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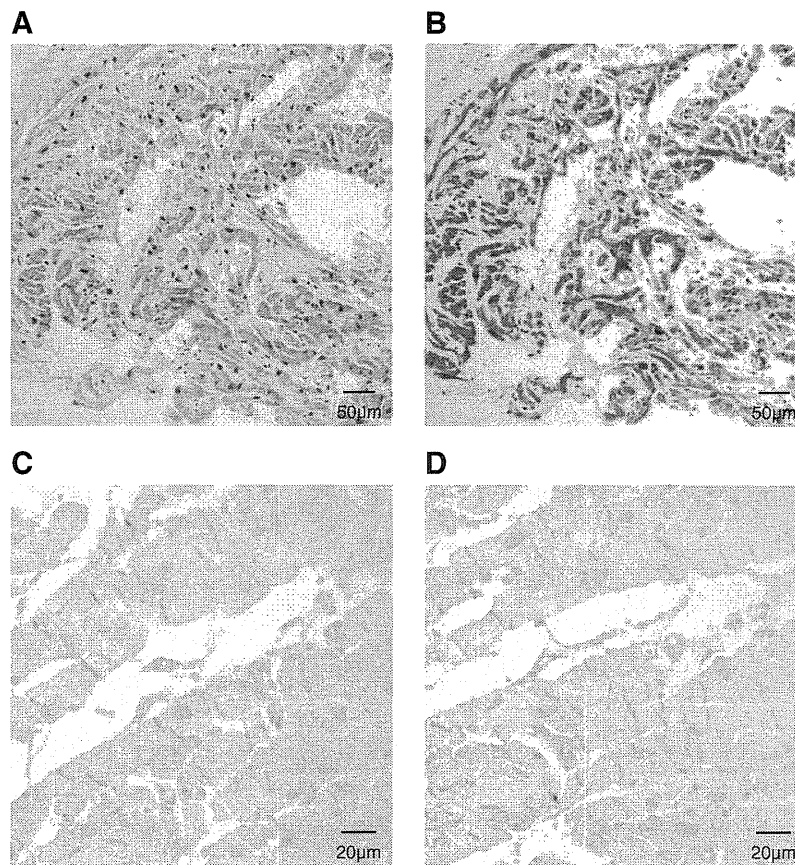
Fig. 2. Photomicrographs of right ventricular endomyocardial biopsy shows disarrangement of cardiomyocytes and intestinal fibrosis (A, hematoxylin and eosin; B, Masson's trichrome). Immunohistochemistry shows normal expressions of (C) plakoglobin and (D) N-cadherin.

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.

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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

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			

Table 1. Baseline Pre-Pregnancy Patient Characteristics

†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 470–500ms. 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 430–470ms.

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 180beats/min with 3 burst ATPs; VF 240beats/min) to 3 zones (VT-1 160beats/min with 3 burst and 3 ramp ATPs; VT-2 180beats/min with 3 burst ATPs; VF 220beats/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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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.

Table 2 SQTS Diagnostic Criteria: Modified Gollob Score	
	Points
QTc interval (ms)	
<370	1
<350	2
<330	3
J point-to-T peak interval <120 ms	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

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. Family history points can be received only once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section to obtain additional points.
  Abbreviations as in Table 1.

leads in the inferior leads (II, III, aVF), lateral leads (I, aVL, V_4 to V_6), anterior leads (V_1 to V_3), or combinations thereof. The contour of the ST segment was classified as having either upsloping or horizontal (downsloping) morphological features. Patients with ICD were assessed for implant indication, delivered therapies, and device complications. We elected to explore the risk-stratifying value of specific variables within the Gollob scoring system. Thus, the diagnostic Gollob score was modified, by excluding clinical events, into a new prognostic score referred to as the modified Gollob score (Table 2).

Statistical analysis. Continuous variables are presented as mean ± SD or median (interquartile range [IQR]: 25th to 75th percentile). Analyzed continuous variables are presented only as medians with IQR and were analyzed using the Wilcoxon rank sum test. Categorical variables are presented as counts with percentages and were analyzed using the Fisher exact test or the chi-square test. Correlation between continuous data was analyzed using the Spearman correlation coefficient. Two-tailed p values of <0.05 were considered statistically significant. Statistical analysis was performed using SAS software version 9.3 (SAS Institute, Inc., Cary, North Carolina).

Results

Clinical data. There were 25 patients and a total of 21 (84%) were male. Their clinical data are presented in Table 3. Patients were followed up for a median of 5.9 years (IQR: 4 to 7.1 years). Patient age at the time of clinical presentation ranged from 1 day to 21 years (13.4 ± 6 years, median: 15 years, IQR: 9 to 18 years), with 9 patients (36%) younger than 12 years.

ECG. The QT interval varied from 160 to 360 ms (279 ± 51 ms, median: 290 ms, IQR: 280 to 300 ms), whereas the QTc interval ranged from 194 to 355 ms (304 ± 41 ms, median:

312 ms, IQR: 286 to 335 ms). The J point-to-T peak interval ranged from 63 to 180 ms (132 ± 35 ms, median: 140 ms, IQR: 119 to 160 ms). Arrhythmias were common: 4 patients had atrial fibrillation, 6 had VF, and 1 had supraventricular tachycardia (SVT) at presentation.

GENETIC TESTING. Genetic testing was undertaken in 21 of the 25 patients, and 5 patients had a confirmed mutation. All gene-positive patients were symptomatic, including a 3-month-old young female with recurrent atrial fibrillation since the age of 4 days and associated sinus and atrioventricular node dysfunction (KCNQ1 V141M). Tables 3 and 4 outline the culprit genes, specific mutations, and associated symptoms and arrhythmias detected in the gene-positive cohort.

FAMILY HISTORY. A personal or familial history of cardiac arrest was present in 16 (84%) of 25 patients. A familial history of SCD, presumed to be arrhythmogenic, was present in 5 symptomatic patients and in 6 asymptomatic patients. These involved 6 siblings (4 young males and 2 young females), 2 uncles, and 1 father. The equal distribution of familial SCD among symptomatic and asymptomatic individuals suggests that SCD alone may not predict prognosis, although numbers were relatively small in this study. Among the entire cohort, there was a positive family history for a clinical diagnosis of SQTS in 17 (68%) patients, equally distributed between parents and siblings. Among the patients with atrial fibrillation, only 1 of 4 had a family history of atrial fibrillation. In the patients with VF, only 1 of 6 had a first-degree relative (father) with SCD. Overall, the prevalence of symptomatic family members did not seem to be more common in symptomatic patients, although a much larger cohort would be required to assess confidently whether a symptomatic family member predicts individual risk. Only 4 of 25 patients had no family history of SQTS or SCD.

