Table 2 Clinical characteristics of LQTS patients with gene mutations

	Compound mutations (N=35)	Single mutations (N=568)	p value
Demographic			
Age at diagnosis (yrs)	19 ± 14 [15, 9–27]	28 ± 19 [22, 12–42]	0.001
Female gender	23 (66%)	330 (58%)	0.394
Proband	26 (74%)	284 (50%)	0.005
Family members	9 (26%)	284 (50%)	0.005
Cardiac events			
cardiac events in all age groups			
Age at first cardiac event (yrs)	10 ± 8 [11, 3.5–13.5]	18 ± 16 [12, 7–19]	0.043
syncope	19 (54%)	235 (41%)	0.161
TdP	10 (29%)	102 (18%)	0.136
cardiac arrest or VF	3 (9%)	44 (8%)	0.748
sudden death	0 (0%)	4 (1%)	1.000
cardiac events before 40 yrs			
syncope or TdP	19 (54%)	205 (37%)	0.043
cardiac arrest or VF	3 (9%)	37 (7%)	0.500
ECG measurements			
RR interval (ms)	866 ± 210	914 ± 174	0.252
corrected QT (ms)	510 ± 56	478 ± 53	0.001
corrected QT >500 ms (%)	23 (66%)	122 (26%)	<0.001
corrected QT <440 ms (%)	3 (9%)	91 (20%)	0.351
corrected QT peak (ms)	385 ± 70	384 ± 50	0.906
corrected QT peak-end (ms)	121 ± 73	95 ± 41	0.081
notched T wave	11 (31%)	200 (37%)	0.540
T-wave alternans	0 (0%)	30 (5%)	0.246
Diagnosis			
Schwartz score	4.2 ± 2.1	3.4 ± 1.9	0.017
Schwartz score ≧4	21 (70%)	219 (47%)	0.026
Therapy			
β-blocker	10 (56%)	175 (33%)	0.006
class Ib antiarrhythmic drugs	3 (9%)	53 (10%)	1.000
pacemaker	1 (3%)	15 (3%)	1.000
sympathectomy	1 (3%)	3 (1%)	0.218
defibrillator	1 (3%)	32 (6%)	0.712

TdP = torsades de pointes, VF = ventricular fibrillation, NS = not significant, corrected QT = QT interval corrected for heart rate with Bazett formula [A, B], A = median, B–C = first interquartile range–third interquartile range.

D85N polymorphism as the "second hit" (Table 1).[11,26] In all age groups of this study, the incidence of cardiac events, such as torsades de pointes or syncope, was similar between single and compound mutation carriers; however, the clinical phenotypes of those with compound mutations before 40 years of age were more serious than in those with a single mutation (Table 2). Thus, phenotypes with compound mutations appear to be more serious than single mutation carriers, regardless of race.

Beta-blocker therapy is first-line treatment for the prevention of cardiac events in LQTS. Beta-blockers have been shown to significantly reduce cardiac events in LQTS patients, especially LQT1 type.[27–29] However, patients with LQT2 or LQT3 have been reported to be less responsive to beta-blocker therapy[27,30] and may require additional therapy, such as pacemaker implantation for LQT2 or a Class Ib antiarrhythmic drug for LQT3. It may be recommended that patients with compound mutations receive additional individual therapy based on their LQTS subtype, for example, the combination of beta-blocker and Class Ib antiarrhythmic drugs for patients with LQT1 and LQT3. In patients who were first diagnosed as LQT1, Kobori et al[31] reported that additional mutations in different LQTS-related genes influenced phenotype severity and reduced beta-blocker effectiveness. Previous reports showed that approximately 20% of LQT1 patients were resistant to beta-blocker therapy. Additional or "latent" mutations may be present in these patients, and conducting a survey for major all LQTS-related genes, even after a possible mutation is identified, is critically important.

Family study analyses are of enormous importance because single mutation carriers in this study tended to have mild phenotypes. Most of the single mutation carriers in families of compound probands remained asymptomatic. However, double hits of these "latent" gene carriers could cause more serious phenotypes.[32,33] Jervell and Lange-Nielsen syndrome is a well-documented LQTS phenotype with an autosomal recessive pattern. The loss of function of I_{Ks} on both alleles generally causes not only more severe clinical phenotypes but also deafness.[9,10] In our study, two of three probands with double *KCNQ1* mutations had no deafness. We speculate that these mutations would functionally cause mild changes without complete loss of I_{Ks}. Westenskow et al[11] reported the molecular mechanism of

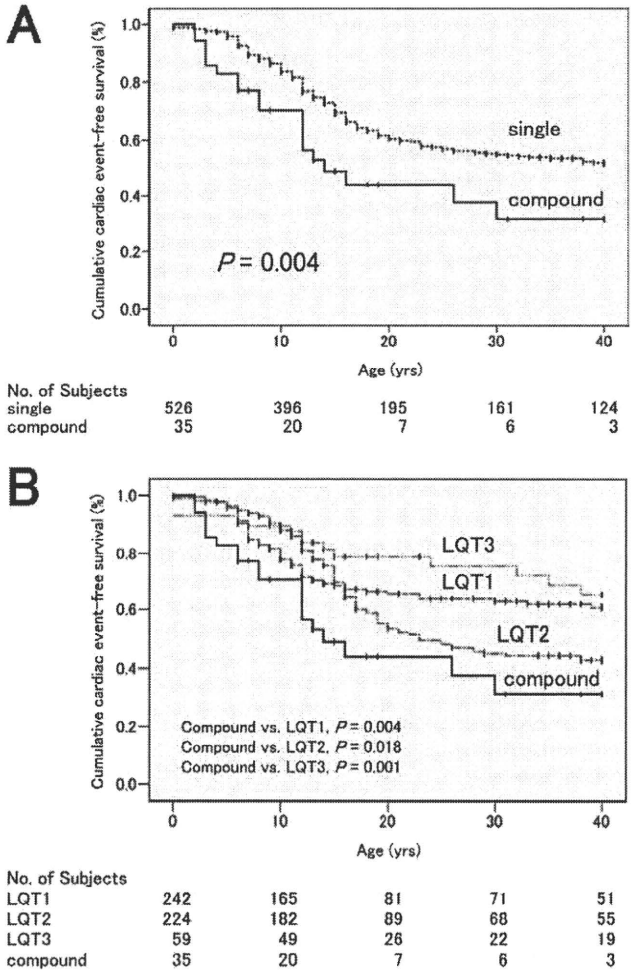

Figure 4 Kaplan-Meier cumulative probability of cardiac event-free survival from birth to age 40 years and before therapy. **A:** Comparison between patients with a single mutation and compound mutations. **B:** Comparison among patients with long QT syndrome type 1 (LQT1), type 2 (LQT2), type 3 (LQT3), and compound mutations.

