipsychotics (SGAs). Some case reports have indicated that SGAs can induce QTc prolongation (Dineen et al., 2003; Vieweg, 2003). However, such anecdotal reports do not provide clear evidence of whether SGAs increase the risk of QTc prolongation, as in first-generation antipsychotics (FGAs), in a real-world setting. This study examined the risk of QTc prolongation of antipsychotic drugs in a large clinical sample from Japan. Japan is known to use higher doses of antipsychotics (Bitter et al., 2003), providing a unique opportunity to investigate the risk of QTc prolongation in a wide range of antipsychotic doses.

2. Methods

2.1. Patients

Clinical information, including data on QTc intervals, was collected from inpatients with schizophrenia who were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) in four independent hospitals. Approval from the ethics committee of each hospital was obtained. Data collection on all inpatients with schizophrenia was begun on the following dates in three psychiatric hospitals Biwako Hospital, Toyosato Hospital, and Minakuchi Hospital: February 2, 2007; February 3, 2007; and July 29, 2007, respectively. In the fourth hospital, the National Center of Neurology and Psychiatry Hospital, clinical records were collected for all patients who were admitted to its psychiatric wards between 1998 and 2007. A total of 1065 inpatients were included from the four hospitals, and all of them underwent ECG screening. Among them, 37 patients were excluded due to hypokalemia (serum potassium <3.5 mEq/L), which can induce QTc interval prolongation (Elming et al., 2003; Taylor, 2003). Two were excluded because of hypothyroidism, and nine because of cardiac disease (four patients with right bundle branch block, two with post-acute myocardial infarction, one with WPW syndrome, one with atrial–ventricular block, and one who underwent surgery for atrial septal defect). The remaining 1017 patients had a mean age of 42.6 years (S.D., 18.2) and were included in the analysis.

2.2. Procedure

A standard 12-lead ECG was recorded at 25 mm/s. Because the QTc interval is influenced by heart rate, it was corrected by Bazett's formula (QTc: $QTc = QT/RR^{1/2}$) (Bazett, 1920). An ECG recording showing the longest QTc interval was selected for each patient whose ECG was recorded two or more times. The QTc was measured automatically by a program on the ECG apparatus (MAC 5500 with 12SL algorithm by GE health care [Amersham Place, Little Chalfont, Buckinghamshire, UK]). For patients with a QTc > 430 ms, QTc and RR intervals were measured manually for the chest lead with the maximal T-wave amplitude, according to Charbit et al. (2006). The end of the T-wave was determined as the intersection between the tangent to the steepest downslope of the T-wave and the isoelectric line. QTc prolongation was defined as a QTc length of more than 470 ms in males and more than 480 ms in females, as 99% of "healthy" people can be excluded by this cut-off value (Taggart et al., 2007). One of the coauthors (M.H.), a cardiologist who specializes in arrhythmias, trained the authors on how to evaluate an ECG recording. Information on drugs administered within 24 h of the ECG recording was obtained. Table 1 shows the distribution of drugs that were administered in more than 3% of the patients and the prevalence of QTc prolongation for each medication. One hundred forty-two patients were drug free when the ECG was recorded, because they were given the test at admission before they had taken any drugs. Two hundred sixty-five patients were on monotherapy. Doses of antipsychotics, antiparkinsonian drugs, and benzodiazepines were converted into those of CP, biperiden, and diazepam equivalents, respectively (Inagaki and Inada, 2006). Subjects who were coadministered medical drugs (i.e., non psychotropic drugs) with an increased risk of producing torsade de pointes were excluded (Chan et al., 2007).

Table 1
Medication and rate of QTc prolongation in 1017 patients. Drugs which were administrated to more than 3% of patients are shown.

Administrated drugs	No. of Patients $n = 1017$ (100%)	Mean dose (SD), mg	No. of patients (%) with QTc prolongation (male: >470 ms, female >480 ms)
Equivalent dose			
CP eq.	875 (86)	963.0 (879.0)	23 (2.6)
Diazepam eq.	672 (66)	14.6 (14.6)	18 (2.7)
Biperiden eq.	645 (63)	3.8 (2.2)	19 (2.9)
Mood stabilizer			
CBZ	74 (7)	478.9 (201.8)	3 (4.1)
VPA	54 (5)	650.0 (334.1)	1 (1.9)
Lithium	47 (5)	587.2 (199.6)	4 (8.5)
Antipsychotics			
HPD	375 (37)	15.9 (12.6)	16 (4.3)
CP	299 (29)	190.5 (198.7)	9 (3.0)
LP	258 (25)	91.9 (94.5)	14 (5.4)
Risperidone	248 (24)	5.6 (3.7)	4 (1.6)
Zotepine	116 (11)	179.9 (124.9)	3 (2.6)
Olanzapine	104 (10)	15.6 (6.4)	0 (0.0)
Quetiapine	60 (6)	375.5 (258.5)	0 (0.0)
Bromperidol	49 (5)	10.7 (8.6)	0 (0.0)
Sultopride	49 (5)	1032.9 (810.2)	10 (20.4)
HPD iv	47 (5)	16.0 (10.5)	8 (17.0)

Abbreviations: eq = equivalent; HPD = haloperidol, CP = chlorpromazine; LP = levomepromazine, CBZ = carbamazepine, VPA = sodium valproate; No. = Number, SD = standard deviation.

2.3. Statistical analyses

First, logistic regression analysis was applied to examine risk factors for QTc prolongation. Age, sex, antipsychotic dose (CP equivalent), benzodiazepine dose (diazepam equivalent), and antiparkinsonian drug dose (biperiden equivalent) were included in the backward stepwise regression model. In the second analysis, age, sex, and individual antipsychotic doses were entered as independent variables in the logistic regression analysis. Then, the adjusted relative risks of important explanatory variables were calculated via the backward stepwise regression analysis. Drugs that were administrated in more than 3% of the patients were analyzed.

Linear regression analysis was used to determine which antipsychotics lengthened the QTc interval in a dose-dependent manner, as the antipsychotic dose was entered as a continuous variable. Then, the adjusted coefficients were calculated using the stepwise selection model. Age, sex, and individual antipsychotic doses were entered as independent variables.

The χ^2 test was used to examine the risk-increasing effect of excessive use of antipsychotics (cut-off points of 1000 or 1500 mg/day of CP equivalent). All statistical analyses were performed using the SPSS, version 13.0 (SPSS Japan, Inc., Tokyo, Japan). All p-values reported are two tailed. Statistical significance was considered when p-value was less than 0.05.

3. Results

The prevalence of QTc prolongation (>470 ms in male and >480 ms in female) was 2.5% (male: 3.7%; female: 1.0%). Logistic regression analysis showed that the antipsychotic dose was a significant risk factor for QTc prolongation (Table 2), whereas antiparkinsonian drugs, benzodiazepines, and mood stabilizers were not risk factors for QTc prolongation. Administration of antipsychotic doses greater than 1000 and 1500 mg/day of CP equivalent was found

Table 2
Result of logistic regression analysis on the risk of QTc prolongation for standardized doses.

	Unadjusted relative risk (95% CI)	Adjusted relative risk (95% CI)
Age	0.97 (0.94–0.99)	
Sex (risk of female)	0.33 (0.12–0.95)	
CP eq. (100 mg)	1.08 (1.05–1.12)*	1.07 (1.04–1.10)*
Diazepam eq. (1 mg)	1.01 (0.98–1.04)	
Biperiden eq. (1 mg)	0.87 (0.72–1.06)	
CBZ (100 mg)	1.00 (1.00–1.00)	
VPA (100 mg)	1.00 (0.99–1.00)	
Lithium (100 mg)	1.00 (1.00–1.01)	
	The Hosmer–Lemeshow Goodness-of-Fit Test $x^2 = 4.77$ df = 8 $p = 0.85$	The Hosmer–Lemeshow Goodness-of-Fit Test $x^2 = 5.15$ df = 8 $p = 0.74$

*$p < 0.001$.
Abbreviations: eq = equivalent, CP = chlorpromazine, CBZ = carbamazepine; VPA = sodium valproate, CI = confidence interval.

to increase the risk of QTc prolongation 1.97 fold (95% CI, 1.48–2.59, $p < 0.001$) and 2.76 fold (95% CI, 1.80–4.18, $p < 0.001$), respectively, when compared to their counterparts. On examination of individual antipsychotics, haloperidol intravenous injection (HPDiv), CP, and sultopride were found to increase the risk of QTc prolongation (Table 3).

In the stepwise selection model of the multiple linear regression analysis, CP, HPDiv, levomepromazine (LP), and sultopride were found to lengthen the QTc interval. Age was also indicated as a risk factor for QTc lengthening. Adjusted coefficients for CP, HPDiv, LP, sultopride, and sex are shown in Table 4. Adding 100 mg of LP, for example, extended the QTc interval by 4.65 ms. Bromperidol, olanzapine, quetiapine, risperidone, and zotepine had no significant lengthening effect on the QTc interval.

Table 3
Result of logistic regression analysis on the risk of QTc prolongation for each antipsychotic drug.