Symptomatic versus asymptomatic patients. Of the entire cohort, 14 (56%) patients had 1 or more clinical features associated with SQTS, including aborted SCD in 6 (24%), unheralded syncope in 4 (16%), and palpitations with documented atrial fibrillation in 4 (16%). The remaining 11 (44%) patients were asymptomatic, 10 of whom were identified through family screening and the remaining through an incidental ECG finding of a very short QTc interval (292 ms). There was no significant difference in median age between symptomatic and asymptomatic patients (median: 15 years, IQR: 8 to 17 years vs. median: 17 years, IQR: 9 to 18 years, p = 0.621). All but 1 of the asymptomatic cases had a family history of SQTS or unexplained SCD.

ECG PARAMETERS. No differences were found in the ECG parameters between asymptomatic and symptomatic patients (Table 3). Although the QTc interval tended to be shorter in symptomatic patients (median: 306 vs. 330 ms), the difference was not statistically significant (p = 0.207).

Table 3   Characteristics of All Patients

Variable	Total (n = 25)	Symptomatic* (n = 14)	Asymptomatic (n = 11)	p Value
Patient age at presentation (yrs)	15 (9–18)	15 (8–17)	17 (9–18)	0.621
Age <12 yrs	9 (36%)	4 (28.6%)	5 (45.5%)	0.434
Male	21 (84%)	11 (78.6%)	10 (90.9%)	0.604
Follow-up duration (yrs)	5.9 (4.4–7.1)	5.7 (4.8–7.4)	6.1 (3.2–6.9)	0.460
Symptoms				
Aborted SCD	6 (24%)	6 (43%)	—	
Unheralded syncope	4 (16%)	4 (28.5%)	—	
Palpitations†	4 (16%)	4 (28.5%)	—	
Modified Gollob score	5 (4–5)	5 (4–6)	4 (4–5)	0.044
Genetic mutation				
KCNH2	2 (8%)	2 (14%)	0	
KCNJ2	2 (8%)	2 (14%)	0	
KCNQ1	1 (4%)	1 (7%)	0	
ECG parameters				
QT (ms)	290 (280–300)	280 (200–300)	295 (280–320)	0.333
QTc (ms)	312 (286–335)	306 (252–329)	330 (292–335)	0.207
J point-to-T peak interval (ms)	140 (119–160)	130 (80–160)	140 (120–160)	0.344
J point-to-T peak interval <120 (ms)	7 (28%)	6 (42.9%)	1 (9.1%)	0.090
Early repolarization	12/24 (50%)	6/14 (43%)	6/10 (60%)	0.680
Family history				0.620
SQTS	8 (32%)	4 (28.6%)	4 (36.4%)	
SCD	4 (16%)	3 (21.4%)	1 (9.1%)	
SCD and SQTS	9 (36%)	4 (28.6%)	5 (45.5%)	
Negative	4 (16%)	3 (21.4%)	1 (9.1%)	
ICD	11 (44%)	8 (57.1%)	3 (27.3%)	0.227
Appropriate shocks	2 (18%)	2 (25%)	0	
Inappropriate shock	7 (63.6%)	4 (50%)	3 (100%)	
Complications‡	9 (81.8%)	6 (75%)	3 (100%)	

Values are median (interquartile range) or n (%). *Only patients with aborted sudden cardiac death, syncope, or documented ventricular or atrial fibrillation at presentation or during follow-up were considered symptomatic for short QT syndrome. †Palpitations and atrial fibrillation or supraventricular tachycardia. ‡Including inappropriate shocks.

ECG = electrocardiography; ICD = implanted cardiac defibrillator; J point-to-T peak interval = interval in milliseconds measured on standard electrocardiography ECG from the J-point to the peak T-wave voltage; SCD = sudden cardiac death. Other abbreviations as in Table 1.

There was a trend toward a higher prevalence of short J point-to-T peak interval (<120 ms) in the symptomatic versus the asymptomatic patients (42.9% vs. 9.1%, p = 0.090). Only 1 of the asymptomatic patients had a short J point-to-T peak interval. The presence of early repolarization did not differ between symptomatic and asymptomatic patients. Early repolarization was found in the anterior (n = 2), anterolateral (n = 2), lateral (n = 1), and anteroinferolateral (n = 1) leads in 43% of symptomatic cases. In 60% of asymptomatic cases, early repolarization was found in the inferolateral (n = 3) cases and in the anterior or lateral leads, or both (n = 3). In all cases, early repolarization had an upsloping ST segment pattern (Fig. 1).

GOLLOB DIAGNOSTIC SCORE FOR SQTS. Asymptomatic patients had Gollob scores ranging from 3 to 5 (median: 4, IQR: 4 to 5), whereas most symptomatic patients had higher Gollob scores ranging from 4 to 10 (median: 6, IQR, 6 to 8, p < 0.001).

A modified Gollob score, excluding clinical events, was assigned to each patient. Asymptomatic patients had modified Gollob scores ranging from 3 to 5 (median: 4, IQR: 4 to 5), whereas most symptomatic patients had higher scores ranging from 3 to 8 (median: 5, IQR: 4 to 6, p = 0.044).

