INTRODUCTION

The past decade has witnessed an explosion of knowledge and radical changes in our understanding of the molecular, ionic, genetic, and pharmacological basis of heritable arrhythmogenic clinical entities, known as primary electrical diseases of the heart. Among the most recently delineated life-threatening electrical diseases of the heart is the Short QT Syndrome (SQTS).

Hereditary and acquired forms of prolonged QT interval have been recognized for their torsadogenic potential and increased risk of sudden cardiac death (SCD) for many years. A short QT interval was noticed in clinical practice mainly in relation to hypercalcemia and digitalis intoxication, and was not considered arrhythmogenic until 2000 after the first description of sporadic cases of: (a) short QT
interval and SCD (Figure 1) and (b) familial short QT interval and paroxysmal atrial fibrillation (Figure 2).\(^1\)

Since its original description, as of April, 2006, the clinical experience with congenital SQTS is based on more than 14 Families world-wide; 35 family members have documented symptomatic SQTS (paroxysmal atrial fibrillation, and/or ventricular tachyarrhythmia, and/or sudden cardiac death (SCD). More than 200 publications are available in the literature. Three major clinical forms of SQTS have been described so far:

(a) Hereditary (familial or sporadic, manifested or concealed)

(b) Acquired (diseases-associated and/or drug-induced)

(c) Paradoxical (deceleration-dependent QT interval shortening).

This lecture will feature and discuss the latest developments in two major areas of SQTS:

(a) Inherited SQTS and drugs

(b) Drugs-induced shortening of the QT interval (iatrogenic SQTS).

Limited to the format of the First Worldwide Internet Symposium on Drug-Induced QT Prolongation, electrophysiological findings, mechanisms, clinical manifestations, and clinical course will not be discussed in-depth in this lecture. Also, the list of literature is limited to 24 references.

**INHERITED SHORT QT SYNDROME AND DRUGS**

**Definition.** We define **inherited SQTS** as a new arrhythmogenic primary electrical disease of the heart that is characterized by:

- Abnormally short QT interval **and**
- Paroxysmal atrial and/or ventricular tachyarrhythmia (atrial fibrillation [AF] and/or ventricular fibrillation [VF])

resulting from an accelerated cardiac (atrial and ventricular) repolarization due to congenital (genetically heterogeneous) cardiac channelopathies

**Short QT Interval as ECG Phenomenon and Clinical Syndrome.** Based upon data from the study by Rautaharju et al,\(^2\) we have previously suggested a short QT interval to be < 350 ms (two standard
deviations below the mean predicted value) and an \textit{abnormally short QT interval} to be $< 320$ ms ($< 80\%$ of mean predicted value), below which SQTS should be strongly considered.\textsuperscript{3} In all published articles about SQTS to date, where the diagnosis was based upon an ECG in a symptomatic patient, the QT interval at a normal heart rate was $\leq 320$ ms, but recent data suggest, that some patients with SQTS may present with QT intervals longer than that, and the question has been raised whether the QT/RR slope would be helpful in making the diagnosis of SQTS in questionable cases with QT intervals in the 310-350 ms range.

The QT interval is traditionally corrected for heart rate, but in patients with SQTS there are only minimal changes in the QT interval with a change in heart rate ($QT \text{"rigidity"}$). Therefore, if the usual correction for heart rate is applied to the QT interval in particular at fast heart rates, a diagnosis of SQTS may be missed. Corrected by Bazett’s formula, at a heart rate of 130–140 beats/min, the corrected QT intervals in our patients were all $> 350$ ms. In order to make a diagnosis of SQTS; the heart rate preferably has to be $< 100$ beats/min. This is particularly important in pediatric population. Recently SQTS was diagnosed in a newborn with bradycardia \textit{in utero} due to atrial fibrillation with slow ventricular response.\textsuperscript{4}

The first indication of the prognostic significance of a relatively short QT interval was from a study in 1993 by Algra et al.\textsuperscript{5} Out of 6693 patients who underwent 24 hour Holter monitoring and followed for two 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 even more than patients with a QTc $> 440$ ms, who had a 2.3 fold increase. The authors argued strongly for the possibility of their finding being a true pathophysiological phenomenon with a relative short QT interval possibly leading to life-threatening arrhythmias.

Visken et al.\textsuperscript{6} compared ECGs of 28 patients with \textit{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.

Short QT interval is also a typical ECG feature of kangaroo and rodents (rat and mouse but not in guinea pig) due to rapid ventricular repolarization.\textsuperscript{1}
In 1999 we presented another form of abnormal shortening of the QT interval duration: 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. We proposed activation of $I_{k_{Ach}}$ 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.

