ABSTRACTS

ABSTRACT AP-517:
What do we know about the QT lately?

Friday, April 29, 2022

8:00 AM - 9:00 AM

AP-517-01

THE LIKELIHOOD OF CLINICALLY SIGNIFICANT QTC PROLONGATION DURING LONG-TERM FOLLOW UP IN PATIENTS WITH CONCEALED LONG QT SYNDROME AND NORMAL QTC AT INITIAL PRESENTATION

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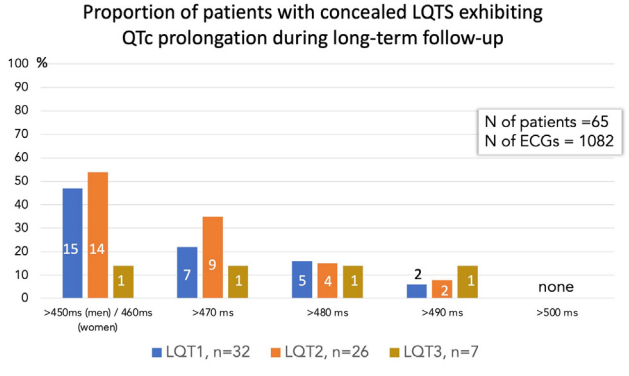
Background: Patients carrying genetic variants associated with long QT syndrome (LQTS) who initially present with normal QTc is a large and growing group of patients who are commonly diagnosed during genetic cascade family screening. Long-term progression of QTc interval in this patient group remains poorly described.
Objective: To assess the risk of QTc prolongation during long-term follow-up in LQTS patients who have normal QTc at first presentation.
Methods: ECGs from adult patients with LQTS followed up at three tertiary care hospitals in Sweden and Denmark were retrieved from regional ECG archives thaht contain ECGs recorded for any reason both in-hospital and in outpatient settings. Patients who had ECGs recorded after 16 years of age with at least two years apart were included. QTc (Bazett) was automatically calculated. Patients with QTc under 450 ms in men or 460 ms in women (upper limits of normal, ULN) at their first presentation were considered as patients with concealed LQTS. The likelihood of observing prolonged QTc above ULN, 480 ms and 490 ms thresholds at any time during follow-up was calculated. Data presented as median [interquartile range].
Results: Out of 207 patients meeting the inclusion criteria, 65 had concealed LQTS at first presentation (LQT1: n=32, age 36 [22-55]; LQT2: n=26, age 29 [18-45]; LQT3: n=7, age 36 [24-44]). In total, 1082 ECGs recorded from patients with concealed LQTS were available for analysis with time between the first and the latest ECGs 6 [3-10] years. Median number of ECGs was 10 [6-20] per patient. During follow up, 35 patients (54%) had QTc remaining under ULN and only 10 (15%) demonstrated QTc prolongation in the interval 480-499 ms (Figure). No significant differences between LQTS genotypes were observed.
Conclusion: Review of large-volume digital ECG archives reveals that vast majority of patients with LQTS who have normal QTc at initial presentation does not demonstrate clinically significant QTc prolongation.



AP-517-02

EFFECT OF INHALED ANESTHETICS ON RHYTHM ABNORMALITIES IN TWIN INFANTS WITH SHORT QT SYNDROME TYPE 2

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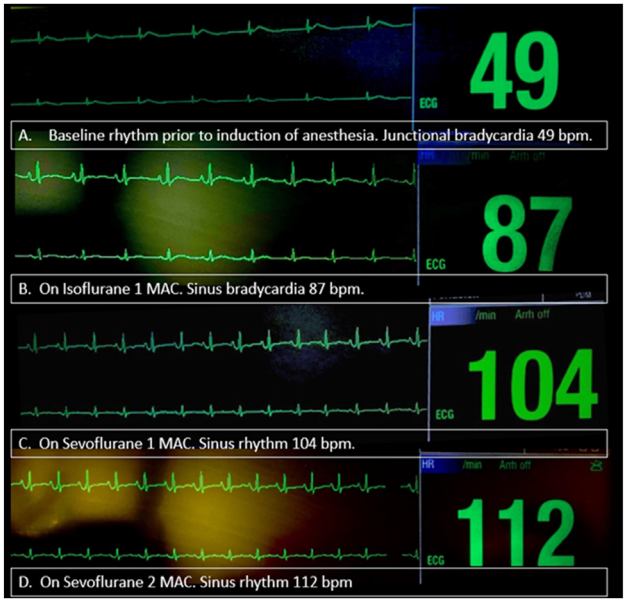
Background: Short QT syndrome (SQTS) is a rare genetic disorder which predisposes patients to a-fib, and sudden cardiac death. We present the case of twin boys with SQTS type 2 who underwent ICD implantation and had unexpected responses to inhaled anesthetics with normalization of heart rhythm.
Objective:
Methods:
Results: Twins A and B are mono-di twins born at 26 5/7 weeks by urgent c-section due to fetal bradycardia. At birth, HR was 40-90 bpm and hypotension was noted. Dopamine and epinephrine drips were initiated with improvement in BP and perfusion, but no effect on HR. Atropine and isoproterenol were also ineffective at raising HR. ECGs on both twins showed junctional bradycardia in the 50-70's with periods of sinus rhythm at 80-130 bpm (Fig. 1). Echo showed normal cardiac structure and function on both. Genetic testing revealed a pathogenic mutation in KCNQ1 (p.V141M) associated with SQTS type 2. Baseline ECGs demonstrated a QT interval of <300 msec and QTc of <330 msec.
Quinidine was initiated with some improvement in bradycardia. After discussion with parents, the decision was made to implant epicardial ICDs once they reached approximately 6 kg. At 6 months of age Twin A was brought to the OR in a junctional bradycardia at a rate of 49 BPM (Fig 2). On isoflurane he was noted to be consistently in sinus rhythm in the 80's without intermittent reversion to junctional rhythm, which had not been observed previously. He was transitioned to sevoflurane at 1 MAC and he remained in sinus rhythm, but the HR climbed to 104 bpm. Sevo was increased to 2 MAC and there was a dose-dependent increase in HR to a rate of 112-118 bpm. A comparable effect was noted in Twin B at the time of his ICD implant.
Conclusion: In SQTS type 2, sinus bradycardia is attributed to the gain of function in K^+ channel Kv7.1, which forms part of the IKs channel complex. In in-vitro studies isoflurane inhibits both IKs and IKr while sevo preferentially inhibits IKs. Both anesthetics

