33
Short QT Syndrome

Preben Bjerregaard and Ihor Gussak

Abstract

Short QT Syndrome (SQTS) is a rare form of channelopathy with a moderately high risk of SCD, but the syndrome is not well-defined and information about long term follow-up still very scarce. A short QT interval is the main component of the syndrome, but because of an abnormal relationship between the QT interval and the RR interval in SQTS patients, the short QT interval in such patients is often only apparent at heart rates close to 60 bpm. Since routine ECGs are often taken at heart rates faster than that, many patients with SQTS may be missed.

Many mutations have been found responsible for SQTS, but in published families a mutation has only been found in one of every four, who has been genetically tested. Most diagnoses are therefore based upon the clinical presentation, which in 90 % of the cases has included a family member with SCD. The treatment of choice is an implantable defibrillator.

Keywords

Short QT interval • Short QT syndrome • Sudden cardiac death • Cardiac channelopathies • Potassium channel mutations • Atrial fibrillation • Implantable defibrillators

Introduction

Since the discovery of Short QT Syndrome (SQTS) less than 12 years ago [1], a lot have been learned about the latest member of the so-called channelopathies, mainly from case reports and research in a few laboratories and clinical centers especially dedicated to this syndrome. Despite the fact that the total number of published cases has just reached 100, the most important aspects of the syndrome have by now been investigated, latest by the addition of a clinical follow-up study of patients with SQTS (Table 33.1) [2–18]. The population of patients with SQTS will continue to grow as evidenced by the fact, that the first patient found with the syndrome has recently given birth to a child, who also has the syndrome. Most impressive is the list of mutations that has been found, in some cases in only a single individual, and the functional testing of these mutations in patch-clamp experiments and *in silico* has greatly improved

P. Bjerregaard, MD, DMSc (✉)
Division of Cardiology, VA Medical Center,
Washington University in St. Louis,
915 North Grand, St. Louis, MO 63106, USA
e-mail: prebenbjerregaard@hotmail.com

I. Gussak, MD, PhD, FACC
Ono Pharmaceutical USA, Lawrenceville, NJ, USA

Department of Internal Medicine, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, USA
e-mail: igussak@newcardio.com

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Table 33–1. Time table for "*First Time Events*" in the short history of short QT syndrome

1999	Discovery of family with SQTS (Bjerregaard P, 1999, personal communication)
2000	Paper describing SQTS (Gussak et al. [1])
2003	High incidence of SCD in families with SQTS (Gaita et al. [2])
	ICD treatment of patients with SQTS (Schrimpf et al. [3])
2004	Mutation found in families with SQTS (Brugada et al. [4])
	Pharmacological treatment of patients with SQTS (Gaita et al. [5])
	Experimental model of SQTS (Extramiana et al. [6])
2005	Review article of mechanism, diagnosis and treatment of SQTS (Bjerregaard et al. [7])
	Successful prevention of SCD by an ICD in patient with SQTS (Schimpf et al. [8])
	SQTS presenting as bradycardia *in utero* (Hong et al. [9])
	SQTS website: shortqtsyndrome.org (Bjerregaard and Collier [10])
2006	Publication of the prevalence of a very short QT interval in the general population (Gallagher et al. [11])
2007	Overlap syndromes of SQTS and Brugada Syndrome (Antzelevitch et al. [12])
	Mutation linking SQTS to SIDS (Arnestad et al. [13])
	Population study of prevalence and prognostic significance of a short QT interval (Anttonen et al. [14])
2008	Animal model: Zebrafish with SQTS (Hassel et al. [15])
2009	Safety issue warning regarding drug induced shortening of the QT/QTc interval (Holbrook et al. [16])
2011	Diagnostic criteria to facilitate clinical recognition of SQTS (Gollop et al. [17])
	Long-term follow-up of patients with SQTS (Giustetto et al. [18])

our understanding of the electrophysiology behind the short QT interval. It is still a challenge to make the diagnosis with certainty and even more of a challenge to rule it out in patients with borderline low QT interval.

Definition and Terminology

By its own definition, any clinical syndrome is a combination of signs and symptoms that occur together and characterize a particular abnormality. In this context, short QT syndrome (SQTS) is best defined as an inheritable, primary electrical heart disease, that is characterized by (*a*) a short QT interval (Fig. 33.1) and (*b*) paroxysmal atrial and/or ventricular tachyarrhythmias resulting from an accelerated cardiac (atrial and ventricular) repolarization due to congenital (genetically heterogeneous) cardiac channelopathies. It requires exclusion of patients with secondary short QT interval [19], and without documentation of associated arrhythmogenic complications in the patient or the patient's family a short QT interval is only an

