

Short QT Syndrome: A Review of Current Literature

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Abstract

The short QT syndrome (SQTS) is a new member of the genetic arrhythmia family (including long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia and familial atrial fibrillation) with a high incidence of syncope, sudden death and atrial fibrillation in all age groups. The cause of this syndrome is mutation in genes that encode for the potassium rectifier channels, leading to a gain of function in these channels and heterogeneous aberration of repolarization, such that patients with this syndrome become prone to ventricular tachyarrhythmias. To date, the implantable cardioverter-defibrillator (ICD) is the only therapeutic option for the prevention of sudden cardiac death. Although many potassium channel (I_{Kr} and I_{Ks}) blocking drugs have been tested for the treatment of this syndrome, only quinidine (and possibly flecainide) has the potential for effective therapy in patients with SQTS and serves as an adjunct to ICD or as a possible alternative treatment (*Iranian Heart Journal 2006; 7 (3):43-51*).

Key words: short QT syndrome ■ genetic arrhythmia ■ sudden cardiac death.

Sudden death occurs predominantly in individuals with structural heart diseases (SHD); however, in approximately 10-20% of all sudden deaths, no SHD can be identified.¹ Cardiac action potentials are generated and propagated through the coordinated activity of multiple ion channels, including voltage-gated sodium channels, calcium channels and potassium channels. Mutations in genes encoding these channels cause familial arrhythmias.²

A correlation between an inherited ion channelopathy and an increased risk of life-threatening arrhythmic events was first reported by Keating et al.³

Each channelopathy or heritable arrhythmia syndrome is capable of causing sudden unexpected death during infancy via a lethal ventricular arrhythmia without a trace of structural evidence left behind for detection during postmortem examination, and are therefore suspects in the etiology of sudden infant death syndrome.⁴

In 1993, after analyzing 6693 consecutive Holter recordings, Algra et al. concluded that an increased risk of sudden cardiac death (SCD) was present not only in patients with long QT interval but also in patients with short QT interval.⁵

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It was not until 2000 that a SQTS was proposed as a new inherited clinical syndrome by Gussak et al.⁶ The initial report was a family with paroxysmal atrial fibrillation (AF) and constantly short QT interval. The familial nature of this sudden death syndrome was confirmed by Gaita et al. in 2003.⁷ They reported two different families with syncope, palpitation, aborted sudden death, family history of sudden death and persistently short QT interval.

Genetic basis and mechanism of QT shortening

The QT interval, first introduced by Einthoven, encompasses both depolarization and repolarization of the ventricular muscle,⁸ and there is a constant relationship between the ventricular effective refractory period and the QT interval.⁹ Ventricular repolarization is determined by the properties and the equilibrium between the inward Na^+ and Ca^{2+} currents and the outward K^+ current. The delayed rectifier K^+ currents (I_K) consist of two components, namely I_{Ks} (slowly activating K^+ current), and I_{Kr} (rapidly activating K^+ current). The duration of the QT interval on the ECG is primarily determined by the duration of the ventricular action potentials (APD). The amplitudes of the rapid and slow components of the delayed rectifier potassium currents are major determinants of the repolarizing forces modulating APD.¹⁰ From a theoretical point of view, the shortening of ventricular repolarization can be the consequence of either an increase in repolarizing currents or a decrease in depolarizing currents during the plateau and/or phase 3 of repolarization.¹¹

Reduced I_K function leads to the prolongation of the cardiac action potential and lengthening of the QT interval. In contrast, an increased activity of I_K could play a role in producing a short QT interval. Among the principal gene candidates proposed to underlie these syndromes were gain of function mutations of I_{Kr} , I_{Ks} , $\text{I}_{K,ACH}$ and $\text{I}_{K,ATP}$ (Fig. 1). $\text{I}_{K,ACH}$ gain of function or other means by which the

influence of the parasympathetic nervous system could be exaggerated was considered as the most likely mechanism to explain the deceleration-dependent variant of the short QT syndrome.¹²

The first gene responsible for the SQTS was reported by Brugada et al. in January 2004 (SQTS-1).¹³ The substitution of lysine for asparagine at position 588 of KCNH2 (N588K) was found to cause a loss of the normal rectification of the current at plateau voltages, thus resulting in a large increase of I_{Kr} during the action potential plateau, leading to marked aberration of the action potential (Table I).¹³ LQT2 has been linked to a mutation causing loss of function in the KCNH2 gene.