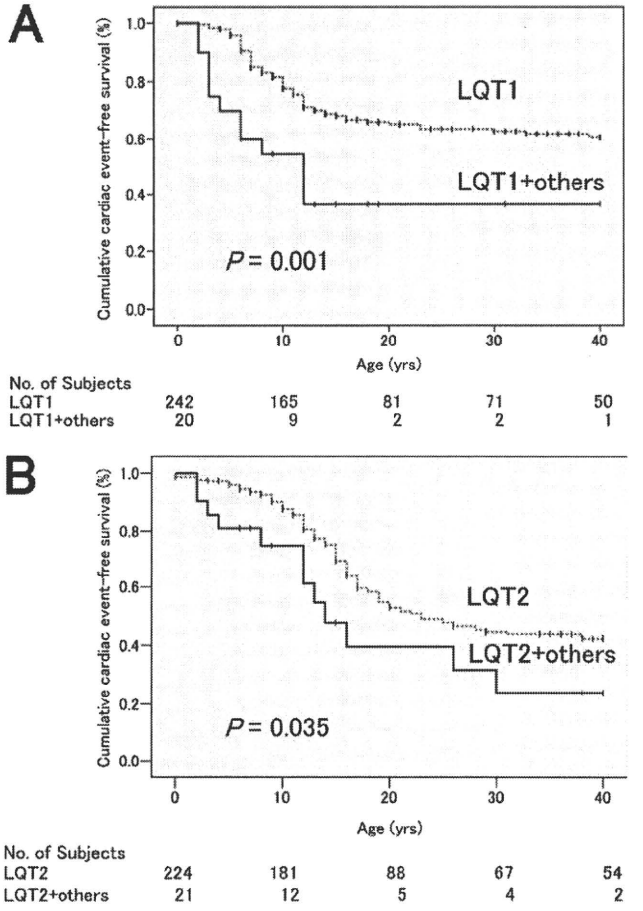

Figure 5 Kaplan-Meier cumulative probability of cardiac event-free survival from birth to 40 years of age and before therapy. **A:** Comparison between patients with long QT type 1 (LQT1_ subtype and compound mutation carriers with LQT1 plus other mutations. **B:** Comparison between patients with long QT syndrome type 2 (LQT2) and those with LQT2 plus other mutations.

increased risk through compound mutations using heterologous expressions in *Xenopus* oocytes. When wild-type and variant subunits were coexpressed in appropriate ratios to mimic the genotype of the probands with mutations, the reduction in current density was equivalent to the additive effects of the single mutations. Coexpression of two mutant subunits caused a significant but incomplete reduction. Thus, either compound mutation seems to be associated with mild functional damage. It is necessary to have "double hits" of these mild mutations in order to produce symptoms.

Study limitations

This study has several limitations. First, six major LQTS candidate genes were examined, but not for minor genes encoding a family of versatile membrane adapters. However, excluding these minor genes from our investigations would not have affected the overall study results, largely because the incidence of these minor gene mutations reportedly is ≤1%. Second, analysis of single mutation carriers in compound mutation families is dominated by their presence in only 35% (9/26) of families. Therefore, there might be a statistical bias due to a mutation-specific effect. Third, Kapa et al[19] reported the need for further studies on whether regions such as the interdomain linker of *SCN5A* could affect the clinical phenotypes of LQTS. In this study, we were able to distinguish mutations from these "genetic noises," especially in the *SCN5A* gene.

Acknowledgment

We thank Professor Pascale Guicheney (INSERM, U956, Group Hospitalier Pitié-Salpêtrière, Paris) for advice and review of the manuscript.

Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.hrthm.2010.06.013.

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Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 56, No. 19, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.06.033

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.

See page 1585

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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Manuscript received April 21, 2010; revised manuscript received June 8, 2010, accepted June 15, 2010.

