In this study, heart rate and cardiac conduction were slower in patients with idiopathic ventricular fibrillation than in healthy controls. Furthermore, His-ventricular interval was prolonged in all of the patients carrying an *SCN5A* mutation. Reductions in heart rate and conduction may result from underlying electrophysiological abnormalities in idiopathic ventricular fibrillation. In addition to the maintenance of the action potential dome, normal impulse generation and propagation are dependent critically on normal sodium channel function,[34] and reductions in heart rate and conduction we observed here can be partially explained by loss-of-function mutations in *SCN5A*. Viskin et al initially reported the association of short QT interval with idiopathic ventricular fibrillation,[35] and the recent study also showed that corrected QT interval is shorter in idiopathic ventricular fibrillation patients with early repolarization than those without early repolarization.[5] In this study, corrected QT interval was shorter in patients with idiopathic ventricular fibrillation than in healthy controls, in line with the previous findings.[5,35] Furthermore, we have previously reported that early repolarization is frequently found in patients with short QT syndrome.[18] There may be the association between short QT interval and early repolarization, although the mechanism is unknown.

Idiopathic ventricular fibrillation associated with early repolarization and Brugada syndrome characterized by J-point/ST-segment elevation in the right precordial leads share genetic, clinical, and pharmacological characteristics.[5,8,12,17,25,33,36–41] Rare variants in genes encoding L-type calcium channel and ATP-sensitive potassium channel have been associated with both diseases.[12,14,36] Defects in *SCN5A* are responsible for Brugada syndrome, and we found that mutations in *SCN5A* were possible causative genetic factors in idiopathic ventricular fibrillation associated with early repolarization. Furthermore, an R367H *SCN5A* mutation identified in this study also has been reported in a family affected by Brugada syndrome.[37] However, the mechanism by which loss of sodium channel function results in either Brugada syndrome or idiopathic ventricular fibrillation associated with early repolarization is unknown, similar to that in other arrhythmia phenotypes caused by loss of function mutations in *SCN5A*, the so called cardiac sodium channelopathies.[42] There may be other genetic or environmental factors that modify the clinical phenotype. Although the association of inferolateral early repolarization with idiopathic ventricular fibrillation has been initially reported,[5] early repolarization in the right precordial leads, where Brugada type electrocardiograms can be seen, also has been associated with idiopathic ventricular fibrillation.[8,25] In this study, 2 of the 3 patients carrying an *SCN5A* mutation showed J-point elevation in the right precordial leads, but did not show diagnostic Brugada type ST-segment elevations in multiple ECG recordings even after sodium channel blocker challenge. Sinus node dysfunction and conduction disorders often are seen in Brugada syndrome, and we observed similar electrocardiographic characteristics in idiopathic ventricular fibrillation.[17,25] Bradycardia-dependent augmentation of J-point amplitude has been reported in both diseases and we observed similar changes of J-wave in a patient carrying *SCN5A* mutation.[43,44] The recent studies have shown that early repolarization is found in 14 to 24% of patients with Brugada syndrome, and that early repolarization is associated with the increased risk of arrhythmia events,[12,45] although the role of early repolarization in Brugada syndrome is not clear. The electrocardiographic manifestations of Brugada syndrome may be unmasked or augmented by sodium channel blockers.[17,25] In our present and prior studies, the administration of sodium channel blockers resulted in the augmentation of J-point amplitude or development of ventricular fibrillation in patients with idiopathic ventricular fibrillation.[46] The efficacy of isoproterenol and quinidine also is common in both diseases.[8,17,25,38–41]

In conclusion, we have shown reductions in heart rate and cardiac conduction in patients with idiopathic ventricular fibrillation associated with early repolarization. We identified *SCN5A* mutations in patients with idiopathic ventricular fibrillation and showed that mutant channels did not generate any currents. These findings implicate that *SCN5A* is a disease gene for idiopathic ventricular fibrillation associated with early repolarization, and that it plays a role in the electrocardiographic characteristics of idiopathic ventricular fibrillation, at least in part.

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CLINICAL PERSPECTIVE

Idiopathic ventricular fibrillation associated with early repolarization is a new arrhythmia syndrome entity, although early repolarization has been considered benign for decades. Early repolarization is a heritable electrocardiographic phenotype and there is a positive family history in 10 to 20% of patients with idiopathic ventricular fibrillation associated with early repolarization. Recent studies have identified the causative genes of the arrhythmia, all of which are associated also with Brugada syndrome. In this study, SCN5A, which encodes the predominant cardiac sodium channel α subunit and is critical for cardiac conduction, was screened in patients with idiopathic ventricular fibrillation associated with early repolarization. The screening identified 3 patients carrying an SCN5A mutation, and His-ventricular interval was prolonged in all patients. All of the mutations are predicted to substitute amino acids highly conserved across species and failed to produce any detectable sodium current. To identify electrophysiological characteristics in idiopathic ventricular fibrillation associated with early repolarization, we compared electrocardiograms between patients with the arrhythmia and healthy controls. We found that patients with the arrhythmia exhibited slower heart rate and slower cardiac conduction properties than controls. Our findings suggest that there are underlying electrophysiological abnormalities resulting in slow heart rate, slow cardiac conduction, early repolarization, and ventricular fibrillation, partially explained by sodium channel dysfunction. Idiopathic ventricular fibrillation associated with early repolarization and Brugada syndrome share genetic, clinical, and pharmacological characteristics, but other factors that modify the clinical phenotypes are unknown. Further studies to identify the modifiers are warranted.

Incidence and Prognostic Value of Early Repolarization Pattern in the 12-Lead Electrocardiogram

Daisuke Haruta, MD, PhD; Kiyotaka Matsuo, MD, PhD; Akira Tsuneto, MD, PhD; Shinichiro Ichimaru, MS; Ayumi Hida, MD, PhD; Nobuko Sera, MD, PhD; Misa Imaizumi, MD, PhD; Eiji Nakashima, PhD; Koji Maemura, MD, PhD; Masazumi Akahoshi, MD, PhD

Background—Early repolarization pattern is a common ECG finding characterized by J-point elevation and QRS notching or slurring in the inferior and/or lateral leads, yet little is known about its incidence and long-term prognosis in Asian populations.

Methods and Results—We reviewed all the ECG records of the 5976 atomic-bomb survivors who were examined at least once during our biennial health examination in Nagasaki, Japan, between July 1958 and December 2004. We defined early repolarization pattern as ≥0.1-mV elevation of the J point or ST segment, with notching or slurring in at least 2 inferior and/or lateral leads. We assessed unexpected, cardiac, and all-cause death risk by Cox analysis. We identified 1429 early repolarization pattern cases (779 incident cases) during follow-up, yielding a positive rate of 23.9% and an incidence rate of 715 per 100 000 person-years. Early repolarization pattern had an elevated risk of unexpected death (hazard ratio, 1.83; 95% confidence interval, 1.12 to 2.97; P=0.02) and a decreased risk of cardiac (hazard ratio, 0.75; 95% confidence interval, 0.60 to 0.93; P<0.01) and all-cause (hazard ratio, 0.85; 95% confidence interval, 0.78 to 0.93; P<0.01) death. In addition, both slurring and notching were related to higher risk of unexpected death (hazard ratio, 2.09; 95% confidence interval, 1.06 to 4.12; P=0.03), as was early repolarization pattern manifestation in both inferior and lateral leads (hazard ratio, 2.50; 95% confidence interval, 1.29 to 4.83; P<0.01).

