existence of antegrade UCP block during AF as opposed to the amelioration of the antegrade AVN conduction.

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Beneficial effects of cilostazol in a patient with recurrent ventricular fibrillation associated with early repolarization syndrome

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Introduction

An early repolarization pattern on the electrocardiogram (ECG), referred to as J-point elevation, which is sometimes followed by ST-segment elevation, has been considered to be a benign ECG manifestation.[1,2] However, clinical problems associated with the early repolarization pattern induced after ventricular fibrillation (VF) were published by Haissaguerre et al[3] in 2008. An early repolarization pattern was reported to occur in 31% of the subjects with idiopathic VF, and VF recurred more frequently in those patients compared to that in healthy subjects. In such patients, this is called early repolarization syndrome (ERS), and an implantable cardioverter-defibrillator (ICD) is the first-line therapy for the prevention of sudden death.[4–6] As an oral medication, the efficacy of quinidine was reported in ERS patients with recurrent VF.[7] However, we experienced a case with recurrent VF associated with ERS refractory to a small dose of quinidine, which was prevented by the oral administration of cilostazol, an oral phosphodiesterase III inhibitor.[8]

Case report

A 64-year-old woman was admitted to the intensive care unit because of VF terminated by an automated external defibrillator in July 2009. After a shock was delivered, her 12-lead ECG showed atrial fibrillation (AF) with a J-point elevation and horizontal/descending ST-segment pattern in leads I, aVL, and V_6 (Figure 1). Additional investigation including echocardiography, coronary angiography, left ventriculography, and cardiac magnetic resonance imaging did not show any structural heart disease. Intravenous infusion of pilsicainide, a sodium channel blocker, at a dose of 50 mg did not lead to any augmentation of a Brugada-like ST-segment elevation. After obtaining written informed consent, an electrophysiological study was performed. There were no abnormal areas in the right ventricle and VF was not induced with triple extrastimuli applied to 2 locations including the right ventricular apex and right ventricular outflow tract. She was diagnosed with idiopathic VF associated with ERS. An ICD (EPIC VR V-196, St Jude Medical, St Paul, MN) was implanted in our hospital, and she was prescribed bisoprolol 1.25 mg/d for heart rate control of her AF before discharge.

During her follow-up, she experienced an inappropriate ICD shock due to AF and digoxin 0.1 mg/d was additionally initiated. Thereafter, she experienced several ICD shocks due to VF during sleep or during the early morning from December 2009 to May 2010 (Figure 2). A low dose of bepridil 100 mg/d was added to prevent VF attacks because of its effectiveness revealed in Brugada syndrome.[9] The frequency of VF episodes decreased, but the VF attacks were not completely prevented. In addition, we tried a low dose of quinidine 200 mg/d, increased the ICD pacing rate from VVI 50 to VVI 70 beats/min, and withdrew the bisoprolol, which failed to prevent subsequent multiple VF attacks. In January 2011, the patient was admitted to our hospital again to reevaluate her condition and to adjust the medication. An echocardiogram revealed no change in the left ventricular function and the 12-lead ECG revealed J-point elevation with a horizontal/descending ST-segment pattern after the ICD pacing rate was reprogrammed to VVI 40. The intravenous application of isoproterenol 1 μg/min led to the attenuation of J-point elevation in leads I, aVL, and V_6 (Figure 3). On the basis of this phenomenon, we tried cilostazol, which was reported to be an effective drug to prevent VF in Brugada syndrome.[10] After cilostazol was initiated, no VF episodes were observed during her hospitalization and cilostazol

KEYWORDS Brugada syndrome; Cilostazol; Early repolarization; J-wave; Quinidine; Ventricular fibrillation

ABBREVIATIONS AF = atrial fibrillation; **ECG** = electrocardiogram; **ERS** = early repolarization syndrome; **ICD** = implantable cardioverter defibrillator; **VF** = ventricular fibrillation (Heart Rhythm 2013;10:604–606)

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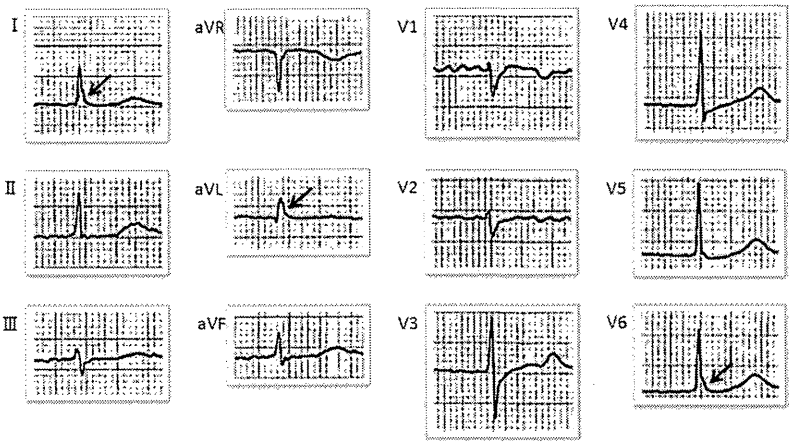

Figure 1 Twelve-lead electrocardiogram (ECG) during the first hospitalization. The ECG showed atrial fibrillation with a J-point elevation and horizontal/descending ST-segment pattern in leads I, aVL, and V_6.

increased her heart rate from 40–45 per minute to 60–80 per minute during sleep and in the early morning during an AF rhythm.

After discharge with cilostazol, the patient has remained asymptomatic with no further tachyarrhythmic episodes requiring device therapy for more than 12 months.

Discussion

To the best of our knowledge, this is the first case report to demonstrate the efficacy of cilostazol therapy in preventing recurrent VF in a patient with ERS as in Brugada syndrome. Early repolarization is characterized by an elevation of the J point, which is thought to be a benign ECG manifestation. However, previous studies revealed a manifest association between an early repolarization pattern and idiopathic VF.[11] Haissaguerre et al reported that 31% of the idiopathic VF patients had an early repolarization pattern in the inferior and lateral leads. Recently, it was reported that ST-segment variations as well as the distribution and magnitude of the early repolarization pattern were related to the risk of arrhythmic death.[4,12] Tikkanen et al[12] showed that horizontal/descending ST-segment patterns with early repolarization are accompanied by an increased risk for arrhythmic death, but early repolarization patterns followed by rapidly upsloping ST segments after the J point are not associated with such a risk. Our patient, who experienced several ICD shocks due to VF during sleep or in the early morning, had a horizontal/descending ST-segment pattern with early repolarization on the 12-lead ECG and was refractory to a low dose of quinidine and bepridil. Ventricular pacing also could not suppress the VF episodes. We initiated the administration of cilostazol, an oral phosphodiesterase III inhibitor, based on the assumption that the mechanism of ERS was likely to be comparable to that in Brugada syndrome.[13] The arrhythmogenic mechanism of ERS is hypothesized to be due to an outward shift in the balance of the membrane ionic currents at the end of phase 2 of the action potential. A prominent I_{to}-mediated action potential notch in the ventricular epicardium, but not in the endocardium, produces a transmural voltage gradient during early ventricular repolarization. Either a decrease in the inward current (I_{Na} and I_{Ca}) or an increase in the outward current (I_{to}) accentuates the notch as a J wave.[2] A further outward shift in the currents during the early phase of the action potential can lead to a loss of the action potential dome, which generates phase 2 reentry and VF[6]; however, different mechanisms of J waves may share the I_{to} and I_{Ca} as a modulator unlike Brugada syndrome based on the different responses to sodium channel blockers.

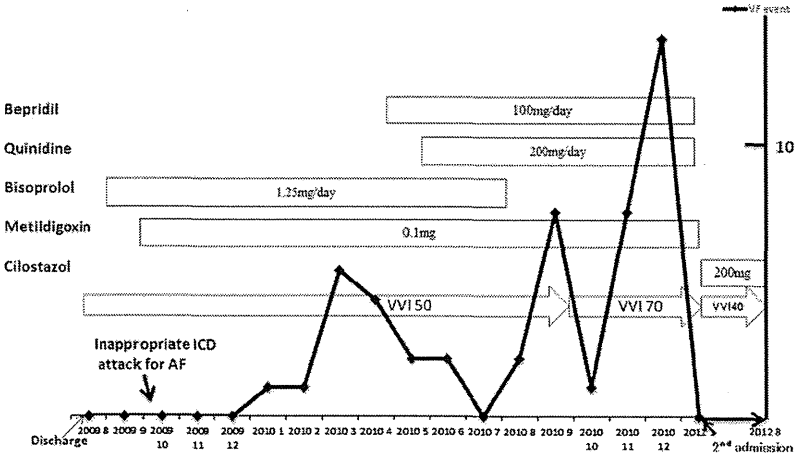

Figure 2 The relationship between the use of a drug and implantable cardioverter-defibrillator (ICD) discharges in the clinical course. The patient experienced several ICD shocks due to ventricular fibrillation (VF), which were refractory to a low dose of quinidine and bepridil. After cilostazol was initiated, no VF episodes were observed during a follow-up of more than 12 months. AF = atrial fibrillation.