Bellocq et al. recently linked a second gene to this syndrome (SQTS-2). A missense mutation in KCNQ1 (KvLQT1) identified a G>C substitution at nucleotide 919 (GTG>CTG), leading to the substitution of valine at position 307 by leucine (V307L), giving rise to a gain of function in I_{Ks} , was identified in this form of the syndrome (Table I).¹⁴ Pacemaker activity can evidently also be disrupted by a gain of I_{Ks} function. Modeling of the V141M mutation predicts a cessation of spontaneous activity of sinoatrial node cells. The effect of the mutation on pacemaker activity in the human heart depends on many factors not included in the rabbit model, but it is clear that gain of I_{Ks} function should affect nodal automaticity.¹⁵ Mutation in the KCNQ1 gene leading to loss of function has been linked to LQT1.

In 1994, the complete human cDNA of an inwardly rectifying K^+ channel gene, KCNJ2 or Kir2.1 , was isolated. The Kir2.1 channels are important regulators of resting membrane potential of the cardiac (and also skeletal) muscle and cellular excitability, since they cause an outflow of K^+ in the hyperpolarized membrane state during the terminal phase of cardiac action potential repolarization.¹⁶ Mutation in gene KCNJ2 (N172) leading to gain of function in the Kir2.1 channel is the basis for SQTS-3 (Table I), which for the first

time was introduced by Priori et al.¹⁷ Interestingly, the shortened repolarization led to an asymmetric T-wave with an exceedingly rapid terminal phase that is unusual and probably an electrocardiographic sign of N172 allele carriers. LQT7 or Andersen syndrome (also Andersen-Tawil syndrome) has been linked to a mutation causing loss of function in the KCNJ2 gene.¹⁶

Table 1. Genetic and molecular mechanism of short QT syndrome

Short QT syndrome	Involved channel	Base pair substitution	Amino acid change
Type 1	HERG (I _{Kr}) HERG (I _{Ks})	C1764A C1764G	N588K N588K
Type 2	KvLQT1 (I _{Ks})	G919C	V307L
Type 3	KCNJ2 (I _{K1})	G514A	D172N

Mechanism of arrhythmogenesis

The electrophysiologic heterogeneity of the left ventricular myocardium is an important finding in ion channelopathies. Three different cell types have been distinguished across the myocardium (epicardial, endocardial, mid-myocardial cells). The different myocardial cell types are characterized by a heterogeneous electrophysiologic profile. For example, of the mid-myocardial cells, (M-cells) have a longer APDs because of a smaller slowly activating delayed rectifier current, I_{Ks} and a larger late sodium current, I_{Na}. Hence, differences in the time course of repolarization between the different cell layers generate a transmural voltage gradient. Heterogeneous abbreviation of the APD and increased transmural dispersion of repolarization in patients with SQTs have been proposed as the potential substrates for the development of ventricular tachyarrhythmias.¹⁸

Under normal conditions, the U-wave is usually buried within the T-wave of the ECG,

probably because of the small conduction delay between the activation of the Purkinje fiber and the ventricles and the difference in repolarization time between the two cell types. However, in patients with SQTs a clear separation of the T and U-wave is often observed. Because of the lower phase 2 voltage, N588K current remains small throughout the APD in Purkinje cells but is increased drastically by the more positive plateau of the ventricular AP.¹⁰

Ventricular cells are, therefore, likely to repolarize more rapidly than Purkinje cells, thus accentuating the difference in APD between Purkinje cells and the ventricle. This phenomenon may help to explain the separation of the U-wave from the T-wave observed on the ECG in SQTs patients but more importantly, the APD difference between Purkinje cells and ventricle will selectively shorten the refractory period of the ventricle. Without a parallel decrease in the APD of Purkinje cells, the shorter refractory period of the ventricle is likely to increase the probability of premature ventricular re-excitation.

