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Short and long QT syndromes: does QT length really matter?☆,☆☆

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Abstract The short and long QT syndromes are inherited diseases associated with an increased risk for life-threatening arrhythmias. The first case of long QT syndrome (LQTS) was reported more than 150 years ago, and the study of this disease led to crucial advancement of our understanding of channelopathies and associated ventricular arrhythmias. Ten years ago, Gussak et al. reported four cases of idiopathic ventricular fibrillation in individuals from a family with a history of sudden cardiac death exhibited very short QT interval and labeled the disease: short QT syndrome (SQTS). Over this decade, the SQTS was found to be a rare inherited syndrome with the potential to provide novel insights into the main mechanisms of cardiac arrhythmogenicity. In this review, we discuss these mechanisms and provocatively question the role of the QT interval duration as a surrogate marker of increased risk for arrhythmia in both the LQTS and the SQTS.

Introduction

The short QT syndrome (SQTS) is an inherited arrhythmia disorder recently described and, associated with family history of sudden cardiac death, short refractory periods, and inducible ventricular fibrillation (VF) in the absence of structural heart disease. Initially, sporadic cases of SQTS were reported by Gussak et al[1] in family-related and unrelated patients with idiopathic VF and history of sudden cardiac death. Subsequently, a clinical investigation of patients with idiopathic VF by Viskin et al[2] reported a significant subgroup of these patients (primarily males) exhibiting electrocardiographic (ECG) tracings with very short QT intervals and peaked T-wave morphologies. Gaita et al[3] confirmed that short QT was associated with familial sudden death, and genetic investigations revealed heterogeneous forms of the SQT syndrome.[4-6] As of today, 5 mutations have been associated with abnormally short QT/QTc intervals. Three mutations are linked to gain function of the potassium channels I_{Kr}, I_{Ks}, and I_{K1} through the KCNH2,[5] KCNQ1,[4] and KCNJ2[6] genes, respectively. The 2 most recent mutations were identified in the CACNA1c and CACNA1b genes[7] and have been associated with loss of function of the L-type calcium channels. The inherited long QT syndromes (LQTSs), on the other hand, have been studies for several decades.[8] Long QT is associated with an increased propensity to arrhythmogenic syncope; polymorphic ventricular tachycardia (torsades de pointes), which itself may lead to VF; and sudden cardiac death. At least 12 different gene mutations have been associated with the LQTS (LQT1-12). The LQT1 and LQT2 are the most prevalent forms of the syndrome, representing an estimated 80% to 90% of the positively genotyped cases. Both LQT1 and LQT2 are associated with loss of function of voltage-gated potassium channels (I_{Ks} and I_{Kr}).[9]

In this essay, we will discuss arrhythmogenic mechanisms in the SQTS in relation to the current arrhythmogenic mechanisms associated with the LQTS for the mutations primarily involving repolarizing potassium currents. L-type calcium channels related reports were associated with moderately shortened QTc intervals (≤360 milliseconds in males and ≤370 milliseconds in females); and thus, their association to an SQTS (<300-320 milliseconds) may be questionable.[7]

Arrhythmogenesis in the LQTSs

In the LQT1 and LQT2 syndromes, the fundamental arrhythmogenic triggering mechanisms are linked to the decreased outward potassium currents. The loss of function in potassium currents results in ventricular repolarization delay increasing the window of vulnerability to arrhythmia. It facilitates the triggering of early after-depolarization (EAD)

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through increased repolarization heterogeneity: global heterogeneity sets conditions for sustained arrhythmia, whereas increased transmural dispersion of action potentials provides a substrate for reentry and prolongs the time window for calcium channels to remain open.

Triggers for LQT1 and LQT2 patients are associated with adrenergic activation; nonetheless, differences are observed. Clinical cases of cardiac events in LQT1 patients generally are preceded by exercise. In LQT2, increased adrenergic tone plays an important role too; but cardiac events in these patients are mainly associated with emotional stress or exposure to auditory stimuli[10-12] and suggest a somewhat different mechanism of arrhythmia generation. Consistent with genotyped specific mechanism, pause-induced EADs have been shown to precede torsades de pointes for LQT2 but not LQT1 patients.[13] The slow component of the potassium repolarizing current (I_{Ks}) is strongly stimulated by activation of β-adrenergic receptors via increase in intracellular cyclic adenosine monophosphate concentrations and activation of protein kinase A.[14] The β-adrenergic stimulation increases I_{Ks} and results in rate-dependent action potential shortening. A decrease in I_{Ks} function due to mutations associated with LQT1 is expected to disrupt this rate-dependent regulation. During exercise, delay of the repolarization at high heart rates combined with an increase in sympathetically activated calcium channel function may predispose to arrhythmias. For LQT2, increased calcium release that follows a pause in rhythm, combined with a prolonged repolarization due to decrease in I_{Kr} function, may contribute to EAD generation; β-adrenergic activation of I_{Ks} may not be fast enough during acute emotional stress and auditory stimuli to compensate for the decreased mutant I_{Kr} currents. Local release of catecholamines and catecholamine-induced EADs has been reported in LQTS patients[15] and may represent the primary arrhythmogenic mechanism in these LQTS types.