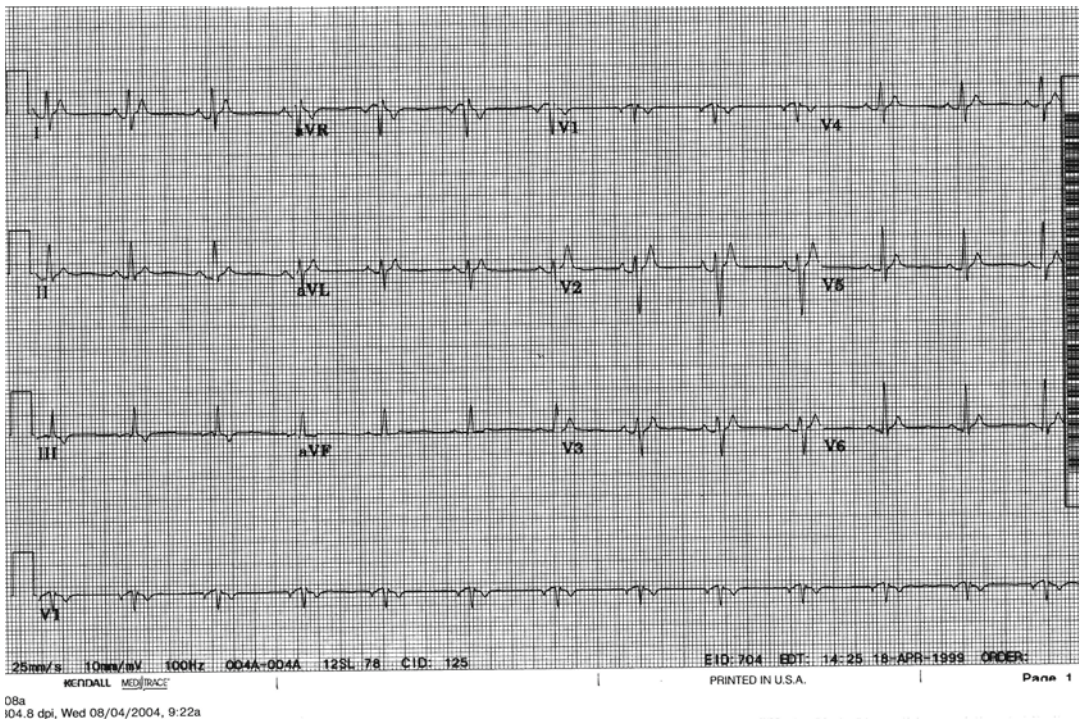

Figure 33–1. Twelve-lead ECG from a patient with SQTS based upon a short QT interval and paroxysmal atrial fibrillation. The ECG shows sinus rhythm at a heart rate of 75 beats/min. The QT interval is 240 ms

ECG abnormality. Unexplained sudden cardiac death (SCD) in a family with members having SQTS would normally be considered a manifestation of SQTS unless proven otherwise.

Before the discovery of SQTS there were no well-defined lower limit for the QT interval, and normal limit for the QT interval was usually given only as an upper limit. Based upon data from Rautaharju et al. study from 1992 of the QT interval in 14,379 healthy individuals, the lower limit for the QT interval (two standard deviations below the mean predicted value) at a heart rate of 60 bpm was 360 ms [20]. More recent studies of apparently normal people have found variable results for the lower limit of QTc probably influences by the population studied and the method used for measuring the interval [11, 14, 21–25], but arguments could be made for a lower limit of the QTc interval of ≤360 ms for men and ≤370 ms for women realizing that these are approximate figures and not a great help in finding patients with SQTS. In our review of the worldwide population of patients with SQTS in 2008 [26] we found among 49 published cases the mean QT interval to be 282 ± 63 (range: 210–340) ms and the mean QTc to be 305 ± 42 (range: 248–345) ms. In a 2011 follow-up study from Europe [18] of 49 patients the QTc was 314 ± 46 ms. In recent years some patients with longer QT intervals have been published as having SQTS (*vide infra*). Since the QT interval in patients with SQTS varies very little with changes in heart rate [7, 27, 28], it is important to realize, that normal correction formulas for the QT interval at heart rates greater than 60 bpm will grossly overestimate, what the OT interval will be at a heart rate of 60 bpm. ***Paradoxically, in patients with SQTS the QTc varies with HR. The faster the HR the longer the QTc and at heart rates 80–90 bpm many patients with SQTS will have a normal QTc.*** At heart rates much above 60 bpm, as often seen in children, there is, therefore, a risk of missing patients with SQTS, when QT correction formulas are used. ***Therefore, SQTS cannot be defined by QTc. In order to get a reliable assessment of the QT interval in a patient suspected of having a short QT interval and possibly SQTS every effort should be made to get an ECG at a heart rate as close to 60 bpm as possible, even by using a drug if necessary.*** The lack of adaptation of QT interval to change in HR in patients with SQTS has been suggested as a diagnostic tool in work up of patients suspected of having SQTS. It is likely, however, that anybody with a short QT interval will have a QT/RR slope lower than people with normal QT intervals. More research in this area is needed before it can be recommended as a reliable diagnostic tool especially in borderline cases, where it would be most needed. Another common finding in the ECG of patients with SQTS in particularly in precordial leads, is tall, peaked T waves, most commonly symmetrical, but in patients with *KCNJ2* mutation asymmetrical with a steep descent [29, 30]. Some studies have pointed out, that the T_{peak}–T_{end} interval and T_{peak}–T_{end}/QT ratio is prolonged in patients with SQTS compatible with an augmented transmural dispersion of repolarization [6, 18].

