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Electro-mechanical dysfunction in long QT syndrome: Role for arrhythmogenic risk prediction and modulation by sex and sex hormones

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ABSTRACT

Long QT syndrome (LQTS) is a congenital arrhythmogenic channelopathy characterized by impaired cardiac repolarization. Increasing evidence supports the notion that LQTS is not purely an "electrical" disease but rather an "electro-mechanical" disease with regionally heterogeneously impaired electrical and mechanical cardiac function.

In the first part, this article reviews current knowledge on electro-mechanical (dys)function in LQTS, clinical consequences of the observed electro-mechanical dysfunction, and potential underlying mechanisms. Since several novel imaging techniques – Strain Echocardiography (SE) and Magnetic Resonance Tissue Phase Mapping (TPM) – are applied in clinical and experimental settings to assess the (regional) mechanical function, advantages of these non-invasive techniques and their feasibility in the clinical routine are particularly highlighted.

The second part provides novel insights into sex differences and sex hormone effects on electro-mechanical cardiac function in a transgenic LQT2 rabbit model. Here we demonstrate that female LQT2 rabbits exhibit a prolonged time to diastolic peak – as marker for contraction duration and early relaxation – compared to males. Chronic estradiol-treatment enhances these differences in time to diastolic peak even more and additionally increases the risk for ventricular arrhythmia. Importantly, time to diastolic peak is particularly prolonged in rabbits exhibiting ventricular arrhythmia – regardless of hormone treatment – contrasting with a lack of differences in QT duration between symptomatic and asymptomatic LQT2 rabbits. This indicates the potential added value of the assessment of mechanical dysfunction in future risk stratification of LQTS patients.

1. Introduction

Long QT syndrome (LQTS) is a rare congenital ion channel disorder of autosomal dominant inheritance with an incomplete penetrance (Napolitano et al., 2015; Roden, 2008). Patients have a prolonged cardiac repolarization phase and may develop potentially lethal ventricular arrhythmia (Priori, 2001). The individual arrhythmogenic risk, however, varies pronouncedly between different LQTS patients – even if they harbour the same mutation (Benhorin et al., 2002). Moreover, pronounced sex differences with an increased arrhythmogenic risk in women affected with LQTS compared to men can be observed (Sauer et al., 2007). A great

Abbreviations: APD, action potential duration (ms); DHT, ovariectomized female LQT2 rabbit with dihydrotestosterone-treatment; EST, ovariectomized female LQT2 rabbit with estradiol-treatment; LQTS, long QT syndrome; LQT1/2/3, long QT syndrome type 1/2/3; Non-VF, LQT2 rabbit without *ex vivo* ventricular fibrillation; OVX, ovariectomized female LQT2 rabbit with placebo-treatment; QTc, heart rate corrected QT interval; QTi, heart rate corrected QT index; SCD, sudden cardiac death; SE, Strain Echocardiography; SF, female LQT2 rabbit with sham surgery and placebo-treatment; SM, male LQT2 rabbit with sham surgery and placebo-treatment; TDI, Tissue Doppler Imaging; TPM, (Magnetic Resonance) Tissue Phase Mapping; TTP, time to peak duration (ms, when heart rate corrected %); VF, LQT2 rabbit exhibiting *ex vivo* ventricular fibrillation; Vr, radial velocity (cm/s); Vz, longitudinal velocity (cm/s).

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challenge for physicians is thus to identify and treat those patients at high arrhythmogenic risk.

On the organ level, cardiac repolarization is prolonged heterogeneously throughout the ventricles, leading to an increased dispersion of repolarization (in addition to the prolonged cardiac repolarization), thus providing an "arrhythmogenic substrate" for life-threatening ventricular arrhythmia in structurally healthy hearts (Antzelevitch, 2007). Due to the underlying ion channel mutations (Moss, 2005) and a globally "normal" structure and mechanical cardiac function (as assessed with standard imaging techniques), LQTS has been perceived for a long time as a primary "electrical" disorder. Therefore, current risk stratification guidelines concentrate on electrical and genetic abnormalities in this syndrome.

Electrical and mechanical cardiac function, however, are inevitably connected via electro-mechanical coupling mechanisms and mechano-electrical feedback (Pfeiffer et al., 2014), suggesting that an impairment of (regional) electrical function should impact on (regional) mechanical cardiac function. Regional mechanical motion can be (subclinically) affected while parameters reflecting global function may still be in the normal range. A high spatiotemporal resolution is required to detect such distinct alterations. M(otion)-Mode echocardiography was the first method used to spot light on mechanical alteration in LQTS patients (Nador et al., 1991). Strain Echocardiography methods (SE) and Magnetic Resonance Tissue Phase Mapping (TPM) emerging in the last years also accomplish high spatiotemporal resolution. In addition, they provide information on regional contractility/relaxation and tissue deformation of the heart.