Mutation N588K induces a large positive voltage shift in the inactivation of HERG channels. As a consequence, I_{Kr} currents electrotonically follow the waveform and amplitude of the cardiac action potential. This will result in larger amplitude I_{Kr} within the ventricle when compared to the Purkinje fibers and, correspondingly, shorter ventricular APs. The net effect is likely to selectively reduce the ventricular refractory period and increase excitability such that smaller transmural dispersion of repolarization within the ventricle combined with relatively longer Purkinje cell action potential may create an arrhythmogenic substrate for SQTs-related arrhythmias.¹⁰

A distinctive ECG feature of the SQTs is the development of tall, peaked T-waves with relatively long T_{peak}-T_{end} intervals, indicative of augmented transmural dispersion of repolarization (TDR). Abbreviation of the QT interval is associated with an increase in

TDR, which creates the substrate for reentry responsible for the development of life-threatening ventricular tachycardia/fibrillation (VT/VF). There is a good association between the level of TDR_{max} and the inducibility of polymorphic VT.¹¹

Patients with a short QT syndrome should be considered as highly vulnerable to premature ventricular beats below 180ms, to which normal hearts would be refractory. The QT interval is most abnormal during low heart rates in patients with a short QT syndrome. Therefore, transmural dispersion of repolarization as the potential substrate for the genesis of ventricular tachyarrhythmias may be most pronounced at low heart rates. Short-coupled premature ventricular beats could be potential triggers, especially during low heart rates at rest and during sleep.¹⁸

In patients with SQT3, the increased outward current resulting from the D172N mutation is expected to reduce the likelihood of early or delayed after-depolarizations. It is reasonable to surmise that the steeper restitution associated with such a mutation would enhance the possibility of T-wave alternans,^{19,20} thereby increasing vulnerability to fibrillation when the heart rate is high.²¹

In addition, as demonstrated by experimental and simulation studies, a significant correlation exists between the stability and frequency of rotors responsible for VF and the magnitude of the outward component of I_{K1} .²²⁻²⁴ Hence, at the range of frequencies of VF, a larger outward current should result in shorter APD to allow higher frequency rotors to stabilize. By inference, SQT3 patients with demonstrated D172N mutation are expected to have an increased vulnerability to sustained VF.¹⁷

Clinical and electrocardiographic manifestations

The hereditary short QT syndrome (SQT3) is a familial clinical-electrocardiographic entity with autosomal-dominant inheritance.²⁵ Patients with SQT3 mostly present with symptoms compatible with atrial and/or

ventricular tachyarrhythmias, such as palpitation, syncope, sudden death or family history of these complaints. The age range of the patients varies from newborn to old age. Because of the low number of reported patients with SQT3 (only 15 patients), the exact incidence, prevalence, and male/female ratio have not been determined, but it seems that idiopathic ventricular fibrillation with short QT interval is more common in males than in females.²⁶

The prominent electrocardiographic feature of these patients is short QT interval. The ST-segment is very short or nearly absent and the T_{end-P} interval appears long.⁸ The ECG can show left anterior fascicular block.²⁵ The cut-off value for diagnosis of short QT interval is still controversial.²⁷ Because important papers distinguishing the normal QT interval from long QT intervals originate from studies by Vincent et al.,²⁸ Vincent's methodology for measuring QT interval has become one of the most prevalent methods. In this method, termination of the T-wave is defined as the point of maximum change in the slope as the T-wave merges with baseline. Three consecutive cycles are measured and the values averaged.²⁸ The typical ECG for determination of QT interval are lead II, aVF or left precordial leads because they often allow a clear distinction of U-waves in the presence of T-wave abnormalities.⁸

There are many different definitions for short QT interval (Table II).

Table II. Different cut-off points for definition of short QT interval

Study	QT interval
Viskin et al. (26)	Male ≤ 360 ms, Female ≤ 370 ms
Schimpf et al. (18)	≤ 320 ms
Priori et al. (27)	< 300 ms

In one of these studies, the following definitions for QT interval were defined in healthy children, middle-aged men, and women: 1) Children: <310 ms (normal range, 370 ± 30 ms); 2) Men: <330 ms (normal range, 400 ± 30 ms); and 3) Women: <330 ms (normal range, 390 ± 30).

