

Short QT interval in clinical practice

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Abstract

The last ten years have seen a growing interest in clinical scenarios, where a short QT interval may play a role, especially because of an increased risk of sudden cardiac death in some situations. One such entity is Short QT Syndrome, which has emerged as a rare, but very malignant disease, in particular when the QT interval is very short. A short QT interval has also been noticed in some patients with other arrhythmic syndromes such as Idiopathic Ventricular Fibrillation, Brugada Syndrome and Early Repolarization Syndrome, but the role of a short QT interval in these settings is so far not known. Hypercalcemia often leads to shortening of the QT interval, but there are no data in humans to suggest an increased risk of sudden cardiac death in this setting. In addition, a shorter-than-usual QT interval has been reported in patients with Chronic Fatigue Syndrome and in response to atropine, catecholamine and Hyperthermia.

When a short QT interval is encountered in daily clinical practice, these various scenarios needs to be considered, but it is still not possible to come up with clear guidelines for how to work up and risk stratify such individuals. Genetic testing is only useful in very few and the value of an electrophysiologic study, Holter monitoring or stress testing to assess QT adaptation to heart rate and T wave morphology analysis may all be helpful, but not well-established, tests in this setting. Published by Elsevier Inc.

Before the discovery¹ of short QT syndrome (SQTS) in 2000 (Fig. 1), very little importance had been attributed to a short QT interval. The increased risk of sudden cardiac death in patients with a long QT interval had been known at least since the first discovery² of a family with syncopal arrhythmias and QT prolongation in 1957, and it was followed by countless publications focusing on the risk involved, when a QT interval was longer than normal.

In this review, we will focus our attention on clinical situations, where a QT interval may shorten and at times be shorter than normal. Issues regarding drug-induced shortening of the QT interval in clinical research and drug development are addressed in another review, “Drug-Induced QT Interval Shortening,” also published in this issue of the journal.³

Lower limit of normal for the QT interval

How to define universally accepted normal limits for the QT interval in an electrocardiogram (ECG) has been very

difficult mainly because of methodological issues and the unpredictable variability of the QT interval with changes in heart rate and influences from the autonomic nervous system. Also, factors like age and sex, temperature, and electrolytes play a role, and so does the decision whether to measure the end of the QT interval at the end of the T wave or where a tangent to the down slope of the T wave crosses the baseline. Instead of using a handheld caliper, newer digital techniques with superimposition of multiple beats from multiple leads have taken over. All these variables may help to explain the differences in lower limit of normal of the QT interval in population studies from the last 20 years (Table 1).^{4–9} Because relatively few males and females have corrected QT intervals (QTc) shorter than 360 and 370 milliseconds, respectively, these values probably should be regarded as “short” (lower limit of normal), as also pointed out by Visken¹⁰ in a recent review of the topic.

Short QT interval and SQTS

Short QT syndrome is a rare form of hereditary channelopathy with an abnormally short QT interval and a high propensity to atrial and ventricular fibrillation (VF).

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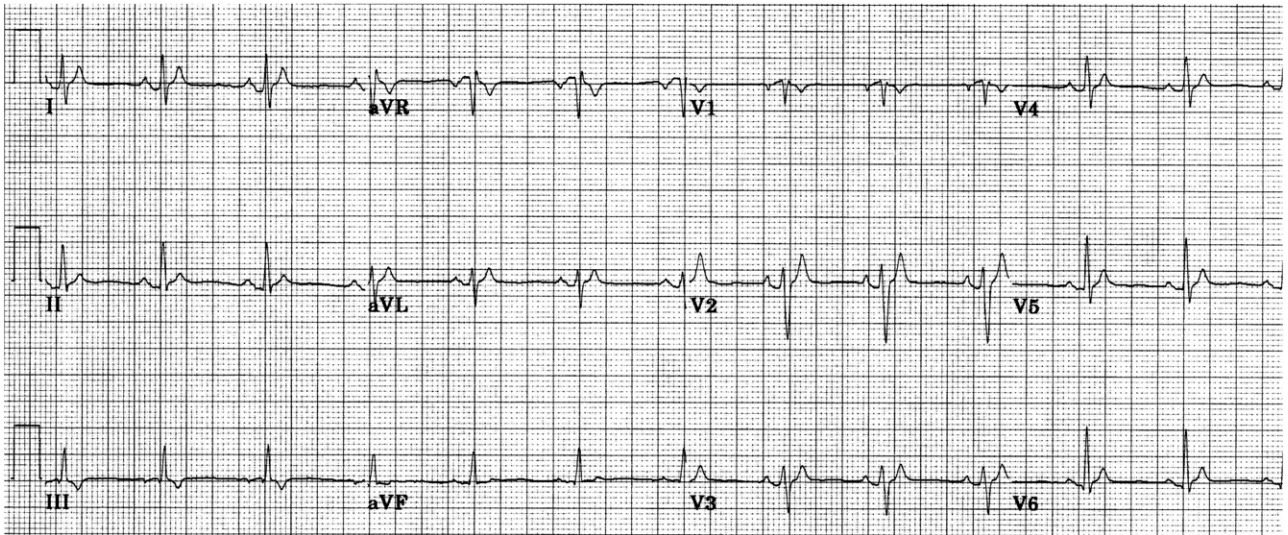