	Unadjusted relative risk (95%CI)	Adjusted relative risk (95%CI)
Age	0.99 (0.96–1.03)	
Sex (risk of female)	0.38 (1.26–1.16)	
HPD (2 mg)	0.99 (0.92–1.06)	
CP (100 mg)	1.37 (1.13–1.67)*	1.37 (1.14–1.64)*
LP (100 mg)	1.55 (0.92–2.61)	
Risperidone (1 mg)	1.01 (0.84–1.12)	
Zotepine (66 mg)	0.91 (0.62–1.34)	
Olanzapine (2.5 mg)	0.00 (0.00 to >100)	
Quetiapine (66 mg)	0.00 (0.00 to >100)	
Bromperidol (2 mg)	0.00 (0.00 to >100)	
Sultopride (200 mg)	1.40 (1.23–1.60)**	1.45 (1.28–1.63)**
HPD iv (2 mg)	1.26 (1.13–1.40)**	1.29 (1.18–1.43)**
	The Hosmer–Lemeshow Goodness-of-Fit Test $x^2 = 5.04$ df = 8 $p = 0.75$	The Hosmer–Lemeshow Goodness-of-Fit Test $x^2 = 17.81$ df = 8 $p = 0.013$

*$p < 0.005$.
**$p < 0.001$.
Abbreviations: HPD = haloperidol, CP = chlorpromazine, LP = levomepromazine, iv = intravenous injection, CI = confidence interval.

4. Discussion

In a large clinical sample, we confirmed that a daily dose of antipsychotics (CP equivalents) was associated with a dose-dependent increased risk of QTc prolongation; however, the use of antiparkinsonian drugs, benzodiazepines, and mood stabilizers did not significantly increase this risk. With regard to individual antipsychotics, CP, HPDiv, and sultopride were shown to significantly increase the risk of QTc prolongation. CP, HPDiv, LP, and sultopride were found to significantly lengthen the QTc interval, whereas HPD, bromperidol, olanzapine, quetiapine, risperidone, and zotepine were not.

Our observation that a daily dose of antipsychotics was associated with a risk of QTc prolongation is consistent with previous studies (Reilly et al., 2000; Warner et al., 1996). In our sample, antipsychotic doses of more than 1000 and 1500 mg/day of CP equivalents were found to increase the risk of QTc prolongation by approximately 2.0 and 3.0 fold, respectively, when compared to their counterparts. Reilly et al. also reported that a high dose (1000 to 2000 mg/day) and a very high dose (>2000 mg/day) predicted QTc prolongation [odds ratio (OR), 5.3 and 8.2, respectively] (Reilly et al., 2000). Warner et al. reported an OR of 4.3 for doses higher than 2000 mg/day (Warner et al., 1996). In contrast to antipsychotics, mood stabilizers showed no significant risk-increasing effect. This is consistent with a previous finding, which showed that lithium or carbamazepine did not significantly increase the risk of QTc prolongation (Reilly et al., 2000). However, a recent study suggested that lithium increases the QTc interval significantly (18.6 ms; 95% CI, 4.8–32.4 ms) (van Noord et al., 2009). Furthermore, lithium is known to cause T-wave changes (Mitchell and Mackenzie, 1982; Reilly et al., 2000) that may lead to torsade de pointes when combined with a QTc-lengthening antipsychotic (Liberatore and Robinson, 1984). Thus, the use of lithium requires careful ECG monitoring. With respect to valproate, our study may be the first to investigate the risk of QTc prolongation for this drug in a clinical setting. With regard to coadministered benzodiazepine and antiparkinsonian drugs, our results suggest no significant effect on QTc prolongation. Although some patients taking diazepam and biperiden equivalent showed QTc interval prolongation (Table 1), the results of logistic regression analysis showed no significant risk-increasing effect of these drugs (Table 2). Therefore, these patients were also taking chlorpromazine equivalent and it was the chlorpromazine equivalent that explained the QTc interval prolongation. Indeed, to our knowledge, there has been no study reporting that these drugs cause QTc prolongation or torsade de pointes.

With respect to individual antipsychotics, previous studies have reported that thioridazine, intravenous droperidol, sertindole, and ziprasidone are associated with a strong risk-increasing effect on QTc prolongation (Czekalla et al., 2001a; Harrigan et al., 2004; Taylor,

Table 4
QTc prolongation effect of each antipsychotic by linear regression model.

	Forced entry model	Stepwise selection model
	Coefficient (95% CI)	Coefficient (95% CI)
Age	0.19 (0.10–0.28)*	0.20 (0.11–0.29)*
Sex (risk of female)	3.22 (−0.01–6.44)	
HPD (2 mg)	0.42 (0.09–0.76)	
CP (100 mg)	3.91 (2.69–5.13)*	3.82 (2.62–5.02)*
LP (100 mg)	4.87 (2.14–7.60)*	4.65 (1.94–7.37)*
Risperidone (1 mg)	0.07 (−0.47–0.61)	
Zotepine (66 mg)	−0.36 (−1.91–1.20)	
Olanzapine (2.5 mg)	0.30 (−0.47–1.08)	
Quetiapine (66 mg)	0.11 (−0.87–1.09)	
Bromperidol (2 mg)	0.08 (−1.00–1.16)	
Sultopride (200 mg)	3.65 (2.48–4.82)*	3.56 (2.41–4.72)*
HPD iv (2 mg)	3.16 (2.36–3.96)*	3.13 (2.34–3.93)*

*$p < 0.001$.
Abbreviations: HPD = haloperidol, CP = chlorpromazine, LP = levomepromazine; iv = intravenous injection, CI = confidence interval.

2003). In Japan, commercial use of thioridazine ended in 2005; intravenous droperidol has not been used in psychiatric treatment; and sertindole and ziprasidone have not been introduced. Thus, we could not confirm the effect of these drugs. However, our results provide robust evidence that HPDiv increases the risk of QTc prolongation. This concurs with Hatta et al. who compared the differences in QTc length among psychiatric emergency patients who received intravenous flunitrazepam alone and those who received intravenous flunitrazepam and haloperidol and found that the latter group showed significantly longer QTc intervals than the former (Hatta et al., 2001). Vieweg et al. (2009) reviewed the literature and identified cases of patients aged ≥60 years who developed QTc interval prolongation, polymorphic ventricular tachycardia/torsade de pointes and/or sudden cardiac death while taking antipsychotic or antidepressant drugs or a combination of these medications. Among such cases, most frequently reported medication was HPDiv (14 out of 37 cases). These findings and ours support the recent alert of the U.S. Food and Drug Administration warning that HPDiv increases the risk of QTc prolongation and torsade de pointes based on at least 28 cases reported in the literature (U.S. Food and Drug Administration Cfdear, 2007). Oral HPD, in contrast, was found to have no statistically significant risk-increasing effect on QTc prolongation, although it had a significant QTc-lengthening effect. Previous findings have suggested that oral HPD at low or moderate doses had no clear effect on QTc, but that it is associated with QTc prolongation and torsade de pointes at higher clinical doses (>20 mg/day) (Czekalla et al., 2001a; Taylor, 2003). Taken together, excessively high blood levels of the drug after an intravenous injection or oral intake of high doses may be critical for the effect of HPD. Regarding bromperidol (oral use only), a chemically similar butyrophenone to HPD, we obtained no evidence for its effect on QTc prolongation or lengthening. To our knowledge, this is the first study to examine bromperidol for such effects. Further studies are warranted to confirm our results. With respect to CP, we detected significant effects on both QTc prolongation and QTc lengthening, which is consistent with previous findings, suggesting an intermediate effect of CP on QTc (i.e., a weaker effect than that of thioridazine, but stronger than oral HPD) (Czekalla et al., 2001a; Mehtonen et al., 1991; Witchel et al., 2003), although there have been some reports of no significant risk-increasing effect of CP (Reilly et al., 2000; Strachan et al., 2004). LP, another phenothiazine, was also found to lengthen the QTc interval in the multiple regression analysis. In the logistic regression, statistical significance was nearly achieved ($p=0.06$, Table 3). These results suggest that LP is likely to increase the risk of QTc prolongation. Although there have been little data on LP in relation to QTc in the literature, an association between sudden death and the use of phenothiazines is prominent, and LP might have been involved in such deaths (Mehtonen et al., 1991). Finally, sultopride, a benzamide derivative, was found to significantly increase the risk of QTc prolongation and QTc lengthening. To our knowledge, this is the first time that such evidence has been obtained for sultopride. Further studies are warranted to confirm our results.

Our results provide no evidence for the possible risk-increasing effect of the examined SGAs (olanzapine, quetiapine, risperidone, and zotepine) on QTc prolongation. Recently, Ray et al. (2009) reported that atypical antipsychotics double the risk of sudden cardiac death when compared with nonusers of antipsychotic drugs, a finding that contradicts our data. However, SGAs can induce weight gain, insulin resistance, and dyslipidemia (Tschoner et al., 2009), all of which are risk factors for ischemic heart diseases. Therefore, the increased sudden death observed by Ray et al. (2009) could be attributable to the increased risk of ischemic heart diseases rather than torsade de pointes due to QTc prolongation. The Pfizer 054 study (2000) reported that SGAs, such as risperidone, quetiapine, ziprasidone, and olanzapine, induced QTc interval prolongation. In the review of Czekalla et al. (2001a), it was suggested that risperidone and quetiapine could lengthen the QTc interval, although the effect observed was smaller than that of thioridazine and chlorpromazine. Olanzapine, in particular, was reported to have little effect on the QTc-interval length (Czekalla et al., 2001b). Dineen et al. (2003) reported the case of a patient who was treated with olanzapine and showed an abnormal QTc interval. Vieweg (2003) reviewed the literature and found nine cases in which QTc prolongation was associated with SGA administration (four cases of risperidone [one case was his original case], three cases of quetiapine, and two cases of ziprasidone). Taken together, although our results suggest that the SGAs (olanzapine, quetiapine, risperidone, and zotepine) are less likely to produce QTc interval prolongation than the FGAs examined herein, the SGAs can also cause QTc prolongation. Thus, further investigations with a more refined methodology are warranted. In particular, the current group-derived formula for correcting QT interval measurements to a heart rate of 60 beats per/min (QTc) are unsatisfactory (Malik, 2001), and, as pointed out by Vieweg (2003), determining the effect of drug-induced change amid the noise of random variation (regression to the mean) will require a new technology.