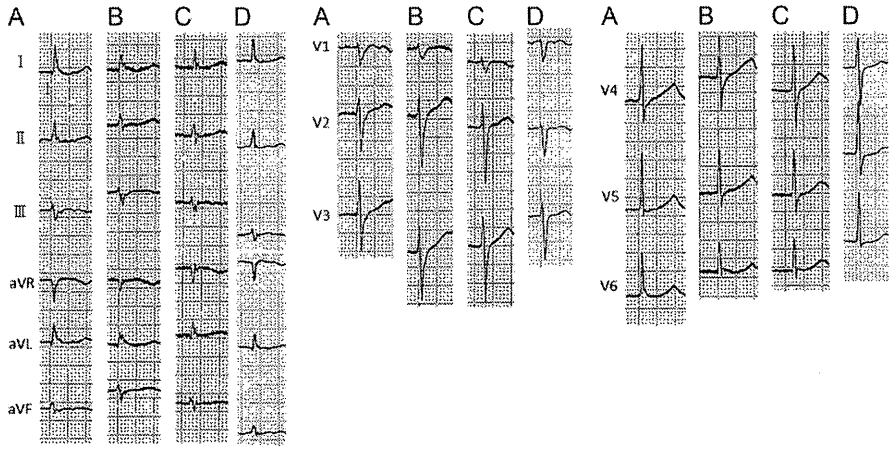

Figure 3 Twelve-lead electrocardiograms (ECGs) during baseline **(A)** and after pilsicainide **(B)**, isoproterenol **(C)**, and cilostazol **(D)**. An intravenous infusion of pilsicainide at a dose of 50 mg did not lead to any augmentation of the Brugada-like ST-segment elevation. After an intravenous application of isoproterenol 1 μg/min, the 12-lead electrocardiogram (ECG) revealed attenuation of the J-point elevation in leads I, aVL, and V_6 as compared to that in the baseline ECG. Oral administration of cilostazol also attenuated the J-point elevation in leads I, aVL, and V_6. ISP = isoproterenol; Pil = pilsicainide.

Quinidine, which inhibits I_{to} and reduces the magnitude of the J wave, was reported to be effective in preventing ventricular tachyarrhythmias in ERS.[7] However, our patient had multiple ICD discharges due to VF even after a small dose of quinidine. Since this case was a rather small-sized woman, we used a low dose of quinidine. The efficacy of quinidine in this ERS case is not conclusive because more than 600 mg of quinidine may be required to control arrhythmic storms in patients with ERS as with Brugada syndrome. Bepridil, a calcium channel blocker, which is also reported to be useful for preventing lethal tachyarrhythmias in Brugada syndrome by suppressing the I_{to}, was also ineffective. An acceleration in the heart rate reduces the I_{to} and is reported to decrease the magnitude of early repolarization (J wave),[14] and an increasing pacing rate from an ICD is reported to be effective in preventing recurrent VF in Brugada syndrome.[15] We tried to prevent the recurrent VF in our patient by increasing the pacing rate of the ICD. However, in this case, VVI pacing at a rate of 70 beats/min by the ICD could not prevent a VF recurrence. Finally, we used cilostazol, a phosphodiesterase type III inhibitor, because it increases the I_{Ca} and diminishes the I_{to} by increasing the intracellular level of the cyclic AMP and heart rate. In fact, cilostazol increased the heart rate from 40–45 per minute to 60–80 per minute during an AF rhythm. After the cilostazol was initiated, no VF episodes were observed during a follow-up of more than 12 months.

Conclusions

We experienced a case with recurrent VF associated with ERS refractory to a low dose of quinidine, which was prevented by the oral administration of cilostazol. Although cilostazol was useful in preventing recurrent VF in our patient with ERS, further studies are necessary to establish the clinical usefulness of this drug in patients with ERS.

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Letter to the Editor

SCN5A mutation associated with ventricular fibrillation, early repolarization, and concealed myocardial abnormalities ☆

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There is increasing evidence that early repolarization or J-wave in the inferolateral leads is associated with an increased risk of ventricular fibrillation and sudden cardiac death [1]. Mutations in ATP-sensitive potassium channel gene *KCNJ8* and L-type calcium channel genes including *CACNA1C*, *CACNB2B*, and *CACNA2D1* have been associated with idiopathic ventricular fibrillation with early repolarization [2,3]. Furthermore, we have recently identified mutations in *SCN5A*, which encodes the predominant cardiac sodium channel α subunit, in patients with idiopathic ventricular fibrillation who had early repolarization in the inferior leads and right precordial leads [4]. Mutations in *SCN5A* have also been associated with cardiomyopathy and concealed myocardial abnormalities [5–7]. Here, we describe a case with a mutation in *SCN5A* who had early repolarization in the inferior leads but not in the right precordial leads, ventricular fibrillation, and structural myocardial alteration.

Genetic testing was performed for mutations in ion channel genes including *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, and *KCNJ8*. Mutations identified were screened in 200 ethnically matched controls in our institutions and 5400 individuals on the Exome Variant Server of NHLBI GO Exome Sequencing Project (http://evs.gs.washington.edu/evs/). The functional effects of mutations were assessed using PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/). Right ventricular endomyocardial biopsy sample was stained with hematoxylin-eosin and Masson's trichrome, and examined by light microscopy. Immunostainings for N-cadherin and plakoglobin were also performed in the endomyocardial sample.

A novel missense mutation R1023C in *SCN5A* was identified in a 28-year-old Japanese man (Fig. 1A). The variant occurs at a residue within the highly conserved cytoplasmic linker between domains two and three (Fig. 1B and C). The mutation was absent in 200 controls. There was no variant affecting R1023 in *SCN5A* in 5400 individuals on NHLBI GO Exome Sequencing Project server, suggesting the pathogenicity of the mutation. The mutation was predicted to have damaging effects on protein functions by PolyPhen-2. The patient lost consciousness suddenly without any prior symptoms while lying on a bed after taking dinner. Ventricular fibrillation was recorded and electrical shock was delivered to restore sinus rhythm by emergency medical services. The physical examination and echocardiography were normal. His electrocardiogram showed prolongation of the PR interval and early repolarization in leads II, III, and aVF (Fig. 1D). A diagnostic type 1 Brugada ECG was not seen spontaneously or after the administration of sodium channel blocker pilsicainide (Fig. 1E). Pilsicainide attenuated early repolarization. During electrophysiologic study, His-ventricular interval was 51 ms and ventricular fibrillation was repeatedly induced by two extrastimuli performed from the right ventricular outflow tract (Fig. 1F). Although coronary angiogram revealed no significant stenosis, coronary spasm was provoked in the right and left coronary arteries by intracoronary administration of acetylcholine. Right ventricular endomyocardial biopsy revealed disarrangement of cardiomyocytes and intestinal fibrosis (Fig. 2A and B). Immunohistochemical analysis did not reveal any abnormalities of expression patterns of plakoglobin and cadherin, that are often affected in arrhythmogenic right ventricular cardiomyopathy (Fig. 2C and D). Left ventriculography, delayed enhanced cardiac magnetic resonance

☆ Disclosures: None.

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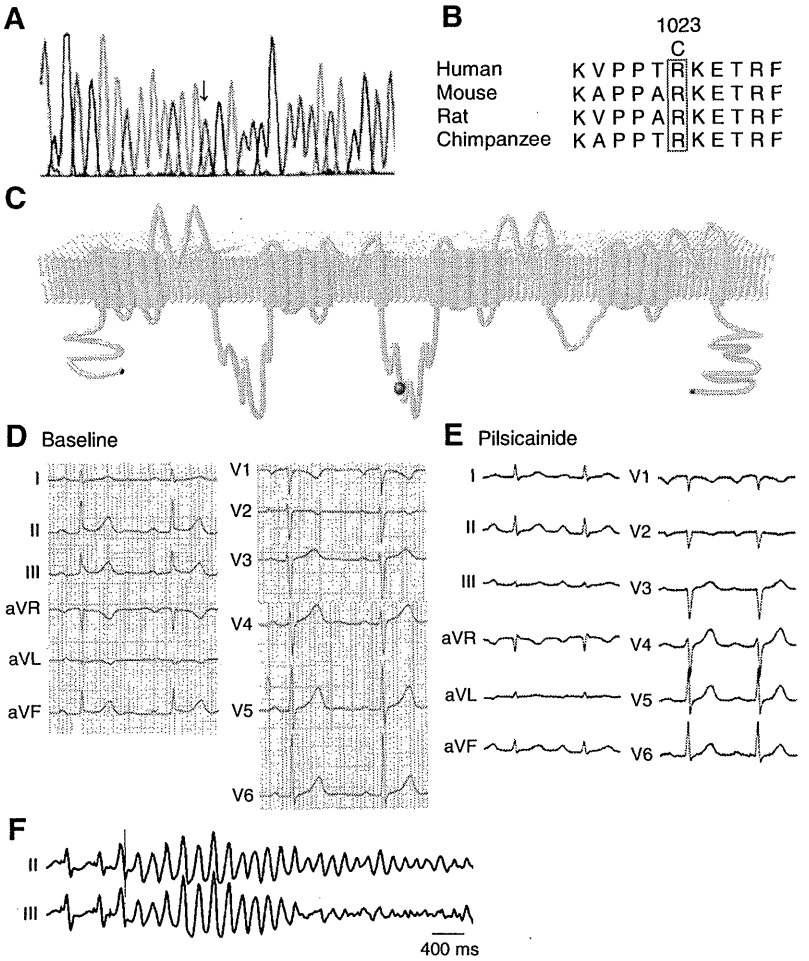

Fig. 1. Genetic and clinical characteristics in a patient with ventricular fibrillation associated with early repolarization. A, The c.3067C→T mutation in *SCN5A* resulting in p.R1023C found in the patient. B, Alignment of amino acids of SCN5A channel across species showing the high conservation of R1023. C, Predictive topology of SCN5A channel. A red circle indicates the location of the mutation. D, Early repolarization was present in the inferior leads. The PR interval was prolonged (250 ms). E, Administration of pilsicainide did not cause J-point elevation or Brugada type electrocardiogram. F, During electrophysiologic study, ventricular fibrillation was repeatedly induced. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

imaging, and thallium/beta-methyliodophenyl pentadecaonic acid (BMIPP) myocardial scintigraphy were normal. He received implantable cardioverter defibrillator. The patient's family history was negative for syncope, sudden cardiac death, and epilepsy. During a follow-up of 8 years, he was free from arrhythmia recurrence or heart failure.