ABORTED SCD. Aborted SCD occurred in 6 (24%) of 25 patients. These patients had a longer follow-up duration

Table 4   Genetic Mutations in the Pediatric Cohort

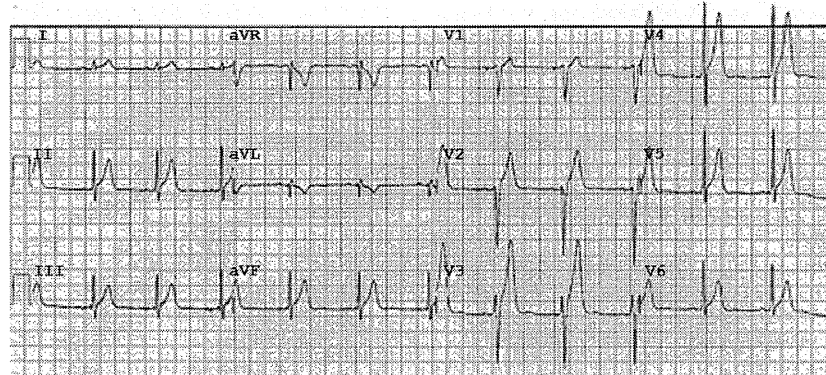| Age (yrs)	Sex	Gene	Mutation	Current	Symptoms	Arrhythmias
3	F	KCNQ1	V141M	IKs	None	Atrial fibrillation, sinus, and atrioventricular node dysfunction
5	F	KCNJ2	M301K	IK1	None	Atrial fibrillation
8	F	KCNJ2	M301K	IK1	None	Atrial fibrillation
14	M	KCNH2	N588K	IKr	Syncope	Ventricular fibrillation
19	M	KCNH2	E50D	IKr	Syncope	None

Figure 1   Representative 12-Lead Electrocardiogram of the Short QT Syndrome

Resting electrocardiogram (ECG) of a 15-year-old young male with aborted sudden cardiac death and a short QT interval (QT interval: 280 ms, QT interval corrected for heart rate [QTc]: 325 ms). There are peaked T waves in most of the precordial leads. The J point-to-T peak interval is 140 ms. There is early repolarization with upsloping ST segment in II, III aVF, and V_2 to V_6.

than those without aborted SCD (median: 7.3 years, IQR: 6.3 to 7.8 years vs. median: 5.3 years, IQR: 4.0 to 6.9 years, p = 0.045). A short J point-to-T peak (<120 ms) was more prevalent among the aborted SCD group (67% vs. 16%, p = 0.032) (Table 5). Five of these 6 patients had implantation of an ICD. In one instance, the parents declined an ICD for a 6-month-old young male (at the time of clinical presentation) with an ultra-short QT interval of 160 ms (QTc interval: 241 ms) who, at 80 months of follow-up, had no recurrent symptoms (Fig. 2). A positive family history of SQTS or SCD did not discriminate between aborted SCD and nonaborted SCD patients because of the high prevalence among the entire cohort. Early repolarization with upsloping ST segment in the anteroinferolateral leads was present in only 1 of the 6 patients with aborted SCD.

Therapy. ICD. Implantation of a cardioverter-defibrillator (ICD) was performed in 11 (44%) of 25 patients, in 6 as primary prevention (unexplained syncope in 2). Indications for ICD in the other 5 patients were aborted SCD or VF. Two (18%) patients had appropriate shocks: a 14-year-old young male (QT interval: 300 ms, QTc interval: 286 ms) with a history of aborted SCD while receiving quinidine at 9 mg/kg daily and a 14-year-old young male (QT interval: 248 ms; QTc interval: 252 ms) with a history of syncope and VF. The latter had no recurrent ICD appropriate shocks while taking quinidine. Two other patients had no shock and 7 (64%) had 1 or more inappropriate shocks. The underlying cause of inappropriate shocks was atrial fibrillation with rapid ventricular conduction (n = 1), sinus tachycardia (n = 3), SVT (n = 1), and ventricular lead fracture (n = 3), including 1 Sprint Fidelis lead (Medtronic, Minneapolis, Minnesota). There was an additional patient with a ventricular lead fracture 6 years after implantation that did not cause an inappropriate ICD shock. Of patients who received an ICD as primary prevention, 4 had inappropriate shocks.

MEDICAL THERAPY. Medical therapy was initiated in 10 (40%) of 25 patients, 4 of whom received multiple agents. Of the 4 patients with paroxysmal atrial fibrillation, 3 received quinidine therapy that proved unsuccessful in preventing recurrences of the arrhythmia. These patients were quite young, including an infant who also had recurrences while receiving propafenone and sotalol, a 5-year-old in whom flecainide also failed, and an 8-year-old. The remaining patient with atrial fibrillation was a 17-year-old young male (QT interval: 320 ms, QTc interval: 355 ms) (Fig. 3A) who was cardioverted at the time of ICD implantation, but continued to experience recurrences despite therapy with digoxin and propafenone. On treatment with digoxin and dofetilide, there was prolongation of the QT interval and return to sinus rhythm without symptomatic recurrences through follow-up (Fig. 3B). However, ICD interrogation identified asymptomatic, short episodes of atrial fibrillation. Two patients with a history of appropriate ICD shocks also received quinidine therapy. The first patient, a 14-year-old young male with aborted SCD, had a therapeutic shock while receiving quinidine 9 mg/kg daily. We were unable to confirm whether lack of compliance was the issue. The J point-to-T peak interval in this patient was 118 ms. He had a Gollob score of 8 with a QT interval of 300 ms (QTc interval: 286 ms). Genetic testing did not identify any known mutation. The second patient had no recurrent shocks while receiving quinidine therapy.

ARRHYTHMIAS ENCOUNTERED DURING FOLLOW-UP. Of the asymptomatic patients, only a 21-year-old man with an ICD as primary prevention had SVT resulting in inappropriate shocks and requiring ICD reprogramming. He had a modified Gollob score of 4. The other 10 asymptomatic cases with Gollob scores of 3 to 5 remained asymptomatic and arrhythmia-free during follow-up. In the group that was symptomatic at presentation, a 19-year-old man receiving no