Female gender is known to be a risk factor for QTc prolongation (Taylor, 2003; Vieweg et al., 2009). However, we failed to detect female gender as a significant risk factor in our sample. Moreover, QTc prolongation was found more commonly in male patients than in female patients. One reason for these results was that the antipsychotic dose was substantially lower in female patients than in male patients (mean CP equivalent dose: 841 vs. 1066 mg/day; frequency of >1500 mg/day: 13.9% vs. 20.8%). In addition, because some previous studies in psychotic patients did not detect the gender difference (Chong et al., 2003; Hatta et al., 2000), such populations may have other factors that attenuate the gender difference.

There are several limitations to the study. First, we did not include medications other than psychotropic drugs in the analysis; however, the subjects included in the analysis were not coadministered other medical drugs that increased the risk for torsade de pointes (Chan et al., 2007). We also excluded patients suffering from cardiac diseases. Furthermore, psychotropic drugs that were administrated to 3% or fewer of the patients in the sample were not included in the analysis. The fact that nearly all patients received multiple drugs and a substantial proportion of participants (69%) were treated with antipsychotic polypharmacy may have made it difficult to obtain a clear result for each drug. However, there is great value in assessing the increased risk of QTc prolongation in such a practical setting. Our participants were all inpatients, and therefore individuals with severe symptomatology and those patients on high doses of antipsychotics were likely to be overrepresented. A recent study reported the possibility that an acute psychotic state itself may be a risk factor for QTc prolongation (Bar et al., 2007). Severe symptomatology might have biased the results toward an increased prevalence of the QTc interval in our subjects.

To screen QTc interval, we used an automated program, which may be fraught with errors. However, Charbit et al. (2006), for example, reported that patients with automatic QTc of <430 ms were at very low risk of having a prolonged QT interval where their definition of prolonged QTc interval was >450 ms in women and >440 ms in men. We measured QTc interval manually for patients with an automated QTc of >430 ms, although our definition of QTc prolongation was >480 ms in women and >470 ms in men. Thus, it was unlikely that we missed patients with QTc prolongation in our study. Furthermore, the reliability of the measurement algorithm of the ECG equipment (MAC 5500 with 12SL algorithm by GE health care [Amersham Place, Little Chalfont, Buckinghamshire, UK]) that we used was reported to be high. The data obtained by this algorithm was within 10 ms of the manual measurement in 95.9% of ECGs and within 15 ms in 99.3% of ECGs (Hnatkova et al., 2006). Thus, the possible effect of the use of the automated program is likely minimal. Another limitation might be that we used the chest lead with the maximal T-wave amplitude because clear T-wave leads are needed for precise

manual measurement. However, Bazett generally used limb lead II to determine his formula.

Despite these limitations, we obtained robust evidence among a large clinical sample in a real-world setting that suggested that a daily dose of antipsychotics is associated with a dose-dependent increased risk of QTc prolongation, whereas that of antiparkinsonian drugs, benzodiazepines, and mood stabilizers is not. With regard to individual antipsychotics, our results suggest that FGAs, such as HPDiv, CP, LP, and sultopride, have a risk-increasing effect on QTc prolongation and that SGAs, such as olanzapine, quetiapine, risperidone, and zotepine, are less likely to produce QTc prolongation than the FGAs. Such information may aid in clinical decision making concerning the choice of antipsychotic medication, particularly in patients who have an increased risk for arrhythmias.

5. Conclusions

We confirmed the statistical effect of chlorpromazine, levomepromazine, and HPDiv on QTc prolongation in a sample of 1017 patients with schizophrenia. Furthermore, statistical evidence for sultopride was obtained for the first time. Furthermore, in the range of the antipsychotic drugs that we examined, the data suggest that SGAs are less likely to produce QTc prolongation than FGAs, which may be useful in guiding the choice of antipsychotic drugs.

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Augmented ST-Segment Elevation During Recovery From Exercise Predicts Cardiac Events in Patients With Brugada Syndrome

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Objectives The goal of this study was to evaluate the prevalence and the clinical significance of ST-segment elevation during recovery from exercise testing.

Background During recovery from exercise testing, ST-segment elevation is reported in some patients with Brugada syndrome (BrS).

Methods Treadmill exercise testing was conducted for 93 patients (91 men), 46 ± 14 years of age, with BrS (22 documented ventricular fibrillation, 35 syncope alone, and 36 asymptomatic); and for 102 healthy control subjects (97 men), 46 ± 17 years of age. Patients were routinely followed up. The clinical end point was defined as the occurrence of sudden cardiac death, ventricular fibrillation, or sustained ventricular tachyarrhythmia.

Results Augmentation of ST-segment elevation ≥0.05 mV in V_1 to V_3 leads compared with baseline was observed at early recovery (1 to 4 min at recovery) in 34 BrS patients (37% [group 1]), but was not observed in the remaining 59 BrS patients (63% [group 2]) or in the 102 control subjects. During 76 ± 38 months of follow-up, ventricular fibrillation occurred more frequently in group 1 (15 of 34, 44%) than in group 2 (10 of 59, 17%; $p = 0.004$). Multivariate Cox regression analysis showed that in addition to previous episodes of ventricular fibrillation ($p = 0.005$), augmentation of ST-segment elevation at early recovery was a significant and independent predictor for cardiac events ($p = 0.007$), especially among patients with history of syncope alone (6 of 12 [50%] in group 1 vs. 3 of 23 [13%] in group 2) and among asymptomatic patients (3 of 15 [20%] in group 1 vs. 0 of 21 [0%] in group 2).

Conclusions Augmentation of ST-segment elevation during recovery from exercise testing was specific in patients with BrS, and can be a predictor of poor prognosis, especially for patients with syncope alone and for asymptomatic patients. (J Am Coll Cardiol 2010;56:1576–84) © 2010 by the American College of Cardiology Foundation

Brugada syndrome (BrS) is recognized as a clinical syndrome that leads to sudden cardiac death (SCD) in middle-aged persons due to ventricular fibrillation (VF) (1). Brugada syndrome is defined by a distinct 12-lead electrocardiogram (ECG) pattern in precordial leads (V_1 to V_3) presenting coved-type ST-segment elevation. Both depolarization and repolarization hypotheses have been reported for the pathogenesis of phenotype in BrS (2–5). Although several indexes have been reported as predictive factors of VF occurrence (6), the recent largest series of BrS patients suggested that there were no reliable predictors of cardiac events except for prior symptoms and spontaneous type 1 ECG (7). However, risk stratification remains disputable, especially for BrS patients without documented VF episodes.

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Autonomic function has been suggested to relate to the occurrence of VF in BrS. It has also been shown that ST-segment elevation in patients with BrS was augmented

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by selective stimulation of muscarinic receptors but mitigated by beta-adrenergic stimulation (8). Heart rate during exercise testing is considered as 1 parameter to evaluate cardiac autonomic function (9). Sympathetic withdrawal and parasympathetic activation occur at early recovery after exercise (10), which are expected to augment ST-segment elevation directly by inhibition of calcium-channel current or by decreasing heart rate (5,11). Two cases of BrS were reported in which ST-segment was augmented during and after exercise (12). Amin et al. (13) recently assessed the ECG responses to exercise in BrS patients with and without *SCN5A* mutations and control subjects. They reported that exercise resulted in an increase of peak J-point amplitude in all groups, including control subjects, and more QRS widening in BrS patients with *SCN5A* mutation. The peak J-point amplitude measured by Amin et al. (13) is thought to represent the depolarization parameter as QRS duration, or at least the combined parameter of both depolarization and repolarization. Therefore, in the present study, we measured several points of ST-segment as a repolarization parameter rather than a depolarization parameter, and tried to investigate the relationship between augmented ST-segment elevation during recovery from exercise testing and prognosis of BrS patients. We also evaluated parasympathetic reactivation by using heart rate recovery (HRR), which is defined as heart rate decay in the first minute after exercise cessation, and its relation with ST-segment change.

Methods

Study population. The study population consisted of 93 consecutive Japanese patients with BrS (91 males; mean age 46 ± 14 years) admitted to the National Cerebral and Cardiovascular Center in Suita, Japan, between 1994 and 2006. Ventricular fibrillation was documented in 22 BrS patients, syncope alone in 35 patients, and the remaining 36 patients were asymptomatic. As control subjects, 102 age-, sex-, and QRS duration-matched healthy subjects were randomly selected from persons who underwent treadmill exercise testing between 2002 and 2007 (97 males; mean age 46 ± 17 years). They included 55 normal subjects with normal QRS duration (<100 ms), 21 with incomplete right bundle branch block (RBBB) (100 ms ≤QRS duration <120 ms), and 26 with complete RBBB (120 ms ≤QRS duration) but without structural heart disease or any ventricular arrhythmias.

