Short QT syndrome

Ramon Brugada, Kui Hong, Jonathan M. Cordeiro, Robert Dumaine

ABSTRACT

The QT interval on an electrocardiogram signifies the time required for the heart to repolarize after depolarization. It has long been appreciated that a long QT interval predisposes patients to life-threatening ventricular arrhythmia. Short QT syndrome is a newly described disease characterized by a shortened QT interval and by episodes of syncope, paroxysmal atrial fibrillation or life-threatening cardiac arrhythmias. The syndrome usually affects young and healthy people with no structural heart disease and may be present in sporadic cases as well as in families. Our understanding of a new disease has rarely been so quickly developed from research in genetics, molecular biology and biophysics. It was first described in 2000 in a handful of patients, and since then 3 different genes associated with the disease and the biophysical basis have been described, and therapy has been made available. Here we review the current understanding of the pathophysiology, clinical presentation and treatment of short QT syndrome.

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Since 2000, there has been increasing evidence that a short QT interval may at times be associated with an increased risk of life-threatening arrhythmic events. That year Gussak and associates\(^1\) described for the first time what has now been defined as a clinical syndrome. They identified a short QT interval in 3 people from the same family, one of whom had several episodes of paroxysmal atrial fibrillation. Similar ECG changes were also documented in another, unrelated patient with malignant arrhythmias and sudden death. The case report showed that a short QT interval could be familial and associated with atrial and ventricular arrhythmias. The definitive link between short QT syndrome and familial sudden death was described by Gaita and associates in 2003, with the clinical report of 2 families with short QT syndrome and a high incidence of sudden cardiac death.\(^2\) Just one year later, in 2004, the genetic and biophysical basis for the disease\(^1\) as well as a possible therapeutic approach were provided.\(^3\)

The role of ion channels

Ion currents, ion channels, structural proteins and gap junctions are all involved in transmitting electrical impulses across cardiac myocytes to achieve a synchronized mechanical function. The discovery of the structure, function and pathophysiology of the ion channels has helped unravel the role played by the different ionic currents in electrical activity and electromechanical coupling.

Ion channels are essential units in cardiac excitability. They are glycoproteins embedded in the membrane of the cardiac myocytes that allow the flux of ions in and out of the cell to modulate the electrical gradient. The depolarizing currents are mediated mainly by channels that allow the entry of sodium and calcium ions into the cell, and the repolarizing currents are mediated by channels that allow the exit of potassium ions. The order of ion channel activation gives rise to the electrical current (Fig. 1). The electrical energy generated is responsible for myocyte excitability. Cardiac action potential requires a well-controlled ionic balance to prevent arrhythmogenesis. Therefore it is not surprising that these channels, when they do not work properly, have a tremendous potential to cause lethal arrhythmia.

Functional analysis of the ion channels involved in generating cardiac action potential explains the basic mechanisms of arrhythmia. However, our understanding of cardiac arrhythmias predisposing to sudden death, like long QT syndrome, Brugada syndrome and short QT syndrome, has also benefited tremendously from the advances in genetics and molecular biology. These familial diseases allow the study of a pure form of a disease, in which a single abnormal protein is the critical factor in the risk of arrhythmogenicity. Genetic research has also provided new insights into how the abnormal and normal genes interact with their environment, drugs, and the damaged heart muscle and trigger the arrhythmia in the acquired forms.

Molecular genetics and electrophysiology

Short QT syndrome, as with most primary familial electrical diseases, is caused by mutations in genes that encode for cardiac ion channels. To date, 3 genes — KCNH2, KCNQ1 and KCNJ2 — encoding different potassium ion channels involved in repolarization have been linked to the syndrome,\(^3\)\(^6\)\(^7\) and the effect of their mutations on the action potential is shown in Fig. 2.

