REVIEW

Short QT syndrome: an update

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INTRODUCTION

In 2000 Gussak et al. first described an idiopathic short QT interval associated with atrial fibrillation (AF) in one family and a sudden death in an unrelated individual[1]. Three years later, in 2003, Gaita et al. reported the association of a short QT interval and sudden cardiac death in two unrelated European families[1]. In recent years a variety of mutations in different genes most likely causative for the short QT interval were identified. The initially reported mutations either caused a gain-of-function of cardiac potassium channels IKr, IKs and IK[1], or a loss-of-function in the cardiac L-type calcium channel (ICa)[3-10]. Meanwhile new mutations have been reported resulting in different alterations of ion channel activity.

Risk of sudden death in patients with a Short QT syndrome has been reported to be high. Also the occurrence of atrial fibrillation at younger ages is not infrequently seen in these patients, most likely caused by short atrial refractory periods.

CLINICAL PRESENTATION

The clinical presentation of patients with SQTS is very heterogeneous. First data were presented from the EUROSHORT registry[10]. 29 patients (21 m, 8 f) were studied. 18/29 were symptomatic at time of enrolment. Nine of the patients had a history of cardiac arrest, 6 had suffered syncope and 7 had documented atrial flutter or atrial fibrillation[10]. Onset of symptoms was very variable ranging from the age of 4 months up to the age of 62 years and it was distributed over all decades of life. Sudden deaths occurred in the youngest patient at the age of 4 months. Thus, SQTS represented also a new cause for the sudden infant death syndrome (SIDS).

Mazzanti et al. studied a population of 47 probands who were referred to the database for cardiac arrest (n=19), syncope (n=9), family history of sudden death (n=2) or an incidentally found short QTc interval[11]. 12/47 had a family history of sudden death in the young and 4 had multiple victims in their family (2.5±0.6.) Among the asymptomatic individuals, the sudden death victims and patients with syncope the QTc interval were not statistically significantly different. The age at time of syncope or sudden death was also comparable with 21±11 vs 25±13 years. Interestingly, the QTc interval in those, in whom a mutation was identified, was significantly shorter (300 vs 335 ms). There was no difference in the likelihood of sudden death between mutation positive and mutation negative probands.

Villafane et al. published a multicentric series of 21 pediatric patients[12,13]. The median age was 15 years. (84% males) 56% of the patients were symptomatic for syncope (n=4) or sudden death (n=6). 16 patients had either a personal or family history of sudden death. The rate of atrial fibrillation was very high for this young cohort with 4/21 patients.

A gene mutation was identified in only 24%. Eleven of 21 patients received an ICD and two patients received an appropriate shock and 64% inappropriate shocks. The authors applied the Gollob score and observed that asymptomatic individuals with a Gollob score of <5 were asymptomatic for VT/VF or sudden death and syncope over a 6 year follow-up. In a Japanese series

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of five Japanese unrelated families symptoms were AF in 2, ventricular fibrillation (VF) in 2, sudden death in 3 patients and severe bradycardia in one new-born. The QTc in this series was between 280 and 340 ms i.e. somewhat longer than in patients with SQT1[14,15].

ELECTROCARDIOGRAPHIC FINDINGS

There is no clear definition of a short QT interval, but a number of authors and the ESC guideline committee has come up with a proposal on where the lower limit of the QT interval should be.

In the following there are some of the works that have tried to determine the upper and lower boundaries of the QTc interval.

In the general population QTc intervals follow a Gaussian normal distribution[16-23]. Normal QT intervals were proposed as QTc intervals within two standard deviations from the mean. QTc shorter than the 2.5th percentile were defined as "short". Following this calculation, QTc of <350 ms for men and QTc <360 ms for women are considered short. In large population based studies the prevalence of a short QT interval was analysed (Anttonen et al.). 10.822 subjects and found short QTc intervals of <340 ms in 0.4% of the subjects[16]. Extremely short QTc intervals <320 ms were seen in 0.1% of the cases. Both, individuals with a short and a very short QTc interval had no cardiac events[8]. In a Japanese cohort of 12.149 subjects 0.01% exhibited a QTc interval within the 2.5th percentile (men QTc <354 ms; females <364 ms) and only 3 male subjects a QTc of <300 ms[17]. Another analysis of 19.53 subjects undergoing biannual health examinations in the follow-up program in Hiroshima and Nagasaki since 1958 the prevalence for a short QT interval (QTc <350 ms) was 0.01%13. Kobza et al. found a similar low prevalence of 0.01% of QTc intervals <320 ms in 41.767 male army conscripts[19].