Table 5 Comparison of Patients With Versus Without Aborted Sudden Cardiac Death

Variable	Aborted SCD (n = 6)	No Aborted SCD (n = 19)	p Value
Patient age at presentation (yrs)	14 (14–15)	17 (8–18)	0.632
Age <12 yrs	1 (16.7%)	8 (42.1%)	0.364
Male	6 (100%)	15 (79%)	0.540
Follow-up duration (yrs)	7.3 (6.3–7.8)	5.3 (4.0–6.9)	0.045
Genetic mutation (n = 21)			
KCNH2	1 (20%)	1 (6.3%)	
KCNJ2	0	2 (12.5%)	
KCNQ1	0	1 (6.3%)	
Negative	4 (80%)	12 (75%)	
Family history			
SCD and/or SQTS	5 (83.3%)	16 (84.2%)	0.999
ECG parameters			
QT interval (ms)	280 (248–300)	295 (280–320)	0.261
QTc interval (ms)	300 (252–325)	312 (291–335)	0.323
QTc interval < 330 ms	5 (83.3%)	11 (57.9%)	0.364
J point-to-T peak interval	109 (80–140)	140 (120–160)	0.130
J point-to-T peak interval <120 ms	4 (66.7%)	3 (15.8%)	0.032
Early repolarization	1/6 (17%)	11/18 (61%)	0.155
Medical therapy with quinidine	3 (50%)	6 (31.6%)	0.344
Documented arrhythmia on follow-up			
Ventricular fibrillation	1 (16.7%)	0	
Polymorphic VT	1 (16.7%)	0	
Atrial fibrillation	0	3 (15.8%)	
SVT	0	1 (5.3%)	
ICD	5 (83.3%)	6 (31.6%)	0.056
Appropriate shocks	2 (40%)	0	
Inappropriate shock	3 (60%)	4 (66.7%)	
Complications*	5 (100%)	4 (66.7%)	

Values are median (interquartile range) or n (%). *Including inappropriate shocks.
SVT = supraventricular tachycardia; other abbreviations as in Tables 1 and 3.

medical therapy and with a history of aborted SCD experienced 2 episodes of nonsustained polymorphic ventricular tachycardia that terminated spontaneously. All cases with atrial fibrillation required ongoing therapy with cardioversion, medical treatment with different antiarrhythmic agents, or both. A 3-month-old young female with an ultra-short QT of 200 ms (QTc interval: 275 ms) had a history of marked sinus bradycardia since birth and atrioventricular node dysfunction with a Wenckebach cycle length of 500 ms. The patient demonstrated atrial fibrillation at 4 days of age, requiring cardioversion. A ventricular pacemaker was implanted at 6 days of age. Despite antiarrhythmic therapy, it eventually progressed into permanent atrial fibrillation. A 5-year-old young female with an ultra-short QT of 172 ms (QTc interval: 194 ms) had mechanically induced atrial and VF during insertion of a Swan Ganz catheter.

Discussion

To our knowledge, this is the longest follow-up cohort of patients with SQTS reported in the literature. It also represents the largest series of pediatric SQTS patients, because the average age in this cohort was 13 years.

Our cohort was predominantly male (84%), reflecting a sex-specific prevalence and possible greater vulnerability to SQTS in young males as compared with young females. Eighty-four percent of patients had a personal or familial history of cardiac arrest. More than half of our patients had symptoms, including aborted SCD (24%) and syncope (16%). The most common symptomatic presentation was cardiac arrest. An additional 11 cases (44% of cohort) were identified through cascade family screening. Twenty percent of cases were identified to have disease-causing mutations. Our cohort included a 6-year-old young male with aborted SCD and a QT interval of 160 ms, the shortest QT interval reported to date. In addition, we report 3 children younger than 8 years with recalcitrant atrial fibrillation and ultra-short QT intervals ranging from 172 to 200 ms and 1 patient, an infant with a QT of 200 ms (QTc interval: 275 ms), who had coexisting sinus and atrioventricular node dysfunction. This patient had sinus bradycardia at birth and demonstrated slow atrial fibrillation at 4 days of age. To our knowledge, the latter clinical scenario associated with a V141M mutation in the KCNQ1 gene has not been reported with SQTS. Another unique finding in this young population has been the high incidence of inappropriate shocks, affecting 64% of ICD recipients, which far exceeded appropriate shocks.

A previously reported study presented the clinical characteristics and outcomes in an adult population of SQTS patients (median age: 26 years) (19). Similar to the observations of our pediatric cohort, most clinically affected adults were men (75%), cardiac arrest as a first presentation was relatively common (32%), a family history of SQTS was present in 50% of patients, and disease-causing mutations were found in 23% of probands. In contrast, our pediatric cohort tended to have a shorter QTc interval (average: 304 ms vs. 314 ms), and although adult and pediatric ICD recipients both received a high inappropriate shock rate, this was more common in pediatric patients (64% vs. 33%).

Gollob et al. (16) proposed diagnostic criteria for SQTS. We found that a modified Gollob score, which excluded points for clinical events, may be useful in identifying patients at a higher risk for unexplained syncope, atrial fibrillation, or aborted SCD. Our patients with a history of these clinical events had a median modified score of 5 (range: 4 to 6) as compared with a median of 4 (range: 4 to 5) in patients who remained asymptomatic (except 1 case of SVT). Patients with a modified Gollob score of 3 (or Gollob score of <5) had a good prognosis during follow-up in this study. Only 1 (7%) of 14 symptomatic patients had a low modified Gollob score of 3.

SQTS is considered a rare electrical abnormality, and recognition of this condition as a cause of unexplained SCD in young children is uncommon, although perhaps under-recognized. A reported series of adult patients with idiopathic VF were noted to have a mean QTc value of 371 ms, significantly less than the QTc value of healthy sex- and age-matched controls (20). These observations suggest that
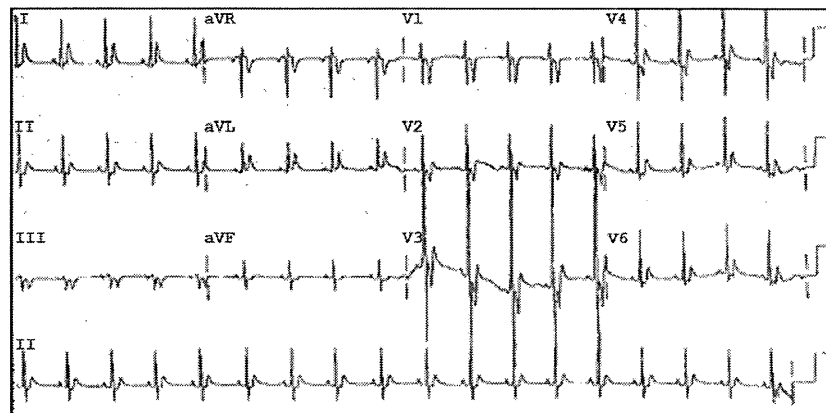
Figure 2 Extreme Abbreviation of QT Interval in a Young, Symptomatic Child

An ultra-short QT interval of 160 ms (QTc interval: 241 ms) in a 6-month-old young male at the time of clinical evaluation after cardiac arrest.

less extreme values of short QTc interval may be part of the SQTS disease spectrum.