Fig. 1. Twelve-lead ECG from the first patient with short QT syndrome showing sinus rhythm at a heart rate of 60 beats/min and QT interval of 230 milliseconds. PR segment depression is noticed in some leads.

Since it was discovered in 2000, only 53 members from 14 families and 10 sporadic cases of the disease have been published. The grave nature of the disease was underscored by the fact that 9 of the probands from the 14 families presented with cardiac arrest, and so did 5 of 10 sporadic cases.¹¹ Initially, a diagnosis of SQTS was considered only in patients with a QT interval of 300 milliseconds or less, but later, a similar clinical picture was observed in some people with slightly longer QT intervals. The range for QT interval in the 49 of 53 patients with SQTS, where numbers for both the QT and the QTc intervals are available, is 210 to 340 milliseconds with a mean ± 2 SD of 282 ± 62 milliseconds. The QTc ranged from 248 to 345 milliseconds with a mean ± 2 SD of 305 ± 42 milliseconds.¹¹ Because there is very little change in the QT interval with heart rate in patients with SQTS, QT correction formulas like the Bazett and the Fredericia formulas are not applicable in patients with SQTS, and QTc values determined by such formulas are not accurate enough for making the diagnosis and especially not for exclusion of a diagnosis of SQTS.

Results from several recent population studies are a testimony to how rare it is to see short QT intervals like these

in the general population. Among 479,120 consecutive ECGs from a hospital population of 106,432 patients, Reinig and Engel¹² found no one with a QTc of 300 milliseconds or less, and Gallagher et al¹³ did not find any one with a QTc of 330 milliseconds or less among ECGs of 12,012 apparently healthy subjects. Using the tangential method to define the end of the QT interval, Anttonen et al⁹ found in ECGs of 10,822 randomly selected middle-aged Finnish subjects 0.1% with QTc of less than 320 milliseconds and 0.4% with QTc less of than 340 milliseconds. Finally, Moriya et al¹⁴ found only 2 with QTc of less than 350 milliseconds in ECGs of 19,153 middle-aged Japanese people.

There have been no data to assess how constant the QT intervals are over time in patients with SQTS, but our limited experience from following 4 patients for more than 5 years is similar to that of Giustetto et al,¹⁵ who found the QT intervals to be very constant even with years between the recording sessions.

To establish a diagnosis of SQTS, symptoms suggesting or ECGs documenting atrial fibrillation or VF in the

Table 1
Lower limit of normal of the QTc interval in population studies from the last 20 years

Authors and year of publication	N	Lower limit of QTc (Mean - 2 SD [ms])		
		Male	Female	All
Merri et al., 1989 ⁴	423			381
Sagie et al. (Framingham Heart Study), 1992 ⁵	5,018	332	344	
Vincent et al., 1992 ⁶	116	380	390	
Rautaharju et al., 2007 ⁷	11,719			395
Mason et al., 2007 ⁸	46,129	356	369	361
Anttonen et al., 2007 ⁹	10,822	348	364	

Table 2
Genetic variants of SQTS

	SQT1	SQT2	SQT3
Year	2004	2004	2005
Authors	R. Brugada et al. ¹⁶	C. Bellocoq et al. ¹⁷	S.G. Priori et al. ¹⁸
Chromosome	7q35	11p15	17q23
Gene	KCNH2	KCNQ1	KCNJ2
Protein	HERG	KvLQT1	Kir2.1
Mutation	N588K	V307L, V141M	D172N
Ion channel	<i>I_{Kr}</i>	<i>I_{Ks}</i>	<i>I_{K1}</i>
Change of function	Gain	Gain	Gain
Families	3		1
Sporadic cases		3	

SQT indicates short QT.

setting of idiopathic very short QT interval (QT/QTc intervals < 340/345 milliseconds) suffice, whereas borderline cases with short QT intervals longer than that may require assessment of QT adaptation to heart rate and attention to T-wave morphology, electrophysiologic (EP) study, or genetic testing. However, none of these tests have been applied to large enough number of individuals with a short QT interval to be able to state their diagnostic accuracy.