Conclusions—Early repolarization pattern is associated with an elevated risk of unexpected death and a decreased risk of cardiac and all-cause death. Specific early repolarization pattern morphologies and location are associated with an adverse prognosis. **(*Circulation.* 2011;123:2931-2937.)**

Key Words: death, sudden ■ epidemiology ■ electrocardiography ■ mortality

Sudden cardiac death is a major health issue, and accounts for 300 000 to 400 000 deaths per year in the United States.[1,2] Coronary artery disease, cardiomyopathy, left ventricular hypertrophy, valvular disease, congenital heart disease, and primary electrophysiological abnormalities are the major causes of sudden cardiac death.[1,2] Approximately 5% of sudden cardiac deaths caused by ventricular tachyarrhythmias occur in the absence of structural heart or coronary artery disease and are attributable to primary electrophysiological abnormalities. Some cases with ventricular tachyarrhythmia show a characteristic 12-lead ECG pattern such as a long-QT interval (long-QT syndrome) and a coved-type ST-segment elevation in the right precordial leads (V_1, V_2, and V_3; Brugada syndrome).[3,4]

Clinical Perspective on p 2937

Early repolarization pattern (ERP) is characterized by an elevation of the QRS-ST junction (J point) and QRS notching or slurring (J wave) in multiple leads, especially in the inferior and/or left precordial leads, and is found in a relatively large proportion (1% to 13%) in previous reports.[5–8] Although conventionally considered benign,[5] it is potentially arrhythmogenic,[9] and in 2 clinical case-control studies, patients with a history of idiopathic ventricular fibrillation (VF) showed an increased prevalence of ERP.[7,8] It has recently been reported that ERP in the inferior leads is associated with increased risk of cardiac death in Western populations.[10] Not much is known, however, about the incidence and long-term prognosis of ERP in Asian populations. Thus, we prospectively examined the incidence and prognostic value of ERP in terms of unexpected death, cardiac death, and all-cause death in Nagasaki Adult Health Study (AHS) subjects.

Methods

General Procedures

Since July 1, 1958, 7564 atomic-bomb survivors (3374 men) in Nagasaki, Japan, have been invited to participate in biennial health examinations as part of a follow-up program conducted by the Radiation Effects Research Foundation (RERF). Detailed descriptions of the program have been published elsewhere.[11,12] Each

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From the Department of Cardiovascular Medicine, Course of Medical and Dental Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki (D.H., K. Matsuo, A.T., K. Maemura); Department of Clinical Studies, Radiation Effects Research Foundation, Nagasaki (D.H., A.T., S.I., A.H., N.S., M.I., M.A.); Department of Statistics, Radiation Effects Research Foundation, Hiroshima (E.N.); and Saikakai Shibatachokodo Hospital, Shimabara (D.H., K. Matsuo), Japan.

Correspondence to Daisuke Haruta, MD, Department of Clinical Studies, Radiation Effects Research Foundation, 1-8-6 Nakagawa, Nagasaki 850-0013, Japan. E-mail harutad@rerf.or.jp

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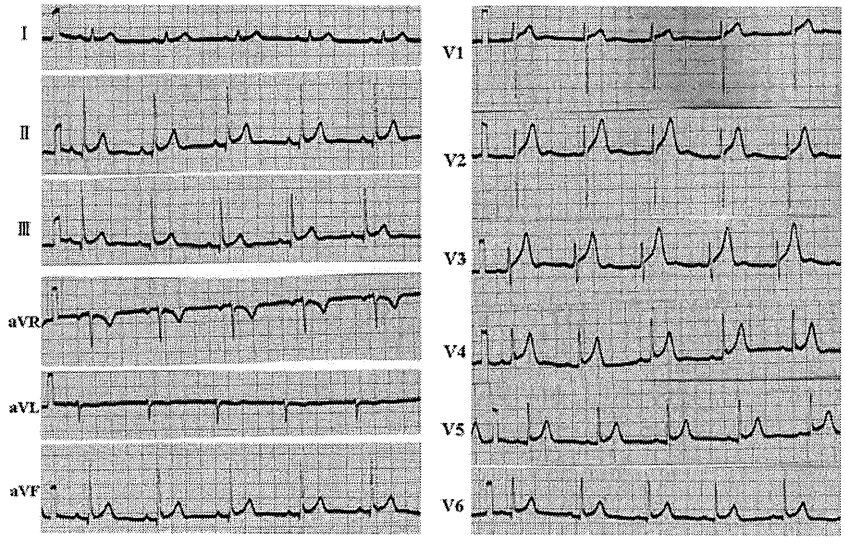

Figure 1. Twelve-lead ECG of a typical pattern of the early repolarization pattern. A slurring morphology is seen in the inferior leads (II, III, aVF), and a notching morphology is seen in leads V_4 through V_6 with ≥0.1-mV elevation from baseline. In our grouping method, this case is classified as both notching and slurring in morphology and as both inferior and lateral leads in lead location, respectively.

examination includes a standard 12-lead ECG obtained by the regular procedure. We extracted 5976 subjects (2612 men) who had been examined at least once between July 1, 1958, and December 31, 2004, and did not have intraventricular conduction disturbances and pacemaker implantation at the first examination and reviewed all the ECG records (12.2±7.5 ECG records per subject) obtained during the follow-up period. The mean length of follow-up for ECG recordings was 23.6±14.7 years. The date of the first examination is different for each individual. During the first 2 years from July 1, 1958, to June 30, 1960, 2912 subjects underwent examination; the remaining 3064 subjects underwent their first examination after that period. We treated subjects who already had ERP at their first examination regardless of the date of examination as prevalent cases and subjects who first showed ERP after their second examination as incident cases. We used the current dosimetry System DS02 to estimate the bone marrow atomic-bomb radiation doses of individual subjects.[13] The Research Protocol Review and Human Investigation Committees of RERF approved the protocol (RP A 14-08).