Brugada syndrome was diagnosed when a coved ST-segment elevation (≥0.2 mV at J-point) was observed in >1 of the right precordial leads (V_1 to V_3) in the presence or absence of a sodium-channel–blocking agent, and in conjugation with 1 of the following: documented VF, polymorphic ventricular tachycardia, family history of SCD <45 years of age, family history of BrS, inducibility of VF with programmed electrical stimulation, syncope, or an nocturnal agonal respiration (6). Structural heart diseases were carefully excluded by history taking, physical examinations, chest roentgenogram, ECG, and echocardiogram.

Abbreviations and Acronyms

AF = atrial fibrillation
BrS = Brugada syndrome
ECG = electrocardiogram
EPS = electrophysiologic study
HRR = heart rate recovery
ICD = implantable cardioverter-defibrillator
RBBB = right bundle branch block
RVOT = right ventricular outflow tract
SCD = sudden cardiac death
VF = ventricular fibrillation

Clinical, laboratory, electrocardiographic, and electrophysiologic study. The following clinical data were collected: family history of SCD (<45 years of age) or BrS, documented atrial fibrillation (AF), documented VF, syncope, age at the first cardiac event, and implantation of implantable cardioverter-defibrillator (ICD).

A 12-lead ECG was recorded in all 93 BrS patients, and RR interval, PR interval (lead II), QRS duration (lead V_5), corrected QT interval (lead V_2), QRS axis, J-point amplitude (leads V_2), and amplitude of several points of ST-segment (leads V_1, V_2, V_3) were measured.

Signal-averaged ECG was recorded and analyzed in 91 patients by using a signal-averaged ECG system (1200EPX, Arrhythmia Research Technology, Milwaukee, Wisconsin). Three parameters were assessed using a computer algorithm: 1) total filtered QRS duration; 2) root mean square voltage of the terminal 40 ms of the filtered QRS complexes (V_{40}); and 3) duration of low-amplitude signals <40 μV of the filtered QRS complexes (T_{40}). Late potential was considered present when the 2 criteria (V_{40} <18 μV and T_{40} >38 ms) were fulfilled.

Electrophysiologic study (EPS) was performed in 79 BrS patients (21 documented VF patients, 30 syncope alone patients, and 28 asymptomatic patients). A maximum of 3 programmed ventricular extrastimuli were delivered from the right ventricular apex and RVOT, unless VF was induced. No patients received antiarrhythmic drugs before EPS. The atrio-His and His-ventricular intervals were measured during sinus rhythm. The EPS was conducted after all subjects gave written informed consent.

Genetic testing for the presence of an *SCN5A* mutation was also conducted.

Exercise testing. Treadmill exercise testing was conducted in all 93 patients with BrS and 102 control subjects. Neither BrS patients nor control subjects used antiarrhythmic agents. A symptom-limited or submaximal (up to 90% of the age-predicted maximum heart rate) graded treadmill exercise testing similar to modified Bruce protocol was used. All 93 BrS patients and 102 control subjects were in normal sinus rhythm, and none had atrioventricular block at the exercise testing. The standard 12-lead ECGs were recorded at rest, at the end of each exercise stage, at peak exercise, and at every minute during recovery. The amplitude of ST-segment from the isoelectric line at the right precordial leads (V_1 to V_3 leads) and QRS width at V_5 lead were manually measured. The ST-segment point was defined as the point

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where the vertical line from the end point of QRS at V_5 lead intersected the precordial leads. We also measured peak J-point amplitude in lead V_2 as a depolarization parameter, and amplitude of the point, which was 40 and 80 ms later than the peak J-points (ST40, ST80) in lead V_2 as a repolarization parameter. Measurements of ECG parameters were performed as the mean of 3 beats by single electrocardiologist who knew nothing about the patients. Significant augmentation of ST-segment elevation was defined as ST-segment amplitude increase ≥0.05 mV in at least 1 of V_1 to V_3 leads at early recovery (1 to 4 min at recovery) compared with the ST-segment amplitude at baseline (pre-exercise). We also recorded heart rate and blood pressure during exercise testing.

The HRR was defined as decay of heart rate from peak exercise to 1 min at recovery.

Follow-up. Follow-up was started after undergoing treadmill exercise testing. All patients with BrS were routinely followed up at the outpatient clinic of our hospital. The ICD implantation was performed in 63 BrS patients (20 documented VF patients, 25 syncope alone patients, and 18 asymptomatic patients). Antiarrhythmic drugs were prescribed for 7 patients; 2 patients who had episodes of VF but refused implantation of ICD (disopyramide 300 mg daily for 1 patient, and amiodarone 200 mg daily for another patient), 2 patients who had AF (quinidine 300 mg daily), and 3 patients who had previous history of both VF and AF and implanted ICD (quinidine 300 mg daily for 1 patient, amiodarone 200 mg daily for 2 patients).

Cardiac events were defined as SCD or aborted cardiac arrest, and VF or sustained ventricular tachyarrhythmia documented by ICD or ECG recordings.

Statistical analysis. Data were analyzed with Dr. SPSS II for Windows software package (SPSS Inc., Chicago, Illinois). Numeric values are expressed as mean ± SD. The chi-square test, Student *t* test, or 1-way analysis of variance was performed when appropriate to test for statistical differences. All p values <0.05 were considered statistically significant. Event rate curves were plotted according to the Kaplan-Meier method, and were analyzed with the log-rank test. Univariate and multivariate Cox regression were performed to assess whether 7 indexes can be significant and independent predictors of subsequent cardiac events. We used the forward step-wise approach with p to enter a value of 0.05 for multivariate analysis. Augmentation of ST-segment elevation at early recovery, family history of SCD or BrS, spontaneous coved-type ST-segment elevation, presence of *SCN5A* mutation, late potential, VF inducibility during EPS, and previous episodes of VF were included as indexes.

Results

There were no significant differences between 93 BrS patients and 102 control subjects with respect to age at exercise testing, sex, QRS duration (lead V_5), and QTc interval (lead V_2), as summarized in Table 1. The RR interval and PR interval (lead II) were significantly longer in BrS patients than in control subjects.

Table 1 Initial Characteristics of Patients and Control Subjects

	Brugada Patients (n = 93)	Control Subjects (n = 102)	p Value
Age at exercise testing, yrs	46 ± 14	46 ± 17	NS
Sex, male	91 (98%)	97 (95%)	NS
Electrocardiographic characteristics, ms			
RR	952 ± 151	903 ± 140	0.020
PR	178 ± 30	165 ± 24	0.001
QRS duration	98 ± 16	98 ± 20	NS
QTc	416 ± 44	406 ± 30	NS

Values are mean ± SD or n (%).
QTc = corrected QT interval.

Response of ST-segment elevation during treadmill exercise testing. Among 93 BrS patients, significant augmentation of ST-segment elevation mostly associated with coved pattern at early recovery phase was observed in 34 BrS patients (37% [group 1]), but not in the remaining 59 BrS patients (63% [group 2]). Conversely, ST-segment augmentation was never observed in any of the 102 control subjects (34 of 93 [37%] vs. 0 of 102 [0%], $p < 0.0001$). Typical responses of ST-segment amplitudes of 3 groups are shown in Figure 1. Composite data of serial changes of ST-segment amplitude in V_1 and V_2 leads during exercise testing are illustrated in Figure 2A. The serial changes of ST-segment amplitude in V_3 lead showed the same trend (not shown). In group 1, ST-segment amplitude decreased at peak exercise and started to reascend at early recovery, and culminated at 3 min of recovery (Figs. 1A and 2A). In contrast, ST-segment amplitude of group 2 patients and control subjects decreased at peak exercise, and gradually returned to the baseline amplitude rather than showing augmentation (Figs. 1B to 1D and 2A). Significant differences were identified between group 1 and group 2 patients in the ST-segment amplitude in leads V_1 and V_2 from peak exercise to 6 min of recovery, whereas no major differences were observed between group 2 patients and control subjects (Fig. 2A). Composite data of serial changes of peak J-point amplitude, ST40, and ST80 amplitudes are presented in Figure 2B. The peak J-point amplitude and ST40 amplitude during recovery showed the same trend as the ST-segment amplitude in Figure 2A. Significant differences were identified between group 1 and group 2 patients in the peak J-point and ST40 amplitudes from peak exercise to 6 min of recovery. The ST80 amplitude showed significant differences between group 1 and group 2 patients at 2, 3, and 4 min of recovery. At peak exercise, the peak J-point amplitude increased in 34 (37%) of 93 Brugada patients and in 26 (26%) of 102 control subjects, although the ST-segment