Loss-of-function mutations in *SCN5A* have been associated with the increased susceptibility to arrhythmia syndromes [8]. In our recent study, mutations in *SCN5A* have been identified in patients with idiopathic ventricular fibrillation who had early repolarization in the right precordial leads in addition to the inferior leads, suggesting the similarities to Brugada syndrome [4]. In this report, a novel mutation in *SCN5A* was identified in a patient who had early repolarization in the inferior leads, but not in the right precordial leads. His electrocardiograms did not show J-point elevation or Brugada electrocardiogram in the right precordial leads even after sodium channel blocker challenge, supporting our hypothesis that mutations in *SCN5A* are responsible for idiopathic ventricular fibrillation associated with early repolarization. Evidence that the mutation is predicted to substitute a highly conserved residue across the spices, resulting in altered sodium channel function, and that there is no variant affecting the residue in a large number of controls suggests the disease causative of the mutation. Another mutation R1023H in *SCN5A*, which affects the same residue, has been associated with Brugada syndrome, further supporting the functional importance of the residue [7].

Mutations in *SCN5A* have been associated with myocardial changes in addition to the increased arrhythmia susceptibility. *SCN5A* is one of the causative genes for dilated cardiomyopathy [5], and using mice expressing the human *SCN5A* mutation associated with dilated cardiomyopathy, we have recently shown that reducing cardiac sodium current is the pathogenic mechanism for cardiomyopathy phenotype [9]. In patients with Brugada syndrome who carry a mutation in *SCN5A*, dilatation and contractile dysfunction of both ventricles have been revealed by cardiac magnetic resonance imaging, and concealed myocardial abnormalities have been frequently identified by endomyocardial biopsy [6,7]. In our patient heterozygously carrying the R1023C *SCN5A* mutation, histology showed myocardial abnormalities and intestinal fibrosis. Furthermore, the R1023H *SCN5A* mutation has been associated with cardiomyopathic changes and aneurysms in both ventricles, suggesting that R1023 may have a critical role in cardiac function in addition to that in electrophysiology [7]. Although the high frequency of inferolateral early repolarization in right ventricular arrhythmogenic cardiomyopathy has been reported [10], cardiac magnetic resonance imaging, histology, and immunostaining for plakoglobin were negative for diagnosis of right ventricular arrhythmogenic cardiomyopathy in our patient.

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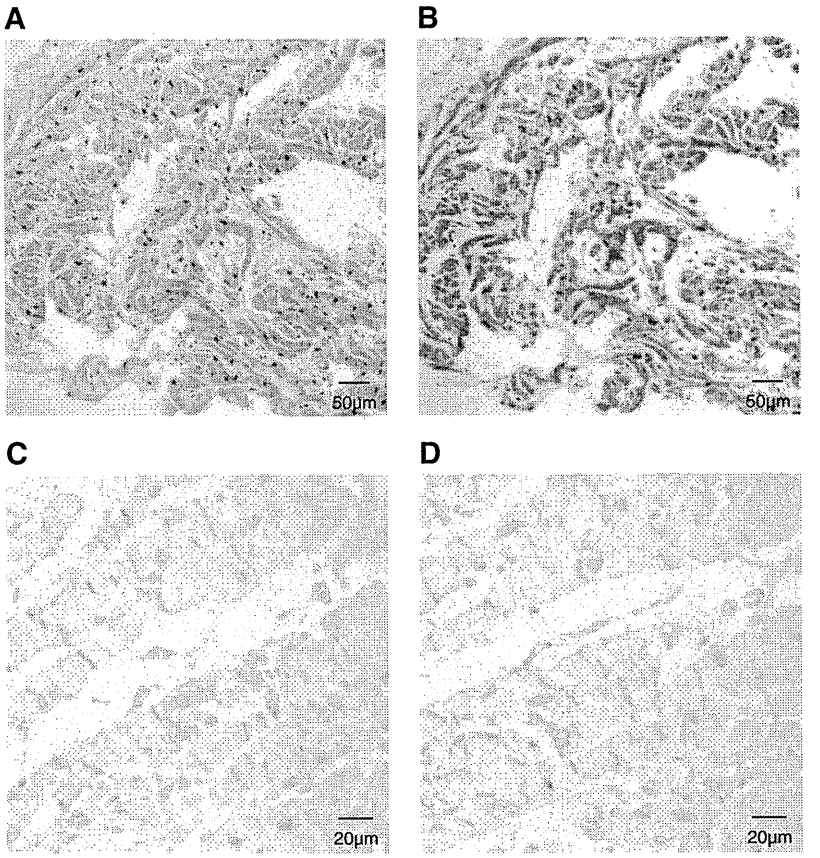

Fig. 2. Photomicrographs of right ventricular endomyocardial biopsy shows disarrangement of cardiomyocytes and intestinal fibrosis (A, hematoxylin and eosin; B, Masson's trichrome). Immunohistochemistry shows normal expressions of (C) plakoglobin and (D) N-cadherin.

In conclusion, our findings support the hypothesis that cardiac sodium channel dysfunction is associated with early repolarization, arrhythmia susceptibility, and myocardial degeneration.

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Safety and Efficacy of Implantable Cardioverter-Defibrillator During Pregnancy and After Delivery

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Background: There are few studies of pregnancy and delivery in patients with an implantable cardioverter-defibrillator (ICD). The purpose of this study was to investigate maternal and fetal outcome in these patients.

Methods and Results: Six pregnant women with an ICD were retrospectively reviewed. All women underwent implantation of an ICD before pregnancy and delivered at the National Cerebral and Cardiovascular Center. The mean age at pregnancy and the mean follow-up period after ICD implantation were 28±3 years old and 5±3 years, respectively. There was no device-related complication during pregnancy. In 4 women, the number of tachyarrhythmias such as non-sustained ventricular tachycardia increased after the end of the second trimester of pregnancy and anti-arrhythmic medications were gradually increased. No patient received discharges or shocks from the ICD during pregnancy, however, and only one required anti-tachycardia pacing at 27 weeks' gestation. Mean gestational age at delivery was 37±2 weeks and all deliveries were by cesarean section, including 5 as emergency deliveries due to a fetal indication. After delivery, 2 mothers had reduced cardiac function and 1 received an ICD shock for the first time.

Conclusions: Pregnancy did not increase the risk of an ICD-related complication under appropriate management. Additional caution might be required in the postpartum period as well as during pregnancy and labor.

Key Words: Beta-blocker; Delivery; Implantable cardioverter-defibrillator; Pregnancy; Ventricular tachycardia

Cardiac disease complicates approximately 1% of all pregnancies, and women with arrhythmias comprise only a small number of these cases.[1] Although arrhythmias are uncommon during pregnancy, they may jeopardize the health of both mother and fetus. Ventricular tachyarrhythmia may be triggered during pregnancy as a result of hemodynamic changes and autonomic nervous system modification.[2,3] Recurrence of malignant ventricular arrhythmias can be treated by defibrillation and anti-tachycardia pacing (ATP) to prevent sudden cardiac arrest.[4] An implantable cardioverter-defibrillator (ICD) improves survival in patients with life-threatening arrhythmias.[5] The number of women with congenital heart disease continues to increase and the use of an ICD has resulted in an increasing number of these women reaching a reproductive age.[6] Natale et al performed a multicenter retrospective analysis of 44 pregnant women with ICDs and found that the majority completed and tolerated pregnancy without serious complications.[7] There are few studies, however, of pregnancy with an ICD managed at a single center and it remains unclear how to manage pregnant women with ICDs. The aim of this study was to investigate the maternal and fetal outcomes in these patients during pregnancy and after delivery.

Editorial p????

Methods

Study Design

The subjects were all pregnant women with an implanted ICD who delivered at the National Cerebral and Cardiovascular Center. Data were retrospectively collected for age at the time of initial ICD implantation and delivery; heart disease and arrhythmia; New York Heart Association class; anti-arrhythmic medications and other anti-arrhythmic treatment; indication

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Table 1. Baseline Pre-Pregnancy Patient Characteristics

Patient	Heart disease	NYHA class	Age at ICD implantation (years)	LVEF at ICD implantation (%)	No. ICD shocks	Anti-arrhythmic medication	Other treatment
1	DCM, VT	2	25	37.5	0	Metoprolol	Catheter ablation
2	DCM, VF	2	23	21.3	2	Carvedilol, Mexiletine, Aprindine, Digoxin	
3	CHD†, VF	1	30	73.4	0	Mexiletine, Propranolol	
4	SSS, VT, PAF	1	26	62.7	16	Propranolol	PMI (DDD)
5	LQTS type 1	1	14	68.2	3	Atenolol	
6	LQTS type 2	1	26	56.5	0	Propranolol	
Mean±SD			25±6	53±20			

†Repair of coarctation of the aorta and patent ductus arteriosus, and aortic valve replacement for congenital bicuspid aortic valve.
CHD, congenital heart disease; DCM, dilated cardiomyopathy; DDD, dual-chamber inhibits and triggers; ICD, implantable cardioverter-efibrillator; LQTS, long QT syndrome; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; PMI, pacemaker implantation; SSS, sick sinus syndrome; VF, ventricular fibrillation; VT, ventricular tachycardia.

for ICD implantation; device information; device-related complications; number of ICD discharges and shocks; gestational age at delivery; mode of delivery; total blood loss at delivery; device status at time of delivery; and fetal and neonatal complications.