If one defines "3 standard deviations from the mean" (encompassing 99% of the values found in non-carriers of long QT mutations) as the normal spectrum, corrected QT (QTc) ≤ 360 ms for males and QTc ≤ 370 ms for females represent abnormally short QT interval and QTc ≤ 300 ms represents very short QT interval, but these values are not exceptional for healthy adults, especially during bradycardia.¹⁴

In all reported patients with SQTS, the QTc were equal or less than 320 ms, so QTc ≤ 320 ms (Bazett) or below 80% of the normal QT interval seems to be a logical definition for short QT interval.¹⁸ It is likely that less-abbreviated repolarizations may also be arrhythmogenic.¹⁴ Viskin et al. recently provided evidence that 35% of their patients affected by unexplained VF are individuals with a short QTc defined as a QTc ≤ 360 ms. This value represents the lowest 0.5% of the distribution in the normal population. Based on Viskin's observations, it is tempting to speculate that the two extremes of the Gaussian distribution of the QT interval may identify individuals at increased risk of VF.¹⁷ Physiologically, the QT interval shortens with the elevation of the heart rate.²⁶ However, in patients with SQTS, lack of adaptation of the QT interval during exercise with increasing heart rate is present.²⁷ Viewing of data suggests that patients with idiopathic ventricular fibrillation have insufficient QT lengthening at slower heart rates.²⁸

Measurements of the QT interval should be performed at resting heart rates as rate correction at high heart rates may lead to pseudonormal QTc. Holter ECGs should be performed to exclude bradycardia-associated shortening of QT interval.¹⁸ Shortening of the QT interval is most prominent at slower heart

rates; therefore, a potential trigger, like short coupled ventricular extrasystoles, may have a greater impact on the induction of ventricular tachyarrhythmias at rest and during sleep.¹⁸

Apart from consistently short QTc, affected patients present with a short or even absent ST-segment and often tall, narrow and symmetrical T-wave in the precordial leads (Fig. 2).

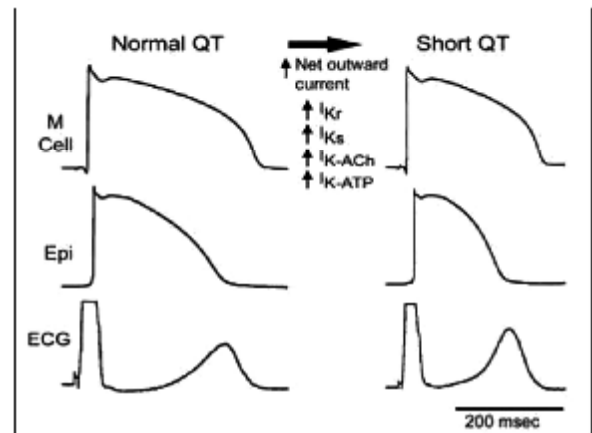


Fig. 1. Schematic diagram illustrating cellular changes attending the abbreviation of the short QT syndrome secondary to an increase in net outward repolarizing current. Epi=epicardium; ECG=electrocardiogram.

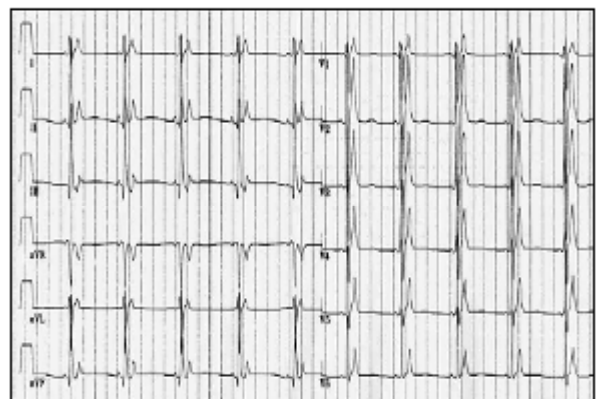


Fig. 2. Twelve-lead surface ECG of a 16-year-old patient with congenital short QT syndrome (QTc=252 ms, paper speed 25 mm/s).