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

JACC Vol. 56, No. 19, 2010
November 2, 2010:1576–84

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

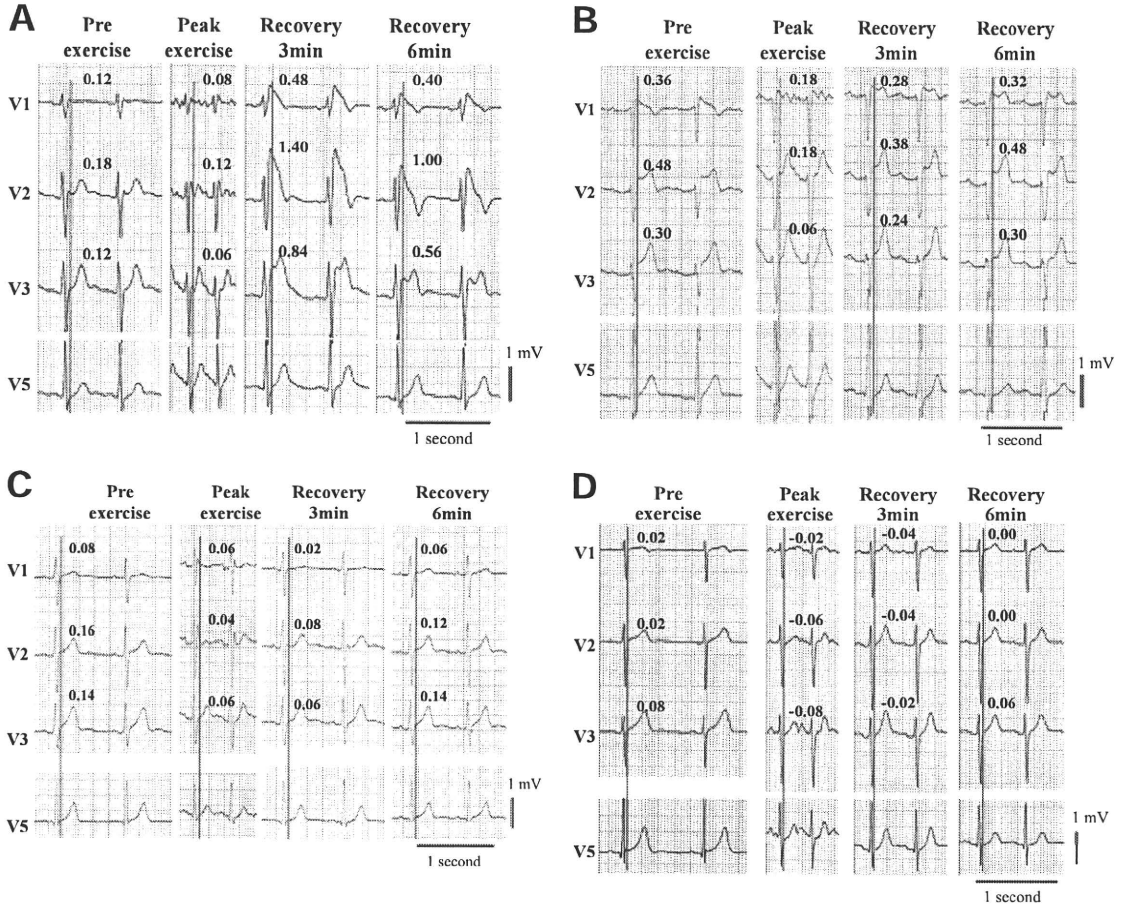

Figure 1 **Typical Responses of ST-Segment Amplitude in Leads V_1, V_2, V_3, and V_5 During Exercise Testing in Brugada Syndrome Patients**

(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 rea-scended 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-

JACC Vol. 56, No. 19, 2010
November 2, 2010:1576–84

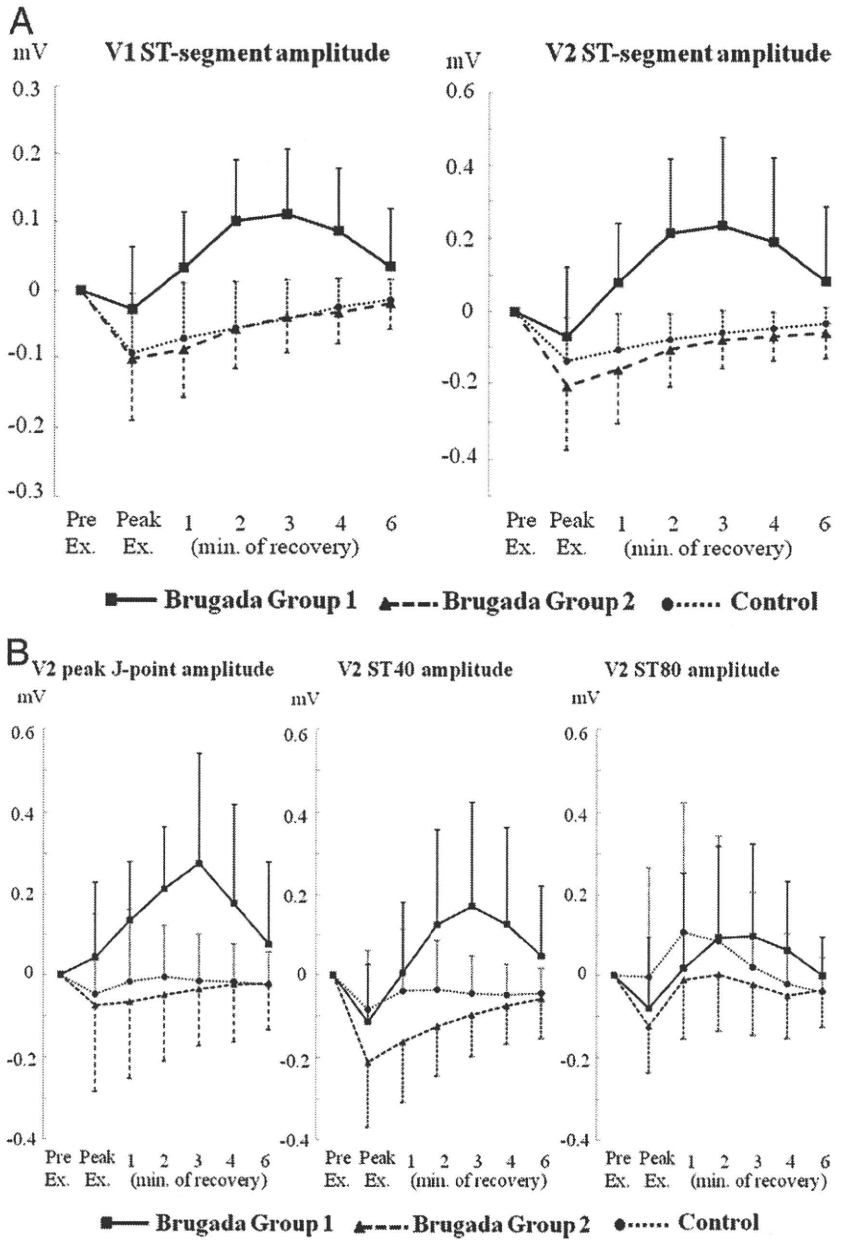

Figure 2 Composite Data of Serial Changes of ST-Segment Amplitude

(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 ($p =$

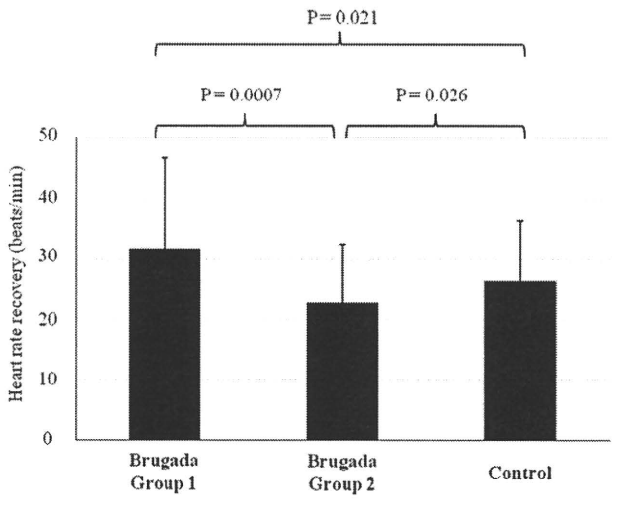

Figure 3 **Comparison of HRR After Exercise Cessation**

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

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.