A recent report on an ECG population sample among 1.7 million persons revealed a QTc of less than 300 ms in 2.7 in 100.000. The risk of dying over a follow up of 8.3 years of follow-up was increased 2.6 fold[21].

The electrocardiogram of the first patients identified with a SQTS (SQT1) showed very short QT intervals and in addition short QT intervals corrected for heart rate (QTc <300 ms). The patients identified as SQT2 – SQT5 exhibited QTc of up to 360 ms. The ECG in SQT1-3 reveals tall, symmetrical and asymmetrical peaked T wave especially in the precordial leads. In most cases a ST segment is absent with the T wave

originating directly from the S wave. Another finding in SQTS is a prolonged Tpeak – Tend interval. Anttonen et al. compared the Jpoint-Tpeak interval in symptomatic patients with SQTS, probands with a short QT interval and a control group of subjects with normal QT interval[24]. Symptomatic patients with SQTS had significantly shorter Jpoint-Tpeak intervals and higher corrected Tpeak-Tend/QTc ratio compared to asymptomatic probands with a short QT interval and subjects with a normal QT interval. Patients diagnosed with SQT4 and SQT5 and carry a mutation in the cardiac calcium channel exhibit shorter than normal QT intervals of 330-360 ms, which is relatively longer than in SQT1-SQT3. These patients additionally displayed J point elevations diagnostic of Brugada syndrome[5].

Villafane et al. reported the data on pediatric patients with a short QT syndrome. The QTc ranged here from 194 to 355ms (mean 312 ms)[12,13].

QT adaptation to heart rate and behaviour during exercise

Another important finding in the initially reported SQT1 patients was the inappropriate adaptation of the QT interval to heart rate. In the first patients with the KCNH2 mutation Wolpert et al. could show that the QT interval did not shorten appropriately compared to normal controls. Treatment with quinidine was able to restore the QTc/heart rate ratio towards the normal range[10,25].

Giustetto and co-workers further studied the usefulness of exercise testing in the diagnosis of short QT in order to see if QT behaviour during exercise helps to differentiate between short QT patients and individuals with a shorter than normal QT interval. They investigated twenty one patients with a short QT syndrome and matched controls. Rest and peak exercise heart rates did not differ between the groups. The baseline QT intervals at rest were 276 vs 364 ms and at peak exercise 228±27 ms vs. 245±26 ms with a mean variation from rest to peak exercise of 48±14 vs. 120±20 ms. The QT/HR slope never exceeded 0.9 ms/bpm. The mean was -0.53 ms/bpm vs. -1.29 ms/bpm.

Electrophysiological findings

Atrial and ventricular effective refractory periods are significantly shortened especially in SQT1 (KCNH2)[29]. Atrial refractory period of 140 ms and ventricular effective refractory period of 150 ms or less are criteria highly suspicious of the SQTS. Inducibility of ventricular fibrillation during programmed ventricular stimulation is high in patients with SQTS 1[16]. The current consensus recommendations and the ESC guidelines

however do not recommend programmed ventricular stimulation for diagnostic purposes or risk stratification. It is only done within research protocols.

RISK STRATIFICATION

The QTc intervals of these patients are ranging from <300 ms up to <360 ms. In summary, a short QT interval on the 12-lead ECG does not predict a risk for life threatening tachy-arrhythmias *per se*. However, the rare finding of a short QT interval should initiate a diagnostic work-up including family members. In the case of a short QT interval together with episodes of atrial fibrillation, sustained palpitation, unexplained syncope, ventricular fibrillation, and/or a positive family history for premature sudden cardiac death, Short QT syndrome should be suspected[30,31].

Gollob et al proposed a SQTS Diagnostic criteria score analogous to the Schwartz-Score for Long QT syndrome in which a high probability of SQTS was reached when more or equal to 4 points were given. In his criteria a QTc of <370 ms was 1 point, <350 ms 2 points and <330 ms equal to 3 points[31].

The 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death provide a class I recommendation for a diagnosis of a SQTS, when the QTc is <340 ms. It should be considered, if the QTc is <360 ms and one or more of the following conditions exists a) a confirmed pathogenic mutation, b) a family history of Short QT syndrome, c) a family history of sudden death at age <40 years or d) survival from a VT/VF episode in the absence of heart disease. The guidelines discourage with a class III indication the EP study for risk stratification[30].

MOLECULAR AND GENETIC MECHANISMS

The SQTS is a genetically heterogeneous disease like long QT syndrome. A number of genes have been described to be associated with Short QT syndrome. The mutations are located on different chromosomes e.g. 7, 10, 11, 12 and 17 and encode for different cardiac ion channels.