**KCNH2**

The KCNH2 gene, often referred to as HERG, the human ether-a-go-go–related gene, expresses a protein that makes
different missense mutations in the same residue in KCNH2 ining rectifier outward current (IKr). Our group identified 2 dif-up the potassium channel responsible for the rapidly activat-

pressed N588K with KCNE2, which encodes a small, single

N588K, alters the outward potassium channel, we coex-

pressed into human cells showed that the mutation abolished

function in the outward current that explains the short QT

played accelerated activation kinetics, which led to the gain of

tated channel activated at more negative potentials and dis-

as the inactivated channels recovered. In contrast, the cur-

dents found in the mutated channels were larger in all phases

of the action potential. The biophysical analysis therefore

showed that the mutation induced a “gain of function” in the

I\textsubscript{o, current, thus shortening the action potential (Fig. 3).}\textsuperscript{3}

We also discovered that although the N588K mutation re-

sults in larger outward potassium currents in the ventricles,

there is no effect on those in the Purkinje fibres\textsuperscript{9} (see the on-

line figure, available at www.cmaj.ca/cgi/content/full

/173/11/1349/DC1). Thus there is selective shortening of the

ventricular action potentials and a substantial reduction in

the refractory period of the ventricles but not of the Purkinje

fibres. This heterogeneity in action potential durations and

refractory periods is likely to create the substrate for reentrant

arrhythmias.

The presence of paroxysmal atrial fibrillation in some af-

ected patients suggests that the increased heterogeneity

would also be present at the atrial level and may be responsi-

ble for the arrhythmia. More recently, our group demon-

strated the definitive link between shortening of the action

potential and atrial fibrillation by identifying the same ge-

netic mutation in a third, unrelated family, in which atrial

fibrillation was the only clinical manifestation of short QT

syndrome.\textsuperscript{9}

**KCNQ1**

The KCNQ1 gene encodes a subunit of the proteins responsi-

ble for the slowly activating delayed outward potassium cur-

rent (I\textsubscript{s}). The mutation was first identified by Bellocq and col-

leagues\textsuperscript{6} in a 70-year-old man with ventricular fibrillation and a

QT interval of 290 ms after resuscitation. The patient had no

inducible dysrhythmias at electrophysiologic study and no

cardiac structural abnormalities.

Biophysical analysis showed that mutation in the KCNQ1
gene produced an outward potassium current with an ampli-
tude similar to that of a normal channel. However, because of

a pronounced shift of the half-activation potential, the mu-
tated channel activated at more negative potentials and dis-
played accelerated activation kinetics, which led to the gain of

function in the outward current that explains the short QT

syndrome phenotype.\textsuperscript{6}

Our group has recently identified a second mutation in

KCNQ1 in a baby girl born at 38 weeks after delivery was

induced because of bradycardia and irregular rhythm.\textsuperscript{10} The

electrocardiogram revealed atrial fibrillation with slow ven-

tricular response and a short QT interval. Genetic analysis

identified a de novo missense mutation in the KCNQ1 gene.

Voltage clamp experiments to characterize the physiologic

up the potassium channel responsible for the rapidly activat-
ing rectifier outward current (I\textsubscript{o}). Our group identified 2 dif-
erent missense mutations in the same residue in KCNH2 in 2

unrelated families.\textsuperscript{3} Both mutations resulted in the same sub-
stitution, of asparagine for lysine at codon 588, an area at the

outer mouth of the channel pore.

To determine the mechanism by which the mutation, N588K, alters the outward potassium channel, we coex-

pressed N588K with KCNE2, which encodes a small, single

transmembrane subunit to the KCNH2 channel. Analysis of

the current generated after the mutated channels were trans-

ferred into human cells showed that the mutation abolished

the inactivation of the KCNH2 channels, which thereby in-

creased the I\textsubscript{o} current. The mutation had similar effects on
currents with and without coexpression of KCNE2.\textsuperscript{3} Analysis of
the current–voltage relation showed that, with and without

KCNE2, the current through the mutated channels failed to

rectify in a physiologic range of voltages. During action po-
tential clamp experiments, the kinetics of outward potassium

flow through normal, or wild-type, channels demonstrated a
typical “hump”-like waveform due to slow activation during

phases 1 and 2 and a rapid increase in current during phase 3

as the inactivated channels recovered. In contrast, the cur-

dents found in the mutated channels were larger in all phases

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identified a de novo missense mutation in the KCNQ1 gene.