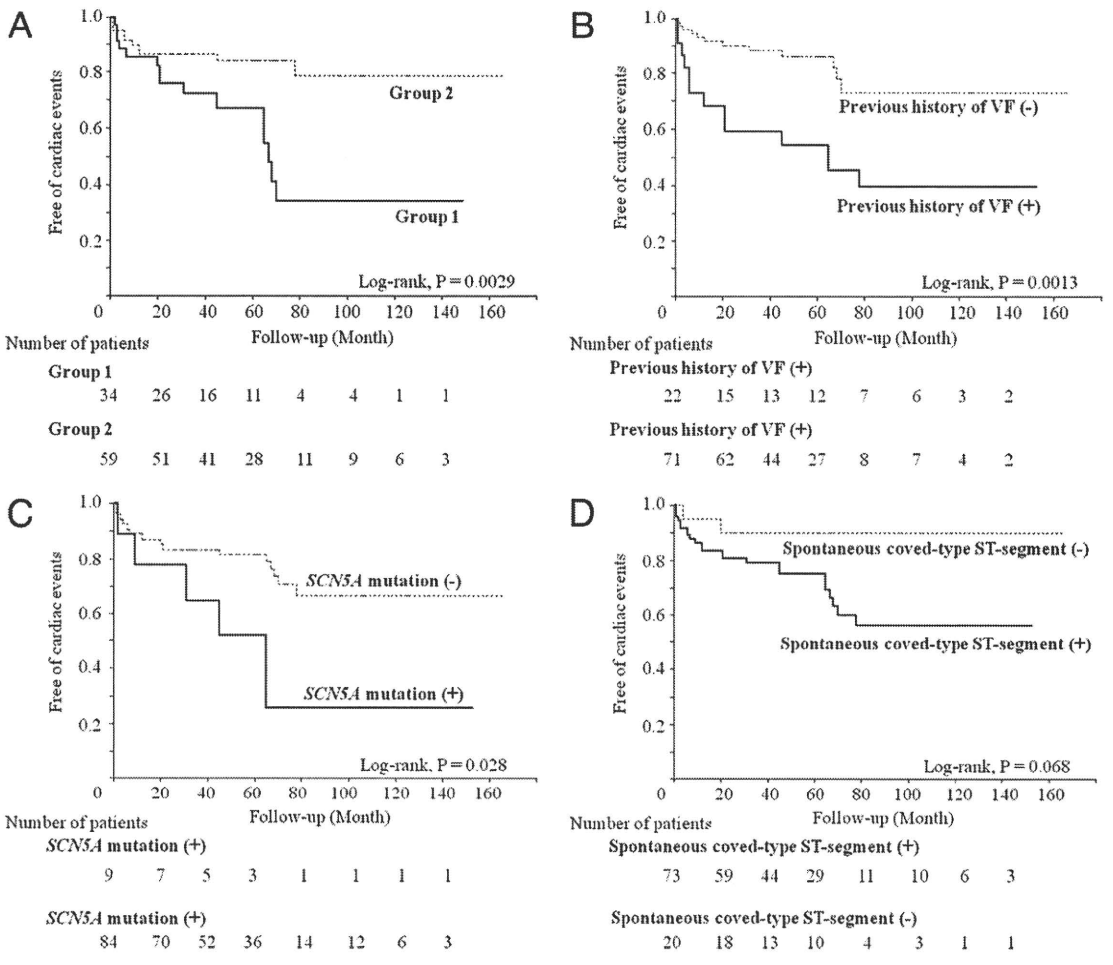

Figure 4 Kaplan-Meier Analysis of Cardiac Events During Follow-Up

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.

Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 57, No. 1, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.07.038

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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Manuscript received May 29, 2010; revised manuscript received July 8, 2010, accepted July 12, 2010.

JACC Vol. 57, No. 1, 2011
December 28, 2010/January 4, 2011:51–9

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.

See page 60

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.

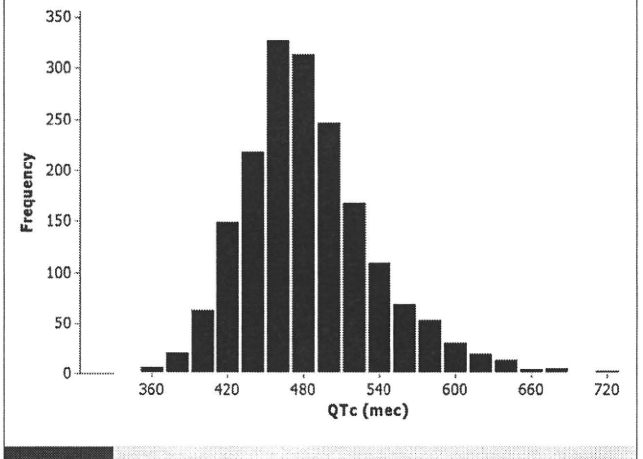

Figure 1 **Distribution of QTc Interval Duration in Genotype-Positive Patients With LQTS**

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

JACC Vol. 57, No. 1, 2011
December 28, 2010/January 4, 2011:51–9

Table 1 Baseline and Follow-Up Characteristics of the Study Population by Genotype-Phenotype

Characteristic	Unaffected Family Members (n = 1,525)	Patients With LQTS With Normal-Range QTc Intervals (n = 469)	Patients With LQTS With Prolonged QTc Intervals (n = 1,392)
Female	52%	48%	61%*†
Family history of SCD	8%	12%	19%*†
QTc interval (ms)			
Mean ± SD	412 ± 22	419 ± 20	501 ± 48
Median (IQR)	420 (400–430)	420 (410–440)	490 (470–520)
Proband	8%	8%	29%*†
RR interval (ms)			
Mean ±SD	793 ± 221	888 ± 236	848 ± 214*†
Median (IQR)	800 (640–930)	900 (740–1,040)	840 (700–1,000)*†
Genotype			
LQT1	NA	40%	39%
LQT2	NA	45%	47%
LQT3	NA	16%	14%
Mutation: TM-MS			
Overall	NA	35%	43%
LQT1	NA	45%	61%
LQT2	NA	16%	29%†
LQT3	NA	64%	31%†
Therapies			
Beta-blockers	6.2%	38%	54%*†
Pacemaker	0.3%	0.6%	5%*†
LCSD	0.1%	0.2%	1.4%*†
ICD	0.6%	6%	14%*†
Events			
Syncope	10%	21%	40%*†
ACA	0.2%	1.3%	8.4%*†
SCD	0.1%	1.5%	4.4%*†
ACA/SCD‡§	0.3%	2.8%	11.3%*

*$p < 0.05$ for the comparison among the 3 genotyped categories. †$p < 0.05$ for the comparison between genotype-positive patients with QTc intervals ≤440 ms and genotype-positive patients with QTc intervals >440 ms. ‡Appropriate ICD shocks constituted 0.04% of ACAs in genotype-positive patients with QTc intervals ≤440 ms and 1.4% of ACAs in genotype-positive patients with QTc intervals >440 ms. §Only the first event for each patient was considered.