The very short QTc and the symmetrical T-wave of high amplitude may depend on increased phase 2 and phase 3 outward

potassium current in all three transmural cell types (epicardial, M-cells, endocardial).²⁹⁻³¹ The exception is SQT3, which is characterized by tall, asymmetrical T waves with an exceedingly rapid terminal phase, and a genetic defect in the KCNJ2 gene that causes a significant increase in the outward component of the I-V relation of I_{K1} . It was hypothesized that such a peculiar ECG appearance may have been related to the sudden acceleration of the final phase of action potential repolarization in the D172N mutant cells.¹⁷

There is a high incidence of AF in patients with SQT; and in one study, about 70% of patients had either paroxysmal or permanent AF.¹⁸ Recent data have indicated a genetic susceptibility in 5% of the patients with AF and up to 15% of the individuals with lone AF.¹⁵ Thus, AF may be the first manifestation of the SQT. Especially in young patients with lone AF, an SQT has to be considered (Fig. 3).



Fig. 3. Chest leads of ECG from a 71-year-old patient with a short QT syndrome with permanent atrial fibrillation. (QT interval=260 ms, QTc=271 ms, paper speed=50 mm/s).

Before arriving at a diagnosis of congenital SQTs, other reversible causes of a short QT interval must be excluded (Table III).³²

Table III. Reversible causes of short QT interval

Metabolic and electrolyte disturbances:	1
Hyperkalemia	A
Hypercalcemia	B
Acidosis	C
Hypermagnesaemia	D
Drugs:	2
Digitalis	A
Acetylcholine	B
Catecholamines	C
Testosterone	D
Hyperthermia	3
Tachycardia	4

Electrophysiologic findings

One of the most prominent features of the patients with SQT at electrophysiologic study (EPS) is extremely short effective refractory periods (ERPs) of the atria and ventricles. Moreover, ventricular tachyarrhythmias, predominantly ventricular fibrillation/flutter, are inducible in a high percentage of patients.¹⁸

Another interesting observation in these patients is the feasibility of VF induction by mechanical stimulation of the ventricle. Although mechanical induction of VT/VF is possible during EPS, it is an extremely rare event.¹⁸

Risk stratification

The 24-Holter monitoring is a useful tool for the evaluation of patients with SQTs, by which one is able to demonstrate the QTI changes during resting and sleeping periods.

The 24-Holter monitoring also is helpful in the detection of ventricular extrasystoles reported in some SQTs with inducible VT/VF.

Exercise testing is useful for the evaluation of QTI changes during activity and higher heart rates.

Finally, EPS can demonstrate patients at higher risk for ventricular tachyarrhythmias (Fig. 4).

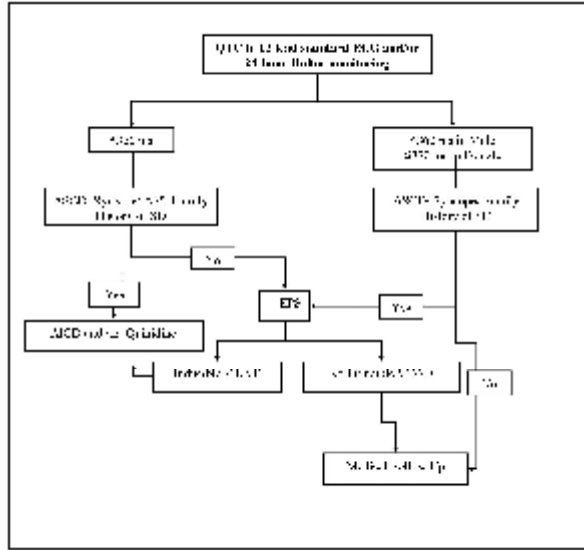


Fig. 4. Algorithm for risk stratification in patients with short QT syndrome.