Voltage clamp experiments to characterize the physiologic
consequences of this mutation revealed an instantaneous and voltage-independent potassium-selective current. This mutation would again lead to gain of function and shorten the action potential duration of ventricular myocytes.

**KCNJ2**

More recently, a third form of short QT syndrome has been linked to mutations in the *KCNJ2* gene, which codes for the channel protein responsible for the inward rectifier current (*I*_κ). The proband and her father, in whom the mutation was discovered, displayed short QT correction intervals of 315 and 320 ms respectively, and electrocardiogram recordings showed asymmetrical T waves with an abnormally rapid terminal phase. The proteins encoded by *KCNJ2* are composed of 2 transmembrane segments linked by a long amino acid chain that forms the channel pore. When expressed in animal cells, the mutated channels generated electrical currents that did not rectify or decrease as much as those of the normal channels, whose functional positive range of potentials was −80 mV to −30 mV. This range of voltages corresponds to the very end of phase 3 repolarization and phase 4. Simulation of the effects of the mutated channels on the morphology of the ventricular action potential showed a selective speeding of late repolarization, which significantly shortened the action potential duration at 90% repolarization.

The findings of 3 forms of short QT syndrome, which link to 3 different potassium channels that alter currents at different voltages, demonstrate the heterogeneity of the disease.

**Clinical manifestations**

Most patients with short QT syndrome have short refractory periods, inducible ventricular fibrillation at electrophysiology study, and a family history of sudden death or atrial fibrillation. The age at onset of clinical manifestations may be extremely young, with reports of malignant forms being responsible for even neonatal sudden cardiac deaths that may sometimes be attributed to sudden infant death syndrome.

The characteristic sign of the disease is the presence of a very short QT interval on electrocardiogram. The T wave remains upright, and the interval between the peak and the end of the T wave is not prolonged (Fig. 4). The appearance of a well-separated U wave has also been reported in several cases. It is difficult to define the normal QT interval because the correcting equations have several limitations. Nevertheless, at a heart rate of 60 beats/min, the uncorrected, or normal, QT interval is usually higher than 360 ms. From the data shown in the familial forms of the syndrome, it is probably safe to say that the presence of a QT interval less than 330 ms should raise high suspicion about the disease.

The severity of the clinical manifestations is highly variable, ranging from no symptoms to atrial fibrillation and from recurrent syncope to sudden death.

**Presence of atrial fibrillation**

As indicated earlier, the first report by Gussak and associates made the link between short QT syndrome and atrial fibrillation. The proband in the family was a 17-year-old woman who, during surgery, developed rapid atrial fibrillation and pulmonary edema. She underwent cardioversion, and on follow-up her QT interval was 280 ms. Her mother was 51 years old and had had 3 episodes of sustained palpitations, 2 of which were later documented as atrial fibrillation. An electrocardiogram showed a QT interval of 230 ms. The proband’s grandfather had died in 1999 at age 84. Later review of his medical records showed long-standing atrial fibrillation with a QT interval less than 300 ms in several electrocardiograms and left ventricular hypertrophy. The proband’s brother, a 21-
year-old with no history of palpitations, dizziness or syncope, was screened with an electrocardiogram and found to have a QT interval of 240 ms. During follow-up he has had some episodes of palpitations and brief episodes of atrial fibrillation with fast ventricular response.

**Presence of sudden death**

The association with sudden death was also provided by Gussak and associates with the description of a single case. A 37-year-old woman who had been found to have a short QT interval died suddenly while awaiting electrophysiologic study. However, the definitive familial link was provided by Gaita and associates with the description of 2 families with typical electrocardiographic patterns, a high incidence of sudden cardiac death at a young age, an absence of structural heart disease, and an abnormally high incidence of paroxysmal atrial fibrillation. The QT interval in the affected members ranged from 240 to 290 ms. The severity of the disease was patent in these families, with 2 members experiencing sudden cardiac death, which was aborted in one, in the first year of life.