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. Twenty-four hour Holter monitoring was used to detect 60 episodes of monomorphic repetitive ventricular tachycardia in 10 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 minutes before at the same heart rates (342 +/- 34 vs 353 +/- 35 msec, P < 0.001). Of the 60 episodes the QT intervals were shortened in 45 (75%) compared to the intervals 40 minutes earlier. The shortening was explained by sudden parasympathetic withdrawal leading to sympathetic predominance and thereby QT shortening. The shortening was considered to play an important role in the pathogenesis of idiopathic VF.

By its own definition, any clinical syndrome is a combination of signs and symptoms that occur together and characterize a particular abnormality. The term “syndrome” is best reserved for a description of clinical manifestation of the disease, while the term “disease” is more comprehensive and embraces (encompass) malfunction/s of organ or system that is typically manifested by distinguishing signs and symptoms as a response to either environmental factors, or specific infective agents, or inherent genetic anomalies, or combinations of these factors. Another word, if “syndrome” is a set of symptoms, then “disease” is an illness (or sickness). In this context, short QT syndrome (SQTS) is best defined as an arrhythmogenic entity that is characterized by: (a) abnormally short QT interval and (b) paroxysmal atrial and/or ventricular tachyarrhythmias. History of idiopathic AF/VF or family history of SCD is apparently important in conformation of the SQTS.
**Genetics and Target Therapy.** Although abnormalities in 3 different potassium channels, (KCNH2, KCNQ1, and KCNJ2) and loss of function mutation in CACNA1C and CACNB2 encoding L-calcium channel subunits have been recognized, it very limited number of patients and likely the main reason why molecular-target based strategies for the management of the short QT syndrome have not yet been successfully developed. Clinical testing of such an approach would not be feasible. Since acceleration of repolarization due to gain of function mutation in cardiac potassium channels appear to be a common theme in the short QT syndrome, pharmacologic blockade of potassium channels could serve as the basis for the development of antiarrhythmic strategy. Triggers and modulating factors that destabilize the underlying substrate of altered repolarization also forms potential targets for drug development.9

In the first two families from Europe with SQTS reported in 2004 by Gaita et al.10 two different missense mutations (C1764A and C1764G) were found to result in the same amino acid change (N588K) in the S5-P loop region of the cardiac IKr channel KCNH2 (HERG).11 It was followed within the same year by a case report from France and the Netherlands of a 70 year old male with idiopathic VF and a short QT interval in whom analysis of candidate genes identified a mutation (V307L) in the KCNQ1 gene encoding the IKs channel KvLQT1.12 Another mutation (V141M) in the KCNQ1 gene leading to SQTS was recently discovered in a newborn with bradycardia in utero secondary to atrial fibrillation with slow ventricular response.4 In 2005 a third genetic mutation was found in an Italian family with SQTS.13 The defect was found in the gene encoding for the inwardly rectifying Kir2.1 (IK1) channel. The affected members had a G514A substitution in the KCNJ2 gene resulting in a change from aspartic acid to aspargine at position 172. Meanwhile in 2005 the genetic mutation in the first reported family with SQTS from USA initially published in 2000 had been determined.14 It turned out to be the same as previously shown in the European family from Germany (missense mutation (C1764G) resulting in an amino acid change (N588K) in KCNH2). A genetic mutation has been found in a total of 13 patients from 5 families with SQTS, but almost as many in other families with SQTS have undergone genetic screening without finding any mutation, which suggests, that other genetic defects may be involved.

Within the last year several cellular electrophysiologic studies and computer models have focused upon the etiology behind arrhythmias in patients with SQTS. Cordeiro et al.15 measured the characteristics of HERG current generated by wild-type KCNH2 and the N588K mutant channel expressed in mammalian
TSA201 cells. They found that the ventricular action potentials were preferentially reduced in SQTS, while the Purkinje fiber action potentials remained unchanged. This would lead to a shortening of the refractory period in the ventricles, but not in the Purkinje fibers. They suggested that the longer action potentials in the Purkinje fibers might re-excite the repolarized endocardial layer of the ventricles and thereby create tachyarrhythmias. This may also explain the wider than usual separation between T and U waves seen in SQTS patients. McPate et al.\textsuperscript{16} examined at physiologic temperature the importance of the S5-P linker for HERG channel function. They demonstrated that N588K-HERG contributes increased repolarizing current earlier in the ventricular action potential due to a \( \sim +60 \) mV shift in voltage dependence of \( I_{\text{HERG}} \) inactivation. This explains the accelerated repolarization and short QT interval in some SQTS patients.