Data for maternal age, gestational age, left ventricular ejection fraction (LVEF), total blood loss during cesarean section, birth weight, and follow-up period are given as mean±SD.

Device Implantation

All ICDs were implanted via transvenous placement of a ventricular lead for defibrillation and pacing using standard techniques under fluoroscopic guidance. Pacing, sensing and defibrillation thresholds were tested during implantation. The devices used were manufactured by Medtronic (Minneapolis, MN, USA), Guidant (St Paul, MN, USA), and Boston Scientific (Natick, MA, USA).

Management of Pregnancy and Delivery

Fetal growth restriction was defined as an estimated fetal body weight <–1.5 SD of the Japanese standard value. Non-reassuring fetal status was diagnosed by cardiotocogram. Induction and augmentation of labor was performed according to obstetric or maternal indications using i.v. oxytocin following mechanical cervical dilation. Epidural anesthesia was electively used to minimize hemodynamic changes arising from pain or bearing down during labor and after cesarean section.

Results

Baseline Characteristics

Six Japanese women with an ICD who delivered between 2006 and 2012 were enrolled in the study. The mean follow-up after ICD implantation was 5±3 years (range, 2–9 years). The baseline pre-pregnancy characteristics of the 6 patients are given in **Table 1**. The indication for ICD implantation was secondary prevention in all women.

Patient 1 had dilated cardiomyopathy (DCM) with spontaneous ventricular tachycardia (VT) causing hemodynamic instability, for which catheter ablation was not effective. Patient 2 had DCM with chronic heart failure and repeated ventricular fibrillation (VF) that required cardioversion. Patient 3 had congenital heart disease, including coarctation of the aorta and patent ductus arteriosus that had been repaired at 2 years old. Aortic regurgitation progressed gradually because of a congenital bicuspid aortic valve and the patient had cardiopulmonary arrest caused by VF at 30 years of age. ICD implantation was performed following aortic valve replacement with a Carpentier-Edwards perimount valve. Patient 4 had sick sinus syndrome with repeated syncope and underwent permanent pacemaker implantation (dual-chamber inhibits and triggers) at 23 years old. This patient had wide QRS tachycardia, and ICD implantation was performed for spontaneous VT causing hemodynamic instability. This patient had experienced 16 ICD shocks in response to VF following paroxysmal atrial fibrillation (PAF) caused by acute pharyngitis. Patient 5 had repeated syncope once a year since 3 years of age and had been diagnosed with long QT syndrome type 1 on genetic testing at 10 years old. After introduction of atenolol at 18 years old, syncope reduced to once every 3 years. The severe long QT syndrome was linked to a double-point mutation in the potassium voltage-gated channel KQT-like subfamily, member 1 in re-testing at 25 years old. Her corrected QT time was 470–500 ms. Patient 6 had experienced repeated syncope since 25 years of age and had been diagnosed with long QT syndrome type 2 on genetic testing at 26 years old. Her corrected QT time was 430–470 ms.

Patients 1 and 4 had implanted dual-chamber ICDs with DDI pacing. The other 4 patients had implanted single-chamber ICDs with VVI pacing. All devices were programmed for the VF zone and 4 (patients 1–4) were also programmed for the VT zone with ATP such as burst and ramp pacing and cardioversion. Patient 2 had inappropriate ICD shocks due to sinus tachycardia, and the VT zone was used only for sensing before pregnancy. Patient 3 had no inappropriate ICD shocks due to discrimination of supraventricular tachycardia. Patient 4 received propranolol before pregnancy to avoid a recurrence of PAF during pregnancy.

Pregnancy and Labor

Baseline pregnancy and labor patient characteristics are given in **Tables 2,3**. There were no device-related complications. In 4 women the number of arrhythmias (patients 1–3, non-sustained VT; patient 4, PAF) increased after the end of the second trimester and anti-arrhythmic medications were gradually increased. During pregnancy, no patient received discharges or shocks from the ICD, and only 1 (patient 1) received ATP at 27 weeks' gestation. After ATP in patient 1, the detection zone was changed from 2 zones (VT 180 beats/min with 3 burst ATPs; VF 240 beats/min) to 3 zones (VT-1 160 beats/min with 3 burst and 3 ramp ATPs; VT-2 180 beats/min with 3 burst ATPs; VF 220 beats/min).

Labor was induced as planned in 3 cases: 2 (patients 1, 2)

Table 2. Baseline Pregnancy Patient Characteristics

Patient	Age at conception	LVEF in pregnancy (%)	NYHA class	No. ICD shocks	LVEF at delivery (%)	Anti-arrhythmic medications (mg/day)			
							1st trimester	2nd trimester	3rd trimester
1	26	61.1	2	0 (29 weeks ATP)	48.4	Metoprolol	40	160	200
2	27	47.7	2	0	44.2	Carvedilol/ Mexiletine/ Aprindine/ Digoxin	5/200/ 20/0.125	10/200/ 40/0.125	10/200/ 50/0.125
3	33	76.1	1	0	72.4	None			
4	29	61.8	1	0	68.8	Bisoprolol	2.5	5	5
5	25	54.8	1	0	51.3	Atenolol	50	50	50
6	28	56.2	1	0	57.3	Bisoprolol	5	5	5
Mean±SD	28±3	60±10			57±11				

ATP, anti-tachycardia pacing. Other abbreviations as in Table 1.

Table 3. Baseline Delivery Patient Characteristics

Patient	During delivery						After delivery		
	Weeks at delivery	ICD mode	Labor	Delivery mode	Indication for CS	Blood loss (ml)	Minimum LVEF (%)	No. ICD shocks	Follow-up period (months)
1	37	Off	Induced	Emergency CS	NRFS	1,190	42.1	1 (ATP 6)	12
2	37	Off	Induced	Emergency CS	NRFS	300	32.6	0	47
3	33	Off	None	CS	FGR	840	64.1	0	26
4	40	Off	Spontaneous	Emergency CS	NRFS	210	61.9	0	16
5	35	Off	Induced	Emergency CS	NRFS	340	59.3	0	12
6	38	On	Spontaneous	Emergency CS	NRFS	400	56.9	0	3
Mean±SD	37±2					547±384	53±13		19±15

Bood loss, total blood loss including amnion at cesarean section; CS, cesarean section; FGR, fetal growth restriction; NRFS, non-reassuring fetal status. Other abbreviations as in Tables 1,2.

Table 4. Baseline Fetus and Neonate Characteristics

Patient	Weeks at birth	Birth weight (g)	Apgar score (1 min)	Apgar score (5 min)	UmA pH	Fetal complications	Neonatal complications
1	37	2,684	7	9	7.312	NRFS	
2	37	2,622	8	9	7.283	NRFS	
3	33	1,240	8	9	7.332	FGR	Hypoglycemia, Hyperbilirubinemia
4	40	2,750	8	9	7.344	NRFS	
5	35	1,776	9	10	7.268	FGR, NRFS	Hypoglycemia, yperbilirubinemia, LQTS type1
6	38	2,188	8	10	6.963	FGR, NRFS	Metabolic acidosis, Hypoglycemia, LQTS type2
Mean±SD	37±2	2,210±603					

UmA, umbilical artery. Oher abbreviations as in Tables 1,3.

for maternal indication of increased non-sustained VT and reduction of cardiac function at 37 weeks' gestation, and 1 (patient 5) for fetal indication of fetal growth restriction and growth arrest at 35 weeks' gestation. All patients delivered by cesarean section under spinal and epidural anesthesia due to fetal indications. The ICD was turned off in patients 1–5 and turned on in patient 6 during labor and cesarean section. Electrocautery was not used during cesarean section. During delivery, there were no syncopal or hypotensive episodes and no patients received ICD discharges or shocks.

After Delivery

Baseline post-delivery patient characteristics are listed in **Table 3**. All but 2 women with DCM (patients 1, 2) breast-fed the neonate. Patient 1 had reduced LVEF before delivery and recovered within 1 month after delivery. She received an appropriate ICD shock after unsuccessful ATP for VT at 6 weeks after delivery. After an increase of β-blockers and construction of 2 more burst ATPs, there were no ICD shocks except for 6 ATP shocks for VT in 1 year after delivery. All ATP shocks were appropriate and successful. Patient 2 had reduced LVEF for 1 week and recovered within 1 month after delivery. In patient 4, PAF increased until 1 week after delivery. In the 2

women (patients 5, 6) with long QT syndrome, the corrected QT time was 505–510 ms and 460–490 ms, respectively; these were almost the same as before pregnancy, and there were no episodes of ventricular arrhythmia after delivery.