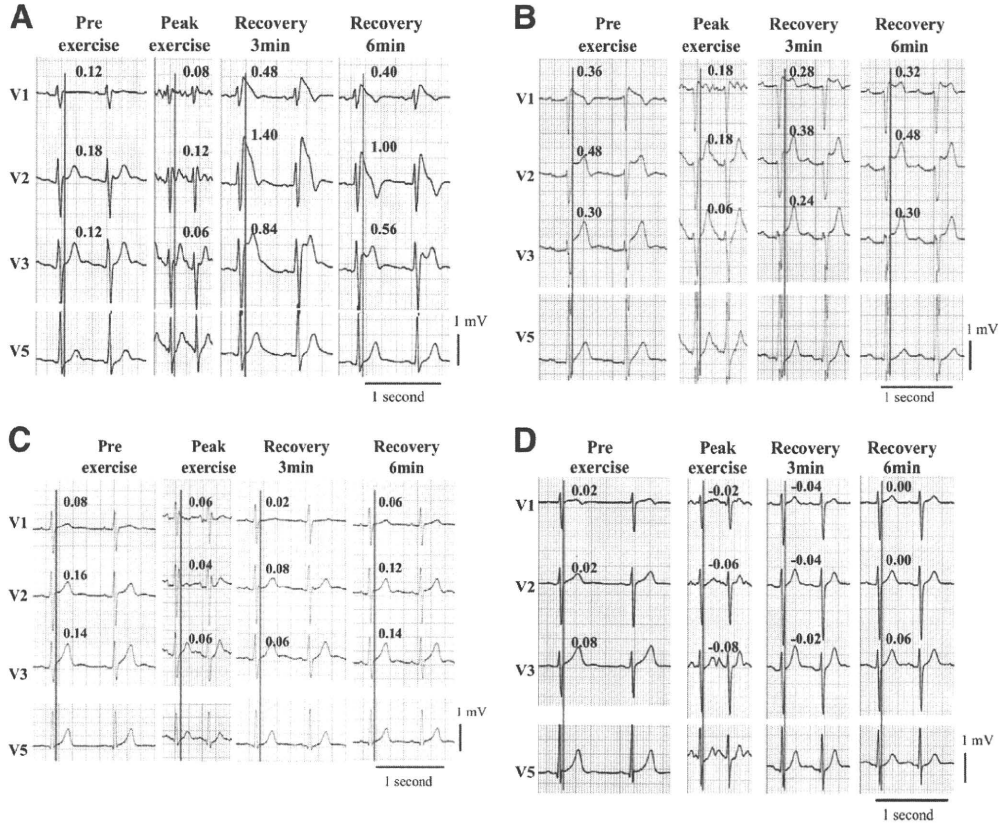

Figure 1 **Typical Responses of ST-Segment Amplitude in Leads V_1, V_2, V_3, and V_5 During Exercise Testing in Brugada Syndrome Patients**

(A) In the group 1 Brugada patient showing saddle-back type ST-segment (lead V_2) at baseline, ST-segment amplitude slightly decreased at peak exercise, but reascended at early recovery (3 min), resulting in typical coved-type ST-segment elevation. **(B, C)** In the group 2 Brugada patient and **(D)** in the control subject, ST-segment amplitude decreased at peak exercise and gradually recovered to the baseline at recovery. It is noteworthy that the peak J-point amplitude in lead V_2 was augmented despite not showing ST-segment augmentation in **A** and **C**. The ST-segment amplitudes are shown as numeric values expressed in millivolts (mV). The **red vertical line** indicates the line from the end point of the QRS interval at electrocardiography lead V_5.

amplitude and ST40 amplitude decreased in most patients of both groups.

Comparison of HRR is shown in Figure 3. The HRR of group 1 patients was significantly larger than that of group 2 patients (32 ± 15 vs. 23 ± 10, p = 0.0007) and control subjects (32 ± 15 vs. 26 ± 10, p = 0.021). The differences of HRR between group 2 patients and control subjects were also statistically significant (23 ± 10 vs. 26 ± 10, p = 0.026).

Although there were no sustained or nonsustained ventricular arrhythmias throughout exercise testing, single premature ventricular complexes were observed during exercise in 8 of the group 1 patients and in 11 of the group 2 patients, and at recovery in 10 of the group 1 patients and in 9 of the group 2 patients. There were no significant differences between groups 1 and 2 in incidences of premature ventricular complexes.

Clinical, laboratory, electrocardiographic, and electrophysiologic characteristics. Comparison of the clinical, laboratory, electrocardiographic, and electrophysiologic characteristics between groups 1 and 2 patients are shown in Table 2. There were no significant differences in these characteristics between groups 1 and 2 except for the presence of *SCN5A* mutation and late potential (*SCN5A* mutation, 17% vs. 5%, p = 0.048; late potential, 82% vs. 53%, p = 0.004).

Follow-up. The mean follow-up period for the 93 BrS patients was 75.7 ± 38.4 months. During follow-up, 25 of all 93 BrS patients (27%) had cardiac events, and the incidence of cardiac events was significantly higher in group 1 than in group 2 patients (44% vs. 17%, p = 0.004). The period from exercise testing to cardiac events ranged from 1 to 78 months (median 12 months). One patient in group 2, who refused implantation of ICD and was taking disopyr-

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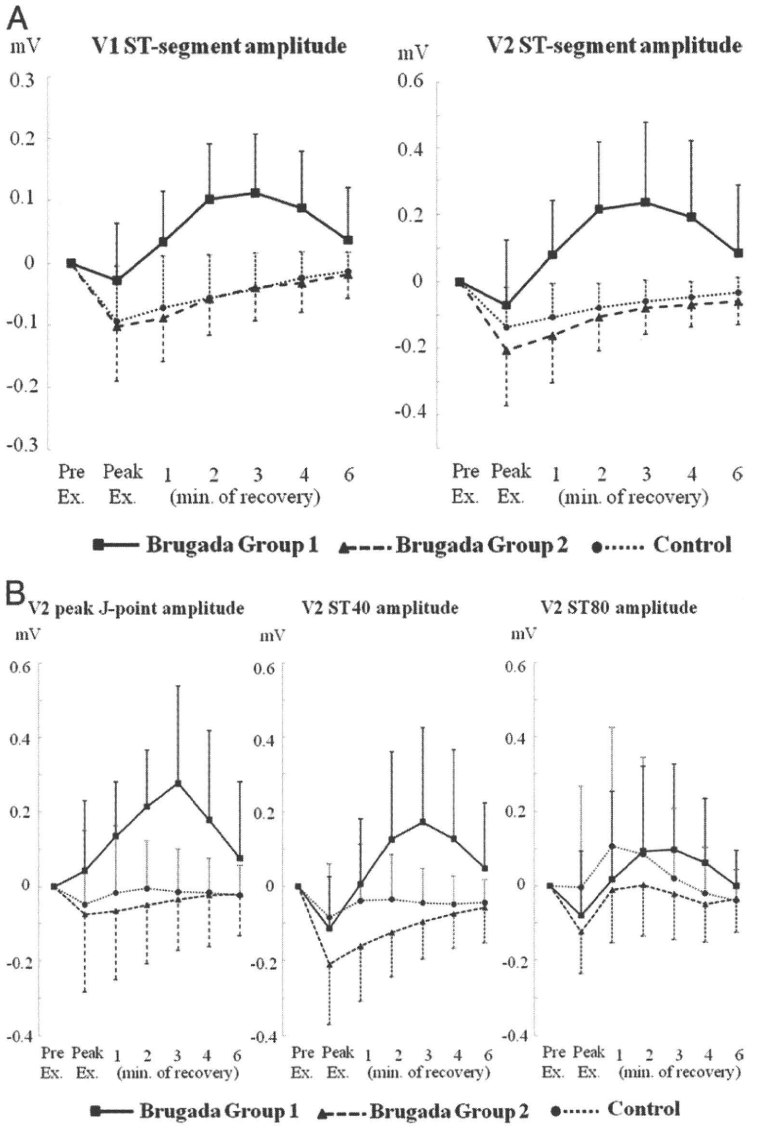

Figure 2 **Composite Data of Serial Changes of ST-Segment Amplitude**

(A) Composite data of serial changes of ST-segment amplitude in lead V_1 **(left)** and lead V_2 **(right)** during exercise (Ex.) testing in group 1 Brugada syndrome patients **(squares)** and group 2 Brugada syndrome patients **(triangles)**, and in control subjects **(circles)**. **(B)** Peak J-point amplitude **(left)**, ST40 amplitude **(middle)**, and ST80 amplitude **(right)** in lead V_2. The ST-segment amplitude decreased at peak exercise and started to reascend at early recovery, and culminated at 3 min of recovery in group 1 Brugada patients. In the group 2 Brugada patients and control subjects, the ST-segment amplitude decreased at peak exercise and gradually recovered to the baseline level during recovery. The peak J-point amplitude and ST40 amplitude during recovery showed the same trend as the ST-segment amplitude. Since ST80 amplitude was influenced by T wave, especially at rapid heart rate, the trends of the 3 groups were somewhat different from ST-segment amplitude or ST40 amplitude. The ST-segment amplitudes are shown as values compared to pre-exercise ST-segment amplitudes. $p < 0.05$.

amide 300 mg daily, died of VF. Three of 7 patients with medication had cardiac events, including 1 death.