Definition and Confirmation of Early Repolarization Pattern and Brugada-Type Electrocardiogram

Using criteria similar to those of Haïssaguerre and colleagues,[7] we defined ERP cases as having (1) an elevation of the QRS-ST junction (J point) in notching formation (positive J deflection inscribed on the S wave) or of the ST segment in slurring formation (smooth transition from QRS complex to the ST segment) in at least 2 leads and (2) an amplitude of QRS-ST junction (J point) or ST-segment elevation ≥0.1 mV above the baseline as QRS notching or slurring in the inferior leads (II, III, aVF), lateral leads (I, aVL, V_4 through V_6), or both[7] (Figure 1) at least once during follow-up. In slurring formation, because the transition from QRS complex to ST segment is smooth or the J point may be hidden in the QRS complex, we used ≥0.1 mV of the ST-segment elevation to indicate high-takeoff QRS-ST junction as the criterion. We classified the time course of the J-point abnormality into 1 of 2 categories: a persistent course showing permanent abnormalities or an intermittent course showing transient disappearance of the J wave itself or normalization of the magnitude of the J point during follow-up (Figure 2). During follow-up, we classified cases by positive-ERP lead location (inferior, lateral, or both) and by J-wave morphology (notching, slurring, or both). We defined the onset of ERP as the date of its first appearance during follow-up and used the age at the onset of ERP in calculating the incidence. One cardiologist (D.H.) reviewed the 12-lead ECGs of all subjects without knowledge of the clinical diagnosis or death certificate information. A second cardiologist (K. Matsuo) blindly reviewed all the ECG records of 200 subjects (50 with ERP and 150 without ERP) who were randomly selected from the 5976 subjects. The concordance rate was 86.0% for ERP diagnosis. Next, he blindly reviewed all the ECG records obtained during follow-up for 194 subjects (94 subjects with only slurring in either inferior or lateral lead and 100 subjects with only notching in either inferior or lateral lead) among the 1429 subjects diagnosed as having ERP by the first cardiologist. The concordance rate was 83.8% for lead location and 81.3% for morphology.

In the diagnostic criteria of Brugada syndrome by consensus reports,[14,15] type 1 characterized by ≥0.2-mV coved-type ST segment elevation is essential, whereas types 2 and 3 characterized by saddleback-type ST elevation are not.[14,15] Therefore, in this study, we defined subjects with type 1 characterized by ≥0.2-mV coved-type ST-segment elevation in ≥1 right precordial leads (V_1 through V_3) at least once during follow-up as Brugada-type ECG cases.

Definition and Confirmation of Sudden Death, Unexplained Accidental Death, and Cardiac Death

The RERF followed the vital status of all participants using Japan's family registration system. We collected all of the death certificates from July 1958 to December 2004 to check the cause and circumstance of death for deceased subjects and defined 3 types of death as we did in our Brugada-type ECG study: sudden death, an out-of-hospital death occurring within 1 hour of the onset of acute symptoms; unexplained accidental death, an accidental death in which VF might have been the cause of the accident; and unexpected death, a sudden death or an unexplained accidental death.[16] We treated death resulting from congestive heart failure and ischemic heart disease as cardiac death.

Statistical Analysis

We calculated the 46.5-year (July 1, 1958, to December 31, 2004) incidence on the basis of the age of incident cases at ERP appearance by a person-year method, stratified according to age. We used Cox regression analysis to assess the long-term prognosis of ERP and Brugada-type ECG cases after controlling for age and sex. We compared ERP and Brugada-type ECG cases with control subjects who had neither ERP nor Brugada-type ECG with respect to unexpected death, cardiac death, and death resulting from all causes. We also assessed unexpected death risk according to lead location and J-wave morphology in ERP cases. Survival time is the time from the date of the first examination for controls and prevalent ERP and Brugada-type ECG cases and the date of the first appearance for incident ERP and Brugada-type ECG cases to the date of death or December 31, 2004, whichever came first. All analyses were conducted with SAS for UNIX (SAS Institute, Cary, NC).[17] We expressed the data as mean±SD and considered $P<0.05$ to be statistically significant.

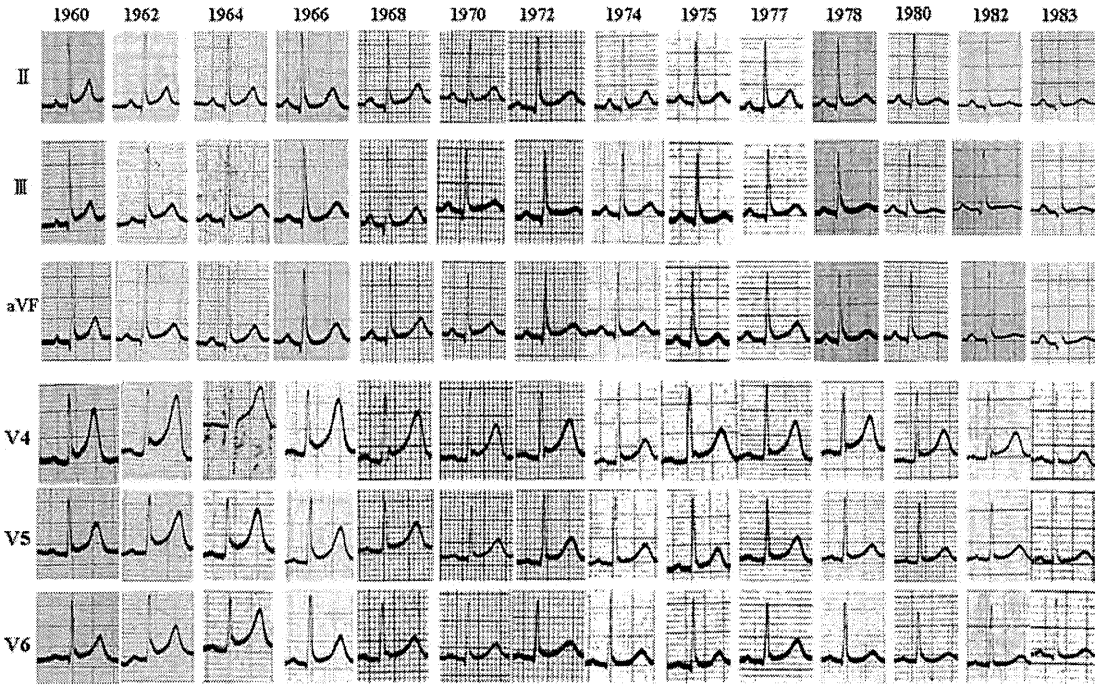

Figure 2. Time course of the ECG (inferior and left precordial leads) in a case of unexpected death in a man. We observed early repolarization pattern with slurring in inferior leads (II, III, aVF) and notching in left precordial leads V_4 through V_6 with ≥0.1-mV elevation from baseline at the first visit in 1960. At the follow-up, the J-wave morphology was consistent in the inferior leads, but the magnitude of ST elevation fluctuated, whereas in the left precordial leads, both the morphology (slurring and notching) and J-point magnitude fluctuated during follow-up. In 1984, the patient died of sudden death at home at 71 years of age.