Since the discovery of SQTS and the significance of a short QT interval the question has been: "when does a short QT interval become clinically significant?"

The first indication of the prognostic significance of a relatively short QT interval was from a study in 1993 by Algra et al. [31]. Out of 6,693 patients who underwent 24 h Holter monitoring and followed for 2 years, patients with a QTc < 400 ms had a 2.4-fold increase in sudden death rate compared to patients with a QTc of 400–440 ms. This was slightly more than patients with a QTc > 440 ms, who had a 2.3-fold increase. The authors argued for the possibility of their finding being a true pathophysiological phenomenon with a relative short QT interval possibly leading to life-threatening arrhythmias.

Evidence that shortening of the QT interval may play a role for the occurrence of idiopathic VT was provided by Fei and Camm in 1995 [32]. Twenty-four hour Holter monitoring was used to detect 60 episodes of monomorphic repetitive ventricular tachycardia in ten patients. Analysis of three consecutive QT intervals immediately before the onset of ventricular tachycardia found these QT intervals significantly shorter than the intervals measured 40 min before at the same heart rates (342 ± 34 vs. 353 ± 35 ms, $P < 0.001$). Of the 60 episodes the QT intervals were shortened in 45 (75 %) compared to the intervals 40 min earlier. The shortening was explained by

sudden parasympathetic withdrawal leading to sympathetic predominance and thereby QT shortening. The shortening was suggested by the authors to play an important role in the pathogenesis of idiopathic VF.

In 1999 we presented a case of paradoxical shortening of the QT interval to 216 ms during severe transient bradycardia in a child with recurrent cardiac arrest and discussed deceleration-dependent shortening of the QT interval as a trigger of arrhythmic events [33]. We proposed activation of Ik_{Ach} due to an unusually high vagal discharge to the heart as a possible mechanism responsible for both slowing of the heart rate and shortening of the QT interval.

Visken et al. [34] compared ECGs of 28 patients with idiopathic VF (17 men and 11 women, age 31 ± 17 years) to those of 270 age- and gender-matched healthy controls. They found that the QTc of males with idiopathic VF was shorter than the QTc of healthy males (371 ± 22 ms vs. 385 ± 19 ms, P = 0.034), and 35 % of the male patients had QTc < 360 ms (range 326–350 ms) compared to only 10 % of male controls (345–360 ms). However, no such differences were found among women. They suggested that QTc intervals shorter than 360 ms might entail some arrhythmic risk.

The limited data available seem to indicate, that the extent of QT interval shortening is associated with the probability of an adverse outcome. In the largest study so far by Giustetto et al. [18] the QTc interval was 300 ± 20 ms in ten patients with cardiac arrest and 309 ± 19 ms in 19 patients with no such event. In our review of the world-wide population of patients with SQTS [26], in 16 patients with SCD or aborted SCD the QT intervals were 271 ± 33 ms compared to 291 ± 55 ms in 26 patients without SCD, aborted SCD and atrial fibrillation. In seven patients with atrial fibrillation only, the QT intervals were 265 ± 49 ms. From these data it is also apparent that the great majority of patients published so far with SQTS have had very short QT/QTc intervals, but because of sporadic cases with somewhat longer QT intervals [12, 28] we are not at a point where the diagnosis can be based upon the duration of the QT interval alone. Even though recently published proposed diagnostic criteria for the diagnosis of SQTS [17] was met by some criticism [35, 36], they very well points out features besides the QT interval, that has to be taken into consideration when making a diagnosis of SQTS, such as clinical and family history in addition to genotyping if possible.

Table 33–2. Gene mutations associated with SQTS

Mutation	Gene	# Families	# Patients
Gene mutations associated with SQTS			
N588K	*KCNH2*	5	≥12
T618I	*KCNH2*	2	≥2
E50D	*KCNH2*	1	2
V307L	*KCNQ1*	1	1
V141M	*KCNQ1*	2	2
I274V	*KCNQ1*	1	1 (SIDS)
D172N	*KCNJ2*	1	2
Gene mutations associated with Short QT and ST-segment changes			
R1135H	*KCNH2*	1	3
S481L	*CACNB2*	1	6
G490R	*CACNA1C*	1	2
A39V	*CACNA1C*	1	1
S755T	*CACNA2D1*	1	3

Genetic Basis of SQTS

SQTS is a genetically heterogeneous disease. In the study by Giustetto et al. [18] the yield of genetic screening in SQTS was 23 % of the investigated index patients in their study. So far a genetic mutation has been found in at least 22 patients from 13 families with SQTS [4, 9, 13, 29, 37–40], and in 15 patients from five families with a short QT interval and ST-segment changes (Table 33.2) [12, 41, 42]. Patients in the later group have ST changes in precordial leads somewhat similar to Brugada Syndrome patients either spontaneously or by provocation, and since there is no clear basis on which to select one syndrome over another, they have been looked upon as a distinct clinical entity. With QTcs ranging from 330 to 360 ms the QT interval in these patients has generally not been as short as reported for patients with only SQTS. Initially mutations in patients with SQTS were found in three genes (*KCNH2*, *KCNQ1* and *KCNJ2*) encoding for potassium channels and the respective syndromes were called SQT1, SQT2 and SQT3 based upon the chronology of their discovery.