Predictors of outcome. Kaplan-Meier analysis demonstrated significant differences in the time to the first cardiac event depending on the presence of ST-segment augmentation during recovery from exercise (Fig. 4A). Group 1 patients had a significantly higher cardiac event rate than group 2 patients (log-rank, $p = 0.0029$). Previous history of VF (Fig. 4B) and positive *SCN5A* mutation (Fig. 4C) also had significant values for occurrence of subsequent cardiac events ($p = 0.0013$ and $p = 0.028$, respectively); however, spontaneous coved-type ST-segment elevation did not predict cardiac events ($p =$

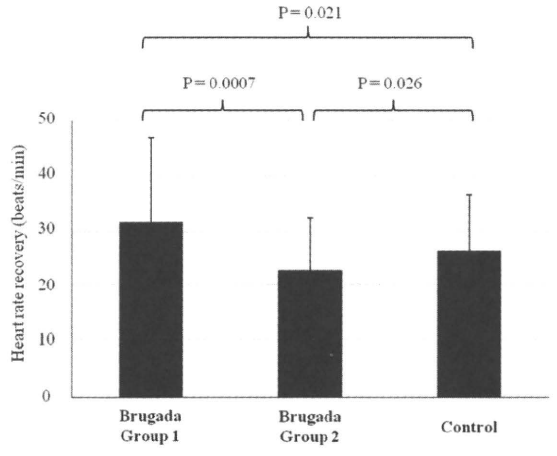

Figure 3 **Comparison of HRR After Exercise Cessation**

Comparison of heart rate recovery (HRR) 1 min after exercise cessation among Brugada syndrome patients of groups 1 and 2 and control subjects. The HRR in group 1 patients was significantly larger than that in group 2 (32 ± 15 beats/min vs. 23 ± 10 beats/min, p = 0.0007) and in control subjects (32 ± 15 beats/min vs. 26 ± 10 beats/min, p = 0.021). The differences of HRR between group 2 patients and control subjects were also significant (23 ± 10 beats/min vs. 26 ± 10 beats/min, p = 0.026).

0.068) (Fig. 4D). The results of Cox regression analysis are shown in Table 3. In univariate analysis, indexes predictive of cardiac events were previous episodes of VF (p = 0.003), ST-segment augmentation at early recovery (group 1; p = 0.005), and presence of *SCN5A* mutation (p = 0.037). In multivariate Cox regression analysis, previous episodes of VF and ST-segment augmentation at early recovery were significant and independent predictors of subsequent cardiac events (p = 0.005 and p = 0.007, respectively).

The incidence of cardiac events during follow-up in the subgroups according to symptoms before exercise testing is shown in Table 4. In the subgroup of 35 BrS patients with syncope alone, group 1 had a significantly higher cardiac event rate than group 2 (log-rank, 6 of 12 [50%] vs. 3 of 23 [13%], p = 0.016). Of note, among 36 asymptomatic patients, only 3 patients (9%) in group 1 experienced cardiac events. The log-rank test also demonstrated higher cardiac event risk in group 1 compared with group 2 (3 of 15 [20%] vs. 0 of 21 [0%], p = 0.039).

Discussion

The major findings of the present study were the following: 1) 37% of BrS patients showed ST-segment augmentation at early recovery during exercise testing; 2) ST-segment augmentation at early recovery was specific in BrS patients, and was significantly associated with a higher cardiac event rate, notably for patients with previous episode of syncope or for asymptomatic patients; and 3) BrS patients with ST-segment augmentation at early recovery showed significantly larger HRR. This is the first systematic report on the relationship between ST-segment augmentation during recovery from exercise and prognosis for BrS patients.

Augmentation of ST-segment elevation and possible mechanism. It is well known that autonomic function influences an extent of ST-segment elevation in BrS (8). The ST-segment elevation is mitigated by administration of β-adrenergic agonists and is enhanced by parasympathetic agonists such as acetylcholine in experimental and clinical investigations (5,14–16). Parasympathetic reactivation is thought to occur at early recovery after treadmill exercise testing, especially in the first minute after cessation of exercise (10,17). In the present study, we measured the ST-segment amplitude as a repolarization parameter rather than a depolarization parameter, and evaluated HRR to investigate the correlation between ST-segment augmentation and parasympathetic activity (9,18). The BrS patients who had ST-segment augmentation had significantly larger HRR compared with patients who did not, suggesting that the ST-segment augmentation was closely related to higher parasympathetic activity. However, it is still unclear whether ST-segment augmentation observed in the 34 BrS patients was simply due to more increased parasympathetic activity or to more increased susceptibility (hypersensitivity) to the parasympathetic reactivation.

Conversely, the *SCN5A* mutation was more frequently identified in group 1. Scornik et al. (19) reported that *SCN5A* mutation can accentuate parasympathetic activity toward the heart directly. It was also reported that specific mutations in the *SCN5A* gene may lead to augmentation of J-point amplitude or ST-segment amplitude during beta-adrenergic stimulation (20,21). Veldkamp et al. (20) demonstrated that a specific *SCN5A* mutation, 1795insD, augments slow inactivation, and delays recovery of sodium channel availability, thus reducing the sodium current and resulting in augmented peak J-point amplitude at rapid heart rate. Increased body temperature induced by exercise can be a risk of life-threatening arrhythmias in patients with BrS (22). A specific *SCN5A* missense mutation, T1620M, was reported to cause a faster decay of the sodium channel but slower recovery from inactivation, resulting in increased ST-segment elevation in precordial leads at higher temperatures during exercise. Although Amin et al. (13) reported that exercise induced augmentation of peak J-point amplitude, a depolarization parameter or at least combined parameter of both depolarization and repolarization, in all subjects tested, the incidence of increase in the peak J-point amplitude at peak exercise was lower (37%) in our Brugada patients. This is probably in part because only 9 (10%) of our 93 BrS patients had the *SCN5A* mutation. We could not identify significant differences in HRR, QRS duration, peak J-point amplitude (lead V_2), and ST-segment amplitude (leads V_1, V_2, V_3) at peak exercise between patients with and without *SCN5A* mutation (not shown), and that may be also due to the small number of BrS patients with *SCN5A* mutation.

Risk stratification in BrS. Implantation of an ICD is a first line of therapy for secondary prevention in patients with BrS who exhibited previous history of VF. The American College

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Table 2 Clinical, Laboratory, Electrocardiographic, and Electrophysiologic Characteristics and Long-Term Follow-Up of Groups 1 and 2 Brugada Syndrome Patients

Characteristic	Group 1 (n = 34)	Group 2 (n = 59)	p Value
Clinical characteristics			
Age at exercise testing, yrs	42 ± 11	48 ± 15	NS
Men	34 (100%)	57 (97%)	NS
Family history of SCD at age <45 yrs or Brugada syndrome	7 (21%)	16 (27%)	NS
Documented AF	7 (21%)	12 (20%)	NS
Documented VF before exercise testing	7 (21%)	15 (25%)	NS
Syncope alone before exercise testing	12 (35%)	23 (39%)	NS
Asymptomatic before exercise testing	15 (44%)	21 (36%)	NS
Age at first cardiac event, yrs.	42 ± 13	45 ± 15	NS
ICD implantation	25 (74%)	38 (64%)	NS
Laboratory characteristics			
SCN5A mutation	6 (17%)	3 (5%)	0.048
Electrocardiographic characteristics			
RR, ms	951 ± 170	953 ± 140	NS
PR, ms	184 ± 28	175 ± 31	NS
QRS, ms	98 ± 14	98 ± 17	NS
QTc, ms	418 ± 46	415 ± 43	NS
ST-segment amplitude (mV) at baseline			
V_1	0.14 ± 0.09	0.16 ± 0.12	NS
V_2	0.41 ± 0.22	0.38 ± 0.26	NS
V_3	0.22 ± 0.13	0.19 ± 0.14	NS
Spontaneous coved-type ST-segment elevation in right precordial leads	30 (88%)	43 (73%)	NS
Signal-averaged electrocardiogram			
TfQRS, ms	122 ± 15	118 ± 17	NS
Late potential	28/34 (82%)	30/57 (53%)	0.004
Premature ventricular complexes during exercise	8 (24%)	11 (19%)	NS
Premature ventricular complexes at recovery	10 (29%)	9 (15%)	NS
Electrophysiologic characteristics			
AH interval, ms	107 ± 24	98 ± 27	NS
HV interval, ms	45 ± 8	44 ± 11	NS
Induction of VF	26/31 (84%)	33/47 (70%)	NS
Follow-up			
Cardiac events	15 (44%)	10 (17%)	0.004
Follow-up period, months	74.1 ± 42.2	76.5 ± 36.4	NS

AF = atrial fibrillation; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; TfQRS = total filtered QRS duration; VF = ventricular fibrillation; other abbreviations as in Table 1.

of Cardiology/American Heart Association/Heart Rhythm Society guidelines refer to BrS patients who have had syncope as having Class IIa indication for ICD therapy (23). However, there is still much room for argument with respect to treatments for patients who have had only syncope, and for asymptomatic patients (24–28). Although inducibility of VF during EPS (25,26), family history of SCD (24), spontaneous type 1 ECG (25,27), and late potential (28) have been proposed as predictors of cardiac events, the availability of these indexes remains controversial (7,29).

In the present study, a previous episode of VF (or aborted cardiac arrest) was the strongest predictor of subsequent cardiac events, as in previous studies (7,30,31). Moreover, ST-segment augmentation at early recovery during exercise testing was a significant and independent predictor of subsequent cardiac events in the present study. The results suggested that parasympathetic activity plays an important role in both ST-segment augmentation and subsequent cardiac events. As previously noted, it remains unclear that the cause of ST-segment augmentation in our 34 patients was a result of more increased parasympathetic activity or of more increased susceptibility of the patients to the increased parasympathetic reactivation.