ACA = aborted cardiac arrest; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LCSD = left cardiac sympathetic denervation; LQT1 = long-QT syndrome type 1; LQT1 = long-QT syndrome type 2; LQT3 = long-QT syndrome type 3; LQTS = long-QT syndrome; MS = missense; NA = not applicable; QTc = corrected QT; SCD = sudden cardiac death; TM = transmembrane.

The clinical characteristics of the total study population by genotype and QTc subgroup are shown in Table 1. The frequency of probands (defined in the registry as the first person in a family, living or deceased, identified to have LQTS by the enrollment center) was highest in patients with prolonged QTc intervals, whereas most patients with normal-range QTc intervals (92%) were asymptomatic at the time of genetic testing. The frequency of female subjects was similar between the unaffected subjects and patients with LQTS with normal-range QTc intervals and higher in patients with prolonged QTc intervals. In mutation carriers, the frequency of the 3 main LQTS genotypes was similar between patients with and without prolonged QTc intervals. However, patients with LQT1 and LQT2 with prolonged QTc intervals had a higher frequency of transmembrane-missense mutations compared with the corresponding genotype carriers who had normal-range QTc intervals. LQTS-related therapies were administered to a significantly higher frequency of patients with prolonged QTc intervals than to subjects in the other 2 subgroups (Table 1).

Clinical course by genotype and QTc subgroup. Kaplan-Meier survival analysis (Fig. 2) demonstrated a relatively low rate of ACA or SCD in patients with LQTS with normal-range QTc intervals (4% at age 40 years and 10% at age 70 years). Event rates were significantly higher in patients with prolonged QTc intervals (15% and 24% at age 70 years; log-rank $p < 0.001$ for the comparison with the normal-range QTc subgroup) and significantly lower in unaffected family members (0.4% and 1% at age 70 years; log-rank $p < 0.001$ for the comparison with the normal-range QTc subgroup and for the overall difference among the 3 subgroups). Notably, life-threatening events in patients with normal-range QTc intervals occurred mostly after age 10 years, whereas patients with prolonged QTc intervals exhibited an earlier onset of life-threatening events (Fig. 2).

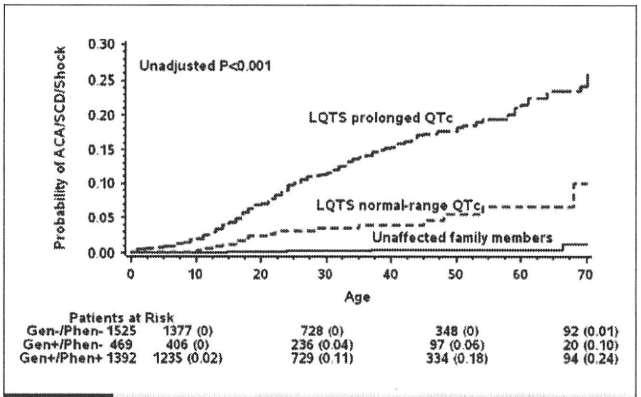

Figure 2 **Rate of ACA or SCD by Genotype and QTc Category**

Kaplan-Meier cumulative probabilities of aborted cardiac arrest (ACA) and sudden cardiac death (SCD) by genotype and corrected QT (QTc) subgroup. LQTS = long-QT syndrome.

After multivariate adjustment for sex, time-dependent beta-blocker therapy, and a family history of SCD in a first-degree relative, patients with LQTS with normal-range QTc intervals were shown to have a significant 72% ($p < 0.001$) lower risk for ACA or SCD compared with patients with prolonged QTc intervals but also exhibited a >10-fold increase in the risk for life-threatening events compared with unaffected family members (Table 2). Histories of syncope were present in 62% of patients with LQTS with normal-range QTc intervals who had life-threatening events during follow-up. Accordingly, when the composite secondary end point of a first cardiac event of any type was assessed (comprising mainly non-life-threatening syncopal episodes), patients with normal-range QTc intervals were consistently shown to be at a lower risk compared with those with prolonged QTc intervals (hazard ratio [HR]: 0.47; 95% confidence interval [CI]: 0.33 to 0.59; $p < 0.001$) and at a higher risk compared with unaffected family members (HR: 5.20; 95% CI: 4.19 to 6.44; $p < 0.001$).

Risk factors for ACA or SCD in patients with LQTS with and without prolonged QTc intervals. Interaction-term analysis demonstrated significant differences in risk factors for life-threatening events between the 2 LQTS subgroups (Table 3). In patients with normal-range QTc intervals, the LQT1 and LQT3 genotypes were associated with respective 10- and 8-fold increases in the risk for life-threatening events compared with the LQT2 genotype. In contrast, in patients with prolonged QTc intervals, the LQT1 genotype was associated with one-half the risk of the LQT2 genotype ($p = 0.002$), with a statistically significant genotype–by–QTc subgroup interaction ($p = 0.006$) (Table 3, first row), and the LQT3 genotype showed a similar risk to the LQT2 genotype, without a statistically significant genotype–by–QTc subgroup interaction (Table 3, second row).

The location and type of the LQTS mutation were shown to be significant risk factors for ACA or SCD in patients with normal-range QTc intervals. In this LQTS subset, transmembrane-missense mutations were associated with a pronounced >6-fold ($p = 0.006$) increase in the risk for ACA or SCD compared with nontransmembrane or nonmissense mutations. In contrast, in patients with prolonged QTc intervals, transmembrane-missense mutations were not independently associated with outcomes (Table 3, third row). Notably, when the secondary end point of cardiac events of any type was assessed, transmembrane-missense mutations were shown to be an independent risk factor in both LQTS subgroups (normal-range QTc interval, HR: 1.71; 95% CI: 1.16 to 2.34; prolonged QTc interval, HR: 1.39; 95% CI: 1.17 to 1.65).