Weiss et al.\textsuperscript{17} have been able to create a computer model of human cardiomyocytes that incorporates modifications in \( I_{\text{Kr}} \) as seen in some SQTS patients. They found a heterogeneous abbreviation of the action potential duration leading to a decreased dispersion of repolarization in heterogeneous tissue.

Repolarization was homogenized and the final repolarization was shifted to epicardial sites. Finally, Tanabe et al.\textsuperscript{18} have been able to create a model based upon fetal rat cardiomyocytes with over-expression of Kv1.5 leading to shortening of the action potential. They have suggested that this model can be used to study the arrhythmogenic substrate of SQTS.

As mentioned earlier, the 3 different potassium mutations identified to date in patients with SQTS have all been investigated \textit{in vitro}.\textsuperscript{19} They all effect potassium channels leading to a gain in function with either a large increase in potassium current with failure to rectify at physiologic membrane potentials, a shift in activation toward an earlier phase of the action potential, or an increased current accelerating the final phase of repolarization. The net effect is an abbreviation of the action potential and refractoriness. Shortening of refractoriness is one of the key elements in the re-entry mechanism behind many tachyarrhythmias and likely the main reason for the increased propensity to atrial and ventricular fibrillation seen in SQTS, but it is also possible that the abbreviation of the action potential may effect different cells differently leading to dispersion of refractoriness as an additional arrhythmogenic factor.\textsuperscript{20} As pointed out by Cerrone et al.\textsuperscript{21} it is likely 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. In the only patient monitored so far during the onset of spontaneous
ventricular fibrillation, where the SQTS was linked to mutations in HERG, the arrhythmia occurred during sleep following a premature beat with a very short coupling interval.22

So far, antiarrhythmic therapy in SQTS patients has mainly been focused on prevention of paroxysmal atrial fibrillation and/or ventricular fibrillation and SCD, particularly, in patients without implanted ICD or those with frequent shocks from an ICD. A clinical experience antiarrhythmic drug in SQTS is very limited. Gaita et al.23 tested the effect of several antiarrhythmic drugs (flecainide, sotalol, ibutilide and hydroquinidine) on the QT interval in 7 patients with SQTS. Flecainide caused a slight prolongation of the QT interval, primarily due to prolongation of the QRS complex, whereas sotalol and ibutilide had no effect on the QT interval. Hydroquinidine caused QT prolongation, with an increase in QT intervals from 263 +/- 12 ms to 362 +/- 25 ms, a normalization of rate adaptation of the QT interval, and ventricular fibrillation was no longer inducible. We have used propafenone (225 Mg TID) in 2 patients with multiple episodes of paroxysmal atrial fibrillation requiring DC-cardioversion for termination without recurrence of the arrhythmia for over two years. Propafenone had no prolonging effect on the QT interval.

IATROGENIC SHORT QT SYNDROME

Short QT interval is a rare occurrence in normal clinical practice. It is well known, however, that various abnormal conditions (e.g. hypercalcemia, hyperkalemia, hyperthermia, acidosis, DC shock) and different cardioactive agents (digitalis, beta-blockers, acetylcholine and catecholamine) can often shorten the QT interval. In addition, early repolarization is often accompanied by shortening of the QT interval.

Most recently, 19 patients with short corrected QT intervals (≤300 ms) irrespective of the etiology were evaluated for cardiac arrhythmias on the same day the short QT interval was detected: atrial fibrillation and/or atrial flutter were detected in 12 cases (63%) and cardiac arrest due to ventricular tachyarrhythmias developed in 32%. After adjusting for age, sex, ethnicity, heart rate, temperature, corrected serum calcium, serum potassium, acid-base status, digitalis use and creatinine, with multivariable logistic regression analysis, patients with short QT interval possess significantly increased risk of arrhythmia (p=0.017).24

Although, (a) the correlation between the degree of QT shortening and arrhythmic event and (b) trigger factors for arrhythmic event are not yet established, some might consider abnormal short QTc as an
independent risk factor for cardiac arrhythmias such as atrial fibrillation, atrial flutter, and ventricular
tachyarrhythmias, and SCD.

**DRUGS-INDUCED SHORTENING OF THE QT INTERVAL**

Drug-induced shortening of QT interval is a significant problem in the area for cardiac safety
testing during drug development due to high arrhythmogenic potential of the inherited form of the SQTS.