Aborted SCD affected 6 of our patients (24%), 5 of them at 15 years of age or younger. One of the current therapeutic options for patients with SQTS includes implantation of an ICD (21–23). Six of our patients received an ICD for primary prevention; however, 4 experienced 1 or more inappropriate ICD shocks. Previous studies have reported an increased risk for inappropriate ICD therapy because of oversensing of short-coupled and prominent T waves resulting in T-wave oversensing (24). In our young cohort with SQTS, inappropriate shocks far exceeded appropriate shocks. Most of our patients had inappropriate shocks secondary to atrial tachycardias, including sinus tachycardia (n = 3), SVT (n = 1), and atrial fibrillation (n = 1). Inappropriate therapies resulting from rapid atrial arrhythmias may be prevented by programming device therapies for heart rates exceeding 210 beats/min, although a formative assessment is needed to evaluate the efficacy of such an approach. In addition, we observed a high prevalence of ventricular lead fracture of 36% (4 of 11 cases) with most (3 of 4) resulting in inappropriate ICD shocks. The high prevalence of ventricular lead fracture in part may be the result of the patients' young ages at implantation. These points together highlight our concerns regarding the use of ICD therapy in asymptomatic young patients.

We identified a higher prevalence of short J point-to-T peak interval (<120 ms) in symptomatic (42.9%) versus asymptomatic patients (9.1%). However, because of the small number of cases, the difference did not reach statistical significance. Watanabe et al. (25) reported a high prevalence (65%) of early repolarization in patients with SQTS that was associated with arrhythmic events. In their cohort, early repolarization was localized in either inferior leads, lateral leads, or both, but the ST segment contour was not described in their paper. Early repolarization with upsloping morphological features can be a benign ECG finding (26),

whereas a horizontal or downsloping ST segment may be associated with VF (27). Early repolarization also was observed in a high percentage of our cohort (50%), and it was localized in anterior, inferior, and lateral leads, or in a combination thereof. This ECG feature was not significantly different between our symptomatic (43%) and asymptomatic (60%) patients. None of our patients with early repolarization had a horizontal or downsloping pattern. Only 1 of our 6 cases of aborted SCD showed early repolarization.

Five of our patients, all symptomatic, had genetic mutations associated with SQTS. The yield of genetic mutation detection was 24% for index patients who underwent genetic testing. This compares with the 23% incidence reported in the literature (16).

Quinidine has been suggested as one of the mainstay therapies for SQTS because of its ability to offset the extreme shortening of repolarization that occurs in SQTS (28). In this cohort, quinidine proved ineffective in managing atrial fibrillation in those patients with frequent recurrences. In addition, while receiving a low dose of quinidine, one patient experienced a therapeutic ICD shock. Therefore, the effectiveness of this antiarrhythmic agent in young SQTS patients awaits further investigation.

Study limitations. Although we describe the largest population of pediatric patients with SQTS with the longest reported clinical follow-up, event rates and risks in later decades of life remain unknown. As a relatively rare or perhaps under-recognized disease, our cohort included only 25 patients. Thus, we must be cautious in reaching conclusions based on such a small group.

Conclusions

SQTS in the pediatric population is associated with a high risk of aborted SCD. The diagnosis seems more common in young males similar to observations in adult SQTS patients. This may reflect protection from ultra-short QT intervals in
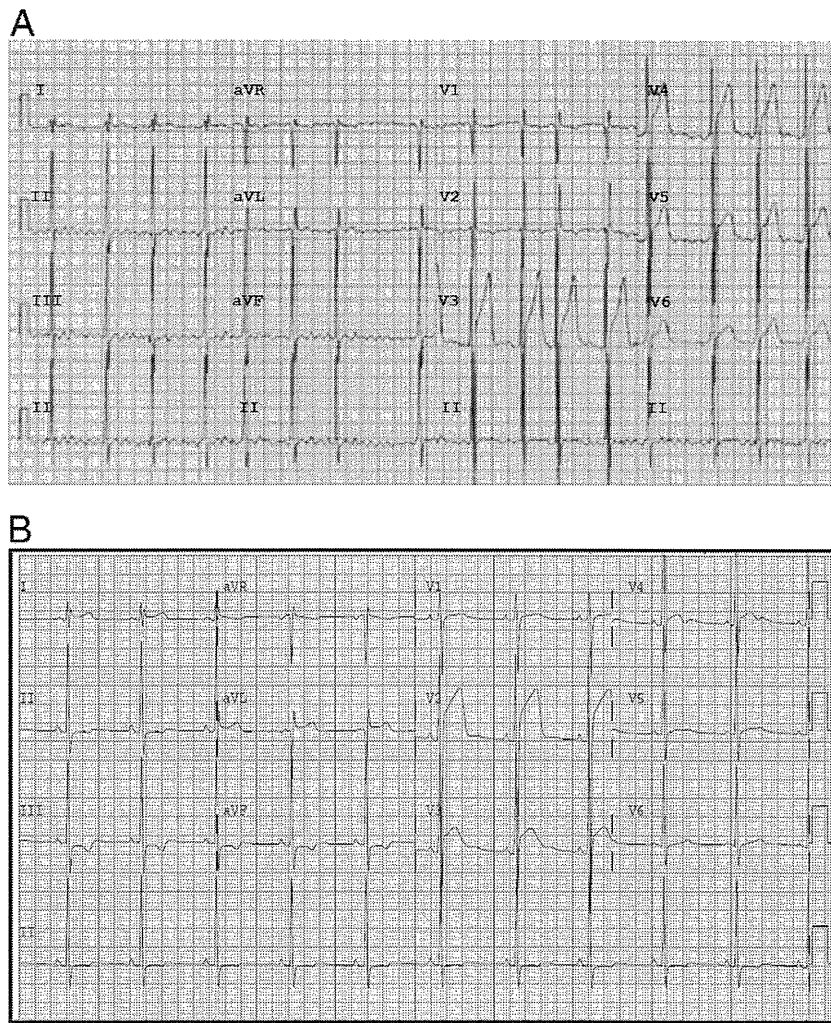
Figure 3 Atrial Fibrillation and the Short QT Syndrome in a 17-Year-Old Young Male Resulting in Conversion to Sinus Rhythm and Prolongation of the QT Interval With Antiarrhythmic Therapy