Using these techniques, it was demonstrated that LQTS patients have a prolonged and heterogeneously affected myocardial contraction duration (Haugaa and Edvardsen, 2011) and that rabbit models of LQTS type 2 (LQT2) have a pronouncedly impaired diastolic relaxation (Odening et al., 2013). These data indicate that LQTS should be considered and assessed not purely as an "electrical" disease but rather as an "electro-mechanical" disease. Therefore, the assessment of regional mechanical alterations may enable alternative risk stratification strategies in LQTS that include regional mechanical parameters (Haugaa et al., 2010). Recent data provide insights into genotype differences in mechanical dysfunction (Leren et al., 2015). No data on potential sex differences and sex hormone effects on mechanical function, however, are available to date.

In this article we hence first review current knowledge on electro-mechanical dysfunction in LQTS, clinical consequences of the electro-mechanical dysfunction for patient characterization, and potential underlying mechanisms.

In the second part, we provide novel insights into sex-specific differences and sex hormone effects on electro-mechanical function in transgenic LQT2 rabbit models.

1.1. Long QT syndrome – clinical symptoms and therapeutic management

LQTS patients are at risk to develop pathognomonic polymorphic ventricular torsades de pointes tachycardia that can lead to emotionally or exercise-triggered syncope, ventricular fibrillation (VF), and sudden cardiac death (SCD) (Priori et al., 2003). The individual arrhythmogenic risk, however, varies pronouncedly between different LQTS patients (incomplete penetrance), even in those carrying the same mutation (Benhorin et al., 2002). The assessment of an individual LQTS patient's risk thus remains a difficult task in daily clinical practice.

The clinical work-up, so far, concentrates on the underlying electrical disorder. The diagnosis is based on the typically prolonged heart rate corrected QT interval (QTc) in the electrocardiogram at rest and arrhythmic events in the patient's personal and family history (syncope, ventricular arrhythmia, aborted cardiac arrest or SCD) (Priori et al., 2003, 2013; Schwartz and Ackerman, 2013). However, since even patients with a high risk phenotype can have a normal QTc, they can be missed by standard screening (Sauer et al., 2007). To substantiate suspicion in those patients, they undergo exercise or pharmacological stress tests, followed by genetic workup and family screening for mutations (Roden, 2008; Schwartz, 2015). To our current knowledge, a "typical" very high risk patient is female, aged 20 years or older, presenting with a QTc $\geq$550 ms, LQT2 genotype, and arrhythmic events before the age of 18 years (Sauer et al., 2007).

To date, mutations in at least 16 different genes have been identified to cause LQTS. Approximately 90% of LQTS patients, however, carry mutations in genes encoding for repolarizing potassium channels or depolarizing sodium channels (*KCNQ1* = LQT1, *KCNH2* = LQT2, *SCN5A* = LQT3) (Tester and Ackerman, 2014). A higher arrhythmogenic risk has been associated with pore region mutations of *KCNH2* and mutations in the cytoplasmatic loop of *KCNQ1* (Moss, 2002). Interactions between the disease-causing mutation and single nucleotide polymorphisms (SNPs) in other genes encoding for other ion channels or modifier-proteins, sex, and age are discussed as genetic modifiers (Napolitano et al., 2015).

Typical arrhythmogenic triggers are physical exercise (LQT1) or emotional stress and startle (LQT2) causing an increase in adrenergic tone (Morita et al., 2008). Hence, patients with LQTS are advised to stop competitive sport, avoid QT prolonging drugs and keep serum electrolyte levels in normal range. Standard treatment consists of beta-blocker therapy. Transvenous or subcutaneous implantable cardioverter defibrillator (ICD) are used for high risk patients after aborted cardiac arrest or in patients remaining symptomatic while on beta-blocker therapy (Schwartz and Ackerman, 2013). Left cardiac sympathetic denervation is an alternative treatment in few patients when ICDs are contraindicated or when beta-blocker therapy is not tolerated or not efficient in preventing arrhythmia. Furthermore, in patients with multiple ICD shocks, left cardiac sympathetic denervation therapy can be considered with a class IIa recommendation according to the ESC Guidelines 2015 (Priori et al., 2015).

1.2. Electrical dysfunction in long QT syndrome – patients and transgenic rabbit models

The hallmark of long QT syndrome is a prolonged cardiac repolarization resulting in a prolonged QTc ($\geq$480 ms) (Priori et al., 2015; Schwartz, 2015). Extended QT interval prolongation is associated with more malignant phenotypes and high-risk patients usually have QTc intervals of at least 500 ms (Schwartz and Ackerman, 2013).

In addition to a "globally" prolonged QT, an increased dispersion of QT and Tpeak-end intervals in the different ECG leads can be observed in LQTS patients, indirectly reflecting pronounced regional and transmural heterogeneities in action potential duration (APD) (Lubinski et al., 1998; Priori et al., 1994). Conflicting data on a possible association of these markers for increased electrical heterogeneities with the arrhythmogenic risk have been published (Antzelevitch, 2005; Castro-Torres et al., 2015; Kanters et al., 2008). Using non-invasive ECG mapping (electrocardiographic imaging, ECGi) in LQTS patients to display the arrhythmogenic substrate, Vijayakumar et al. could additionally directly demonstrate regions with steep repolarization dispersion due to heterogeneous APD in LQTS patients (Vijayakumar et al., 2014).

With the help of transgenic rabbit models, we further evaluated mechanisms underlying the heterogeneously prolonged

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