Arrhythmogenesis and short QT interval

Before the discovery of SQTS, there was neither in isolation nor in connection with other electrocardiographic abnormalities any indication that a short QT interval was a risk factor for tachyarrhythmias and sudden cardiac death, but in the first family with SQTS, all members had atrial fibrillation at one time or another while the clinical presentation in other families primarily was ventricular tachyarrhythmias and often sudden cardiac death.

However, SQTS was found to be a genetically heterogeneous disease with gain-of-function mutations in some of the patients in the *KCNH2*, *KCNQ1*, or *KCNJ2* genes, giving rise to SQT1, SQT2, and SQT3 forms of SQTS (Table 2),^{16–18} but most patients have not been genetically categorized. Therefore, the cellular basis for arrhythmogenesis differs between different families with SQTS. In an experimental model of the SQT1 (which is the subgroup of SQTS studied most), Patel and Antzelevitch¹⁹ found shortening of APD, QT interval, and ERP but an increase in the $T_{\text{peak}}-T_{\text{end}}$ interval and transmural dispersion of repolarization (TDR) in canine left ventricular wedge preparations. Preferential abbreviation of epicardial APD was responsible for the increase in TDR and $T_{\text{peak}}-T_{\text{end}}$ interval. Reversal of the direction of activation of the left ventricular wall by pacing from the epicardium instead of the endocardium increased TDR and exaggerated the effect of the I_{Kr} agonist used in the study to increase TDR, thus facilitating the induction of polymorph ventricular tachycardia (pVT). Quinidine was found to prevent the induction of pVT by reversing the effect of a selective I_{Kr} agonist on the QT interval and ERP, but not on TDR. These results suggest that a gain of function of I_{Kr} predisposes to pVT via an abbreviation of ERP as well as an augmentation of TDR.

Morphologic changes in T waves have been observed in many patients with SQTS. Priori et al¹⁸ noticed asymmetrical T waves with a rapid descending limb in the first family with SQT3 syndrome, and later, tall T waves were found to be a problem for oversensing in SQTS patients receiving an implantable cardioverter-defibrillator (ICD) leading to inappropriate shocks.²⁰ Using principal component analysis, Anttonen et al²¹ found markedly abnormal T-wave loops among some symptomatic patients with mutation-negative SQTS and suggested that such analysis might be helpful in identifying patients with SQTS. As pointed out later in this article, a short QT interval has been seen in some patients with Brugada syndrome, and recently, Watanabe et al²² found a high prevalence of early repolarization in patients

with SQTS. How much these various arrhythmogenic markers contribute to arrhythmias, when they occur simultaneously, is unknown, but findings by Watanabe et al²² suggest that early repolarization may be useful for assessment of risk of cardiac events in patients with SQTS.

Short QT interval and idiopathic VF

The notion that there might be patients with SQTS who have QT intervals longer than hitherto published with that syndrome stems primarily from observations by Viskin et al.²³ They compared the ECGs of 28 patients with idiopathic VF (17 men and 11 women; age, 31 ± 17 years) with those of 270 age- and sex-matched healthy control subjects. The QTc of men with idiopathic VF was shorter than the QTc of healthy men (371 ± 22 vs 385 ± 19 milliseconds; $P = .034$), and 35% of the male patients had a QTc of less than 360 milliseconds (range, 326–350 milliseconds) compared with only 10% of male controls (345–360 milliseconds). However, no such differences were found among women.

Considering the difficulties in measuring the QT interval, it will always be difficult to define a disease by a specific limit for the QT interval, and whether some patients being diagnosed as idiopathic VF are patients with SQTS will probably have to be determined by other means. Whether genetic testing or the results from EP studies including determination of atrial and ventricular refractory periods will be helpful in this regard is not known.