In the first two families from Europe with SQT1 reported in 2004 by Gaita et al. [2] two different

missense mutations (C1764A and C1764G) were later discovered and found to result in the same amino acid change (N588K) in the S5-P loop region of the cardiac I_{Kr} channel *KCNH2* (HERG) [4]. Within the same year the first patient with SQT2 was reported, when a mutation (V307L) in the *KCNQ1* gene encoding the I_{Ks} channel KvLQT1 was found in a 70 year old male with idiopathic ventricular fibrillation and a short QT interval [38]. Another *KCNQ1* mutation was later found in two unrelated patients with bradycardia *in utero* and born with atrial fibrillation and high degree atrio-ventricular block in addition to a very short QT interval [9]. Genetic testing showed a missense mutation, G to A substitution at nucleotide 421 (g421a). This mutation results in substitution of valine by methionine at position 141 (V141M) adjacent to a previously described S140G mutation for familial AF [43]. Finally, in 2007 a third gain-of-function mutation (I274V) was found in *KCNQ1* in a patient with SIDS [44].

In 2005 in an Italian family a *KCNJ2* gene mutation was found in a 5-year old girl with a short QT interval (SQT3). Genetic analysis by Priori et al. led to the identification of a single base pair substitution (G514A) in *KCNJ2*, resulting in an amino acid change from aspartic acid to asparagine at position 172 in the Kir2.1 potassium channel (I_{K1}) [29]. From these initial findings an interesting concept emerged, that LQTS and SQTS had closely related genetic basis and could be considered "allelic diseases". Indeed, all three SQTS genes were known to also cause LQTS. Since then eight additional mutations responsible for shortening of the QT interval have been found (Table 33.2).

Cellular Basis of Arrhythmogenesis in SQTS

Mutations effecting potassium channels all leads to a gain-of-function. There is general agreement that gain-of-function from the N588K-HERG mutation in patients with SQT1 leading to an increase in the repolarizing currents active during phase 2 and 3 of the AP stems from severely compromised inactivation. McPate et al. found a ~ +60 mV positive-shift in voltage dependence of I_{HERG} inactivation [45]. Not all cells are affected to the same degree and Cordero et al. found that ventricular Purkinje cells were minimally affected [46]. Grunnet et al.'s patch clamp experiments showed that the biophysical characterization of the short QT mutation HERG-N588K was compatible with a mixed gain-and loss-of-function [47]. The most prominent loss-of-function property was reduced tail currents, but also slower activation and faster deactivation kinetics leading to reduced ability to conduct current at the end of repolarization. The authors pointed out that in patients carrying HERG-N588K the loss-of-function of repolarization current and diastolic HERG current might be at least as pro-arrhythmic as the gain-of-function of plateau current. All information on the likely consequences for I_{Kr} -kinetics of N588K-HERG mutation comes from studies of the HERG1a isoform. Recent evidence suggests, however, that native cardiac I_{Kr} may not be comprised of HERG1a alone, but rather of HERG1a heteromerically expressed with an alternative transcript, HERG1b, an isoform with a truncated N-terminus. This lead McPate el al. to conduct a study to determine the effects of the N588K-HERG SQT1 mutation on co-expressed HERG1a/1b channels [48]. Their data showed that the inactivation-attenuation effects of the N588K mutation were markedly greater when co-expressed HERG1a and 1b were studied, than when HERG1a alone was studied. The study also confirmed the differential effect the N588K-HERG mutation has on current during ventricular and Purkinje AP's as initially suggested by data from the study by Cordeiro et al. [46] and McPate et al. [45].

Another mutation, which effects the plateau phase of the action potential is V307L-KCNQ1 seen in SQT2 patients. Bellocq et al. did conventional patch-clamp experiments using COS-7 cells and showed faster activation at more negative potentials for V307L channels compared to wild-type (WT) while kinetics for deactivation were similar [38]. Computer simulations with findings from the patch-clamp experiments incorporated clearly showed diminished AP duration favoring the association of a short QT interval with the V307L-KCNQ1 mutation.