Study limitations. First, BrS patients were confined to those who were hospitalized in our hospital for close investigation. That indicates these patients can be biased toward relatively high risk. Second, the present study is based on data from a small population of 93 patients; hence, it was not sufficient to evaluate the prognosis, and there also was a small number of events. Although we adopted a step-wise approach, the limited number of events can lessen the precision of the consequences for multivariate Cox regression analysis.

Conclusions

The presence of *SCN5A* mutation was a significant predictor of subsequent cardiac events by univariate Cox regression analysis. However, multivariate Cox regression analysis showed it was not a significant predictor of prognosis.

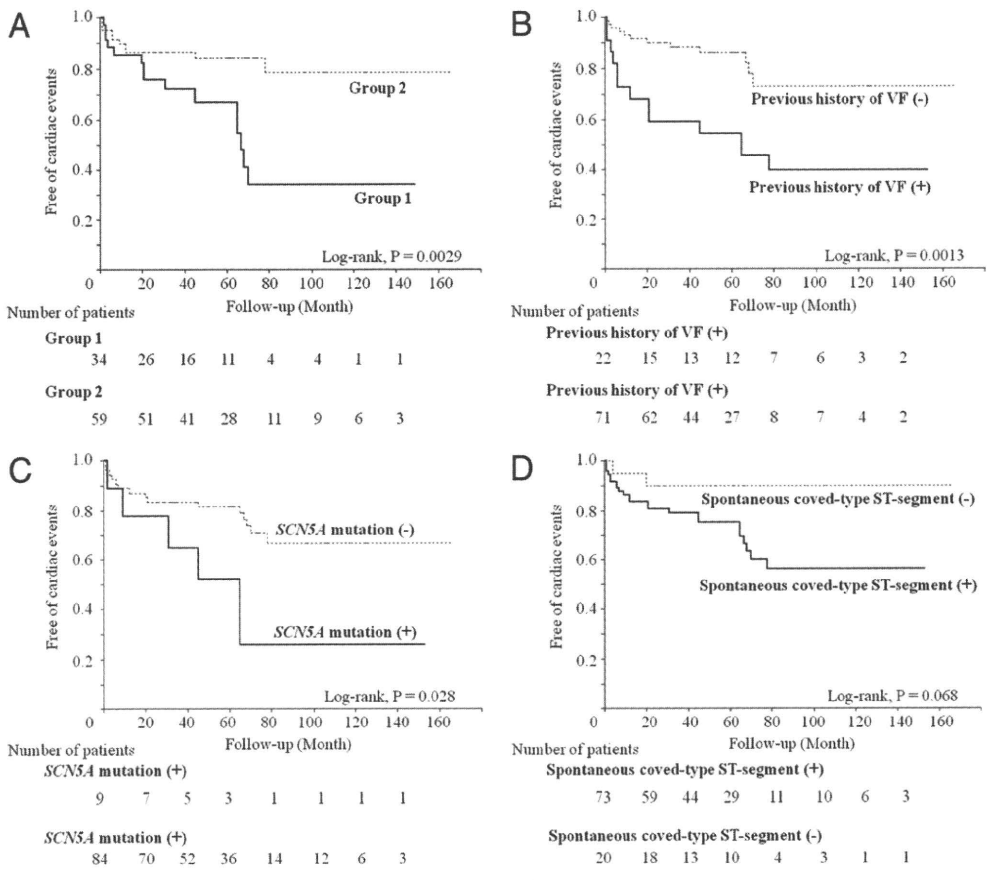

Figure 4 Kaplan-Meier Analysis of Cardiac Events During Follow-Up

Kaplan-Meier analysis of **(A)** cardiac events during follow-up, depending on patterns in response to ST-segment elevation during exercise test (groups 1 and 2), **(B)** incidence of previous episode of ventricular fibrillation (VF), **(C)** *SCN5A* mutation, and **(D)** spontaneous coved-type ST-segment elevation. Group 1 Brugada patients had a significantly higher cardiac event rate than did group 2 Brugada patients (log-rank, p = 0.0029). Brugada patients with previous episodes of VF or with *SCN5A* mutation had significantly greater values for occurrence of subsequent cardiac events than did patients without VF episodes or *SCN5A* mutation (p = 0.0013, p = 0.028, respectively), whereas spontaneous coved-type ST-segment elevation in Brugada patients did not predict cardiac events compared with patients not having such ST-segment elevation (p = 0.068).

Further study with a larger number of BrS patients will be required to evaluate the significance of the index as a predictor of subsequent cardiac events.

As for BrS patients with only syncope, subsequent cardiac events occurred in 50% (6 of 12) patients who exhibited ST-segment augmentation at early recovery. Asymptomatic

Table 3 Predictive Capabilities of Cardiac Events

		Univariate Analysis		Multivariate Analysis	
	Positive, n (%)	HR (95% CI)	p Value	HR (95% CI)	p Value
Previous episodes of VF	22 (24%)	3.40 (1.54–7.53)	0.003	3.25 (1.43–7.37)	0.005
Augmentation of ST-segment elevation at early recovery phase	34 (37%)	3.17 (1.42–7.09)	0.005	3.17 (1.37–7.33)	0.007
SCN5A mutation	9 (10%)	2.86 (1.07–7.66)	0.037		
Spontaneous coved-type ST-segment	72 (77%)	3.51 (0.83–14.9)	0.089		
Late potential	58/91 (64%)	2.25 (0.84–5.99)	0.11		
VF inducible in EPS	59/78 (76%)	0.73 (0.30–1.75)	0.48		
Family history of SCD or BrS	23 (25%)	1.19 (0.47–3.02)	0.72		

BrS = Brugada syndrome; CI = confidence interval; EPS = electrophysiologic study; HR = hazard ratio; other abbreviations as in Table 2.

Table 4 Incidence of Cardiac Events According to Symptoms Before Exercise Testing

Type	n	Treadmill Exercise Test	n	VF Occurrence	p Value (vs. Group 1)
Documented VF	22	Group 1	7	6 (86%)	
		Group 2	15	7 (47%)	0.14
Syncope alone	35	Group 1	12	6 (50%)	
		Group 2	23	3 (13%)	0.016
Asymptomatic	36	Group 1	15	3 (20%)	
		Group 2	21	0 (0%)	0.039

The p value was calculated according to the log-rank test.
VF = ventricular fibrillation.

patients who had ST-segment augmentation at early recovery had a higher incidence of cardiac events than patients who did not. These data suggested the potential utility of exercise testing to predict cardiac events for patients with BrS who have had previous episodes of only syncope but not VF or who have had no symptoms.

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Key Words: Brugada syndrome ■ exercise testing ■ ST-segment elevation.

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Risk for Life-Threatening Cardiac Events in Patients With Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals

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Objectives This study was designed to assess the clinical course and to identify risk factors for life-threatening events in patients with long-QT syndrome (LQTS) with normal corrected QT (QTc) intervals.

Background Current data regarding the outcome of patients with concealed LQTS are limited.

Methods Clinical and genetic risk factors for aborted cardiac arrest (ACA) or sudden cardiac death (SCD) from birth through age 40 years were examined in 3,386 genotyped subjects from 7 multinational LQTS registries, categorized as LQTS with normal-range QTc (≤440 ms [n = 469]), LQTS with prolonged QTc interval (>440 ms [n = 1,392]), and unaffected family members (genotyped negative with ≤440 ms [n = 1,525]).

Results The cumulative probability of ACA or SCD in patients with LQTS with normal-range QTc intervals (4%) was significantly lower than in those with prolonged QTc intervals (15%) ($p < 0.001$) but higher than in unaffected family members (0.4%) ($p < 0.001$). Risk factors ACA or SCD in patients with normal-range QTc intervals included mutation characteristics (transmembrane-missense vs. nontransmembrane or nonmissense mutations: hazard ratio: 6.32; $p = 0.006$) and the LQTS genotypes (LQTS type 1:LQTS type 2, hazard ratio: 9.88; $p = 0.03$; LQTS type 3:LQTS type 2, hazard ratio: 8.04; $p = 0.07$), whereas clinical factors, including sex and QTc duration, were associated with a significant increase in the risk for ACA or SCD only in patients with prolonged QTc intervals (female age >13 years, hazard ratio: 1.90; $p = 0.002$; QTc duration, 8% risk increase per 10-ms increment; $p = 0.002$).

Conclusions Genotype-confirmed patients with concealed LQTS make up about 25% of the at-risk LQTS population. Genetic data, including information regarding mutation characteristics and the LQTS genotype, identify increased risk for ACA or SCD in this overall lower risk LQTS subgroup. (J Am Coll Cardiol 2011;57:51–9) © 2011 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ACA = aborted cardiac arrest
ECG = electrocardiographic
LQTS = long-QT syndrome
LQT1 = long-QT syndrome type 1
LQT2 = long-QT syndrome type 2
LQT3 = long-QT syndrome type 3
QTc = corrected QT interval
SCD = sudden cardiac death

Congenital long-QT syndrome (LQTS) is an inherited channelopathy characterized by a prolonged corrected QT interval (QTc) at rest that is associated with an increased predisposition for polymorphic ventricular arrhythmias and sudden cardiac death (SCD) in young subjects without structural heart disease (1). To date, more than 500 mutations have been identified in 12 LQTS-susceptibility genes, with the long-QT syndrome type 1 (LQT1), long-QT syndrome type 2 (LQT2), and long-QT syndrome type 3 (LQT3) genotypes constituting more than 95% of genotype-positive LQTS and approximately 75% of all LQTS (2). Risk assessment in affected patients with LQTS relies primarily on a constellation of electrocardiographic (ECG) and clinical factors, including QTc interval and age-sex interactions (3–6). In addition, there is increasing evidence that genetic information and the molecular and cellular properties of the LQTS-causative mutation may identify subjects with increased risk for cardiac events (7–10). Despite these recent advances, however, currently there are limited data regarding the clinical course and risk factors for life-threatening events in patients with LQTS with normal resting QTc values, so-called silent mutation carriers, concealed LQTS, or normal–QT interval LQTS.