Short QT interval and Brugada syndrome

Brugada syndrome is generally associated with either normal or a slightly prolonged QT interval particularly in the right precordial leads, but in 2007, Antzelevitch et al²⁴ described a new syndrome consisting of familial sudden cardiac death syndrome in which a Brugada syndrome phenotype is combined with a short QT interval. By screening 82 consecutive probands with Brugada syndrome for ion channel gene mutations, they found 3 probands displaying ST-segment elevation in V_1 through V_3 and QTc of 360 milliseconds or less among 7 who had mutations in genes encoding the cardiac L-type calcium channel. Corrected QT interval values ranged from 330 to 370 milliseconds among probands and clinically affected family members. Rate adaptation of QT interval was reduced and Quinidine normalized the QT intervals and prevented stimulation-induced VT. Genetic and heterologous expression studies revealed loss-of-function missense mutations in *CACNA1C* (A39V and G490R) and *CACNB2* (S481L) encoding the α_1 - and β_{2b} subunits of the L-type calcium channel.

Recently, Itoh et al²⁵ identified a novel mutation (R1135H) in *KCNH2*, the gene encoding the α -subunit of the rapid delayed rectifier K^+ channel (I_{Kr}), in a patient with short QT interval (QTc = 329 milliseconds) and Brugada-type ECG.

Short QT interval and early repolarization

Early repolarization is electrocardiographically characterized by an increase of 0.1 mV or higher of the QRS-ST junction (J-point) with slurring or notching of the end of the QRS complex with or without a J wave or J deflection and with or without ST-segment elevation. The changes are most commonly seen in mid-to-lateral precordial leads or inferior leads (II, III, and aVF). It is seen in 1% to 6% of the general population and usually regarded as a normal variant. Several reports within the last few years have suggested, however, that such a finding in certain individuals may be an indication of an increased risk of death from cardiac causes and, in particular, from sudden cardiac arrest.²⁶ In this context, it is of interest to observe that the QT intervals in patients with early repolarization are relatively short. In the study by Haissaguerre et al²⁷ of subjects resuscitated after cardiac arrest due to VF, early repolarization was found in 32%, and the duration of the QTc was statistically significantly shorter in patients with early repolarization compared with patients without such a finding.

In a study of ECGs from 102 065 patients (52 779 males and 49 286 females) at Shiga University Hospital in Japan,²⁸ 275 patients (215 males and 60 females), or 0.27%, had a QTc of less than 360 milliseconds. Of these 275 individuals, 107, or 39%, had early repolarization compared with an overall prevalence of early repolarization in this study of 1.7%.

Short QT interval and hypercalcemia

Hypercalcemia (mild, when serum calcium is <12.5 mg/dL; moderate, 12.5–13.9 mg/dL; and severe, when serum calcium is \geq 14.0 mg/dL) is most commonly seen in malignancies with osteolytic bone metastases, hyperparathyroidism, renal disease, and from medications such as thiazide diuretics, lithium, and vitamin D and is probably the best known reason for secondary short QT interval in clinical practice, described as early as 1922 by Carter and Andrus.²⁹

The basis for the shortening of the QT interval in hypercalcemia is the shortening of phase 2 of the action potential possibly brought about by a decrease in I_{Ca} and augmentation of the calcium-activated I_{Cl} . In addition to shortening of the QT interval, the electrocardiographic manifestations of hypercalcemia consists of PR prolongation, QRS widening, flat or biphasic T waves, and the appearance of J waves.^{30,31} An increase in QRS amplitude has been noticed by some.³² Some of the shortening of the QT interval can, in rare cases, be offset by the widening of the QRS complex or by congenital long QT syndrome as shown in a patient with hypercalcemia and Williams syndrome.³³

Several studies have examined the relationship between either total serum calcium or serum ionized calcium and the duration of the QT interval.^{34–36} It was discovered early on that the best correlation was between serum calcium or serum ionized calcium and the corrected interval from the

origin of the Q wave to the apex of the T wave ($Q_{-a}T$ interval) instead of using the usually corrected interval from the origin of the Q wave to the end of the T wave ($Q_{-c}T$ interval). The usefulness of the QTc as a clinical indicator of hypercalcemia was found, however, to be limited mainly because of all the other factors known to affect the QT interval.

Corrected QT intervals as short as seen in patients with SQTS have been reported in several patients with severe hypercalcemia, but it is currently not known whether a short QT interval secondary to hypercalcemia is a risk factor for arrhythmias the same way a congenital short QT interval is.