Fetus and Neonate Outcome

Baseline characteristics of fetuses and neonates are given in **Table 4**. Five neonates were born by emergency cesarean section due to non-reassuring fetal status. We observed persistent late decelerations in 3 fetuses and prolonged decelerations in 2 fetuses during labor on cardiotocogram. One neonate (patient 6) had metabolic acidosis that required infusion of bicarbonate. Two neonates (patients 3, 5) were born preterm and 3 (patients 3, 5, 6) were small for date. The 2 neonates of mothers with long QT syndrome (patients 5, 6) were also diagnosed with long QT syndrome on genetic testing. No major complications were observed in the observation period.

Discussion

To our knowledge, this is the largest single-center retrospective study to investigate the outcome of pregnancy in women with an ICD. According to the present 6 cases, pregnancy did not increase the risk of an ICD-related complication under appropriate management (eg, increase of β-blockers and change of the ICD setting), even though the number of ventricular arrhythmias increased after the end of the second trimester of pregnancy. Additional caution might be required in the postpartum period, as well as during pregnancy and labor.

Pregnancy and Ventricular Arrhythmia

Pregnancy is associated with reversible increases in blood volume, heart rate and cardiac output.[8,9] In some instances, these changes can trigger maternal cardiac deterioration during pregnancy.[10–13] Some studies have suggested that pregnancy may have an adverse effect on subsequent maternal cardiac outcome, perhaps as a result of the hemodynamic burden on ventricular structure and function during pregnancy.[14–17] Clearly, special caution is required for patients with an ICD with regard to cardiac function and arrhythmias. In this context, pregnancy can be thought of as a physiological stress test, and complications during pregnancy identify women at high risk for late events.[18] We monitored the ICD settings from before pregnancy to prevent inappropriate ICD discharges due to heart rate increases during pregnancy. In 1 case, β-blockers were introduced before pregnancy to avoid a recurrence of PAF during pregnancy. Although the number of tachyarrhythmias increased in all women after the end of the second trimester except in 2 with long QT syndrome, ICD discharges were not precipitated during pregnancy, when anti-arrhythmic medications were gradually increased and the setting of the ICD was changed.

Balint et al recommended that women at high cardiac risk should receive closer surveillance both during pregnancy and late after delivery.[19] Adverse events during pregnancy are associated with higher rates of late events, which makes it important to re-evaluate the cardiac status of women with pregnancy cardiac events more closely after pregnancy.[19] In the present study, 1 woman who had ATP at 27 weeks' gestation received her first ICD shock and several ATP events after delivery despite an increase of anti-arrhythmic medications and a change of the ICD setting. This suggests that additional caution may be required in the postpartum period, as well as during pregnancy and labor.

ICD Mode During Delivery

It remains unclear whether an ICD should be on or off during delivery. In the present study, no arrhythmias or ICD discharges were precipitated during delivery, as also reported by Natale et al.[7] In this respect, the status of the ICD during delivery appears to have no effect on the overall outcome. Recurrence of VT, however, decreases placental perfusion due to maternal hypotension and could be dangerous for the fetus. In contrast, ICD shocks are a concern for the safety of the fetus, although the amount of energy transferred to the uterus is very small and the fetal heart has a high fibrillatory threshold.[7,20] Based on these considerations, we have recently changed our policy to leave the device turned on during vaginal delivery or cesarean section, with the proviso that electrocautery is not used. Because elevated heart rate during labor may cause inappropriate ICD shock, a multidisciplinary approach involving specialists in maternal fetal medicine, cardiology and anesthesiology is needed for total management during labor and delivery for pregnant woman with an ICD. This management needs to be designed specifically to meet these needs at each hospital.

Fetal and Neonatal Complications

Three of the present fetuses (50%) had fetal growth restriction. Gelson et al found a significant reduction in fetal growth rates associated with maternal heart disease, and concluded that the presence of maternal cyanosis and reduced cardiac output are the most significant predictors of this condition.[21] These findings, however, are not necessarily applicable to the present cases.

In the present study, 5 patients (83%) were given β-blockers, and 2 of these experienced fetal growth restriction. Beta-blockers are considered to be reasonably safe for use during pregnancy, but may rarely cause fetal growth restriction, bradycardia, apnea, hypoglycemia, and hyperbilirubinemia of neonates.[22–25] Five patients delivered by emergency cesarean section due to non-reassuring fetal status (ie, hypoxia of the fetus or severe cord compressions in the uterus, which also occurs during labor in those without an ICD). Beta-blockers are thought to have little effect in the unstressed fetus, but adverse effects may become apparent during fetal distress because these drugs impair fetal response to distress.[25] Although the number of cases is small, β-blockers may have been related to fetal and neonatal complications, but these drugs are clearly effective for preventing life-threatening arrhythmias and inappropriate ICD shocks.[26] We consider use of β-blockers permissible during pregnancy on the condition that efficacy surpasses complications. Furthermore, as few drugs as possible and the safest drugs at the lowest effective doses should be chosen for use in pregnancy.

Study Limitations

There are several limitations in the study, including its retrospective design and the relatively small sample size. First, the present 6 patients were relatively low risk: ICD shocks were delivered before pregnancy only in 3 of the 6 patients; clinically documented ventricular arrhythmias were heterogeneous (VT in 2 patients and VF in the other 4 patients); and LVEF was preserved in 4 of the 6 patients. Because risk of recurrence of ventricular arrhythmias would be strongly associated with the clinical and arrhythmia background of pregnant women, further investigation is needed, including in patients with high risk for VT and VF. Second, it may be safe to leave the device turned on during vaginal delivery or cesarean section, but the sample size may have been too small to prove this

point. There were no ICD shocks during pregnancy, and therefore we are unable to determine whether ICD shocks are safe for the fetus. Third, the follow-up period after delivery was insufficient to permit analysis of long-term morbidity and mortality, which prevented evaluation of potential long-term benefits and the risks of use of an ICD after delivery. The present study, however, is worthwhile as a report of a single-center experience of a rare condition that we were able to follow up in 5 patients (83%) more than 1 year after delivery.

Conclusions

In the present 6 patients with an ICD, pregnancy did not increase the risk of an ICD-related complication under appropriate management (ie, increase of β-blockers and changing of the ICD setting). Additional caution may be required in the postpartum period as well as during pregnancy and labor. Guidelines are required for pregnancy and delivery in patients with an ICD. Further large prospective studies are needed to establish the most appropriate treatment strategies.

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Disclosure

None of the authors have a conflict of interest to disclose.

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Prognostic implications of mutation-specific QTc standard deviation in congenital long QT syndrome

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BACKGROUND Individual corrected QT interval (QTc) may vary widely among carriers of the same long QT syndrome (LQTS) mutation. Currently, neither the mechanism nor the implications of this variable penetrance are well understood.

OBJECTIVES To hypothesize that the assessment of QTc variance in patients with congenital LQTS who carry the same mutation provides incremental prognostic information on the patient-specific QTc.

METHODS The study population comprised 1206 patients with LQTS with 95 different mutations and ≥ 5 individuals who carry the same mutation. Multivariate Cox proportional hazards regression analysis was used to assess the effect of mutation-specific standard deviation of QTc (QTcSD) on the risk of cardiac events (comprising syncope, aborted cardiac arrest, and sudden cardiac death) from birth through age 40 years in the total population and by genotype.

RESULTS Assessment of mutation-specific QTcSD showed large differences among carriers of the same mutations (median QTcSD 45 ms). Multivariate analysis showed that each 20 ms increment in QTcSD was associated with a significant 33% ($P = .002$) increase in the risk of cardiac events after adjustment for the patient-specific QTc duration and the family effect on QTc. The risk associated with QTcSD was pronounced among patients with long QT syndrome type 1 (hazard ratio 1.55 per 20 ms increment; $P < .001$), whereas among patients with long QT syndrome type 2, the risk associated with QTcSD was not statistically significant (hazard ratio 0.99; $P = .95$; P value for QTcSD-by-genotype interaction = .002).

CONCLUSIONS Our findings suggest that mutations with a wider variation in QTc duration are associated with increased risk of cardiac events. These findings appear to be genotype-specific, with a pronounced effect among patients with the long QT syndrome type 1 genotype.

KEYWORDS Long QT syndrome; Corrected QT interval; Sudden cardiac death

ABBREVIATIONS **CI** = confidence interval; **ECG** = electrocardiogram/electrocardiographic; **HR** = hazard ratio; **LQTS** = long QT syndrome; **LQT2** = long QT syndrome type 2; **QTc** = corrected QT interval; **QTcSD** = QTc standard deviation; **SNP** = single nucleotide polymorphism

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Introduction

Congenital long QT syndrome (LQTS) is an inherited ion channelopathy that results in the prolongation of the repolarization phase of the cardiac action potential, predisposing affected individuals to potentially serious arrhythmic events and sudden cardiac death. LQTS is caused by a mutation in one of the several cardiac ion channels.[1] Overall, more than

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600 mutations have been identified in 13 genes, with long QT syndrome type 1 (LQT1), LQT2, and LQT3 comprising more than 95% of genotyped cases.[2]

Although the genetics of LQTS are well established, patients who share the same mutation may show a large variance in the duration of the corrected QT interval (QTc) and in the risk of cardiac events.[3,4] Currently, neither the mechanism nor the implications of this variable penetrance are well understood. It is possible that LQTS mutations that exhibit a wider range of QTc durations are more likely to be affected by modifier genes and/or environmental factors, which have been shown to increase predisposition to ventricular tachyarrhythmic events.[5] The present study was designed to examine QTc variance among patients with identical mutations and its association with the risk of LQTS-related cardiac events. We hypothesized that the assessment of QTc variance among carriers of the same LQTS mutation may provide incremental prognostic information on the patient-specific QTc.