The high inducibility of ventricular arrhythmias during EPS in SQTs patients with paroxysmal AF points to an increased risk for SCD, justifying the implantation of a defibrillator.³³

Therapy

To date, the implantable cardioverter-defibrillator (ICD) is the only therapeutic option for the prevention of sudden death in patients with SQTs and a history of sudden death or syncope. Whether patients without a family history of sudden death or symptoms need an ICD cannot yet be answered, and requires further investigations.³⁴ One of the fairly common problems in patients with SQTs who undergo ICD implantation is inappropriate shock delivery due to double counting of the R-wave and short coupled high amplitude T-waves.³⁵

This problem can be corrected by programming to lower sensitivity and longer decay delay (Fig. 5).^{12, 35}

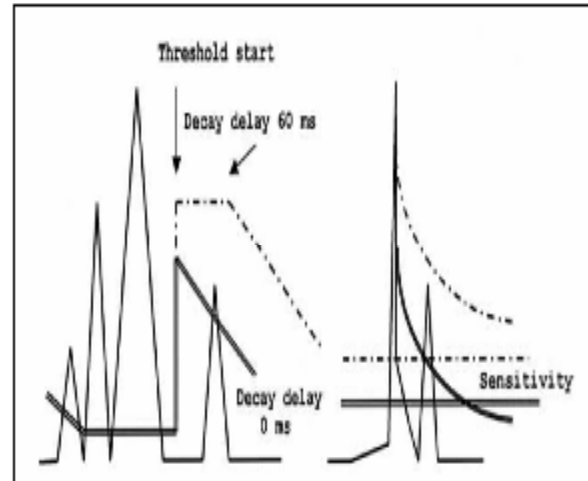


Fig. 5. Reprogramming to reduce T-wave oversensing. Schematic ECG curve of integrated intracardiac ECG signal (solid line), initial programming (double line), and final programming (dashed line).

Left: Prevention of T-wave oversensing by programming a decay delay starting after the ventricular refractory period and a higher start threshold (St. Jude Medical Inc. algorithm).

Right: Programming of a diminished sensing level and start value of exponential sensing delay (Medtronic Inc. algorithm).

Although ICD in patients with SQTs is the therapy of choice, antiarrhythmic drug therapy may constitute a potential adjunct or an alternative therapy in children or in newborns in whom ICD implantation is not feasible.¹⁸

The antiarrhythmic effects of I_{Kr} -blockers such as sotalol and ibutilide have been tested with inconsistent results. Flecainide (Na^+ channel-blocker, I_{Kr} -blocker and transient outward K^+ current blocker) leads to an increase in ventricular ERP, but only slight prolongation of the QT interval.³³

In contrast to sotalol and ibutilide, quinidine has shown ability to normalize the QT interval at resting heart rates^{33, 36} and also during exercise.

The persistent effect of the drug during exercise is significant, because sudden death in at least one case is reported to have occurred during strenuous exercise.³

The basis of the greater effectiveness of quinidine in comparison to sotalol is not fully understood. A greater affinity of quinidine for open state of the HERG channel, its ability to block the I_{Ks} that contributes to the repolarization, and its anticholinergic activity could explain the effect of the prolongation of the QT interval.

One of the characteristics of the patients with SQTS is the lack of dependence of QT interval on heart rate. Quinidine can restore the heart rate dependence of the QT interval toward on adaptation range of normal subjects. It rendered VT/VF noninducible. Quinidine's effect in reducing inducibility most likely is due to its actions in restoring homogeneity and increasing the wavelength for reentry.³⁶

Quinidine may serve as either an adjunctive to ICD therapy in the treatment of paroxysmal AF and recurrent ventricular tachyarrhythmias, or as an alternative in very young patients (Table IV).

Table IV. Role of quinidine in the therapy of patients with SQTS.

Adjunctive	Alternative
1- Treatment of paroxysmal AF	1- Very young children
2- Treatment of ventricular tachyarrhythmias in those who are getting frequent ICD shocks	2- Patients who refuse an ICD

However, the useful effects of quinidine have only been shown for patients with mutation in HERG, and could vary in patients carrying different mutations leading to SQTS.¹⁸ Flecainide may be the second choice when quinidine is not tolerated.³³

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