Consistent results demonstrating an association between transmembrane-missense mutations and the risk for ACA or SCD in patients with normal-range QTc intervals were shown when the reference group (comprising nontransmembrane or nonmissense mutations) was further divided into 3 subcategories, including nonmissense mutations in the transmembrane region, missense mutations in the nontransmembrane region, and nonmissense mutations in the nontransmembrane region (HR >4.0 for all 3 comparisons). Accordingly, patients with normal-range QTc intervals with transmembrane-missense mutations experienced a relatively high rate of ACA or SCD during follow-up (9% at age 40 years and 21% at age 70 years), whereas patients with normal-range QTc intervals with other mutations had a very low event rate (1% at age 40 years and 5% at age 70 years; log-rank p for overall difference = 0.005) (Fig. 3A). In contrast, in patients with prolonged QTc intervals, there was no statistically significant difference in the rate of ACA or SCD between the 2 mutation categories (16% and 14% at 40 years, respectively, $p = 0.18$) (Fig. 3B).

Clinical and ECG factors, including sex and QTc duration, were shown to be associated with a significant increase in the risk for ACA or SCD only in patients with prolonged QTc intervals (Table 3, rows 4 to 6). In contrast, in patients

Table 2 **Multivariate Analysis: Risk for ACA or SCD Among the 3 Genotype and QTc Categories***

Genotype and QTc Subgroup	HR	95% CI	p Value
LQTS with prolonged QTc interval vs. unaffected family members	36.53	13.35–99.95	<0.001
LQTS with normal-range QTc interval vs. unaffected family members	10.25	3.34–31.46	<0.001
LQTS with normal-range QTc interval vs. LQTS with prolonged QTc interval	0.28	0.16–0.49	<0.001

*Model also adjusted for sex (female age >13 years) and time-dependent beta-blocker therapy.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

Table 3 Risk Factors for ACA or SCD in Patients With LQTS by QTc Interval Category*

Variable	LQTS and Normal-Range QTc Interval		LQTS and Prolonged QTc Interval		p Value for Interaction
	HR (95% CI)	p Value	HR (95% CI)	p Value	
Genotype					
LQT1 vs. LQT2	9.88 (1.26–37.63)	0.03	0.53 (0.35–0.79)	0.002	0.006
LQT3 vs. LQT2	8.04 (0.85–36.03)	0.07	1.07 (0.70–1.63)	0.77	0.08
Mutation location and type					
TM-MS vs. non-TM-MS	6.32 (1.71–23.33)	0.006	1.24 (0.88–1.76)	0.22	0.02
Sex					
Female age >13 yrs vs. male age >13 yrs	1.32 (0.42–4.17)	0.64	1.90 (1.26–2.86)	0.002	0.53
QTc interval (ms)					
Per 10-ms increase	1.20 (0.81–1.78)	0.35	1.08 (1.05–1.10)	<0.001	0.58
≥Median vs. <median†	1.03 (0.36–2.98)	0.95	2.96 (2.06–4.26)	<0.001	NA

*Cox proportional hazards regression modeling was carried out in models that included all patients with genotype-positive LQTS (n = 1,861). Covariates in the models included QTc category (≤440 ms vs. >440 ms), genotype, mutation location and type, sex, QTc interval (assessed as a continuous measure [per 10-ms increase]), time-dependent beta-blocker therapy, and a family history of SCD; the effect of each covariate in patients with normal-range (≤440 ms) and those with prolonged (>440 ms) QTc intervals was assessed by interaction-term analysis, with interactions tested 1 at a time. Estimates of predictor hazard ratios in the separate normal-range and prolonged QTc interval groups were obtained using these interactions. Virtually identical results for all pre-specified risk factors were also obtained from the models that did not include appropriate ICD shocks as part of the composite end point. †Results were obtained from separate models that assessed the risk associated with QTc values greater than or equal to the median in patients with LQTS with normal-range QTc intervals (median 420 ms) and prolonged QTc intervals (median 500 ms).

Abbreviations as in Tables 1 and 2.

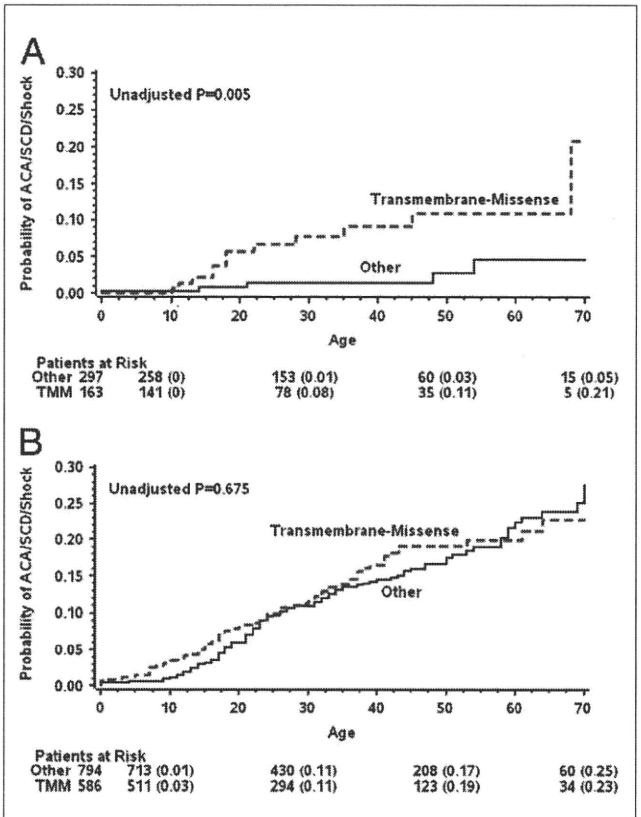

Figure 3 Rate of ACA or SCD in Patients With Normal-Range and Prolonged QTc Intervals by Mutation Location and Type

Kaplan-Meier cumulative probabilities of aborted cardiac arrest (ACA) and sudden cardiac death (SCD) by mutation location and type in patients with long-QT syndrome (LQTS) with **(A)** corrected QT (QTc) intervals ≤440 ms and **(B)** QTc intervals >440 ms.

with normal-range QTc intervals, sex was not a significant risk factor, and QTc duration was not independently associated with a significant increase in the risk for ACA or SCD when assessed as a continuous measure or when dichotomized at the median value (≥420 ms).