The first mutation identified to be causing short QT syndrome (SQT1) was a gain of function mutation leading to an increase of the rapid component of the delayed rectifier potassium current (IKr)[7]. Two different missense mutations were identified resulting in the same amino acid change in HERG (KCNH2). These mutations at nucleotide 1764 in the KCNH2 gene substitute the asparagine at codon 588 for a positively charged lysine (p.N588K). The p.N588K mutation causes a loss of the normal rectification of the current at plateau voltages, which results in a significant increase of IKr during phase 2 and 3 of the action potential leading to abbreviation of the action potential and both, atrial and ventricular refractoriness. Bellocq et al. shortly after reported on a mutation in a single sporadic case of a 70-year-old patient with SQTS (QTc 302 ms) and sudden cardiac arrest. They identified a gain of function mutation (p.V307L) in the KCNQ1 gene which encodes the slow component of the delayed rectifier potassium channel (IKs) (SQT2). A further missense mutation in the same was identified in a baby with bradycardia and atrial fibrillation *in utero*[6]. The ECG of the new-born revealed a shortened QT interval and episodes of atrial fibrillation.

Priori and co-workers later identified in two relatives without sudden cardiac arrest a gain of function in KCNJ2, encoding the inward rectifier potassium channel (IK1) causing abbreviation of the QT interval and asymmetrical T waves with a rapid terminal downslope[4].

Later, we, together with Antzelevitch and co-workers, further described novel mutations of the cardiac L-type calcium channel genes responsible for shortening of the QT interval in families characterized by sudden cardiac death, atrial fibrillation together with a Brugada type 1 ECG pattern[5]. Functional analyses revealed loss-of-function missense mutations of the CACNA1C and CACNB2b genes encoding the pore forming of Cav1.2 α1- and β2b-subunits of the cardiac L-type calcium channel. The decreased net current of the cardiac L-type calcium channels led to an abbreviation of the plateau phase of the action.

Recently new patients have been identified who suffer from mutations in KCNH2 and KCNQ1. A Japanese group and a Chinese group identified a novel mutation in KCNH2 that resulted in a 2.5-fold increase in peak current density in COS-7 cells and a mutation in KCNH2-p.T618L[14].

Moreno et al presented a male individual with a family history of sudden death with a QTc of 356 ms who carried a mutation in the S5 segment of the KCNQ1 that impaired its association with KCNE[19]. Suzuki reported a case of a asymptomatic 10-year old boy who displayed a QTc interval of 260 ms. In molecular genetic screening they found a mutation in the KCNH2-p.N588K, identical to the one identified in the first two unrelated families in 2000 and 2003 when the syndrome was described first in detail[32].

Table 1. Short QT genetic subtypes

SQT	Gene	Channel
SQT1	KCNH2	IKr
SQT2	KCNQ1	IKs
SQT3	KCNJ2	IK1
SQT4	CACNA1C	ICa
SQT5	CACNB2b	ICa

Deo et al described a mutation in KCNJ2 that resulted in an enhanced IK1 outward current leading to a phenotype of an extremely abbreviated QT interval and atrial fibrillation[33].

A French group presented a family with inherited L-carnitine deficiency, in which a short QT interval was found in all affected members. After substitution of carnitine the QT interval was significantly prolonged towards normal range[34].

PHARMACOLOGIC THERAPY OF SHORT QT SYNDROME

Most of the experiences *in vitro* and *in vivo* are available for patients with SQT1. Heterogeneous expression studies exhibited that the p.N588K mutation increased the density of IKr and reduced the affinity of IKr blockers like d-sotalol 20-fold. McPate et al. could demonstrate that the effect of E-4031, a specific IKr blocker, was also significantly attenuated by the p.N588K mutation, whereas quinidine was less and disopyramide the least affected by p.N588K-HERG[40]. Cordeiro et al. could nicely show that these findings are based on the +90 mV shift in the voltage-dependence of inactivation of the HERG channels. Most IKr-blockers interact with the HERG channels in the inactivated state. Thus, a failure of inactivation of the HERG channel leads to the inefficacy of the specific IKr blockers[41]. Recently, McPate et al. could demonstrate that besides disopyramide and quinidine also propafenone and amiodarone were only slightly inhibited by the mutant p.N588K[41]. Thus these drugs may represent an additional option in the pharmacologic treatment of SQT1.