could thereby inhibit overactive K^+ channels and result in improvement in sinus bradycardia. There are no effective IV medications to treat SQTS and associated sinus bradycardia is often refractory to sympathomimetic medications. It is possible that inhaled anesthetics may provide a temporizing rescue therapy for Short QT patients with hemodynamically significant and drug-refractory bradycardia.



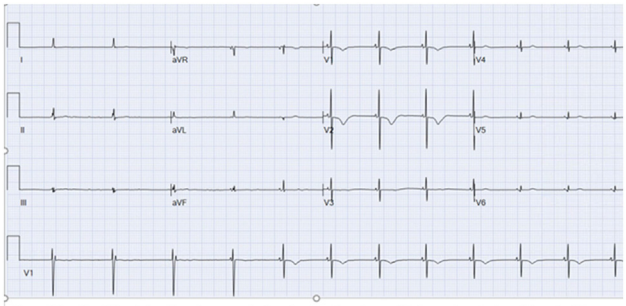


Figure 1. Baseline ECG at 1 day of age demonstrating junctional bradycardia transitioning to sinus rhythm with marked T wave abnormality. QT 280msec, QTc 317msec

AP-517-03

WHOLE EXOME SEQUENCING IDENTIFIES TWO NOVEL EXTREMELY RARE CANDIDATE VARIANTS ASSOCIATED WITH THE SHORT QT SYNDROME IN TWO LARGE PEDIGREES

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Background: Short QT syndrome (SQTS) is caused by pathogenic variants predominantly in the *KCNQ1*, *KCNH2*, *KCNJ2* genes and genes encoding for different subunits of the L-type calcium channel. Recently, a variant in the *SLC4A3* gene has been associated with the SQTS as well.

Objective: To identify the genetic background causing SQTS using whole exome sequencing (WES) and co-segregation analysis in two large pedigrees.

Methods: Genetic testing of the index patient 1 and molecular autopsy of the index patient two was performed using NGS. Family screening was performed with cardiologic work-up and genetic cascade screening.

Results: Index case 1 was diagnosed with SQTS at the age of 28 years after a syncopal event. Work-up revealed a markedly shortened QTc interval (340ms). Family history revealed peripartum death of one relative. Genetic testing of all known implicated genes was initially negative. WES was performed, which revealed a novel rare heterozygous missense variant (p.(Arg370Cys)) in a highly conserved region of the *SLC4A3* gene. Cardiac and genetic work-up of 5 relatives suggested co-segregation of the candidate variant (pedigree 1) with the SQTS. Index case 2 had sudden cardiac death (SCD) at 17 years of age and had a positive family history for SCD before the age of 40 in three cases. A previously recorded 12-lead ECG revealed a QTc of 340ms in the index patient. Post-mortem genetic testing of all known implicated genes was initially negative. In light of our previous findings, reanalysis was performed including the *SLC4A3*gene, which revealed a second rare novel heterozygous missense variant(p.(Ser1039Arg)). Cardiac and genetic work-up of 10 relatives suggested co-segregation of the candidate variant with the SQTS (pedigree 2).

Conclusion: WES and co-segregation analysis in two families with the SQTS revealed two novel candidate variants in the *SLC4A3* gene with high penetrance. Alteration of the protein encoded by the *SLC4A3* gene may lead to increased intracellular pH and shortened action potential duration leading to the SQTS. Functional work-up of these two variants is under way.