It is noteworthy that different mutations within the same gene (hERG or KCNQ1) can lead to different phenotypic expression and carry different level of risks. An increasing number of investigations support the concept that certain mutations, their location, and their topology are more arrhythmogenic than others (pore, nonpore region,[10] transmembrane or cytoplasmic domains).[16-18] These emerging investigations are likely to unravel further the arrhythmogenic mechanisms involved in these syndromes.

In the acquired and congenital forms of the LQTS, there is a clear clinical consensus about the boundary for QTc interval duration (>500 milliseconds) above which the risk for ventricular arrhythmias is of concern. However, the definition of a lower boundary of QTc in the SQTS and its association with increased cardiac risk are less clear. The threshold for the lower boundary of QTc suggesting the syndrome was, in earlier work, described by the ratio of QT/QTp not exceeding 80%,[19] with QTp being the predicted QT based on the formula of Rautaharju et al,[20] whereas in an earlier report, Viskin et al[2] proposed gender-specific thresholds of QTc: less than 360 milliseconds in males and less than 370 milliseconds in females, based on 28 patients with idiopathic VF. Another example of a remarkable endeavor to define QTc shortening threshold for the SQTS is from Watanabe et al.[21] This group conducted a large retrospective analysis of ECGs in a general hospital (Nigaata, Japan) from a database consisting of 86 068 ECGs acquired between 2003 and 2009. The patients without history of cardiac events or cardiovascular disease, or any medication were reviewed for short QTc interval. Forty-four individuals were found with QTc less than 330 milliseconds, representing 0.3% of this population. This group was compared with a group of patients with QTc less than 360 milliseconds and documented VF, resuscitated sudden cardiac death and syncope, or SQTS genotyping. The ECG parameters such as QT apex, T-peak to T-end (TpTe) interval, and QTc interval were compared between these 2 groups. The TpTe interval prolongation was the most significant parameter between these 2 groups, but not the QTc interval. Today, a QTc less than 320 milliseconds is definitely accepted as an abnormal QTc value[20]; yet the prevalence of a short QT interval in 12-lead standard resting ECGs of the general population is not systematically associated with cardiac risk. As reported by Anttonen et al[24] in a group of middle-aged randomly selected individuals from Finland (N = 10 957), 0.1% of the studied population was associated with QTc less than 320 milliseconds; and this short QT was not associated with life-threatening events. This lack of association between abnormally shortened QTc interval and cardiac events was confirmed by another large independent study from Japan,[22] published shortly after, in which 26 350 ECGs were reviewed. Using a threshold of QTc less than 300 milliseconds, 0.03% of the population exhibited a short QT interval; and none of these individuals had the dangerous clinical symptoms of the SQTS. Consequently, the short QT interval in the SQTS seems to be a phenotypic expression lacking association with arrhythmia risks. Importantly, one would note that the use of heart rate correction formula and the method used for measuring the QT interval may have nonnegligible effect in the studies that have described the abnormal lower boundary for QTc interval in the SQTS.

Interestingly, an ECG pattern associated with the SQTS, and commonly reported, is the lack of an ST segment and the presence of peaked and tall T waves. Unfortunately, none of the reports investigating short QT reported information related to T-wave amplitude or other morphologic aspect of the T wave. The late portion of the T wave, that is, the TpTe interval, is statistically prolonged in most SQTS reports; so the role of repolarization heterogeneity (global or transmural) as the primary arrhythmogenic mechanism involved in the SQTS syndrome may carry more clinically relevant information than the QT/QTc interval duration. We will discuss 2 aspects: transmural dispersion associated with the shortening of the actions potentials and early repolarization (ERP) patterns.

Wedge experiments supporting the role of transmural dispersion and TpTe interval prolongation as a surrogate marker of arrhythmogenic risks

Because of the limited number of reported cases with the SQT syndrome, the characteristics and the arrhythmogenic

mechanisms of this syndrome are not well understood. Yet, interesting investigations have been reported in ventricular-wedge model developed by Extramiana and Anztelevitch[23] in 2004. Their experiment demonstrated that heterogeneous distribution of action potential shortening within the left ventricle and associated with transmural dispersion facilitates the induction of polymorphic ventricular tachycardia. Interestingly, the shortening of the QT interval was not sufficient to trigger the arrhythmia: transmural dispersion was found to be an arrhythmogenic requirement. An additive β-adrenergic stimulation (isoproterenol) to their wedge experiment led to abbreviate further the QT interval and prolong more the TpTe interval duration. These experimental conditions led to systematic triggering of polymorphic ventricular tachycardia in their models.

