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Short and Long QT Syndromes: does QT length really matter?

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Introduction

The short QT syndrome (SQTS) is a recent inherited arrhythmia disorder associated with family history of sudden cardiac death, short refractory periods, and inducible ventricular fibrillation (VF) in absence of structural heart disease. Initially, sporadic cases of SQTS were reported by Gussak et al. in family-related and unrelated patients with idiopathic VF and history of sudden cardiac death¹. Subsequently, a clinical investigation of patients with idiopathic VF by Viskin et al. reported a significant subgroup of these patients (primarily males) exhibiting ECG tracings with very short QT intervals and peaked T-wave morphologies². Gaita et al. confirmed that short QT was associated with familial sudden death³, and genetic investigations revealed heterogeneous forms of the SQT syndrome^{4–6}. As of today, five 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 two most recent mutations were identified in the *CACNA1c* and *CACNA1b* genes⁷, and have been associated with loss of function of the L-type calcium channels. The inherited long QT syndromes (LQTS), on the other hand, have been studied for several decades⁸. Long QT is associated with an increased propensity to arrhythmogenic syncope, polymorphic ventricular tachycardia (torsades de pointes), which itself may lead to ventricular fibrillation, 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 80–90% 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 msec in males and ≤ 370 msec in females) and thus their association to a short QT syndrome (<300 – 320 msec) may be questionable.⁷

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Arrhythmogenesis in the long QT syndromes

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) through increased repolarization heterogeneity: global heterogeneity sets conditions for sustained arrhythmia while 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 preceded by exercise or swimming. 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. Consistently to genotyped specific mechanism, pause induced EADs have been shown to precede TdP for LQT2 but not LQT1 patients¹³. The slow component of the potassium repolarizing current (I_{Ks}) is strongly stimulated by activation of β -adrenergic receptors via increase in intracellular cAMP concentrations and activation of protein kinase A (PKA).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, increase 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, beta-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 have been reported in LQTS patients¹⁵, and may represent the primary arrhythmogenic mechanism in these LQTS type.

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, non-pore region¹⁰, 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 long QT syndrome, there is a clear clinical consensus about the boundary for QTc interval duration (>500msec) 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 is less clear. The threshold for the lower boundary of QTc suggesting the syndrome was, in earlier work, described by the ratio of QT/QTp $\leq 80\%$ ¹⁹, with QTp being the predicted QT based on Rautaharju's formula²⁰. While in an earlier report, Viskin et al. proposed gender-specific thresholds of QTc: <360 msec in males and QTc <370 msec 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. 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 <330 msec representing 0.3% of this population.²¹ This group was compared to a group of patients with QTc <360msec and documented ventricular

fibrillation, resuscitated SDC and syncope, or SQTs genotyping. The electrocardiographic parameters such as QT apex, TpTe interval and QTc interval were compared between these two groups. The T-peak to T-end interval prolongation was the most significant parameter between these two groups, but not the QTc interval. Today, a QTc <320 msec is definitely accepted as an abnormal QTc value²⁰, 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. in a group of middle-aged randomly selected individuals from Finland (N=10,957), 0.1% of the studied population was associated with QTc <320 msec [21], 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 Japan²², published shortly after, in which 26,350 ECGs were reviewed. Using a QTc <300 msec threshold, 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 the use of heart rate correction formula and the method used for measuring the QT interval may have non-negligible effect in the studies that have described the abnormal lower boundary for QTc interval in the SQTs.

Interestingly, an electrocardiographic 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 morphological aspect of the T-wave. The late portion of the T-wave i.e. the T-peak to T-end interval (TpTe) 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. I will discuss two aspects: transmural dispersion associated with the shortening of the action potentials and early repolarization 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 in 2004.²³ 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 non-genotyped SQTs patients by Anttonen et al. using the Tpeak to Tend 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.²⁴ As noted earlier, TpTe interval was significantly prolonged ($p<0.001$) in SQTs patients from a Japanese cohort of 37 patients compared to normal subject with short QTc (<330 msec). 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_{K_r} -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 early repolarization pattern in short QT syndrome: 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. reported a high prevalence of early repolarization 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 early repolarization (odds ratio equal to 5.6, $p=0.001$) in comparison to subject with short QT but no history of cardiac events. Early repolarization is a 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 electrocardiography (elevation 0.1 mV or >0.2 mV in more than two leads). Tikkanen et al. investigated the relationship between the presence of ERP and long-term outcome in 10,864 middle-aged individuals²⁵. 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 ventricular fibrillation²⁶ or patients with inducible VF²⁷. 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. whom described the heterogeneity of action potential domes as the main mechanism producing the manifestation of the electrocardiographic J-wave. In parallel, the propagation of the action potential dome in a heterogeneous manner was associated with local reexcitation i.e. extrasystolic activity and phase 2 reentry. This mechanism was observed in canine epicardium exposed to K^+ channel openers such as pinacidil. Finally, Antzelevitch et al. proposed the concept of the “J-wave syndrome”²⁸ to encompass a spectrum of disorders associated with the genesis of J-wave. With three 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 $QTc > 470$ in males and $QTc > 480$ in females. Nonetheless, increased risk for arrhythmias is only associated with $QTc > 500$ ms in this population. In a similar manner, for SQT, although < 320 ms 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, apico-basal or lateral to posterior heterogeneity are likely to all

contribute in a complex mechanism that can generate specific or non-specific ECG patterns. In this discussion, TpTe interval prolongation and early repolarization patterns/J wave are presented as interesting electrocardiographic manifestations of the short QT syndrome, yet these patterns remain to be further investigated. The availability of large database of ECGs from patients with this syndrome (such as the LQST ECG database of LQTS genotyped patients available in the Telemetric Holter ECG Warehouse³²), 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 electrocardiographic phenotype to the morphology of the T-wave/T-loop, as it was done in the congenital and acquired form of the LQTS^{29–31}.

As a final remark, the prolongation or the shortening of the QT interval revealed to be imperfect surrogate markers 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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