(A) 12-lead ECG of a symptomatic 17-year-old young male with atrial fibrillation. There is a short QT interval (QT interval: 320 ms, QTc interval: 355 ms), peaked T waves, and early repolarization. (B) After treatment with dofetilide and digoxin, there was prolongation of the QT interval (QT interval: 380 ms, QTc interval: 380 ms). The patient remained asymptomatic and on sinus rhythm except for short bouts of atrial fibrillation.

women because of the QT prolonging effects of estrogen (29). A modified Gollob score may be useful in identifying patients at a higher risk of clinical events and may prove useful for risk stratification, although larger cohort studies are necessary. Although ICD therapy proved useful in some patients, it was fraught with inappropriate shocks. One of 2 appropriate ICD shocks occurred despite a low dose of quinidine. Quinidine monotherapy did not prove to be effective in treating atrial fibrillation.

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Key Words: arrhythmias ▪ atrial fibrillation ▪ short QT syndrome ▪ sudden cardiac death.

ORIGINAL ARTICLE

Usefulness of scintigraphy to predict electrical storms in severe idiopathic dilated cardiomyopathy

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Abstract

Background Although several predictors of an electrical storm (ES) are indicated in patients with idiopathic dilated cardiomyopathy (IDCM), whether the severity of the myocardial tissue damage (SMTD) evaluated by myocardial perfusion SPECT (MPS) has an association with an ES remains unclear. The purpose of this study was to elucidate the clinical significance of SMTD for the prediction of ES in IDCM patients with an ICD.

Methods Thirty-seven (27 men, mean age 58 ± 15 years) IDCM patients receiving ICD implantations for secondary prevention with preoperative MPS were enrolled in this study. The medical history, physical and laboratory findings, electrocardiograms, echocardiograms and MPS findings were evaluated. The SMTD was assessed by the summed scores of 17 segments using a 4-point system (0, normal ~3, severe defect).

Results During a mean follow-up of 43.9 ± 30.7 months, an ES developed in 12/37 (32.4 %) patients. The SMTD score predicted an ES with a 92 % sensitivity and 56 % specificity, at a cut-off score of 10. In addition, a multivariate analysis showed that the SMTD score remained an independent predictor of an ES (HR 1.09/score 1 increase, 95 % CI 1.01–1.19, $p = 0.02$). The SMTD score was significantly associated with three indices of late potentials on the signal-averaged electrocardiograms, and was significantly higher in patients with positive late potentials ($p = 0.0006$).

Conclusion SMTD score assessed by MPS has a strong correlation to the late potentials and higher SMTD score may increase the risk of ES among patients with IDCM and an ICD.

Keywords Idiopathic dilated cardiomyopathy · Implantable cardioverter defibrillator · Electrical storm · SPECT · Myocardial tissue damage

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Introduction

Implantable cardioverter defibrillators (ICDs) provide an established therapeutic option for reducing the risk of sudden cardiac death, and have a high success rate in terminating life-threatening ventricular arrhythmias including ventricular tachycardia (VT) or ventricular fibrillation (VF) [1, 2]. About 40–60 % of patients with an ICD will receive an appropriate ICD therapy for VT/VF within 3 years of the implantation [3–5]. Such therapy is usually limited to antitachycardia pacing or a small amount of shocks for targeted ventricular tachyarrhythmias. However, some

patients experience multiple shock therapies, which significantly compromise the quality of life of ICD recipients and increase the risk of subsequent death [6].

Due to the increase in the number of patients with ICD indications, electrical storm (ES), which is defined as 3 or more separate episodes of ventricular tachycardia (VT) and/or ventricular fibrillation (VF) terminated by ICD therapies within 24 h, have become an important issue because of the clinical, psychological and economical consequences involved. Although we and several investigators have reported the incidence, predictive factors and clinical prognosis of an ES in patients with idiopathic dilated cardiomyopathy (IDCM) [1, 3–5, 7–9], the significance of the severity of the myocardial tissue damage (SMTD) as a predictor of an ES remains unclear. We attempted to elucidate the clinical value of SMTD in predicting an ES in patients with IDCM and an ICD.

Methods

Study population

Forty-eight consecutive IDCM patients received an ICD for secondary prevention between 1998 and 2004 at the National Cerebral and Cardiovascular Center. In addition to the examinations necessary for the precise diagnosis, MPS prior to the ICD implantation was routinely performed in IDCM patients during this period unless it was rejected by the patient. The medical records including the clinical characteristics, medications, and electrocardiographic, echocardiographic and MPS findings were analyzed.

Patients with a history of hypertension were excluded from this study to carefully rule out hypertensive heart disease. Coronary angiography and echocardiography were performed in all patients to rule out ischemic cardiomyopathy and valvular heart disease. Other modalities including specific biochemical tests, magnetic resonance imaging, nuclear imaging, cardiac biopsy, and genetic testing were added if required according to the patient's history, to exclude other secondary cardiomyopathies including infectious cardiomyopathy, toxic cardiomyopathy, peripartum cardiomyopathy, tachycardia-mediated cardiomyopathy, autoimmune cardiomyopathy, infiltrative cardiomyopathy, and hereditary cardiomyopathy. Finally, patients with diffuse left ventricular dysfunction and enlargement of the left ventricle with an unknown etiology were defined as having IDCM.

In these patients, an ICD was implanted for secondary prevention of sudden cardiac death after one or more episodes of confirmed sustained ventricular tachyarrhythmias or under the context of any presumed tachyarrhythmic syncopal attacks. The implanted devices included Medtronic 7221CX, 7223CX, 7227CX, 7229CX, 7271, 7273, and 7278, and CPI/Guidant 1790 and 1861 devices. The ICD was programmed according to the documented or induced arrhythmia with at least two detection zones. Antitachycardia pacing including more than one burst pacing and one ramp pacing therapy followed by cardioversion were programmed in the VT-zone, whereas the maximum shocks were programmed in the VF-zone. Written informed consent was given before the ICD implantation.