Results

Incidence of Early Repolarization Pattern

We identified 1429 ERP cases (815 men) among 5976 AHS subjects during the whole study period (July 1, 1958, to December 31, 2004); 650 cases (413 men) were classified as prevalent cases and 779 cases (402 men) were classified as incident cases (mean±SD age at first appearance of ERP, 47.2±15.4 years), yielding a follow-up positive rate of 23.9% (1429 of 5976) and an incidence of 715 per 100 000 person-years (Table 1). Incidence was highest in the second decade of life for men and women and was almost identical between the sexes, whereas the male preponderance became obvious thereafter, leading to twice as high an overall incidence for men (Table 1). Radiation dose was not associated with ERP in both prevalent and incident cases (P=0.89, data not shown).

We identified 30 Brugada-type ECG cases (see Table 2). Brugada-type ECGs showed a J-point elevation in the anterior precordial leads. Among them, 6 cases had both ERP and Brugada-type ECG (Figure 3).

Lead Location and Morphology of the J Wave

Table 3 shows the morphology and lead location of the J wave observed during the follow-up period. Almost all of the

Table 1. Number of Subjects at the First Examination for Each Individual and Incidence From July 1958 to December 2004

	Subjects, n		Person-Years*		Incident ERP Cases, n		Incidence, n/100 000 Person-y	
Age, y	Men	Women	Men	Women	Men	Women	Men	Women
≤19	160	155	287	358	9	12	3136	3352
20–29	432	551	1798	2532	38	41	2113	1619
30–39	609	1250	5434	10 024	96	103	1767	1028
40–49	492	598	7009	14 811	71	77	1013	520
50–59	533	478	9199	16 573	75	59	815	356
60–69	296	236	8718	14 724	79	59	906	401
70–79	80	78	4810	8858	29	24	603	271
≥80	10	18	1292	2587	5	2	387	77
Total	2612	3364	38 547	70 467	402	377	1043	535
	5976		109 014		779		715	

ERP indicates early repolarization pattern.

*Aggregate numbers of years contributed to each age category from 1958 to 2004 by all subjects remaining at risk for ERP.

Table 2. Cause of Mortality in Subjects With Early Repolarization Pattern, Brugada-Type ECG, and Neither Early Repolarization Pattern nor Brugada-Type ECG

		Cause of Death		
	Subjects, n	All	Unexpected	Cardiac
ERP (with Brugada-type ECG)	1429 (6)	628 (4)	27 (0)	100 (0)
Brugada-type ECG without ERP	24	14	4	1
Neither ERP nor Brugada-type ECG	4523	2262	45	434
Total	5976	2904	76	535

ERP indicates early repolarization pattern.

ERP cases (98.3%) showed intermittent manifestations, and both characteristics changed over time (Figure 2).

Mortality From Unexpected Death, Cardiac Death, and All-Cause Death

Table 2 shows the breakdown of the 5976 subjects into ECG category and their cause of death. The 27 ERP cases with or without Brugada-type ECG (19 men; age at death, 68.6±19.1 years; age range, 20.7 to 96.1 years), 4 Brugada-type ECG cases without ERP (3 men; age at death, 59.5±12.4 years; age range, 42.3 to 71.7 years), and 45 controls (23 men; age at death, 65.6±16.3 years; age range; 24.2 to 95.8 years) had unexpected death. Age at unexpected death was not different among the 3 groups. The time interval between the first ECG appearance of ERP and unexpected death based on 16 incident ERP cases was 21.7±13.8 years (range, 2.5 to 42.3 years). In Cox proportional hazards analysis, ERP predicted unexpected death (hazard ratio [HR], 1.83; 95% confidence interval [CI], 1.12 to 2.97; $P=0.02$) and had a favorable effect on cardiac (HR, 0.75; 95% CI, 0.60 to 0.93; $P<0.01$) and all-cause (HR, 0.85; 95% CI, 0.78 to 0.93; $P<0.01$) death (Table 4).

With respect to lead location and J-wave morphology, ERP cases with a broad range of J-wave–positive leads (both inferior and lateral) had a significantly higher HR for unexpected death (HR, 2.50; 95% CI, 1.29 to 4.83; $P<0.01$) and both slurring and notching predicted unexpected death (HR, 2.09; 95% CI, 1.06 to 4.12; $P=0.03$) when we used controls as the reference group (Table 4). We saw no unexpected deaths for patients with ERP with Brugada-type ECG and so could not calculate that HR for unexpected death.

Table 3. Lead Location and Morphology of the J Wave During Follow-Up Among Subjects With Early Repolarization Pattern

	Morphology, n patients			
	Notching	Slurring	Notching and Slurring	Total
Lead location				
Inferior	337	44	41	422
Lateral	335	54	172	561
Inferior and lateral	141	50	255	446
Total	813	148	468	1429

Brugada-type ECG cases had the highest HR for unexpected death (HR, 27.15; 95% CI, 9.35 to 78.85; $P<0.01$), whereas in contrast to ERP cases, it had no favorable effects on cardiac and all-cause death (Table 4). Radiation dose was not associated with unexpected death ($P=0.45$; data not shown).

Discussion

As far as we know, this 5-decade study is the first Asian population–based study of the incidence and prognosis of ERP. We learned that ERP was a common ECG finding, with a follow-up positive rate of 23.9% and an incidence of 715 in 100 000 person-years, and was associated with a higher risk of unexpected death and a lower risk of cardiac and all-cause death. Although the subjects were atomic-bomb survivors, radiation dose was not associated with ERP or unexpected death, so the results should be generalizable.

Incidence of Early Repolarization Pattern

The prevalence of ERP has been reported to be 1% to 13%.[5–8] However, because ERP (defined by the modified criteria of Haïssaguerre and colleagues[7]) appeared intermittently, we based

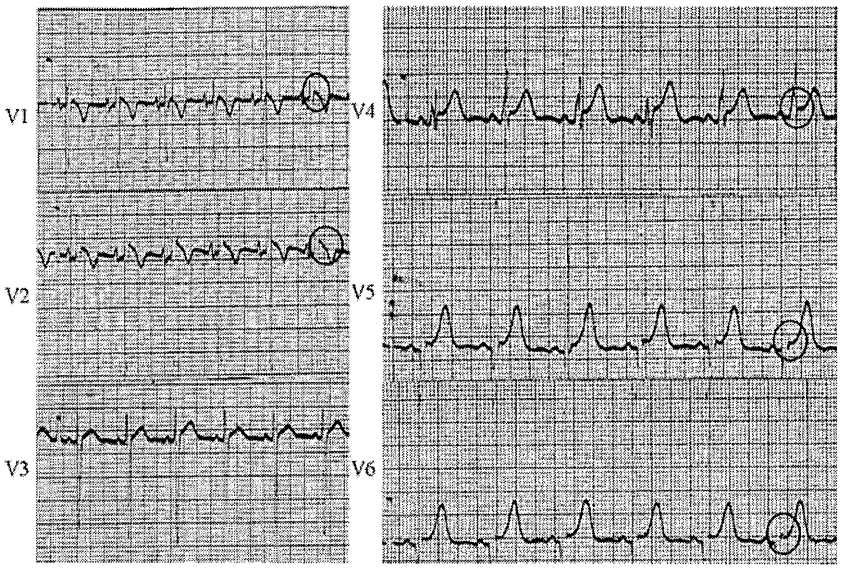

Figure 3. A case with both early repolarization pattern and Brugada-type ECG in chest leads V_1 through V_6. Coved-type ST elevation with 0.2 mV at the J point was seen in V_1 and V_2, and early repolarization pattern with notching morphology 0.1 mV at the J point was seen in V_4 through V_6. Coved-type ST elevation of Brugada-type ECG (V_1 and V_2) and notching morphology of early repolarization pattern (V_4 through V_6) at the last recorded beat are highlighted by circles.