As suggested previously (15), the presence of a family history of SCD in any first-degree relative was not shown to be an independent predictor of ACA or SCD in patients with either normal-range QTc intervals (HR: 0.89; 95% CI: 0.63 to 1.25; p = 0.50) or prolonged QTc intervals (HR: 1.40; 95% CI: 0.32 to 6.17; p = 0.65) after adjustment for genetic and clinical factors.

Beta-blocker therapy was administered to 38% of patients who had normal-range QTc intervals compared with 54% of the patients who had prolonged QTc intervals (p < 0.001) (Table 1). Treatment with beta-blockers was associated with an overall significant 25% reduction in the risk for ACA or SCD in the total study population (95% CI: 0.70 to 0.80; p < 0.001), with similar effects in patients with normal-range QTc intervals and those with prolonged QTc intervals (p for beta-blocker–by–LQTS subset interaction = 0.45).

Characteristics of fatal or near-fatal cases with a normal-range QTc intervals. The characteristics of patients with normal-range QTc intervals who experienced ACA or SCD during follow-up are shown in Table 4. The mean age at occurrence of the lethal or near-lethal event in this population was 25.9 ± 4.5 years. Nine of the patients (53%) who experienced events were women, and 4 (24%) were treated with beta-blockers are the time of the events. In patients with normal-range QTc intervals with available data regarding therapies and triggers at the time of the events, none were reported as being treated with a QT interval–prolonging drugs at the time of ACA or SCD, and the majority of the lethal or near-lethal events were not associated with exercise or arousal triggers (Table 4).

Table 4 Characteristics of ACA and SCD Cases With Normal-Range QTc Intervals

Case	Event	Event Age (yrs)	Female	QTc Interval (ms)	BB†	LCSD†	PM†	ICD†	QT PD	Trigger*	Genotype	Mutation Location and Type
1	SCD	0.5	–	390	–	–	–	–	–	NA	LQT3	Non-TM-MS
2	ACA	10		430	–	–	–	–	–	Exercise	LQT1	TM-MS
3	ACA/shock	11	+	400	–	–	–	+	–	Non-E/A	LQT1	TM-MS
4	SCD	13	–	440	+	–	–	–	NA	NA	LQT1	TM-MS
5	ACA	14	–	410	–	–	–	–	–	Exercise	LQT1	Non-TM-MS
6	SCD	16	+	420	–	–	–	–	–	Non-E/A	LQT3	TM-MS
7	ACA	16	+	440	–	–	–	–	–	Arousal	LQT1	TM-MS
8	SCD	18	–	430	+	–	–	–	–	Non-E/A	LQT1	TM-MS
9	ACA	18	+	410	–	–	–	–	–	Exercise	LQT1	TM-MS
10	SCD	21	+	380	–	–	–	–	–	Arousal	LQT2	Non-TM-MS
11	SCD	22	–	440	–	–	–	–	NA	NA	LQT1	TM-MS
12	SCD	28	–	410	–	–	–	–	–	Exercise	LQT1	TM-MS
13	ACA	35	+	420	–	–	–	–	–	Non-E/A	LQT3	TM-MS
14	ACA	46	+	440	+	–	–	–	NA	NA	LQT2	TM-MS
15	SCD	48	–	430	+	–	–	–	–	Non-E/A	LQT2	Non-TM-MS
16	ACA	54	+	420	–	–	–	–	–	Non-E/A	LQT3	Non-TM-MS
17	SCD	69	–	380	–	–	–	–	NA	NA	LQT1	TM-MS

*Data regarding triggers for cardiac events and treatment with QT interval–prolonging medications were available for study patients who were enrolled in the U.S. portion of the International LQTS Registry.
†At time of event. ‡Implanted or performed before event.
BB = beta-blocker therapy; E/A = exercise/arousal trigger for event; NA = not available; PM = pacemaker; QT PD = QT interval–prolonging drug; other abbreviations as in Tables 1 and 2.

Discussion

In this study, we assessed the clinical courses and risk factors for life-threatening events in LQTS patients with genetically-confirmed LQTS who do not exhibit the disease's phenotypic hallmark of QT interval prolongation, otherwise referred to as concealed LQTS, normal–QT interval LQTS, or genotype-positive/ECG phenotype–negative LQTS. Similar to prior studies (16), we have shown that patients with LQT1 to LQT3 exhibit a wide QTc distribution, with approximately 25% having QTc intervals well within the normal range. The rate of ACA or SCD in patients with LQTS with normal-range QTc intervals was shown to be very low (4% from birth through age 40 years, corresponding to an approximate event rate of 0.13% per year). Comparatively, however, this very low risk subset of the LQTS population still exhibited a >10-fold increase in the risk for life-threatening events compared with genetically and phenotypically unaffected family members. Importantly, predictors of life-threatening events were shown to be significantly different between LQTS patients with and without prolonged QTc intervals. In the latter LQTS subgroup, genetic data, including knowledge of genotype and mutation characteristics, were shown to identify the risk for ACA or SCD, whereas in the former LQTS subgroup, female sex in the post-adolescence period and QTc duration were identified as the predominant risk factors for life-threatening events.

The clinical courses of patients with LQTS are variable because of incomplete penetrance (17). They are influenced by age, genotype, sex, environmental factors, therapy, and possibly other modifier genes (1–10). Recent studies from the International LQTS Registry that assessed the risk for life-threatening events in patients with LQTS have consistently demonstrated that ECG and clinical risk factors, including the QTc interval and age-sex interactions, identify increased risk in the LQTS population (3–5). These studies, however, included mainly phenotype-positive patients with LQTS with QTc intervals ≥ 450 ms. Thus, the effect of genetic data on outcomes in these studies was not statistically significant after adjustment for the ECG and clinical factors. The present study population, comprising 1,861 genetically confirmed patients with the LQT1 to LQT3 genotypes, extends the data derived from prior studies and demonstrates that risk factors for life-threatening events are significantly different between patients with LQTS with and without QTc prolongation. Consistent with prior studies, we have shown that in patients with LQTS who exhibit prolonged QTc durations, ECG information and clinical factors can be used to identify the risk for life-threatening events. In contrast, in mutation-positive subjects with normal-range QTc intervals, genetic factors, including knowledge of the LQTS genotypes and the mutation location and type, identified patients who were at an increased risk for ACA or SCD after adjustment for ECG and clinical data.