The study protocol according to the ethical guidelines of the 1975 Declaration of Helsinki was approved by the Institutional Review Board at National Cerebral and Cardiovascular Center, and were announced to the patients. The patient privacy was completely protected by anonymization of the entire data.

Definition of ES

Three expert electrophysiologists randomly reviewed the intracardiac electrograms to avoid delivering inappropriate therapies. The occurrence of 3 or more separate episodes of VT/VF terminated by an appropriate ICD therapy within a 24-h period was defined as an ES [8]. The appropriate ICD therapy consisted of antitachycardia pacing as well as low- and high-energy shocks for the targeted ventricular tachyarrhythmias. Repetitive ineffective shocks were not categorized as an ES.

Follow up

The patient follow-up started after the implantation. The patients visited the outpatient clinic every 1–2 months as a follow-up with a routine blood test and electrocardiogram. Furthermore, the ICD was checked every 3–6 months. They were also encouraged to visit whenever palpitations, pre-syncope or shocks occurred. The interrogation part of the device follow-up was performed to evaluate the number and type of episodes from the stored intracardiac-electrograms during each check. Patients encountering an ES were admitted to the hospital for a detailed investigation of the cause including a blood analysis (electrolytes, blood cell count, and the thyroid, creatinine, C-reactive protein, creatinine kinase, and troponin levels), echocardiography and coronary angiography if necessary.

SMTD scores using myocardial perfusion SPECT

Rest MPS was performed at least 1–3 months before the ICD implantation with a stable condition of chronic heart failure (CHF). One hour after the intravenous injection of 600 MBq of technetium-99m (^{99m}Tc) sestamibi, the patients consumed a light meal or milk before image acquisition to remove the tracer retention in the liver and

4-point scoring system

0, Normal

1, Mild defect

2, Moderate defect

3, Severe-total defect

Left Ventricular Segmentation

1. basal anterior
2. basal anteroseptal
3. basal inferoseptal
4. basal inferior
5. basal inferolateral
6. basal anterolateral

7. mid anterior
8. mid anteroseptal
9. mid inferoseptal
10. mid inferior
11. mid inferolateral
12. mid anterolateral

13. apical anterior
14. apical septal
15. apical inferior
16. apical lateral
17. apex

Cerqueira MD. et al. Circulation 2002;105:539-54

(a) High-SMTD case   (b) Low-SMTD case

Vertical Long Axis (Seg 17)

Short Axis (Seg1-16)

Summed Defect Score   Summed Defect Score
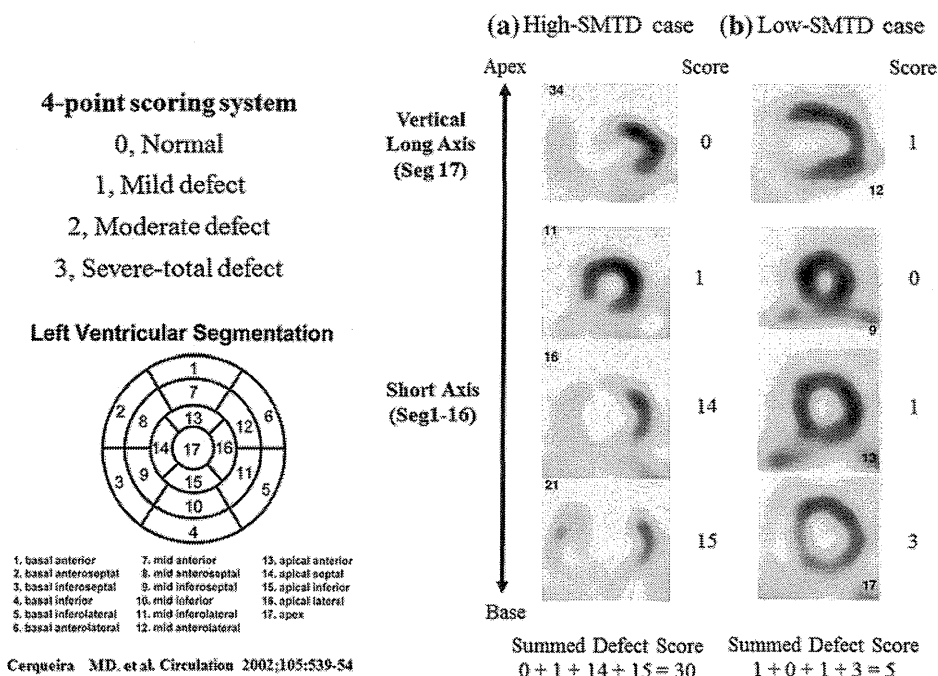0 + 1 + 14 + 15 = 30   1 + 0 + 1 + 3 = 5

Fig. 1 Semiquantitative visual analysis using a myocardial 17-segment model. Tracer uptake in each segment was evaluated using a 4-point scoring system (0, normal; 1, mild; 2, moderate; 3, severe reduction or absence of radioisotope uptake). The short-axis view was used for assessing segments *1–16*, and the vertical long-axis view was used for assessing segment *17*. **a** Typical case with high-SMTD scores (summed defect score = 30). Severe-total defects were identified through the basal to mid-ventricular levels, especially in anterior, inferior, and septal walls. This patient experienced an electrical storm. **b** Typical case with low-SMTD scores (summed defect score = 5). Only mild defects were seen in basal level and apex. This patient did not experienced an electrical storm

gallbladder. Thirty projection images were obtained over 180° in 6° increments with 50 beats per view, using a dual-headed SPECT system (VERTEX; ADAC Laboratories, Milpitas, CA, USA) equipped with a low-energy general-purpose collimator. The image resolution in the transaxial plane was 16 mm full-width at half-maximum and data were stored in a 64 × 64 matrix. Energy discrimination was centered on 141 keV with a 20 % window. Transaxial tomograms were generated from the projection data and oblique angle tomograms were reconstructed using a ramp filter and a Butterworth filter (order 8, cut-off 0.27 cycle/pixel).