Harchi et al. using perforated-patch voltage-clamp recordings (Chinese Hamster Ovary cells) at 37 °C of whole-cell current with epicardial ventricular AP waveform carried by co-expressed *KCNQ1* and *KCNE1* showed a marked (−36 mV) shift in half-maximal activation for V307L compared to WT-KCNQ1 [49]. In contrast to Bellocq et al. [38], they also found a significant slowing of current deactivation. They also looked at the effect of the mutation on atrial cells and found peak repolarising current significantly augmented for V307L-KCNQ1 compared to WT for both ventricular and atrial AP commands, consistent with an ability of the V307L mutation to increase repolarising I_{Ks} in both regions. Although atrial fibrillation was not reported for the patient in whom the V307L-KCNQ1 mutation was first identified [38], SQTS patients especially with the N508K-HERG mutation do experience atrial fibrillation at a higher incidence than expected by chance alone [18]. Atrial fibrillation was also part of the clinical picture in patients with the V141M-*KCNQ1* mutation [9, 26]. These patients presented with bradycardia *in utero* and were born with a short QT interval and atrial fibrillation with a very slow heart rate suggesting high degree AV block. The inability to restore sinus rhythm in one of the patient and the inability to maintain sinus rhythm for more than a few hours in the other patient suggested possibly sick sinus syndrome as well. Hong et al. [9] injected oocytes from *Xenopus laevis* with WT or *V141M-KCNQ1* cRNA with or without KCNE1 cRNA and 2–3 days later exposed them to two electrode voltage clamp recordings. The V141M mutation did not noticeably alter the gating of KCNQ1 channels expressed alone in oocytes. The WT-*KCNQ1*/*KCNE1* channels exhibited a voltage-dependent threshold of activation near −50 mV and activated very slowly. In sharp contrast, the *V141M-KCNQ1*/*KCNE1* channel current developed instantly at all voltages tested, consistent with the interpretation that these channels were constitutively open. Computer modeling showed decrease in peak voltage and shortening of APD consistent with shortening of the QT interval. The effect of the V141M gain of function mutation was also modeled in a computer model of rabbit sinoatrial node cells. The results indicated that the enhanced outward I_{Ks} causes cessation of spontaneous activity and a stabilization of the resting membrane potential at a level positive to the normal maximum diastolic potential of these cells. The exact mechanism behind the bi-nodal dysfunction seen in these patients needs, however, further exploration. A third mutation in *KCNQ1* has been considered a possible cause for sudden infant death syndrome. In a patient with sudden infant death Arnestad et al. [13] found a 1,274 V-*KCNQ1* mutation and Rhoades et al. [44] presented electrophysiological data from patch clamp recordings (Chinese hamster ovary cells) showing that I274V-*KCNQ1* in the presence of *KCNE1* causes gain of function in I_{Ks} characterized by increased current density, faster activation, slower deactivation, and accumulation of instantaneous current during repeated stimulation. To test the hypothesis that I274V may promote a short QT syndrome phenotype, computerized modelings of ventricular action potentials were performed comparing WT-Iks to heterozygous I274V-Iks. At all cycle length the AP was shorter for I274V-Iks supporting the prediction that I274V-KCNQ1 will cause a short QT phenotype, and, therefore, may be a plausible explanation for sudden death in an infant carrying this mutation.

SQT3 patients are characterized by a mutation in the KCNJ2 gene [29]. Whole-cell patch-clamp studies of the heterologously expressed human D172N channel have demonstrated larger outward I_{K1} than the WT at potentials between −75 and −45 mV, with the peak current being shifted in the former with respect to the later (WT, −75 mV; D172N and −65 mV). Co-expression of WT and mutant channels to mimic heterozygous condition of the proband has yielded an outward current that is intermediate between WT and D172N. The authors hypothesized that the tall and asymmetrical T-waves with an exceedingly rapid terminal phase seen in these patients and not seen in SQT1 or SQT2 patients might be related to a more sudden acceleration of the final phase of action potential repolarization in patients with the D172N mutation.

Shortening of refractoriness is one of the key elements in the re-entry mechanism behind many tachy-arrhythmias and likely the main reason for the increased propensity to atrial and ventricular fibrillation seen in SQTS, but as pointed out, it has also been shown that the abbreviation of the action potential can effect

different cells differently leading to dispersion of refractoriness as an additional arrhythmogenic factor [6, 46, 50]. It is conceivable, however, that the mechanisms that lead to electrical instability and eventually results in VF in patients carrying mutations in HERG or KvLQT1 would be different from those resulting from gain-of-function substitutions in Kir2.1. The discrepancy between heart rate and QT interval duration is most pronounced during bradycardia and at least two observations suggest that the potential for developing life-threatening tachy-arrhythmias is highest at slow heart rates. In the study by Sun et al. [40] all four patients from a family with SQTS dying suddenly, died during sleep, and the first patient reported saved from VF by an ICD also had the episode at night during sleep. However, in the follow-up study by Giustetto et al. it was not possible to find a uniform trigger for arrhythmic events since cardiac arrest and syncope occurred both at rest and during effort [18].

Mutations effecting L-type calcium channels all lead to a loss-of-function due to a trafficking defects with a decrease in amplitude of the inward calcium current causing both a short QT interval and various degrees of ST-segment changes [12, 41, 42]. Similar overlap syndromes among channelopathies are well known from long QT syndrome and Brugada syndrome [51] and recently also early repolarization syndrome and short QT syndrome. Watanabe et al. [52] studied the later combination in three cohorts: (1) 37 SQTS patients (12 new patients with QTc ≤ 330 ms plus an arrhythmic event and/or genetic mutation, and 25 patients with SQTS from the literature), (2) 44 control cohort with QTc ≤ 330 ms and no symptoms, and (3) 185 control cohort with normal QTc and no sign or symptoms of heart disease. They found the prevalence of early repolarization to be 65 % in cohort 1, 30 % in cohort 2 and only 10 % in cohort 3. In a multivariable model early repolarization was associated with arrhythmic events in the SQTS cohort whereas neither QT nor QTc duration were associated with arrhythmic events, and they concluded that there is a high prevalence of early repolarization in patients with SQTS, and early repolarization may be useful in identifying risk of cardiac events in patients with SQTS.