The concept of increased transmural dispersion was evaluated in a couple of nongenotyped SQTS patients by Anttonen et al[24] using the TpTe interval normalized by the QT interval (TpTe/QT). The study revealed an increased TpTe/QT ratio at lower heart rate in SQTS patient, yet these values were primarily driven by the QT interval shortening than TpTe interval prolongation. As noted earlier, TpTe interval was significantly prolonged ($P < .001$) in SQTS patients from a Japanese cohort of 37 patients compared with normal subjects with short QTc (<330 milliseconds). Therefore, there are both animal experiments and clinical investigations that have sought to confirm the concept of transmural dispersion as a primary arrhythmogenic mechanism in I_{Kr}-related arrhythmia. The current findings did support this arrhythmogenic concept, yet one would caution that if this mechanism is demonstrated in the wedge experiment, clinical reports did not consistently described TpTe interval prolongation in SQT syndrome patients.

The prevalence of ERP pattern in SQTS: reinforcing the role of transmural dispersion through J-point elevation manifested in leads with inferior or laterally directed positive poles

A very recent publication from Watanabe et al[21] reported a high prevalence of ERP in a large retrospective study involving 25 cases of SQTS patients. The review of the ECG tracings from this group evidenced a statistically significant higher occurrence of ERP (odds ratio = 5.6, $P = .001$) in comparison to subjects with short QT but no history of cardiac events. *Early repolarization* is an ECG finding associated with very different prognosis; it is defined as an elevation of the QRS-ST junction (J point) in leads other than V_1 through V_3 on 12-lead ECG (elevation 0.1 mV or >0.2 mV in >2 leads). Tikkanen et al[25] investigated the relationship between the presence of ERP and long-term outcome in 10 864 middle-aged individuals. The association between an increased risk of death and the ERP was significant after adjustment for QTc and left ventricular hypertrophy. ERP independent predictive value from arrhythmic events was already reported in survivors of primary VF[26] and patients with inducible VF.[27] The genesis of the ERP remains to be elucidated, but the cellular basis for the J point was investigated in 1996 by Yan et al who described the heterogeneity of action potential domes as the main mechanism producing the manifestation of the ECG J wave. In parallel, the propagation of the action potential dome in a heterogeneous manner was associated with local reexcitation, that is, extrasystolic activity and phase 2 reentry. This mechanism was observed in canine epicardium exposed to K^+ channel openers such as pinacidil. Finally, Antzelevitch and Yan[28] proposed the concept of the "J-wave syndrome" to encompass a spectrum of disorders associated with the genesis of J wave. With 3 proposed types depending on the location of leads presenting a J wave, the arrhythmogenic substrate in several mutations of the SQTS could lead to increase of outward potassium currents and develop arrhythmia vulnerability according to the described mechanism.

Conclusion

To conclude, ventricular repolarization deficiency associated with perturbation of the repolarizing potassium current, and primarily its slow and rapid components (gain or loss of functions), is associated with profound effect on the electrical activity of the heart and predisposes the individual for life-threatening arrhythmias. There is no doubt that more mutations will be discovered for both the SQTS and LQTS. These syndromes represent rare but important conditions that will, over time, help to elucidate important factors involved in the triggering and maintaining of arrhythmias. It is important to stress that abnormal QT intervals are not always associated with an increased risk for cardiac events. *Long QT* is defined as QTc greater than 470 milliseconds in males and greater than 480 milliseconds in females. Nonetheless, increased risk for arrhythmias is only associated with QTc greater than 500 milliseconds in this population. In a similar manner, for SQT, although less than 320 milliseconds is considered abnormal, the correlation between QTc and risk has not yet been established. It is possible that very short QTc (200-260) may be associated with an increase in cardiac risk; but nonetheless, for both syndromes, there is a wide range of QTc that is considered abnormal, without a significant increase in risk. In particular, for this population, it is very important to look at additional markers to identify patients at risk. Transmural dispersions and apicobasal or lateral to posterior heterogeneity are likely to all contribute in a complex mechanism that can generate specific or nonspecific ECG patterns. In this discussion, TpTe interval prolongation and ERP patterns/J wave are presented as interesting ECG manifestations of the SQTS; yet these patterns remain to be further investigated. The availability of a large database of ECGs from patients with this syndrome (such as the LQTS ECG database of LQTS genotyped patients available in the Telemetric Holter ECG Warehouse[29]) or an international SQTS registry would help addressing this important clinical question. Finally, because the ECGs of patients with the SQTS are also described as "peaked T wave with large amplitude," one may consider extending the analysis of ECG phenotype to the morphology of the T wave/T loop, as it was done in the congenital and acquired forms of the LQTS.[30-32]

As a final remark, the prolongation or the shortening of the QT interval was revealed to be an imperfect surrogate marker of an increased risk for arrhythmic events. The current concepts for the underlying arrhythmogenic mechanisms involved in the triggering of life-threatening arrhythmias for these syndromes do not systematically require the presence of abnormal duration of the QT/QTc interval.

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