Table 4. Age- and Sex-Adjusted Hazard Ratio for Each Group (Cox Analysis)

			HR (95% CI)		
	Subjects, n	Unexpected Deaths, n	Unexpected Death	Cardiac Death	All-Cause Death
Control*	4523	45	1.00	1.00	1.00
ERP	1429	27	1.83 (1.12–2.97)	0.75 (0.60–0.93)	0.85 (0.78–0.93)
P			0.02	<0.01	<0.01
Lead location					
Inferior	422	8	1.91 (0.88–4.14)		
P			0.10		
Lateral	561	7	1.37 (0.61–3.04)		
P			0.45		
Both	446	12	2.50 (1.29–4.83)		
P			<0.01		
Morphology					
Notching	813	11	1.36 (0.70–2.65)		
P			0.37		
Slurring	148	5	1.60 (0.61–4.24)		
P			0.34		
Both	468	11	2.09 (1.06–4.12)		
P			0.03		
Brugada-type ECG	24	4	27.15 (9.35–78.85)	0.47 (0.07–3.35)	1.09 (0.65–1.85)
P			<0.01		
Total	5976	76		0.45	0.74

HR indicates hazard ratio; CI, confidence interval; and ERP, early repolarization pattern.
*Subjects with neither ERP nor Brugada-type ECG.

our calculation on both prevalent and incident cases and found that 23.9% manifested ERP at least once during follow-up, indicating that ERP was not a rare ECG finding. In past studies, only the prevalence, not incidence, of ERP has been reported because longitudinal studies covering the period before the diagnosis of ERP were lacking. We report the incidence of ERP for the first time here and reveal that the incidence of ERP was highest in the second decade of life in men and women and decreased thereafter (Table 1). It is possible that the difference in the age distribution of the subjects in the target cohort and the intermittent appearance of ERP may have affected the reported prevalence of ERP. It is also possible that if we used criteria other than the modified criteria of Haïssaguerre and colleagues, we would have found different incidence values.

The incidence of ERP that we observed (Table 1) was ≈50 times as high as the incidence reported for Brugada-type ECG (14.3/100 000 person-years),[16] whereas the male/female incidence ratio for ERP (1.95) was about one-fifth that of Brugada-type ECG (8.97),[16] but the incidence of both ERP and Brugada-type ECG is high at a relatively young age. Because our cohort of atomic-bomb survivors did not include subjects who were <12 years of age on July 1, 1958, and the appearance of ERP was intermittent, it is necessary to follow up a large number of the population who are <10 years of age to arrive at a more precise value.

Prognostic Value of Early Repolarization Pattern

Sinner et al[18] recently reported in a prospective cohort study that ERP was associated with a ≈2- to 4-fold increased risk of cardiac mortality, which was determined through the use of death certificates. They did not mention the association between ERP and unexpected death because cardiac death was assumed in the ninth version of the *International Classification of Diseases* codes 390 to 429 and 798.[18] On the other hand, Haïssaguerre et al[7] reported that ERP in the inferior or lateral leads was more frequent among patients with idiopathic VF than among control subjects. Rosso et al[8] reported a similar association between ERP and idiopathic VF. Those studies were cross-sectional; here, in a prospective cohort study, ERP predicted unexpected death. How ERP did that, however, is unclear. It has been reported that 11% of Brugada syndrome patients show ERP in the inferior-lateral leads and that drug challenge tests provoke a coved pattern in the inferior-lateral leads in 4.6% of Brugada syndrome patients.[19] Those observations suggest that ERP and Brugada syndrome overlap in phenotype and electrophysiological similarities. The presence of a prominent I_{to}-mediated action potential notch (spike and dome) in the epicardium, but not the endocardium, generates a transmural voltage gradient during the early phase of repolarization, which manifests J-wave and J-point elevation in the surface ECG in both ERP and Brugada syndrome.[20] Heterogeneous loss of the action potential dome produces phase 2 reentry, leading to polymorphic ventricular tachycardia/VF.[20] It is possible that ERP has a vulnerability to arrhythmias that is due to transmural heterogeneity of ventricular repolarization and that ERP is affected by such factors as testosterone and drugs through ion channel activity.

A J-wave manifestation in both inferior and lateral leads was associated with a higher risk of unexpected death. A J-wave manifestation in many leads suggested that electric instability caused by heterogeneity of repolarization was occurring in broad regions of the ventricles. Merchant et al[21]

reported that notching in lateral leads is significantly more prevalent among ERP patients with idiopathic VF, but they did not assess morphological changes over time. In our study, we defined slurring, notching, and slurring and notching, taking morphological changes into account during follow-up, and found that manifestation in both slurring and notching has an important implication for risk stratification.

In this study, ERP cases had a lower risk of cardiac and all-cause mortality. On the other hand, it has also been reported that ERP in the inferior leads is associated with an increased risk of cardiac death, (HR, 1.28; 95% CI, 1.04 to 1.59; P= 0.03),[10] and ERP in any localization was associated with an increased risk of all-cause death (HR, 1.87; 95% CI, 1.03 to 3.37; P=0.038).[18] Thus, the association between ERP and mortality other than unexpected death is still controversial. We proposed a hypothesis that testosterone may modulate cardiac and total mortality in ERP cases. Various reports indicate that testosterone may be associated with ERP and Brugada syndrome. Early repolarization pattern showed male preponderance[7,8,10]; the typical coved-type Brugada ECG disappears after surgical castration for prostate cancer[22]; and male Brugada syndrome cases have significantly higher plasma testosterone levels than age-matched male controls.[23] It has been suggested that testosterone may increase the outward repolarizing potassium currents such as I_{K1}, I_{Kr}, I_{Ks} and I_{to}, inhibiting inward L-type Ca^{2+} current.[24–26] Such effects help to induce an outward shift of current in the epicardium, aggravate transmural voltage gradient between epicardium and endocardium, and lead to the J-point and ST-segment elevation seen in ERP and Brugada syndrome. These reports suggest that testosterone is associated with ERP and Brugada syndrome through ion channel activity. On the other hand, several studies reported that low serum testosterone level was associated with an increased risk of cardiovascular and all-cause mortality and cardiovascular risk factors in men (abnormal lipid profiles, impaired glucose metabolism, and high blood pressure).[27–29] Thus, elevated serum testosterone level may influence the prognosis of patients with ERP by increasing the risk of sudden death through a more prominent transmural voltage gradient, which leads to phase 2 reentry and ventricular tachycardia/VF, while decreasing the risk of cardiac and all-cause death, probably through protective effects. However, this hypothesis should be supported by more direct evidence of the association between testosterone and ERP.