Methods

Study population

The study population was derived from the International LQTS Registry and comprised 1205 patients with LQTS with 95 different mutations from 174 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. The selection criteria included patients who (1) were genetically tested and found positive for only a single known LQT1–3 mutation and (2) shared that mutation with at least 4 other individuals from the registry who were included in the study. Patients with >1 mutations, as well as those with congenital deafness, were excluded from the study.

Data collection

Routine clinical and rest electrocardiographic (ECG) parameters were acquired at the time of enrollment for all study patients. Measured parameters on the first recorded ECG included QT and RR intervals in milliseconds, with QT corrected for heart rate by using the Bazett formula.[6] Clinical data were collected on prospectively designed forms, with information on demographic characteristics, personal and family medical history, ECG findings, therapies, and events during long-term follow-up. Data common to all LQTS registries involving genetically tested individuals were electronically merged into a common database for the present study.

The *KCNQ1*, *KCNH2*, and *SCN5A* mutations were identified with the use of standard genetic tests performed in academic molecular-genetic laboratories, including the Functional Genomics Center, University of Rochester Medical Center, Rochester, NY; Baylor College of Medicine, Houston, TX; Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN; Boston Children's Hospital, Boston, MA; Laboratory of Molecular Genetics, National Cardiovascular Center, Suita, Japan; and Department of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands.

Definitions and end point

Mutation-specific QTc standard deviation

We assessed the standard deviation of the mean QTc (QTcSD) among patients carrying the same mutation (ie, the square root of QTc variance among patients with the same mutation). In the analyses, QTcSD was used as both a continuous measure and a categorical covariate. The approximate median value of the mutation-specific QTcSD was used to dichotomize patients with mutations exhibiting a high ($\geq$45 ms) and a low ($<$45 ms) QTcSD.

Individual QTc

The QTc for each patient (patient-specific QTc) was dichotomized at 500 ms on the basis of prior studies and was also assessed as a continuous measure.

Family-specific QTcSD

To differentiate between the effect of mutation-specific QTcSD on the risk of cardiac events and that of QTc variance among family members, all findings were further adjusted for the family-specific QTcSD.

Individual QTcSD during follow-up

In an additional analysis, we evaluated the effect of the degree of QTc variance in an individual during follow-up (defined as patient-specific QTcSD during follow-up) on the risk of cardiac events. This analysis was carried out in a subset of 360 study patients who had $\geq$3 ECGs obtained during follow-up.

The primary end point of the study was the occurrence of a first cardiac event, comprising syncope (defined as transient loss of consciousness that was abrupt in onset and offset), aborted cardiac arrest (requiring external defibrillation as part of the resuscitation), or LQTS-related sudden cardiac death (death 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), whichever occurred first, from birth through age 40 years. The consistency of the results was assessed in a secondary analysis that also included a first appropriate implantable cardioverter-defibrillator shock in the composite cardiac event end point.

Statistical analysis

The clinical characteristics of the patients in the study were compared by QTcSD category (dichotomized at the median value). Comparisons were performed by using χ^2 tests for categorical variables and Mann-Whitney-Wilcoxon and t tests for continuous variables.

The Kaplan-Meier estimator was used to assess the time to first cardiac event and the cumulative event rates by QTcSD and by combined assessment of QTcSD with individual QTc, and groups were compared by using the log-rank test.

Multivariate Cox proportional hazards regression analysis was carried out in the total study population to evaluate the effect of QTcSD, patient-specific QTc, and family-specific QTcSD on the risk of a first cardiac event. Additional covariates in the multivariate models included sex, time-dependent beta-blocker therapy, and the LQTS genotype. 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. The patient-specific QTc and QTcSD were assessed both as continuous measures and as categorical covariates in 2 separate models. In a secondary analysis, findings were also adjusted for the individual QTc variance during follow-up in a subset of 360 patients who had ≥3 follow-up ECGs.

The association of QTcSD with the risk of cardiac events among patients with LQT1 and LQT2 was assessed by including a QTc-by-LQTS genotype interaction term in the multivariate model that included patients with LQT1 and LQT2 (n = 953). Patients with the LQT3 genotype were not included in this analysis owing to sample size limitations (n = 163).

Because almost all the subjects were first- 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.[7] 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, NC). A 2-sided $P = .05$ significance level was used for hypothesis testing.

Results

The approximate median value of mutation-specific QTcSD was 45 ms (range 12 ms to a maximum of 101 ms; interquartile range 35–53 ms).

The clinical characteristics of study patients compared by QTcSD category are summarized in Table 1. Patients who were carriers of mutations with a high QTcSD (≥45 ms) also had a significantly higher mean individual QTc and were treated with LQTS therapies at a higher frequency compared with patients who were carriers of mutations with a low QTcSD. A LQTS genetic subtype analysis also revealed differences between the 2 groups: patients with LQT2 comprising a higher frequency of mutations with a high QTcSD (Table 1).

Risk of cardiac events by mutation-specific QTcSD

Patients with a high QTcSD had a higher frequency of cardiac events during follow-up (Table 1). Kaplan-Meier survival analysis showed that the cumulative probability of cardiac events from birth through age 40 years was significantly higher among patients who were carriers of mutations with a high QTcSD (50%) as compared with those who were carriers of mutations with a lower QTcSD (34%; $P < .001$ for the overall difference during follow-up; Figure 1). Furthermore, patients who had both high individual QTc (>500 ms) and mutation-specific QTcSD (≥45 ms) experienced a significantly higher rate of cardiac events during follow-up as compared with patients who had a lower range of either or both of those values (Figure 2).

Consistent with those findings, multivariate analysis showed that the mutation-specific QTcSD was independently associated with a significant increase in the risk of cardiac events after adjustment of the patient's individual QTc and the family-specific QTcSD (Table 2). When assessed as a continuous measure, each 20 ms increment in QTcSD was shown to be independently associated with a significant 33% ($P = .02$) increase in the risk of cardiac events after adjustment for the patient-specific QTc duration (Table 2). Similarly, when dichotomized at the median value, QTcSD ≥45 ms was independently associated with a significant 48% increase in the risk of cardiac events (hazard ratio [HR] 1.48; 95% confidence interval [CI] 1.02–2.14).

Table 1 Characteristics of study patients compared by QTcSD category

Characteristic	Low QTc variance (QTcSD <0.45 ms) (n = 606)	High QTc variance (QTcSD ≥0.45 ms) (n = 599)	P
Sex: female	58%	56%	.52
QTc (ms)	471 ± 38	489 ± 60	<.001
RR interval (ms)	833 ± 215	824 ± 239	.37
LQTS subtype			
LQT1	50%	48%	.50
LQT2	35%	40%	.001
LQT3	15%	12%	.002
Therapies*			
Beta-blockers	13%	18%	.02
Pacemaker	3%	6%	.02
LCSD	1%	1%	.78
ICD	13%	14%	.56
Cardiac events			
Syncope	27%	40%	<.001
Appropriate ICD Shocks†	0.4%	1.6%	.03
ACA/SCD	7%	13%	.01

Data are presented as percentages or as mean ± SD. All cardiac event subtypes are defined as the incidence of any event observed during the follow-up period.

ACA = aborted cardiac arrest; ICD = implantable cardioverter-defibrillator; LCSD = left cardiac sympathetic denervation; LQT1, 2, 3 = long QT syndrome types 1, 2, and 3, respectively; QTc = corrected QT interval; QTcSD = QTc standard deviation; SCD = sudden cardiac death.

*The percentage of patients treated with each of the therapies at any time during follow-up (ie, from birth through age 40 years).

†Frequency within the total study population.

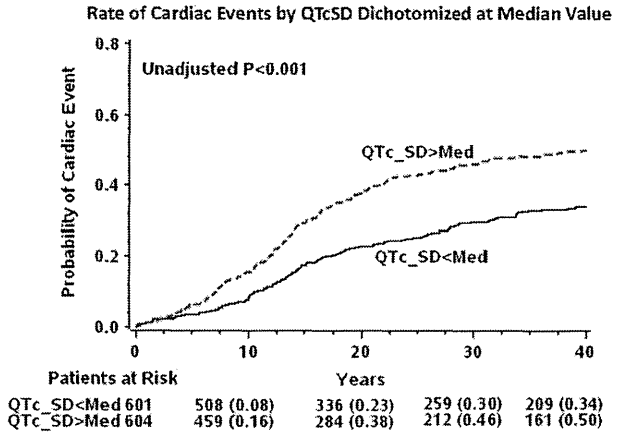

Figure 1 Kaplan-Meier estimates of the cumulative probability of a first cardiac event by QTcSD, categorized at the median value. QTc = corrected QT interval; QTcSD = QTc standard deviation.

In a secondary analysis comprising 360 patients who had ≥3 follow-up ECGs, we evaluated the association of mutation-specific QTcSD with the risk of cardiac events after further adjustment for patient-specific QTcSD during follow-up. This analysis showed that the mutation-specific QTcSD, when dichotomized at the median value of ≥45 ms, was still a statistically significant independent predictor of cardiac events (HR 1.17; 95% CI 1.00–1.87) while the risk associated with QTcSD during follow-up was not statistically significant (HR 1.61 per 20 ms increment in QTcSD in each patient during follow-up; 95% CI 0.73–3.55).