Electrophysiologic Findings

Except for sporadic case reports the main information about electrophysiology studies in patients with SQTS comes from two studies. Watababe et al. [52] did not report any detailed results from programmed stimulation of 18 patients with SQTS, but stated there was no difference in inducibility of ventricular tachyarrhythmias between patients with arrhythmic events (73 %) and those without arrhythmic events (72 %). In the long-term follow-up study by Giustetto et al. [18] 28 patients underwent an electrophysiologic study. The ventricular effective refractory periods at the right ventricular apex were shortened and varied between 140 and 200 ms (mean: 166 ± 21 ms). No difference was found between patients with a history of cardiac arrest or syncope and those without. VF was induced in 16 patients (57 %), in seven by mechanical induction during catheter positioning. The atrial effective refractory periods also were shortened and ranged between 120 and 200 ms (mean: 163 ± 22 ms). Atrial fibrillation was induced in 36 %. Patients with HERG mutation had shorter refractory periods than those without. From these data it is apparent that an electrophysiologic study is not useful in predicting cardiac arrest having a sensitivity of only 37 %.

Clinical Manifestations and Clinical Course

It was an article from 2003 by Gaita et al. [2] that brought attention to the high incidence of SCD in families with short QT interval. Both families were later found to have a *HERG* gene mutation. In a family from Italy six members had died suddenly. Of those six, one had documented short QT interval. Two living members also were known to have short QT interval. In the other family, which was from Germany, three members had died suddenly, one with documented short QT interval in an ECG taken prior to death. Two members of that family with short QT interval were alive. The most comprehensive report about clinical manifestations of SQTS can be found in the recently published follow-up study from Giustetto et al. [18] of 53 patients with SQTS.

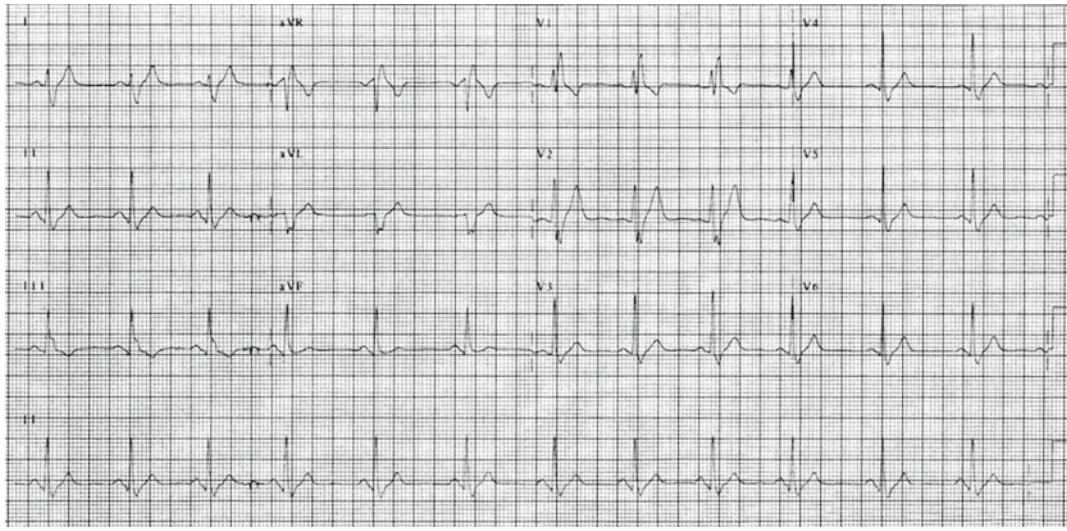

Figure 33–2. Twelve-lead ECG from asymptomatic female with SQTS based upon a short QT interval and sibling with aborted SCD due to SQTS. The ECG shows sinus rhythm at a heart rate of 81 beats/min, RBBB and R axis deviation. The QT interval varies between different leads from 320 to 360 ms. Twenty-four-hour Holter monitoring showed a QT/RR slope of 0.1 both during the day and during the night suggesting minimal variability in QT interval with changes in heart rate. The person had an ICD implanted for primary prevention of SCD