In case reports, severe hypercalcemia secondary to hyperparathyroidism has been associated with sinus arrest,³⁷ atrio-ventricular (AV) block,^{36,37} atrial fibrillation,³⁷ right ventricular outflow tract tachycardia,³⁸ and VT in ischemic heart disease.³⁹ Such arrhythmic events are mainly seen in patients with severe hypercalcemia. In a study by Rosenquist et al⁴⁰ of 20 patients with moderate hypercalcemia, only mild shortening of the QT interval was seen and without any significant effect upon cardiac conduction or incidence of cardiac arrhythmias. They reported 9 cases from the literature where patients with severe hypercalcemia all had arrhythmias in terms of AV block in 7, sinus arrest in 4, and atrial fibrillation in 4 and the severity of the conduction disorder seemed to correlate with the degree of hypercalcaemia.

It is known that the effect of hypercalcemia on various electrophysiologic properties of the heart is very much dependent upon other electrolyte disturbances, in particular the serum potassium concentration. Thus, in acute hyperparathyroidism, where severe hypercalcemia often is accompanied by hypokalemia, a very high incidence of sudden death has been reported supposedly from VF,⁴¹ whereas reports of ECG-documented VF secondary to hypercalcemia in humans without other electrolyte disturbances have been difficult to come by. In dogs, isolated hypercalcemia has been shown to produce VF.⁴²

Hypercalcemia potentially has arrhythmogenic effects that go beyond shortening of the QT interval in the form of early repolarizations as well as delayed after-depolarizations and possibly cyclic AMP-mediated triggered activity.

Short QT interval in other clinical situations

In addition, a shorter-than-usual QT interval has been reported in patients with chronic fatigue syndrome⁴³ and in response to atropine,⁴⁴ catecholamine,⁴⁵ and hyperthermia.⁴⁶

Paradoxical (deceleration-dependent) shortening of the QT interval

A few sporadic observations from the literature have confirmed the existence of situations where slowing of the heart rate is accompanied by shortening of the QT interval and not the normal response of prolongation of the QT interval. Thus, in 1999, we presented a 4-year-old African

American girl with shortening of the QT interval during bradycardia.⁴⁷ She was hospitalized with complications related to her premature birth, including developmental delay and several episodes of cardiac arrest. An episode of severe transient bradycardia was documented during Holter monitoring, with the ECG rhythm strip showing a paradoxical gradual shortening of the QT interval to 216 milliseconds. In an earlier report by Kontny and Dale,⁴⁸ an episode of idiopathic VF with spontaneous termination after 17 seconds was shown. During the postfibrillation period with severe bradycardia, the QT interval was very short compared with the QT interval during normal sinus rhythm immediately before the episode.

Takahashi et al⁴⁹ described paradoxical shortening of the QT interval in 2 patients during bradycardia while Holter monitored, and Strasburger and Maron⁵⁰ presented in “Images in Clinical Medicine” an ECG rhythm strip from a 13-year-old boy resuscitated after commotio cordis during a baseball game. The QT interval duration during both bradycardia and sinus tachycardia immediately after defibrillation was approximately 200 milliseconds.

There are no data from clinical studies to indicate how often paradoxical shortening of the QT interval occurs in a clinical setting, but the existence of the phenomenon has been documented in experiments with dose-dependent effects of acetylcholine on the heart. It has been shown that, in addition to muscarinic modulation of the heart rate, a very high concentration of acetylcholine also activates $I_{k,ACh}$, resulting in a marked shortening of the action potential duration. It is therefore possible that unusually high concentrations of acetylcholine in certain situations could be responsible for both bradycardia and shortening of the QT interval in humans. After VF, the shortening of the QT interval might also be related to high intracellular calcium levels as a consequence of hypoperfusion and ischemia.

Suggested clinical implications

By definition, a short QT interval (QTc < 360 milliseconds in males and <370 milliseconds in females) is rare and is therefore a finding that should always lead to a search for a potential etiology. In daily clinical practice, most episodes of a short QT interval are a normally variant, with hypercalcemia and early repolarization next on the list. The most significant feature of a short QT interval is the occasional connection to an increased risk of sudden cardiac death. Because of the limited number of patients with a short QT interval and lack of studies to help us make the correct diagnosis in each individual, it is not possible to come up with clear guidelines for how to work up and risk stratify such individuals. A positive genetic testing will be able to confirm the diagnosis, and a history of symptoms suggesting tachyarrhythmias, a family history of SQTs, or sudden cardiac death would seem to be strongly in favor of a diagnosis of SQTs. The value of an electrophysiologic study, Holter monitoring, or stress testing to assess QT adaptation to heart rate and T-wave

morphology analysis may all be helpful, but not well-established, tests in this setting.

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