Sex was not a significant risk factor for cardiac events in patients with normal-range QTc intervals. Furthermore, patients with normal-range QTc intervals displayed a similar frequency of women as unaffected family members, whereas the frequency of women was significantly higher among patients with prolonged QTc intervals. These findings are in accordance with earlier evidence of longer QTc intervals in LQTS women than in men (18), resulting in a marked female predominance in phenotypically affected patients (3–5). The biologic basis for this sex difference might be the down-regulation of expression of cardiac potassium-channel genes by female

JACC Vol. 57, No. 1, 2011
December 28, 2010/January 4, 2011:51–9

sex hormones, which have been shown to prolong the QT interval in both congenital and drug-induced LQTS (19,20). These hormonal effects may explain the present findings of a lower frequency of LQTS women with normal-range QTc intervals.

Recent genotype-phenotype studies have shown that missense mutations located in the transmembrane region, which is responsible for forming the ion conduction pathway of the channel, are associated with a significantly higher risk for cardiac events compared with mutations that are located in other regions of the LQTS channel (9,10). The present study also shows that transmembrane-missense mutations are associated with a significantly higher risk for cardiac events of any type (predominated by syncopal episodes) in patients with LQTS with both normal-range and prolonged QTc intervals. However, our findings suggest that data regarding mutation characteristics are important for the assessment of life-threatening events (comprising ACA and SCD) mainly in patients with normal-range QTc intervals, in whom information derived from ECG and clinical data is more limited. In this LQTS subset, missense mutations located in the transmembrane region were shown to be associated with a >6-fold increase in the risk for life-threatening events and with a clinically meaningful rate of ACA or SCD (9%) from birth through age 40 years.

The mechanisms relating to the occurrence of life-threatening ventricular tachyarrhythmias in phenotype-negative patients with LQTS are not clear. In the present study, none of the patients with normal-range QTc intervals who experienced ACA or SCD took QT interval–prolonging medications at the time of the events. Furthermore, most events in patients with normal-range QTc intervals were not related to exercise or arousal triggers (Table 4). An ECG tracing from a patient with the LQT1 genotype who developed arrhythmic events despite a normal-range QTc interval showed spontaneous generation of polymorphic ventricular tachycardia without preceding extrasystolic pauses or sudden sinus rate acceleration (Fig. 4), possibly explaining the occurrence of ACA or SCD in study patients with normal-range QTc intervals who were treated with beta-blockers at the time of the events.

Study limitations. Most study patients did not undergo comprehensive genetic testing for all currently known mutations that may predispose to arrhythmic risk. Thus, it is possible that the coexistence of modifier genes affected the outcomes of patients with LQTS with normal-range QTc intervals who experienced life-threatening cardiac events. In addition, to provide an estimation of event rates among unaffected family members, we included in the control group subjects who were both genotype negative and also had normal-range QTc intervals (and excluded genotype-negative subjects with prolonged QTc intervals due to possible unidentified mutations in this subset). Therefore, the overall frequency of genotype-positive subjects in the total population may not represent the true penetrance of LQTS in affected families.

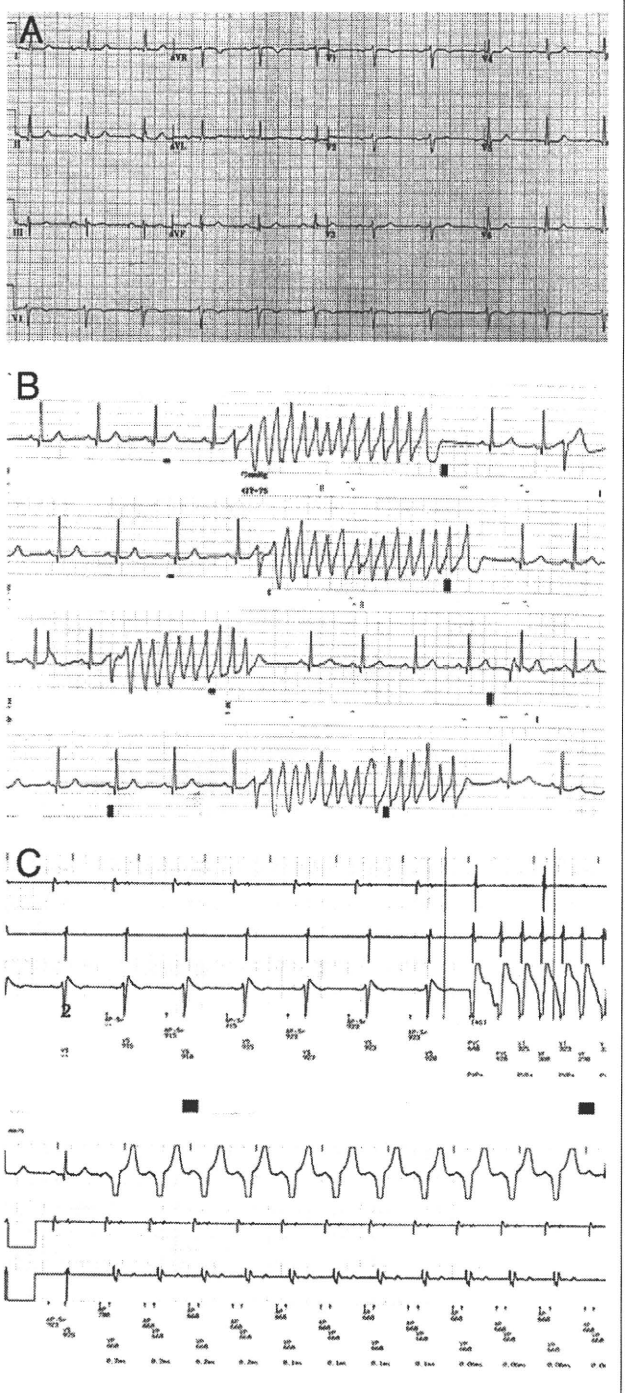

Figure 4 **Polymorphic Ventricular Tachycardia in a Patient With a Normal-Range QTc Interval**

Spontaneous generation of polymorphic ventricular tachycardia in a patient with long-QT syndrome type 1 with a normal-range corrected QT (QTc) interval. **(A)** The patient had a QTc duration of 410 ms on baseline electrocardiography. **(B)** Electrocardiographic tracing at the time of arrhythmic event demonstrates sinus rate with an RR interval of 1,000 ms without significant QT prolongation before the arrhythmia. **(C)** The patient was treated with nadolol and received an implantable cardioverter-defibrillator but continued to exhibit arrhythmic episodes that were recorded on implantable cardioverter-defibrillator interrogation.