Almost 90 % of the patients had a personal or familial history of SD, and 33 (62 %) had symptoms at presentation: 4 had died suddenly, 13 had an aborted SCD, 8 had syncope and 13 palpitations. Cardiac arrest had a similar prevalence in males and females (35 % vs. 30 %), but in patients carrying a *HERG* mutation a greater proportion of affected females (55 % vs. 18 %; $p = 0.04$) and a higher prevalence of atrial fibrillation (36 % vs. 3.6 %; $p = 0.02$) were observed compared with non-*HERG* patients. The high incidence of atrial fibrillation in patients with *HERG* mutation in this study is in accordance with observations in the first family with SQTS, where all four members with SQTS and a HERG mutation had atrial fibrillation [39]. A few cases of SQTS have been reported in children. Morphett JAM [53] reported a 3 week-old neonate who presented with episodes of apnea. The ECG showed QT-interval of 210 ms. During ECG monitoring sinus node dysfunction in terms of sinus bradycardia, sinus arrest and atrial and ventricular standstill was observed. The case was interpreted as SIDS with SQTS in which sinus node dysfunction was an important aspect of the pathophysiology. In the study by Giustetto et al. [18] one of the patients had a history of aborted SCD at the age of 8 months (mutation unknown). These two cases combined with the finding of a gain-of-function *KCNQ1* mutation in a patient with SIDS [13], suggest that SQTS is a possible explanations for sudden death in infants. Atrial fibrillation with high degree AV block and a heart rate mostly in the 40s has been found in two babies with bradycardia *in utero* and a V141M-*KCNQ1* mutation [9, 26]. DC cardioversion was unable to restore persistent sinus rhythm suggesting a sick sinus node as well as AV nodal disease. Conduction system disease has also been present in other patients with SQTS. Left anterior hemiblock was observed in two asymptomatic subjects with SQTS and RBBB in two other patients, including a 25-year old sister to a patient with SQTS and aborted SCD (Fig. 33.2) [26]. She also had left posterior hemiblock with a QRS duration of 140 ms and the QT interval at a heart rate of 54 beats/min was 340 ms. The occurrence of this type of conduction disturbance in young adults is unexpected and suggests that conduction system disease may be part of the clinical picture of SQTS and possibly related to specific gene mutations. The two patients with left anterior hemiblock both had a HERG mutation [18], where as the mutation in patients with RBBB and RBBB + LPH is unknown.

During a follow up of 47 patients over 64 ± 27 months by Giustetto et al. [18] there were

no death. Among 24 patients with an ICD there were two, who was successfully defibrillated and three who had episodes of non-sustained ventricular tachycardia. Among 14 previously asymptomatic patients who received no treatment there was one who had a syncopal episode. Two patients who had previously had syncope, but opted for no treatment were asymptomatic during follow-up. If we assume that the two patients who were appropriately shocked by the defibrillator would have died without being treated, the incidence of SCD in the study by Giustetto et al. [18] is compatible with an intermediate risk of SCD in a mixed population with SQTS of approximately 0.8/100 pt-yrs. Just like in patients with LQTS [54] it is very likely that factors such as gender, QT-interval duration, type of mutation and a history of syncope will all have an impact upon the risk for the individual SQTS patient.

Treatment

The Implantable Cardioverter-Defibrillator (ICD)

Patients with SQTS belong to a category of patients at high risk of sudden cardiac death who are all candidates for prophylactic ICD implantation as long as features for individual risk stratification are not known and the benefit from medical treatment not proven. A characteristic finding in some patients with SQTS is tall peaked T waves, which may lead to double counting of the ICD and inappropriate shocks. This was encountered in four of the very first SQTS patients who received an ICD [3], but not been a clinical problem since then because of the ability to program ICDs in such a way that it can be avoided. Other complications to ICD treatment in patients with SQTS was presented in the long-term follow-up study from the European SQTS registry [18]. Among 24 patients who received an ICD 14 (58 %) had complications. As already mentioned four had T wave oversensing, but there were no recurrences following reprogramming of the ICD. Four had inappropriate shocks during supraventricular tachycardias, four patients needed ICD lead replacement: three because of lead fracture and one because of infection of the ICD system. One patient had early replacement of the ICD because of a recall. Finally, there was one patient who had severe psychological distress from having an ICD. During the approximately 5 years of follow-up, two patients were successfully defibrillated. One had initially presented with cardiac arrest and the other with syncope.

Pharmacological Therapy

Antiarrhythmic therapy in patients with SQTS has mainly been necessary for paroxysmal atrial fibrillation and as prophylaxis against ventricular tachycardia or fibrillation in patients with an ICD in order to reduce the number of shocks to a minimum. In the study by Giustetto et al. [18] hydroquinidine was initially used in 22 patients, but in ten it had to be discontinued because of poor compliance in six, no QT prolongation in two and gastrointestinal side-effects in two. Twelve patients (three with history of cardiac arrest, three with history of syncope and six previously asymptomatic) took hydroquinidine for a mean period of 76 ± 30 months without having any arrhythmic events. The use of quinidine was based upon limited data from previous studies. In 2004 Gaita et al. [5] had tested Flecainide, Sotalol, Ibutilide and Hydroquinidine in six patients with SQTS. Flecainide, Sotalol and Ibutilide did not produce any significant QT prolongation. Only hydroquinidine prolonged the QT interval from 263 ± 12 to 362 ± 25 ms with prolongation of the ventricular effective refractory period to >200 ms and VF was no longer inducible. The slight prolongation of the QT interval following Flecainide was mainly due to QRS prolongation. The lack of QT prolongation following selective I_{Kr}-blocking agents like Ibutilide and Flecainide suggested that the (N588K) mutation in the KCNH2 channel in these patients with SQT1 might have caused loss of some of the physiologic regulatory mechanisms, and the ion channel was no longer sensitive to a drug that normally has a specific action on it. Quinidine was recommended as the drug of choice for medical therapy while Flecainide because of some increase in the effective refractory period could be the second choice. Wolpert et al. [27] later performed exercise testing of quinidine in three patients with SQTS caused by a mutation in HERG and showed that the