Beta-blocker therapy was associated with a significant 49% ($P < .001$) reduction in the risk of cardiac events among patients with QTcSD ≥45 ms and with a corresponding 39% ($P < .001$) risk reduction among patients with a lower QTcSD (P value for the difference = .22).

Assessment of mutation-specific QTcSD by genotype

The association of QTcSD with the risk of cardiac events was shown to be significantly different between patients with LQT1 and patients with LQT2. Kaplan-Meier survival analysis showed that among patients with LQT1, those with a high mutation-specific QTcSD experienced a pronounced increase in the cumulative probability of cardiac events as compared with those with a lower mutation-specific QTcSD (55% vs 31%, respectively, at age 40 years; $P < .001$ for the overall difference during follow-up; Figure 3A). In contrast, among patients with LQT2, the rate of cardiac events during follow-up was similar between those with a high vs a low QTcSD (46% vs 41%, respectively, at age 40 years; $P = .23$ for the overall difference during follow-up; Figure 3B). Consistent with those findings, multivariate analysis (Table 3) showed that among patients with LQT1 each 20-ms higher mutation-specific QTcSD was associated with a significant increase in the risk of cardiac events (55% per 20 ms increment in QTcSD; $P < .001$]) whereas among patients with LQT2 the effect of mutation-specific QTcSD was not statistically significant (HR 0.99; $P = .95$). Similar findings were obtained in the multivariate models in which QTcSD was categorized at the median value of 45 ms, showing that among patients with LQT1 a high QTcSD was associated with a significant 90% ($P = .003$) increase in the risk of cardiac events after adjustment for the individual QTc (Table 3).

Discussion

The present results provide several important implications for risk assessment in this population: (1) patients with LQTS with identical mutations may exhibit a wide variance in the QTc duration; (2) a high mutation-specific QTcSD has important prognostic implications that are independent of those related to the individual's own QTc; and (3) the risk associated with a higher QTcSD is pronounced among patients with LQT1, but was not observed among patients with LQT2, with a statistically significant interaction effect by genotype. These findings suggest that data regarding mutation-specific characteristics should be incorporated in the risk assessment of patients with LQTS.

Congenital LQTS is an inherited disorder caused by more than 600 known mutations in 12 cardiac ion channels.[2] The mutations lead to QTc prolongation because of the modulation of cardiac ion channel function. Although QTc has been well established as an important clinical predictor of

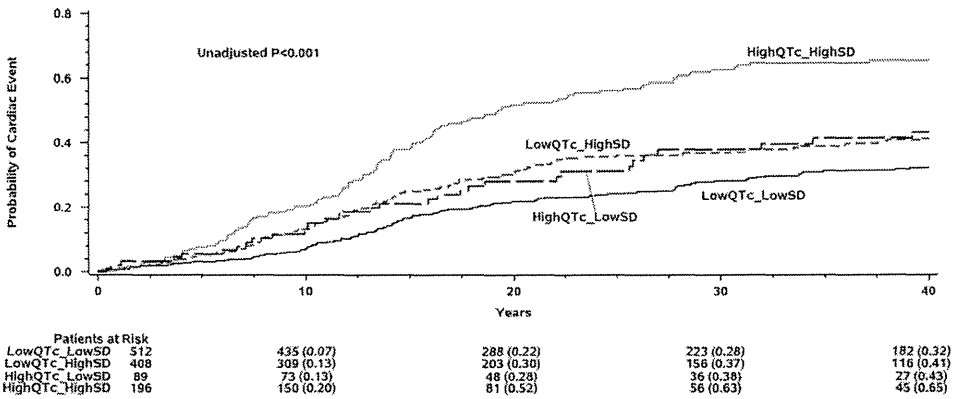

Figure 2 Kaplan-Meier estimates of the cumulative probability of a first cardiac event by a combined assessment of QTcSD and individual QTc dichotomized at 45 ms (median value) and 500 ms, respectively. QTc = corrected QT interval; QTcSD = mutation-specific QTc standard deviation.

Table 2 Multivariate analysis: Effect of patient-specific baseline QTc, mutation-specific QTcSD, and family-specific QTcSD on the risk of cardiac events in the total study population*

Predictor	HR	95% CI	*P*
Mutation-specific QTcSD (per 20 ms increment)	1.33	1.23–1.59	.002
Individual baseline QTc (per 20 ms increment)	1.13	1.09–1.17	<.001
Family-specific QTcSD (per 20 ms increment)	0.64	0.40–1.02	.06

CI = confidence interval; HR = hazard ratio; QTc = corrected QT interval; QTcSD = QTc standard deviation.

*All findings are further adjusted for age and sex (ie male vs female risk before and after age 13 years), time-dependent beta-blocker therapy, and the LQTS genotype; similar results were obtained in a secondary analysis in which the composite cardiac event end point also included the occurrence of a first appropriate implantable cardioverter-defibrillator shock.

adverse cardiac events,[1,8,9] it may lead to risk under- or overestimation if used alone.[10] Age and sex both have also been demonstrated as important clinical factors that modulate risk in a patient with congenital LQTS.[11] However, even risk assessment that incorporates these 3 clinical parameters remains incomplete, and it has been shown that mutation-related factors, such as the location and biophysical function, also contribute to the risk of cardiac events independently of the phenotypic expression in an individual patient.[12,13] Our findings extend these data and suggest that mutations that express a high variance in QTc duration among affected individuals identify those with increased risk of cardiac events, with a pronounced effect among patients with the LQT1 genotype.

The mechanism underlying our findings regarding the independent prognostic implications of mutations-specific QTc variance may relate in part to the increased susceptibility of certain LQTS mutation to the effects of modifiers of ion-channel activity. These may include environmental and biological factors, such as differences in the level of exercise activity or QT-prolonging drugs. We have recently shown that the standard Bazett QT correction formula does not adjust sufficiently for heart rate in patients with LQT1, with patients carrying this genotype requiring a greater degree of QT correction for heart rate for risk assessment than do patients with LQT2.[14] Thus, it is possible that mutations in the LQT1 gene with a wider QTc variance are more sensitive to heart rate changes, resulting in an increased susceptibility to cardiac events even among patients with a lower individual QTc.

Possible effects of modifier genes may relate to the risk of arrhythmic events in patients with LQTS from different families who carry the same mutation. As our knowledge of genomics has grown, it is now evident that each individual's genetic disease risk is the result of an immense collection of gene variants including those inherited from ancient ancestors, more recent ancestors, and mutations occurring de novo. Furthermore, because significantly deleterious mutations are eliminated over a long period of time through natural selection, recently inherited and de novo mutations (although occurring at a lower frequency) are likely to have a greater effect on an individual's overall disease susceptibility.[15] Crotti et al[16] showed that the common single nucleotide polymorphism (SNP) *K897T* exaggerates the electrophysiological consequences of the LQT2 *A1116V* mutation. Furthermore, it was recently shown that SNPs in the 3′ untranslated region of *KCNQ1* modify disease severity in LQT.[16] Thus, it is possible that some LQTS mutations are more sensitive to the effects of certain common SNPs, possibly leading to increased QTc variance related to the copresence of SNPs and a higher risk of arrhythmic events among patients who carry both more sensitive mutations and SNPs.

We have previously shown that the maximum QTc during follow-up in an individual provides incremental prognostic information on the baseline QTc.[17] Our study extends this information and shows that certain high-risk LQTS mutations (with increased QTcSD) are associated with increased risk of arrhythmic events independently of the QTc present in an individual or a sibling.

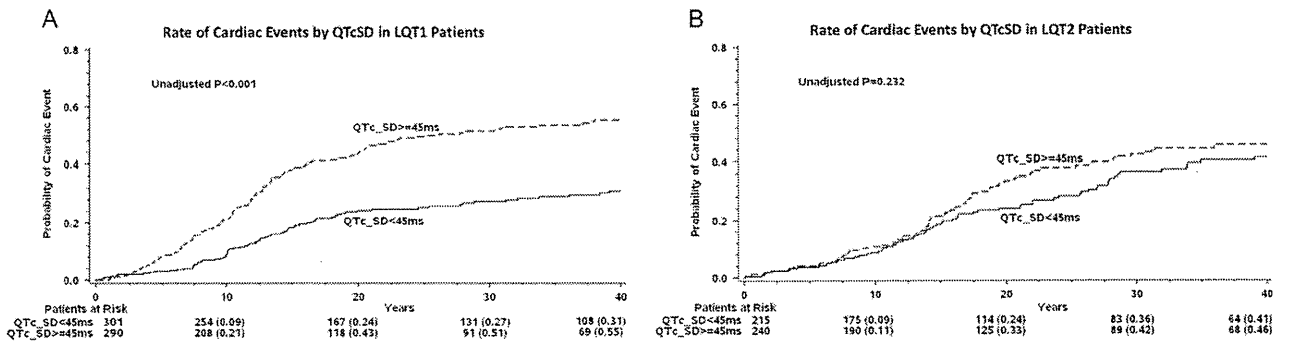

Figure 3 Kaplan-Meier estimates of the cumulative probability of a first cardiac event by QTcSD dichotomized at 45 ms (median value) in (**A**) patients with LQT1 and (**B**) patients with LQT2. LQT1, 2 = long QT syndrome types 1 and 2, respectively; QTc = corrected QT interval; QTcSD = mutation-specific QTc standard deviation.

