TRIGGERED SYNCOPE AND THE RISK FOR SUBSEQUENT LIFE THREATENING EVENTS IN LONG QT SYNDROME

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Background: Syncope, associated with specific triggers, is the most powerful predictor for life-threatening events (LTE) in patients with congenital long QT syndrome (LQTS).

Objective: We aimed to evaluate the association between adrenergic/non-adrenergic syncope and the risk for subsequent LTE.

Methods: The study population comprised 3,147 genetically confirmed LQT1-LQT3 patients from the International LQTS registry. Multivariate Cox regression was used to determine the association of adrenergic (exercise, arousal, swimming, etc.) or non-adrenergic (during rest, pregnancy, medications, etc.) triggered-syncope on the risk of subsequent LTE (aborted cardiac arrest, LQTS related death, or appropriate shock) in each genotype group separately.

Results: In LQT1 patients (n=1,410) syncope occurred in 444 (31%) subjects and was triggered mostly by adrenergic triggers 55%. Syncope preceded 78% of LTEs. Syncope occurred in 394 (33%) subjects and was triggered by non-adrenergic (during rest, pregnancy, medications, etc.) in 28% and by non-adrenergic (during rest, pregnancy, medications, etc.) in 45%. Syncope preceded 71% of LTEs. Non-adrenergic syncope was associated with 124% risk increase in LTE (HR 2.05; 95%CI 1.2; 3.42; p=0.001), whereas the risk associated with syncope events during non-adrenergic triggers was non-significant (HR 0.82). In LQT2 patients (n=1,217), syncope occurred in 394 (33%) subjects and was triggered by adrenergic triggers in 28% and by non-adrenergic in 45%. Syncope preceded 71% of LTEs. Non-adrenergic syncope was associated with 124% risk increase in LTE (HR 2.24; 95%CI 1.22-4.11; p=0.010), whereas adrenergic syncope was associated with a trend of 105% increase (HR 1.2; 95%CI 0.25-5.7; p=0.82). In LQT3 patients (n=1,410) syncope occurred in 78% (33%) subjects and was triggered mostly by adrenergic triggers 55%. Syncope preceded 78% of LTEs. Syncope was associated with a trend of 105% increase (HR 1.22-4.11; p=0.001), whereas the risk associated with syncope events during non-adrenergic triggers was non-significant (HR 0.059). In contrast, LTE was the first clinical presentation in the majority of LQT3 patients (81%). The residual rate of LTE despite beta-blocker therapy was highest in LQT1 patients with prior syncope triggered by adrenergic triggers (Figure).

Conclusion: We show for the first time that trigger-specific syncope episodes confer different risk for subsequent LTE and response to therapy by genotype.

THE EFFECT OF CHANGES IN EXTRACELLULAR CALCIUM LEVELS ON THE SMALL-CONDUCTION CA2+-ACTIVATED K+ CHANNEL OF METABOLIC SYNDROME

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Background: Metabolic syndrome (MetS) is associated with increased cardiac arrhythmia and mortality. Small conductance Ca\(^{2+}\)-activated K\(^{+}\) (SK) channels link intracellular calcium transients to membrane potential changes and play an essential role in atrial repolarization. Regulation of the SK channels is still not fully discovered.

Objective: To determine the interaction between extracellular calcium and MetS on the activity of SK channel in MetS.

Methods: We used the high-fat diet (45%) to induce MetS in mice. Optical mapping was performed in Langendorff perfused mice hearts with alteration of extracellular calcium to measure the atrial action potential duration (APD), calcium transient duration (CaTD) and conduction velocity (CV). The selective SK blocker, apamin, has revealed multifaceted functions of the SK channel in atria of MetS.

Results: Under high and normal extracellular calcium, apamin prolonged APD and CaTD both in MetS and control mice. However, the apamin only prolonged APD and CaTD in MetS but not in control mice in low extracellular calcium, meaning that both high extracellular calcium and MetS contribute to the upregulation of SK channels. A reverse relationship between CV and extracellular calcium was found in control mice but not in MetS mice. Additionally, the number of phase singularity during atrial fibrillation was larger in MetS than in control mouse.

Conclusion: We suggest extracellular Ca\(^{2+}\) and MetS both upregulate SK currents in the atria. The effect of extracellular calcium on the atrial CV is different between MetS and CTL mouse. Apamin-sensitive SK current may play an important role in the atrial repolarization of MetS and associated arrhythmogenesis.

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EFFECTS OF RENAL DENERVATION TO SLEEP APNEA AND CARDIAC ARRYTHMIA IN RATS WITH MYOCARDIAL INFARCTION

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Background: Sympathetic hyperactivity and poor sleep quality are reported in MI patients. Sleep is an important modulator of cardiovascular function, both in physiological and pathological states.

Objective: We aimed to evaluate the effects of renal denervation (RDN) on cardiac autonomic activity and disordered sleep pattern in a MI rat model.

Methods: Wireless transmission of polysomnographic recording was performed in sham (n=12) and MI (n=15) rats during normal daytime sleep before and after RDN treatment. Spectral analyses of the electroencephalogram (EEG) and electromyogram (EMG) were evaluated to define active waking (AW), quiet and paradoxical sleeps (QS, PS). Cardiac autonomic activities were measured by analyzing the power spectrum of heart rate variability. Central sleep apnea (CSA) events were measured by analyzing the EMG of the diaphragm (DEMG).

Results: In MI group, there was a higher LF/HF ratio during sleep, and LF/HF ratio was reduced significantly after RDN treatment in all sleep stages, when compared to that before RDN treatment (Fig A), respectively. The percentage of QS stage significantly decreased, and the frequency of sleep interruption was increased in MI rats compared to sham, respectively (Fig C, D). CSA events were significantly increased in MI rats (Fig E). Those changes were ameliorated and restored to baseline after RDN treatment in MI rats.

Conclusion: Our results demonstrate a significant sleep fragmentation with sympathetic hyperactivity after MI, and RDN restores the autonomic dysfunction and disordered sleep pattern to normal physiological status. The findings suggest that RDN may improve sleep-related arrhythmia and sudden cardiac death after MI by restoring autonomic homeostasis.

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ELUCIDATION OF ALG10B AS A NOVEL LONG QT SYNDROME SUSCEPTIBILITY GENE

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Background: Long QT syndrome (LQTS) is characterized by QT prolongation and increased risk for syncope, seizures, and sudden cardiac death. The majority of LQTS stems from pathogenic variants in either KCNQ1, KCNH2, or SCN5A. However, ~10% of patients clinically diagnosed with LQTS remain genetically elusive. Here, we used genome sequencing (GS) to identify a novel LQTS genetic substrate in a multi-generational “genotype negative” LQTS pedigree with a LQT2-like phenotype.

Methods: We used genome sequencing (GS) to identify a novel LQTS substrate in a multi-generational “genotype-negative” LQTS pedigree. GS was performed on 5 affected family members. Only rare (minor allele frequency < 5x10\(^{-5}\) in gnomAD) non-synonymous variants present in all affected family members were considered. The candidate variant was characterized functionally in gene-edited, variant-corrected, isogenic control and patient-derived pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) using western blot, immunocytochemistry, patch-clamp, and multielectrode array (MEA) technologies.

Results: A missense variant (p.G6S) was identified in ALG10B-encoded alpha-1,2-glucosyltransferase B as the most likely candidate. ALG10B is a known interacting protein of KCNH2-encoded Kv11.1. Compared with isogenic control, p.G6S-ALG10B iPSC-CMs showed 1) decreased protein expression of