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In the present study we used combined data from 7 national LQTS registries to: 1) compare the clinical courses of patients with LQTS and normal-range QTc intervals to those of patients with prolonged QTc intervals and of genotype-negative unaffected family members; and 2) identify specific clinical and genetic risk factors for life-threatening cardiac events in patients with LQTS with normal-range QTc intervals.

Methods

Study population. The study population comprised 3,386 genotyped subjects drawn from the Rochester, New York, enrolling center (center 1) of the International LQTS Registry (n = 2,630), the Netherlands LQTS Registry (n = 391), and the Japanese LQTS Registry (n = 205), as well as from data submitted by other investigators specifically for this collaborative mutation analysis project from Denmark (n = 90), Italy (n = 28), Israel (n = 25), and Sweden (n = 17). Patients were derived from 552 proband-identified *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) families. The proband in each family had otherwise unexplained, diagnostic QTc prolongation or experienced LQTS-related symptoms. Patients were excluded from the study if they had: 1) >1 LQTS identified mutation (n = 70); 2) Jervell and Lange-Nielsen syndrome with deafness and 2 *KCNQ1* mutations or 1 known *KCNQ1* mutation and congenital deafness (n = 2); and 3) no identified mutation on genetic testing with prolonged QTc interval (>440 ms [n = 428]).

Data collection and end point. Routine clinical and rest ECG parameters were acquired at the time of enrollment in each of the registries. Measured parameters on the first recorded electrocardiogram included QT and R-R intervals in milliseconds, with QT interval corrected for heart rate using Bazett's (11) formula. Clinical data were collected on prospectively designed forms with information on demographic characteristics, personal and family medical histories, ECG findings, therapies, and events during long-term follow-up. Data common to all LQTS registries involving genetically tested subjects were electronically merged into a common database for the present study. In addition, information regarding QT interval–prolonging medications and triggers for cardiac events was collected through a specific questionnaire for patients enrolled the U.S. portion of the registry.

The primary end point of the study was the occurrence of a first life-threatening cardiac event, comprising aborted cardiac arrest (ACA; requiring external defibrillation as part of the resuscitation or internal defibrillation in patients with implantable cardioverter-defibrillators) or LQTS-related SCD (abrupt in onset without evident cause, if witnessed, or death that was not explained by any other cause if it occurred in a nonwitnessed setting such as sleep). In the multivariate models, follow-up was censored at age 41 years to avoid the influence of coronary disease on the occurrence of cardiac events. We also evaluated a secondary end point that included the occurrence of a first cardiac event of any type during follow-up (comprising syncope [defined as transient loss of consciousness that was abrupt in onset and offset], ACA, or SCD).

Phenotype characterization. For the purpose of this study, the QTc interval was categorized as normal range (≤440 ms) or prolonged (>440 ms) according to accepted criteria for the phenotypic definition of LQTS (12). Using this definition, the study population were categorized into 3 genotype and QTc subgroups: 1) LQTS with normal-range QTc interval (n = 469), comprising patients identified to have LQT1 to LQT3 mutations with QTc intervals ≤440 ms; 2) LQTS with prolonged QTc interval (n = 1,392), comprising patients with LQT1 to LQT3 mutations with QTc intervals >440 ms; and 3) unaffected family members (n = 1,525), comprising registry subjects from genotype-positive proband-identified families who were genetically tested and found to be negative for the LQTS-associated mutation, with QTc intervals ≤440 ms (i.e., genetically and phenotypically unaffected family members).

Genotype characterization. The *KCNQ1*, *KCNH2*, and *SCN5A* mutations were identified with the use of standard genetic tests performed in academic molecular genetics laboratories, including the Functional Genomics Center, University of Rochester Medical Center, Rochester, New York; Baylor College of Medicine, Houston, Texas; Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, Minnesota; Boston Children's Hospital, Boston, Massachusetts; the Laboratory of Molecular Genetics, National Cardiovascular Center, Suita, Japan; the Department of Clinical Genetics, Academic Medical Center, Amsterdam, the Netherlands; and the Molecular Cardiology Laboratory, Policlinico S. Matteo and University of Pavia, Pavia, Italy.

Genetic alterations of the amino acid sequence were characterized by location and by the type of the specific mutation. The transmembrane region of each of the 3 LQTS channels was defined as: 1) amino acid residues from 120 through 355 in the *KCNQ1*-encoded Kv7.1 channel (S1 to S6 region); 2) amino acid residues from 398 through 657 (S1 to S6 region) in the *KCNH2*-encoded Kv11.1 channel; and 3) amino acid residues 129 through 417, 713 through 940, 1201 through 1470, and 1523 through 1740 in the *SCN5A*-encoded Nav1.5 channel (13). On the basis of prior studies that demonstrated the functional and clinical importance of missense mutations that are located in the transmembrane region of these LQTS-associated channels (9,10), mutation categories were pre-specified in the primary analysis as transmembrane-missense (mutations of the missense type in any of the 3 transmembrane regions described previously) versus nontransmembrane or nonmissense (i.e., any other identified LQT1 to LQT3 mutation that was not transmembrane-missense).

Statistical analysis. The clinical characteristics of study patients were compared by genotype and QTc categories using chi-square tests for categorical variables and *t* tests and Mann-Whitney-Wilcoxon tests for continuous variables. The Kaplan-Meier estimator was used to assess the time to a first life-threatening event and the cumulative event rates by risk groups and risk factors, and groups were compared using the log-rank test.

Cox proportional hazards regression analysis was carried out in the total study population and separately in the subset of patients with genotype-positive LQTS. Pre-specified covariates in the total population model included the 3 genotype and QTc categories, sex, and time-dependent beta-blocker therapy. The models comprising genotype-positive patients included the following pre-specified covariates: QTc category (normal range [≤440 ms] vs. prolonged [>440 ms]), the LQT1 to LQT3 genotypes, mutation location and type, sex, QTc duration (assessed both as a continuous measure [per 10-ms increase] and as a categorical covariate [dichotomized at the median value of each QTc category and assessed in separate models]), time-dependent beta-blocker therapy, and a family history of SCD in a first-degree relative. The effect of each covariate on outcome in each QTc category (i.e., in patients with LQTS with normal-range and prolonged QTc intervals) was assessed using interaction-term analysis, with interactions tested 1 at a time. Estimates of predictor hazard ratios in the separate normal and prolonged QTc categories were obtained using these interactions. To avoid violation of the proportional hazards assumption due to sex-risk crossover during adolescence, we used an age-sex interaction term in the multivariate models.

Because almost all the subjects were first-degree and second-degree relatives of probands, the effect of lack of independence between subjects was evaluated in the Cox model with grouped jackknife estimates for family membership (14). All grouped jackknife standard errors for the covariate risk factors fell within 3% of those obtained from the unadjusted Cox model, and therefore only the Cox model findings are reported. The statistical software used for the analyses was SAS version 9.20 (SAS Institute Inc., Cary, North Carolina). A 2-sided significance level of 0.05 was used for hypothesis testing.

Results

The spectrum and number of LQT1-associated, LQT2-associated, and LQT3-associated mutations by the pre-specified location and type categories are presented in Online Table 1. Totals of 100, 177, and 41 different mutations were identified in the *KCNQ1*-encoded Kv7.1, *KCNH2*-encoded Kv11.1, and *SCN5A*-encoded Nav1.5 ion channels, respectively. Study patients with identified LQTS mutations exhibited a very wide QTc interval distribution (Fig. 1), ranging from a minimum of 350 ms to a maximum of 800 ms (mean 450 ± 56 ms; median 440 ms; interquartile range: 410 to 480 ms). QTc distribution was similar among the 3 LQTS genotypes. Four hundred sixty-nine LQTS mutation–positive patients exhibited normal-range QTc intervals, constituting 25% of identified cases.

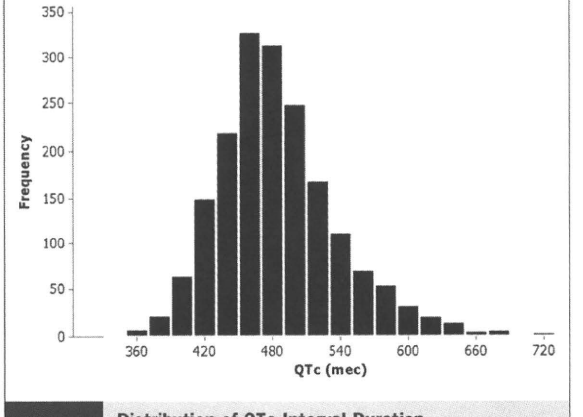

Figure 1 **Distribution of QTc Interval Duration in Genotype-Positive Patients With LQTS**

Distribution of corrected QT (QTc) interval durations in genotype-positive study patients. LQTS = long-QT syndrome.