Table 3 Multivariate analysis: Effect of mutation-specific QTc variance and individual-specific QTcSD on the risk of cardiac events by genotype*†

Predictor	HR	95% CI	P
	Patients with LQT1 (n = 532)		
QTc and QTcSD assessed as continuous measures			
Mutation-specific QTcSD (per 20 ms increment)	1.55	1.20–2.00	<.001
Individual baseline QTc (per 20 ms increment)	1.14	1.09–1.18	<.001
QTc and QTcSD assessed as categorical variables			
Mutation QTcSD ≥45 ms vs <45 ms	1.90	1.25–2.90	.003
Individual QTc >500 ms vs ≤500 ms	1.83	1.20–2.80	<.001
	Patients with LQT2 (n = 421)		
QTc and QTcSD assessed as continuous measures			
Mutation-specific QTcSD (per 20 ms increment)	0.99	0.84–1.17	.95
Individual baseline QTc (per 20 ms increment)	1.14	1.10–1.18	<.001
QTc and QTcSD assessed as categorical variables			
Mutation QTcSD ≥45 ms vs <45 ms	0.87	0.61–1.14	.44
Individual QTc >500 ms vs ≤500 ms	2.50	1.94–3.22	<.001

CI = confidence interval; HR = hazard ratio; LQT1, 2 = long QT syndrome types 1 and 2, respectively; QTc = corrected QT interval; QTcSD = QTc standard deviation.

*All findings are further adjusted for age and sex (ie, male vs female risk before and after age 13 years) and time-dependent beta-blocker therapy; similar results were obtained in a secondary analysis in which the composite cardiac event end point also included the occurrence of a first appropriate implantable cardioverter-defibrillator shock.

†Findings are obtained from an interaction model in which patients with LQT1 and LQT2 were included; *P* value for genotype-by-QTcSD interaction = .002; because of small number of patients with LQT3 (n = 163), analysis by genotype was carried out only in patients with LQT1 and LQT2.

Study limitations

The present study includes an analysis of 95 unique mutations from 174 proband identified LQTS families. Thus, it is possible that some of the findings relating to the association of mutation-specific QTcSD are related to a family effect. The fact that our results persisted after adjustment for a family effect on QTcSD further supports the consistency of the present findings.

We have shown that patients who harbor mutations with a high QTcSD experience a significant increase in the risk of cardiac events after adjustment for the individual QTc both at baseline and during follow-up. However, mutations with a high QTcSD comprise a larger proportion of patients with a higher individual QTc (as shown in Table 1). Thus, despite the independent findings after multivariate adjustment, it is still possible that the effect of a high mutation-specific QTcSD on clinical outcomes may be related (at least in part) to the presence of a larger proportion of patients with a higher individual QTc in this higher risk subset.

Conclusions and clinical implications

The present results suggest that mutation-specific QTcSD may be used to identify certain LQTS mutations that harbor increased arrhythmic risk independently of the phenotypic expression in an individual. This observation is consistent with our recent data, indicating that risk stratification in patients with LQTS should rely on combined assessment of both clinical and mutation-specific factors.

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Long-Term Follow-Up of a Pediatric Cohort With Short QT Syndrome

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Objectives The purpose of this study was to define the clinical characteristics and long-term follow-up of pediatric patients with short QT syndrome (SQTS).

Background SQTS is associated with sudden cardiac death. The clinical characteristics and long-term prognosis in young patients have not been reported.

Methods This was an international case series involving 15 centers. Patients were analyzed for electrocardiography characteristics, genotype, clinical events, Gollob score, and efficacy of medical or defibrillator (implantable cardioverter-defibrillator [ICD]) therapy. To assess the possible prognostic value of the Gollob score, we devised a modified Gollob score that excluded clinical events from the original score.

Results Twenty-five patients 21 years of age or younger (84% males, median age: 15 years, interquartile range: 9 to 18 years) were followed up for 5.9 years (interquartile range: 4 to 7.1 years). Median corrected QT interval for heart rate was 312 ms (range: 194 to 355 ms). Symptoms occurred in 14 (56%) of 25 patients and included aborted sudden cardiac death in 6 patients (24%) and syncope in 4 patients (16%). Arrhythmias were common and included atrial fibrillation ($n = 4$), ventricular fibrillation ($n = 6$), supraventricular tachycardia ($n = 1$), and polymorphic ventricular tachycardia ($n = 1$). Sixteen patients (84%) had a familial or personal history of cardiac arrest. A gene mutation associated with SQTS was identified in 5 (24%) of 21 probands. Symptomatic patients had a higher median modified Gollob score (excluding points for clinical events) compared with asymptomatic patients (5 vs. 4, $p = 0.044$). Ten patients received medical treatment, mainly with quinidine. Eleven of 25 index cases underwent ICD implantation. Two patients had appropriate ICD shocks. Inappropriate ICD shocks were observed in 64% of patients.

Conclusions SQTS is associated with aborted sudden cardiac death among the pediatric population. Asymptomatic patients with a Gollob score of <5 remained event free, except for an isolated episode of supraventricular tachycardia, over an average 6-year follow-up. A higher modified Gollob score of 5 or more was associated with the likelihood of clinical events. Young SQTS patients have a high rate of inappropriate ICD shocks. (J Am Coll Cardiol 2013;61:1183–91) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ECG = electrocardiography

ICD = implantable cardioverter-defibrillator

IQR = interquartile range

QTc = corrected QT interval for heart rate using the Bazett formula

SCD = sudden cardiac death

SQTS = short QT syndrome

SVT = supraventricular tachycardia

VF = ventricular fibrillation

The short QT syndrome (SQTS) is a primary cardiac electrical disease and one of the recent additions of inherited arrhythmias associated with sudden cardiac death (SCD). Although believed to be a rare condition, the entire disease spectrum continues to emerge with newly recognized cases, and as we continue to understand the disease better and to characterize it more fully, a broader disease spectrum may be revealed. The underlying pathophysiological features involve shortening of myocardial repolarization, which creates the electrical substrate for atrial and ventricular tachyarrhythmias (1). The arrhythmogenic potential of a short QT interval was described first by Gussak et al. (2). To date, genetic studies have shown that SQTS is associated with gain-of-function mutations in 3 different potassium channels (3–6) and 3 loss-of-function mutations in the L-type cardiac calcium channel, although forms of short QT interval associated with calcium channelopathies show phenotypic overlap with Brugada syndrome (7,8).

In SQTS, the corrected QT interval for heart rate using the Bazett formula (QTc) in most reported cases to date usually is <340 to 360 ms, with rare exceptions (9). A normal QT interval has been reported as 370 ± 30 ms in children (10) and 385 ± 24 ms in adults (11), with a slightly longer QT interval in post-pubescent females (12). According to population studies (13), a QTc interval of 340 to 360 ms has been proposed as the lower limit of normal. However, as demonstrated with long QT syndrome, there is an overlapping range of QT intervals between affected individuals (14) and apparently healthy subjects (15). It is likely SQTS cases with longer QTc interval exist. In contrast, the presence of a short QT interval in isolation may not always be indicative of SQTS. Thus, Gollob et al. (16) proposed diagnostic criteria for SQTS (Table 1).

The therapeutic approach to SQTS is not well defined. An implantable cardioverter-defibrillator (ICD) may be considered as primary therapy, given the known risk of SCD (17). However, the risk-to-benefit ratio of such an approach remains unknown, particularly in the young. Although hydroquinidine has demonstrated some benefit in a limited number of patients (18,19), there is limited experience with medical therapy.

To date, the long-term prognosis in young SQTS patients has not been reported. We set out to define the clinical characteristics and long-term outcomes of a pediatric cohort diagnosed with SQTS.

Methods

Study population. Pediatric SQTS patients (≤21 years of age at clinical presentation) from 15 centers in North and South America, Europe, and Japan were characterized clinically and were followed up beginning in 2007. Entry criteria included: 1) QT interval of 330 ms or less; or 2) QTc interval of 360 ms or less with 1 or more of the following: syncope, atrial fibrillation, ventricular fibrillation (VF), aborted SCD, positive family history of SQTS or unexplained SCD, or a combination thereof. A total of 28 patients were enrolled, of whom 25 met the inclusion criteria for this study: 1) a Gollob diagnostic score of 3 or more (indicating a moderate to high probability of SQTS); and 2) clinical follow-up longer than 1 year. Patient demographic data were collected. The ECG parameters analyzed included: QT interval, QTc interval, J point-to-T peak interval, and early repolarization. The QT interval was measured manually. The QTc interval was calculated using Bazett's formula. The J point was defined as the end of the QRS interval and the beginning of the ST segment. The T peak was measured at the highest point of the T-wave. Early repolarization was defined as an elevation of more than 0.1 mV of the J point from baseline in at least 2 contiguous

Table 1 SQTS Diagnostic Criteria: Gollob Score

	Points
QTc interval (ms)	
<370	1
<350	2
<330	3
J point-to-T peak interval <120 ms	1
Clinical history*	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

High-probability SQTS: ≥4 points, intermediate-probability SQTS: 3 points, low-probability SQTS: ≤2 points. Electrocardiogram must be recorded in the absence of modifiers known to shorten the QT interval. J point-to-T peak interval must be measured in the precordial lead with the greatest amplitude T-wave. Clinical history events must occur in the absence of an identifiable cause, including structural heart disease. Points can be received only for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope. Family history points can only be received once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section to obtain additional points.

QTc = corrected QT interval for heart rate using the Bazett formula; SQTS = short QT syndrome; VF = ventricular fibrillation; VT = ventricular tachycardia.

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