**History of Drug-induced QT Interval Shortening.** The history of iatrogenic SQTS is short yet
several important milestones have been identified by Dr. Rashmi Shah:

1980  Use of primidone to shorten QT in LQT patients (Moss et al)
1998  Use of nicorandil to shorten QT in LQT patients (Aizawa et al)
1993-99  Levocromakalim shortens APD and induces VF (de la Coussaye et al, 1993; Tosaki et al,
1993; Robert E et al, 1997, 1999)
2000  Idiopathic Short QT syndrome (Gussak et al)
2002  Familial and proarrhythmic (Gussak et al)
2004  Pinacidil shortens QT and is proarrhythmic (Antzelevitch et al)
2004  Gain in function mutation of KCNH2 (IKr) (Brugada et al)
2004  Gain in function mutation of KCNQ1 (IKs) (Bellocq et al)
2005  Gain in function mutation of KCNJ2 (IKi) (Priori et al)
2005  hERG channel activating drug RPR260243 (Kang et al)
2005  hERG channel activating 3 other molecules (Zhou et al)
2006  Mallotoxin is a hERG channel activator (Zeng et al)
2007  Loss of function mutation in CACNA1C and CACNB2 encoding L-calcium channel
subunits (Antzelevitch et al).

De la Coussaye et al. (1993) found that levocromakalim, IK\textsubscript{ATP} potassium channel opener, led to
death of 6 of 6 dogs (100%) after 0.3 mg/kg, 2 of 8 dogs (25%) after 0.1 mg/kg and 1 of 7 dogs (14%)
after 0.03 mg/kg. QT interval and monophasic action potential were significantly shortened in a dose-
dependent manner. Robert E et al. (1997, 1999) tested levocromakalim in 44 Langendorff-perfused rabbit
hearts induced spontaneous VF in all hearts at 50 μM, whereas only one VF occurred at 500 μM nicorandil.

After analyzing 60 compounds tested in hERG and in canine Purkinje fibre preparations (courtesy of Dr. Leslie Patmore, Quintiles Ltd and Dr. Rashmi Shah), it appears that:

- Of the hERG negative: 44% shortened action potential duration (APD)
  - 33% no effect on APD
  - 19% prolonged APD
  - 4% bell-shaped APD

- Of the hERG positive: 43% shortened APD
  - 18% no effect on APD
  - 28% prolonged APD
  - 11% bell-shaped APD.

It was also documented that:

(a) In the rabbit heart, repolarization disturbances in the presence of shortened (APD) are more proarrhythmic than in its absence or in the presence of prolonged APD (Hondeghem L et al, 2001).

(b) Shortening of APD becomes highly profibrillatory when it is combined with triangulation and slowed conduction (nearly 100% of the cases; unpublished observation in more than 18,600 experiments; Shah RR and Hondeghem L, 2005).

Currently, there is no universal or unique mechanism that can explain the drug-induced shortening of the cardiac repolarization and QT interval, in particular, and its arrhythmogenic potential. Extramiana and Antzelevitch (2004) noted that pinacidil, IKATP potassium channel opener, can produce heterogeneous shortening of APD among the different cell types across the ventricular wall and increases transmural dispersion of repolarization from 27.0 ms to 64.9 ms, thus creating the substrate for the genesis of ventricular tachycardia under conditions associated with short QT intervals (from 303.7 ms to 247.3 ms). Interestingly, the effects of pinacidil were completely reversed by glybenclamide (10 mol/L, n=4) and partially reversed by E-4031 (5 mol/L, n=5), which prevented induction of polymorphic ventricular tachycardia in 3 of 5 preparations.
INSTEAD OF CONCLUSIONS

The search for the most appropriate therapeutic strategy in the prevention of the arrhythmogenic complications of the Short QT Syndrome is in its very initial phase. However, it seems that in the cases of inherited and iatrogenic SQTSs:

- Not all drugs that prolong the duration of cardiac repolarization and QT interval are antiarrhythmic
- Not all drugs that reduce the duration of cardiac repolarization and QT intervals are antiarrhythmic
- Antiarrhythmic affect of the drugs might not always be associated with the prolongation of cardiac repolarization and QT intervals

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Figure 1. Twelve-lead ECG recorded from the first patient with short QT syndrome and sudden cardiac death. Of note, QT interval duration of 266 msec (or 63% of predictive value) in 37-year old female with syncopal episodes who had an ECG taken shortly before she died suddenly in 1997. ECGs recorded from her father, mother and sister in 2004 – normal (Courtesy of Drs. Adriaca and Brugada)
Figure 2. Three ECGs from the first family with Short QT syndrome. Of note, Panel A – ECG from 84-year old grandfather (QT=280 ms or 71% of predictive value), Panel B – ECG from 51-year old mother with episodes of dizziness (QT=272 ms or 66% of predictive value), Panel C – ECG from 21-year old brother (QT=260 ms or 69% of predictive value) (from Reference #1)
REFERENCES