In the present study, the HR for unexpected death was lower for ERP (1.83) than for Brugada-type ECG (27.15), and may not directly lead to the recommendation of implantable cardioverter-defibrillator treatment. However, because the number of ERP cases (1429) was much larger than the number of Brugada-type ECG cases (24), the unexpected death rate was greater for ERP cases (27 of 76, 35.5%) than for Brugada-type ECG cases (4 of 76, 5.3%), suggesting a greater public health implication for ERP and a careful evaluation of the past history of syncope and the family history of sudden death or syncope. Further epidemiological and electrophysiological studies are needed to clarify what characteristics among the large number of ERP cases are predictive of high risk.

Study Limitations

In this study, only 1 cardiologist reviewed all the ECG records obtained during follow-up in 5976 subjects. However, the accuracy of the diagnosis was ensured because all the ECG records (12.2±7.5 ECG records per subjects) during follow-up were reviewed for each subject. A second cardiologist blindly reviewed all the ECG records obtained during follow-up in 200 subjects (50 with ERP and 150 without ERP) and 194 ERP cases, and the concordance rate was 86.0% for ERP diagnosis, 83.8% for lead location, and 81.3% for morphology.

We could not deny the effect of structural heart diseases on ERP because we did not perform echocardiography and cardiac catheterization in this epidemiological study.

We did not assess the risk of unexpected death by the nature of the manifestation of ERP (intermittent/persistent), because almost all of the ERP cases (98.3%) showed the intermittent course. Because the magnitude of the J point fluctuated over time in ERP cases, the most elevated values of J point were biased, depending on how many times the ECG was recorded. Thus, we did not assess the effects of the magnitude of J point on unexpected death. For the same reason, other ECG characteristics such as QRS duration and QTc interval were not used as covariates in Cox regression analysis.

With respect to Brugada-type ECG, we did not include 10 patients with types 2 and 3 in the Brugada-type ECG group. We cannot deny the possibility that they might have changed into type 1 if they had drug challenge tests, which could not be performed in our cohort study. We observed 3 unexpected deaths among 10 patients with types 2 and 3.

Age at unexpected death was relatively high in both ERP cases and controls. Uncertainty of the cause of sudden or unexplained accidental death without autopsy information, especially for coronary heart disease, may limit the present results, but this possible bias would be equal for ERP cases and controls.

Because the number of unexpected deaths in ERP cases by lead location and morphology subgroup and in Brugada-type ECG cases was small, such data might limit efforts to draw a definitive conclusion about effects of ERP by lead location and morphology subgroup and Brugada-type ECG on unexpected death.

Conclusions

In this 5-decade population-based study, we described the epidemiology and long-term prognosis of ERP. Early repolarization pattern was a common ECG finding; ERP appeared intermittently, and its location and J-wave morphology changed over time. Early repolarization pattern was associated with an elevated risk of unexpected death and a decreased risk of cardiac and all-cause death. The manifestation of both slurring and notching and the manifestation of the J wave in both inferior and lateral leads were associated with the higher risk of unexpected death. Further clinical and experimental studies are needed to define the characteristics of high-risk ERP cases so that they can be singled out for preventive measures.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Recent studies have suggested a potential arrhythmogenicity and a higher risk of cardiac or all-cause death of early repolarization pattern (ERP) in Western populations. But, the incidence and prognosis of ERP in an Asian population have not yet been elucidated. We investigated 5976 atomic-bomb survivors followed up for ≈5 decades. Early repolarization pattern was a very common finding throughout the survivors' entire lives, yielding a lifetime positive rate of 23.9%, an incidence rate of 715 per 100 000, and male predominance. In this study, ERP patients had an increased risk of unexpected death and a decreased risk of cardiac and all-cause death. The ERP manifestation of both slurring and notching and the manifestation of the J wave in broad leads were associated with unexpected death. The hazard ratio for unexpected death in ERP was lower than that in Brugada-type ECG. However, because ERP is a very common finding, ERP has a greater public health implication.

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

Ilan Goldenberg, MD,* Samuel Horr, MA,* Arthur J. Moss, MD,* Coeli M. Lopes, PHD,† Alon Barsheshet, MD,* Scott McNitt, MS,* Wojciech Zareba, MD, PHD,* Mark L. Andrews, BBA,* Jennifer L. Robinson, MS,* Emanuela H. Locati, MD,§ Michael J. Ackerman, MD, PHD,¶ Jesaia Benhorin, MD,‖ Elizabeth S. Kaufman, MD,# Carlo Napolitano, MD,**†† Pyotr G. Platonov, MD, PHD,§§ Silvia G. Priori, MD, PHD,**†† Ming Qi, MD,‡ Peter J. Schwartz, MD,‡‡ Wataru Shimizu, MD, PHD,‖‖ Jeffrey A. Towbin, MD,¶¶ G. Michael Vincent, MD,*** Arthur A. M. Wilde, MD, PHD,## Li Zhang, MD***

Rochester and New York, New York; Milan and Pavia, Italy; Tel Aviv, Israel; Rochester, Minnesota; Cleveland, Ohio; Lund, Sweden; Suita, Japan; Houston, Texas; Amsterdam, the Netherlands; and Salt Lake City, Utah

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

From the *Cardiology Division of the Department of Medicine, University of Rochester Medical Center, Rochester, New York; †Cardiovascular Research Institute University of Rochester Medical Center, Rochester, New York; ‡Department of Pathology, University of Rochester Medical Center, Rochester, New York; §Cardiovascular Department De Gasperis, Niguarda Hospital, Milan, Italy; ‖Heart Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; ¶Departments of Medicine, Pediatrics, and Molecular Pharmacology and Experimental Therapeutics/Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic College of Medicine, Rochester, Minnesota; #The Heart and Vascular Research Center, MetroHealth Campus, Case Western Reserve University, Cleveland, Ohio; **Molecular Cardiology, Fondazione S. Maugeri, University of Pavia, Pavia, Italy; ††Leon Charney Division of Cardiology, New York University School of Medicine, New York, New York; ‡‡Department of Cardiology, Fondazione Policlinico S. Matteo IRCCS and University of Pavia, Pavia, Italy; §§Department of Cardiology, Lund University, Lund, Sweden; ‖‖Division of Cardiology, Department of Internal Medicine National Cardiovascular Center, Suita, Japan; ¶¶Department of Pediatric Cardiology, Baylor College of Medicine, Houston, Texas; ##Department of Cardiology, Academic Medical Center, Amsterdam, the Netherlands; and the ***Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah. This work was supported by research grants HL-33843 and HL-51618 from the National Institutes of Health. The authors have reported that they have no relationships to disclose.