In vivo, several class I and III antiarrhythmic drugs have been tested in patients with a mutation in HERG (SQT1). Neither d-sotalol nor ibutilide were able to prolong QT interval in the first series of type I Short QT syndrome patients. Flecainide, a Na+-channel blocker, which has in addition a blocking effect on IKr and on the transient outward potassium current (Ito), led to a slight increase in ventricular effective refractory periods, but failed to effectively prolong the QT interval[42]. In contrast quinidine was able to normalise the QT interval and to prolong the ventricular effective refractory period in patients with a SQT1[29]. Further quinidine restored the heart rate dependence of the QT interval towards the normal range and rendered ventricular tachyarrhythmias non-inducible in patients in whom baseline electrophysiological studies demonstrated reproducible inducibility of ventricular fibrillation. Following the positive effects of disopyramide in in vitro experiments disopyramide has also been shown to be effective in a pilot study in patients with a SQT1 by Schimpf et al.

The most frequently used drug for treatment of VF prevention or recurrences was quinidine. No patient on quinidine therapy suffered from ventricular fibrillation or a recurrence of atrial fibrillation during midterm follow-up in the Short QT registry[10,38]. A subset from one SQT-1 family published by Bjerregaard et al. treated with propafenone is free of recurrences of atrial fibrillation without prolongation of the QT interval. However, it is not known if the fact, that they did not suffer from ventricular fibrillation during follow up is caused by the effect of the drug or incidental (personal communication).

Whether the effects of the investigated class I and III drugs can be translated to SQT2 – SQT5 is not clear. However, in a patient with SQT4 quinidine was equally able to prolong QT interval and suppress paroxysms of atrial fibrillation as seen in SQT1.

Due to the electrophysiologic and genetic heterogenity of the SQTS therapy may have very different effects depending on the type of mutation and the affected channel. Further studies of pharmacologic therapy are needed to elucidate the potential long term benefit of pharmacologic treatment for both prevention of atrial fibrillation and sudden death.

The 2015 ESC guidelines recommend quinidine or sotalol when patients refuse an ICD or have a contraindication and in asymptomatic patients and a family history with a class IIb indication. Finally, however, some drug combinations have been successfully used in patients, that are not mentioned in the guidelines and to some extent the treatment of this very heterogeneous patients will remain individual[30].

ICD THERAPY

To date the only reliable treatment to prevent patients from sudden cardiac death is the implantation of an implantable cardioverter-defibrillator (ICD). In symptomatic patients with SQTS the ICD is the therapy of choice, while antiarrhythmic drug therapy may re-
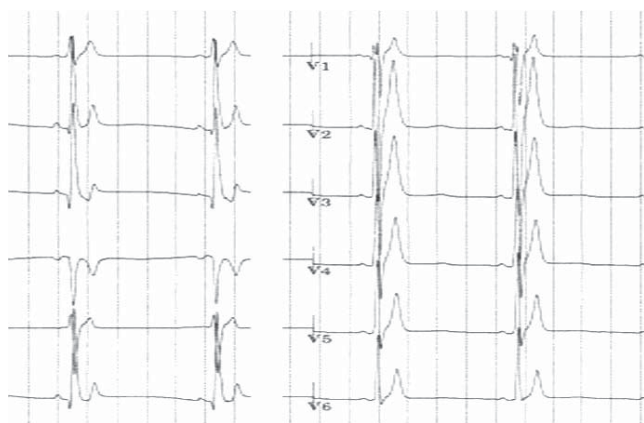
Figure 1. The figure displays the ECG of a young patient with Short QT syndrome.

present only an adjunct or an alternative therapy in children or in newborns, where ICD implantation is often associated with high morbidity. The risk for inappropriate ICD discharges due to T wave oversensing is increased in patients with SQTS compared to other conditions with ICD implanted, since intra-cardiac T waves are high and closely coupled to the preceding R wave. This problem can be solved by individual ICD programming of the sensing parameters and selection of specific devices depending on the T wave suppression algorithms of the different manufacturers. Additionally, quinidine therapy prevents T wave oversensing by increasing the QT interval[43]. The importance of careful ICD programming is underlined by the high incidence of inappropriate shocks especially in the pediatric cohort.

Risk stratification in short QT syndrome is based on the QTc-interval, family history of sudden death <40 years of age in a relative and symptoms. An ICD is indicated following to the 2015 ESC guidelines for survivors of sudden death or patients with a spontaneous documented VT.

SUMMARY

The SQTS is one of the primary electrical diseases of the heart with a high incidence of syncope and sudden cardiac death. The hallmark for the diagnosis is a short QT interval. Since the disease presentation is quite heterogeneous, a strong genotype-phenotype correlation and a conclusive risk stratification is still very difficult to achieve.

Patients with SQTS should be referred for genetic counselling, molecular genetic analysis and initiation of family screening in specialized centers in order not to miss affected individuals at risk or to over diagnose patients with a shorter than normal QTc who are not at risk of sudden death.

Conflict of interest: none declared.

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