linear relationship between QT_{peak} and increasing heart rate seen in normal persons did not exists in patients with SQTS and the slope of QT_{peek} in these patients was much less steep than in a control group. Quinidine was, however able to bring the HR/QT relationship in patients with SQTS close to normal. Recently Pirro et al. [55] reported a 5-year old child with SQTS and an N588H-*HERG* mutation who had been on hydroquinidine since she was 9 days old. She was followed by frequent ECG and plasma concentration of hydroquinidine with a target QTc interval >360 ms and a plasma concentration between 0.6 and 2.0 μg ml^{-1}. No cardiac symptoms or major side effects were observed during follow-up. Sun et al. tested the effect of quinidine and Sotalol on the mutant T618I-HERG channels expressed in HEK 293 cells and found for both drugs a much smaller loss of inhibitory effect than previously shown on N588K-HERG channels suggesting that SQTS patients with the T618I mutation may not be resistant to these drugs. Disopyramide is another drug considered as therapy for SQTS patients. McPate et al. [56] used whole-cell patch clamp recordings from Chinese Hamster Ovary cells expressing HERG with a N588K mutation to demonstrate, that the HERG-blocking potency of disopyramide was reduced only 1.5-fold. Since other studies had shown that Quinidine's blocking effect of N588K-HERG channels was reduced 5.8-fold and Sotalol's 20-fold, the study provided a rational basis for further evaluation of disopyramide as a treatment for SQTS. There are, however, at this point only a few case reports about the clinical effect of disopyramide in patients with SQTS and the results have been mixed [18, 57, 58]. Other drugs used sporadically with some success includes amiodarone [59], and propafenone [7, 60], but as with any of the other drugs, there are just not enough patients with SQTS to make drug testing possible.

Concluding Remarks

Everything stated about SQTS has to be seen in light of the fact that patient number 100 was published just recently and the fact that most of our knowledge stems from patients who have very short QT and QTc intervals (<340 ms) [18, 26]. Much more information is needed before our current knowledge about SQTS can be applied to patients with longer, but still short QT intervals, regarding risk of arrhythmic events and heritability, and we will have to wait quite a bit longer before more specific criteria for diagnosing and treating this syndrome can be made. The importance of a short QT interval in the setting of other arrhythmia syndromes such as Brugada Syndrome and early repolarization syndrome is still unknown. In the meantime it would seem prudent that work up of patients with a short QT interval is done in consultation with centers with special interest and knowledge of QT interval related diseases in order to avoid some of the diagnostic miscues observed in patients with congenital long-QT syndrome [61]. If possible, genetic testing should always be done whenever SQTS is suspected. If it is positive, it is a great help in making the diagnosis, also in family members. Clinical situations with secondary shortening of the QT interval are rare, but needs to be ruled out [19]. It is important to take several ECGs at different heart rate and especially as close to 60 bpm as possible and attempts should be made to evaluate the QT/RR relationship either by stress-testing or Holter monitoring. Minimal change in the QT-interval reflecting in an increase in QTc with an increase in heart rate is typical for SQTS. The presence of very tall and peaked T waves especially in precordial leads favors a diagnosis of SQTS, and the same is true for very short atrial and ventricular refractory periods obtained by an electrophysiologic study. The diagnostic and prognostic value of VF or VT induction by programmed electrical stimulation is questionable, but induction of VF by simple positioning of the electrode-catheter in the RV is a phenomenon rarely seen in a normal heart, but a common occurrence in patients with SQTS [7, 18]. Once the diagnosis of SQTS is made the treatment of choice is an ICD. Medical treatment with QT prolonging antiarrhythmic drugs may offer some protection against SCD and several drugs have shown some therapeutic benefit and so far without any proarrhythmic side effect in SQTS patients. They, therefore, could be alternatives to an ICD in patients who do not want to have an ICD or in small children where implantation of

an ICD may have a high risk. Non-cardiac side effects to quinidine and difficulties in getting the drug anymore may, however, hinder its use. Other anti-arrhythmic drugs which have been used in isolated patients with SQTS includes disopyramide, amiodarone, propafenone and sotalol.

Even though the incidence of life-threatening ventricular tachy-arrhythmias during follow up of patients with SQTS so far has been low, it is important to realize that most of the patients published have been relatively young and only followed for a few years. The risk important to these patients is the risk during a lifetime, and that may be quite high.

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