Of the 6 people in the 2 families with short QT syndrome, 5 were inducible into ventricular fibrillation during electrophysiologic study, and all 6 received an implantable cardioverter defibrillator because of the strong family history of sudden cardiac death.

**Disease management**

Robust genotype–phenotype correlation data are not yet available for short QT syndrome, and thus clinical management must rely on clinical findings.

The disease is clinically highly heterogeneous, as indicated by the tremendous variation in symptoms and presentation in the 3 families with the same mutation and one isolated case. Preliminary data have shown that there may be effective pharmacologic therapy; the high incidence of sudden cardiac death, however, warrants the implantation of a cardioverter defibrillator, especially in people in whom sudden death has been aborted. The syndrome confers a risk of sudden death on young children, in whom implantation is not feasible. Recently, concern has been raised about inappropriate shocks, especially in relation to the presence of short-coupled prominent T waves. The adaptation of programming with decreased sensitivity levels and decay delays is warranted in these situations to prevent T-wave oversensing.

**Pharmacologic therapy**

Numerous drugs block the repolarizing outward potassium current, including methanesulfonanilides, phosphodiesterase inhibitors, macrolide antibiotics, antifungal agents, and antihistamines; this is the basis for their prolonging effect on the QT interval and potential arrhythmogenicity. Because shortening of the QT interval is likely due to an increase in the outward current, blocking the current with class III antiarrhythmic drugs (which are known to increase the QT interval) may be a therapeutic approach for treating short QT syndrome. No large randomized trials have been conducted to date on drug therapies for the syndrome. The current evidence is derived from small studies.

In our study, sotalol, a class III antiarrhythmic with potent 

![](image)

**Fig. 3.** Current–voltage relationship for steady state current measured at the end of the activating pulse. Steady state current amplitudes were measured at the end of the 800-ms test pulses. Mutation N588K removes rapid inactivation and significantly increases the amplitude of the rapid delayed rectifier current in a physiologic range of membrane potentials. In wild type, or normal, currents, the current amplitude increased up to a test potential of –10 mV and then gradually decreased past –10 mV as the channels inactivated. In contrast, the N588K current increased linearly and did not rectify. N588K currents were much larger than wild type past 0 mV in the range of the ventricular action potential plateau. Reprinted, with permission, from ref. 8.
cainide, ibutilide or sotalol did not modify the QT interval. Consistent with these findings, electrophysiologic studies in heterologous expression systems showed that the N588K mutation reduced the affinity of the channels for quinidine by 5.8-fold, from 0.75 µmol/L in normal channels to 4.4 µmol/L in mutated channels, compared with a 20-fold reduction in affinity for D-sotalol, which provides evidence that quinidine may be superior to D-sotalol for treating the first form of the syndrome. Clinical follow-up in one family with paroxysmal atrial fibrillation indicates that the episodes respond well to treatment with class Ic agent propafenone.9

Future directions

In summary, 3 forms of short QT syndrome have been discovered to date. Each form is linked to mutations in different channels, which likely makes the therapeutic options unique to each form. Patients who present with atrial or ventricular arrhythmias and whose electrocardiogram shows a short QT interval that is not related to a correctible cause should be suspected as having short QT syndrome, especially if the family history suggests an inherited factor. These patients should be referred to a cardiologist with expertise in arrhythmia management for a correct diagnosis and treatment strategy. The severity of the disease, which may cause sudden cardiac death at a very young age, highlights the importance of aggressive risk stratification of patients and family members.

The first line of therapy, especially in people recovered from sudden cardiac death or with a history of syncopal episodes, is the implantation of cardioverter defibrillator. Although antiarrhythmics that prolong the QT interval, such as sotalol or quinidine, may be suitable for the first form of the syndrome, no known blocker can specifically target the other 2 forms. This establishes the syndrome’s multigenic nature, which is similar to that of long QT syndrome, and highlights the need to identify the form, whether by genetic screening or clinical means, so that the right pharmacologic approach can be determined. Although the pharmacologic interactions for each form are not yet well identified or developed, knowing the genes and mechanisms involved hold the promise of a higher therapeutic specificity.

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