SPECT images were semiquantified using a myocardial 17-segment model. Segments 1–16 were assigned to four evenly spaced regions of apical slices, with six each of mid-ventricular and basal slices in the short-axis views. Segment 17 was assigned to the extreme tip of the ventricle where there is no longer cavity present assessed by vertical long-axis view (Fig. 1) [10]. The tracer uptake in each segment was scored using a 4-point system (0, normal; 1, mild; 2, moderate; 3, severe reduction or absence of radioisotope uptake). A summed defect score was obtained by adding each score of the 17 segments, and served as an index of the severity of the myocardial tissue damage. Three experienced observers, who were blinded to the clinical findings, determined the summed defect scores of each segment. The averaged score was adopted for analysis as a SMTD score. Examples of patients with typical high- and low-SMTD scores assessed by one observer were represented in Fig. 1.

Signal-averaged ECG

Ventricular late potentials (LPs) were analyzed using a signal-averaged ECG system (Arrhythmia Research Technology model 1200 EPX, Austin, TX, USA). The analysis was based on quantitative time-domain measurements of the filtered vector magnitude of orthogonal Frank X, Y, and Z leads. This system consisted of a vector magnitude with a bidirectional bandpass filter set between 40 and 250 Hz combined with the standard bipolar orthogonal (X, Y, Z) leads. Signals from 200 to 300 beats were averaged to obtain a diastolic noise level of <0.5 μV. The following parameters were assessed using a computer algorithm: (1) total filtered QRS (TFQRS) duration, (2) root-mean-square voltage of the terminal 40 ms of the filtered QRS complex (RMS40), and (3) duration of the terminal low amplitude signals of <40 μV in the terminal-filtered QRS complex (LAS40). An LP was considered to be positive when at least two of the following criteria were met: (1) TFQRS

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>120 ms, (2) RMS40 <20, and (3) LAS40 >38 ms [11] in patients with a normal QRS duration, and (1) TFQRS >170 ms, (2) RMS40 <20, and (3) LAS40 >45 ms [12] in patients with bundle blanch block.

Statistics

All data were statistically analyzed using JMP 7.0.1 software. Data are expressed as the mean ± standard deviation (SD) for continuous variables, and as frequencies and ratios (%) for categorical variables. The significance of the baseline variables with respect to the outcome was assessed using univariate Cox proportional hazards models. A multivariate analysis was performed with an adjustment for the age, sex, BMI, NYHA functional class, and LVEF. Observations were censored at the time of the last known follow-up when an ES did not occur or at the time of death. A receiver operating characteristic (ROC) curve analysis was used to determine the appropriate cut-off value of the SMTD score. Event-free survival curves were calculated according to the Kaplan–Meier method. The significance of differences between curves was determined using a log rank test. A p value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Finally, 37 (27 men and 10 women) patients who agreed to undergo MPS were enrolled in this study. Table 1 shows the baseline characteristics of the study patients. The mean age at the time of the ICD implantation was 58 ± 15 years and the mean NYHA functional class was 2.7 ± 1.1. Over 80 % of the patients were prescribed with beta-blockers, and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs). Class III antiarrhythmics were prescribed to 23 (59.5 %) patients. When class III antiarrhythmics were used, amiodarone was selected first, and changed to sotalol in case of amiodarone intolerance. Single- and dual-chamber devices were implanted in 14 (37.8 %) and 23 (62.1 %) patients, respectively.

Electrical storm

During a mean follow-up of 43.9 ± 30.7 months (median of 42.0 months, ranging from 1 to 118 months), 12 (32.4 %) patients experienced at least one ES episode (mean 5 ± 5.1 episodes; median of 3.5 episodes per patient) and 7 (58.3 %) of those 12 experienced two or more. The mean duration between the first ES occurrence

and the ICD implantation was 30.8 ± 33.6 months (median 17.0 months, ranging from 1 to 84 months). The ES was apparently generated by exacerbated heart failure in 3 (25.0 %) patients, low potassium levels in 2 (16.7 %), infection in 1 (8.4 %), and non-specific causes in the remaining 6 (50 %).

Risk factors for an ES

Tables 2 and 3 show the results of the univariate and multivariate analyses regarding the occurrence of an ES. An univariate Cox proportional regression analysis indicated that the NYHA functional class ($p = 0.04$), monomorphic VT as an index arrhythmia ($p = 0.03$), QRS duration ($p = 0.04$) and QTc interval ($p = 0.02$) on the electrocardiogram, LVDd ($p = 0.03$) and posterior wall thickness ($p = 0.04$) on the echocardiogram, and the SMTD on the MPS ($p = 0.01$) were significant predictors of an ES occurrence. However, when these parameters were adjusted for the age, sex, BMI, NYHA functional class, and LVEF, only the SMTD on the MPS remained as a significant predictor of an ES occurrence ($p = 0.02$, HR 1.09/score 1 increase, CI 1.01–1.19).

Significance of the SMTD score as a predictor of an ES

The sensitivity–specificity analysis used receiver operating characteristics (ROC) curves, with a cut-off value of the SMTD score being set at 10 to optimize the capability of predicting an ES (Fig. 2). At a cut-off score of 10, the area under the curve was 0.802, and the SMTD score predicted an ES with 92 % sensitivity, 56 % specificity, and positive and negative predictive values of 52 % and 94 %. Figure 3 shows the Kaplan–Meier curves for the freedom from ES events between the groups with SMTD scores of ≥10 and <10. The ES event-free rate at 1, 3, and 5 years was 76.4, 66.2, and 57.9 % in the group with an SMTD score of ≥10, and was stable at 93.3 % in those with an SMTD score of <10. The patients with IDCM had a significantly higher risk of an ES occurrence when the SMTD score was ≥10.

Relationship between the SMTD score and LPs

Thirty-six (97.3 %) patients received a signal-averaged ECG to assess late potentials. Figure 4 shows the relationship between the SMTD score and LPs. Among 36 patients, positive LPs were observed in 22 (61.1 %), and the SMTD score was significantly larger in the patients with LPs than in those without (16.1 ± 9.4 and 6.1 ± 4.7, respectively; $p = 0.0006$). In addition, the SMTD score was significantly correlated with each index of the SAECG such as the TFQRS ($r^2 = 0.27$, $p = 0.0013$), LAS40