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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.

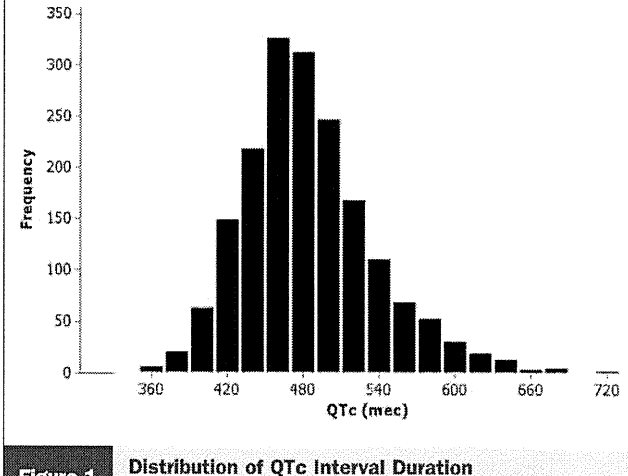

Figure 1 Distribution of QTc Interval Duration in Genotype-Positive Patients With LQTS

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

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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).

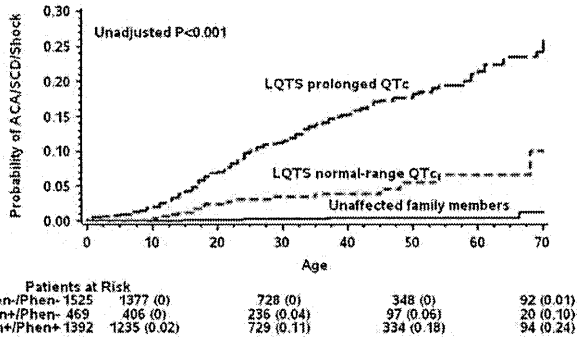

Figure 2 Rate of ACA or SCD by Genotype and QTc Category

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.

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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		
	HR (95% CI)	p Value	HR (95% CI)	p Value	p Value for Interaction
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.

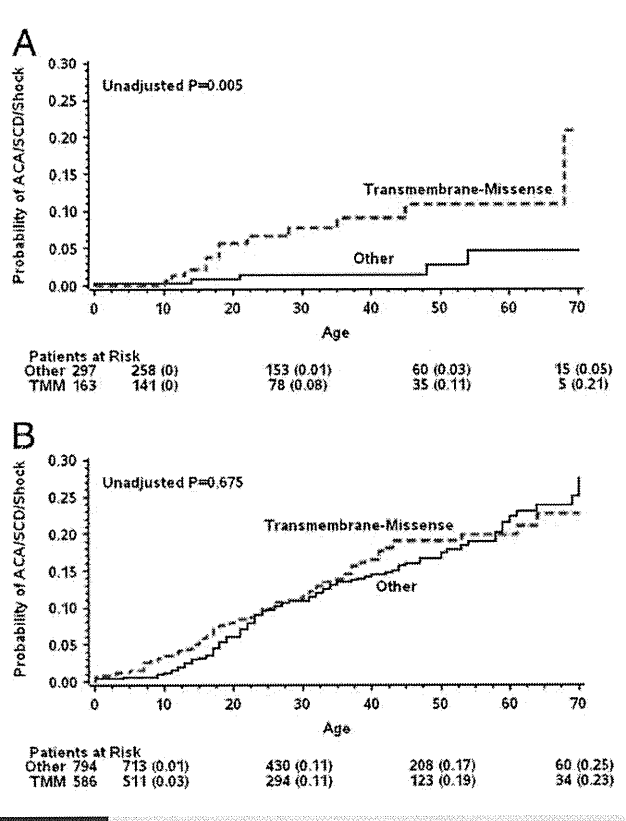

Figure 3 Rate of ACA or SCD in Patients With Normal-Range and Prolonged QTc Intervals by Mutation Location and Type

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

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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.

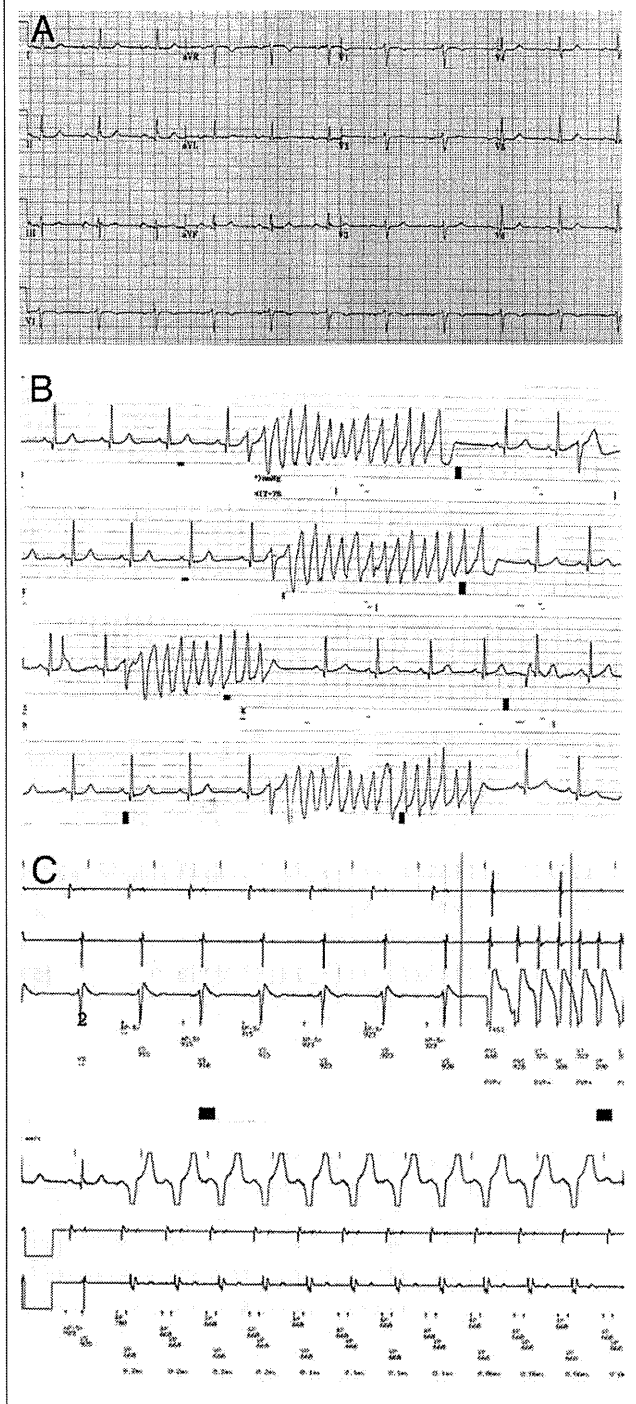

Figure 4 **Polymorphic Ventricular Tachycardia in a Patient With a Normal-Range QTc Interval**

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.

The threshold value of 440 ms for the definition of a normal-range QTc in the present study was based on the diagnostic criteria for LQTS proposed by Schwartz et al. (12), which define a prolonged QTc interval as ≥450 ms in male patients and ≥460 ms in female patients. We chose to use a uniform approach by selecting 440 ms as the upper limit of normal rather than having separate phenotypic definitions for male and female patients. It should also be noted that 2.5% of infants and 10% to 20% of adults exceed this cutoff (21). Thus, the 440-ms value is not meant to suggest an LQTS diagnosis on its own.

Conclusions

The present study shows that patients with LQTS who exhibit normal-range QTc intervals constitute approximately 25% of the LQTS population and have a significantly lower risk for life-threatening events compared with phenotypically affected patients but also exhibit a significant increase in the risk of ACA or SCD compared with unaffected family members. Missense mutations in the transmembrane regions of the ion channels, mainly in patients with LQT1 and LQT3, were shown to identify patients with normal-range QTc intervals who have an increased risk for ACA or SCD. In contrast, increments in QTc duration were not shown to be significantly associated with increased risk for life-threatening events in this population. These findings suggest that: 1) risk assessment in phenotype-negative family members of LQTS probands should include genetic testing, because a positive genetic test result in a family member with a normal-range QTc interval implies an overall >10-fold increase in the risk for ACA or SCD compared with a negative test result in an unaffected family member; 2) genetic data may be used to identify phenotype-negative patients with LQTS who are at increased risk for fatal ventricular tachyarrhythmias independently of QTc duration; and 3) LQTS mutation–positive patients with normal-range QTc intervals who are identified as having increased risk for life-threatening events on the basis of genotype and mutation characteristics (i.e., LQT1 and LQT3 with transmembrane-missense mutations) should be carefully followed and receive a similar management strategy as phenotype-positive patients with LQTS, including avoidance of QT-prolonging medications (22), routine therapy with beta-blockers, and possibly implantable cardioverter-defibrillator therapy in those who remain symptomatic despite medical therapy. Conversely, patients with the lowest risk profile of already low risk, concealed LQTS (i.e., concealed LQT2 and non-transmembrane-missense LQT1 and LQT3) may represent the nominally near zero risk subpopulation(s) of LQTS in need of only preventative health recommendations such as QT drug avoidance.

Reprint requests and correspondence: Dr. Ilan Goldenberg, Heart Research Follow-Up Program, Box 653, University of Rochester Medical Center, Rochester, New York 14642. E-mail: ilan.goldenberg@heart.rochester.edu.

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Key Words: corrected QT interval ▪ long-QT syndrome ▪ sudden cardiac death.

APPENDIX

For a table about *KCNQ1*, *KCNH2*, and *SCN5A* mutations by amino acid coding, frequency, location, and type, please see the online version of this article.

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Electrophysiological Characteristics of Idiopathic Ventricular Tachycardia in Children

Junji Fukuhara, MD; Naokata Sumitomo, MD, PhD; Takahiro Nakamura, MD; Rie Ichikawa, MD; Masaharu Matsumura, MD; Osamu Abe, MD; Michio Miyashita, MD, PhD; Kazuo Taniguchi, MD; Hiroshi Kanamaru, MD; Mamoru Ayusawa, MD, PhD; Kensuke Karasawa, MD, PhD; Hideo Mugishima, MD, PhD

Background: Idiopathic ventricular tachycardia (VT) has been reported to have a good prognosis, but there still might be the potential risk of sudden death.

Methods and Results: The 46 consecutive children (mean age 11.7±3.4 years) with idiopathic VT were enrolled in this study. Monomorphic VT was detected in 39 patients and polymorphic VT in 7 patients. The VT originated from the right ventricle (RV) in 22 patients, and left ventricle (LV) in 17 patients. The VT was induced by exercise in 68% of the RVVT, 41% of the LVVT, and 100% of the polymorphic VT. The VT was induced by programmed ventricular stimulation in 41% of the RVVT, 35% of the LVVT, and none of the polymorphic VT. Adenosine tri-phosphate terminated the VT in 9 of 15 patients (60%). The mechanism of the VT was suspected to be triggered by activity in 36.4%, automaticity in 40.9%, and re-entry in 22.7% of the RVVT, whereas it was 52.9%, 5.9%, and 41.2% of the LVVT, respectively.

Conclusions: The exercise inducibility was higher in polymorphic VT than the RVVT and LVVT, but no difference in the programmed stimulation. The sensitivity to adenosine tri-phosphate was not different between the RVVT and LVVT. In some patients with idiopathic VT, a non-verapamil sensitive re-entry was documented, which was more common in patients with ischemic heart disease or cardiomyopathy.

Key Words: Idiopathic ventricular tachycardia; Monomorphic ventricular tachycardia; Polymorphic ventricular tachycardia; Ventricular fibrillation

Idiopathic ventricular tachycardia (VT) is a clinical entity observed in children and adults without any structural heart disease detected by conventional diagnostic evaluations. Idiopathic VT has been reported to have a good prognosis,[1] but there might still be some risk of sudden death or congestive heart failure.[1] We evaluated patients with idiopathic VT using electrophysiological studies (EPSs) in children.

Editorial p???

Methods

From July 1987 to June 2008, consecutive patients referred to our institutes for EPSs or catheter ablation of VT were studied. Organic heart disease was excluded by physical examination, chest radiography, and echocardiography. The 46 children (18 males, 28 females) with a mean age of 11.7±3.4 years (4–19) were included in this study. Their mean body weight was 41.6±14.2 kg (17.9–71.6 kg), mean body length 147.1±18.3 cm (109.4–178.0 cm), and mean body surface area 1.30±0.30 m^2 (0.74–1.85 m^2). Of those patients, 34 had symptoms, and 12 were asymptomatic. Of the symptomatic patients, 8 had syncope, 1 had dizziness, 17 had palpitations or chest pain, and 8 had other symptoms during the tachycardia. Syncope was noted in 6 patients with CPVT, and 2 with monomorphic VT. None of these patients developed sudden death. Anti-arrhythmic agents were used in 26 patients. In 19 of the 26 patients, the VT was not controlled by anti-arrhythmic medication, and consequently they underwent catheter ablation. Eight asymptomatic patients were found by a school mass screening, and 4 by auscultation or an electrocardiogram during medical check-ups for other diseases.

After written informed consent was obtained from the child's parent or guardian, an EPS was performed under intravenous anesthesia. All anti-arrhythmic drugs were discontinued for at least 5 half-lives prior to the EPS. Electrode

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Department of Pediatrics and Child Health, Nihon University, School of Medicine, Tokyo, Japan
Mailing address: Naokata Sumitomo, MD, PhD, Department of Pediatrics and Child Health, Nihon University, School of Medicine, 30-1 Oyaguchi Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan. E-mail: sumitomo.naokata@nihon-u.ac.jp
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