Tissue Phase Mapping analysis of IKr-blocker E4031 effects on mechanical cardiac function in transgenic long-QT syndrome type 1 rabbits

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Target audience: radiologists, cardiologists and medical physicists interested in cardiac function

Purpose: Long-QT syndrome (LQTS) is an inherited cardiac channelopathy, in which mutations in cardiac ion channels cause a prolongation of cardiac repolarization (prolonged QT interval) and predispose patients to ventricular tachycardia and sudden cardiac death. Drugs that block IKr-currents can mimic this disease, causing acquired LQTS, a serious side effect of a variety of different drugs. Thus far, LQTS was considered a purely "electrical" disorder of the heart. However, we have recently demonstrated also a mechanical dysfunction in transgenic LQT type 2 rabbits (loss of IKr currents) – due to electro-mechanical coupling [1].
The aim of this study was to investigate whether IKr-blocking drugs (E4031) similarly affect mechanical cardiac function. We therefore used transgenic LQT type 1 rabbits (loss of IKs) with a particularly high susceptibility to IKr-blocking drugs and compared them to wild-type littermate controls (LMC).

Methods: Transgenic LQT1- and LMC-rabbits (both n=11, male) were anesthetized with ketamine/xylazine, which does not affect electro-mechanical cardiac function [2]. They were subjected to tissue phase mapping (TPM) before (Baseline, BL) and during E4031-infusion (1µg/kg/min, intravenous) on a 1.5T Avanto MR-scanner (Siemens) with a 15-channel knee coil [3]. A black-blood prepared and 3-directional velocity encoded gradient echo sequence was used (temporal resolution 7.6 ms, spatial resolution 1.0×1.0×4.4 mm; venc [in-plane]=10 cm/s, venc [through-plane]=15 cm/s, 4 averages; prospective ECG gating; free breathing; kt-accelerated PEAK-GRAPPA: R=3 [4]) for acquiring 3 short-axis slices (base, mid, apex). Data post-processing (Matlab) included eddy current correction, semi-manual segmentation of the left ventricle (LV) and a transformation of the measured in-plane velocities (V_x,V_y) into perpendicular (V_r) and tangential (V_φ) to the inner heart wall in-plane velocities. For segmental analysis the LV was divided according to the AHA 16-segment model (Fig. 3 & 4). Global (averaged over the entire slice, Fig. 1 & 2) and segmental velocity time courses were derived, systolic and diastolic peak velocities (AMPsys/AMPdia) and according Time-To-Peak (TTPsys/TTPdia) were extracted. Velocity data (for LQT1/LMC) before and during E4031-infusion were compared using paired t-tests (*p<0.05; **p<0.01; ***p<0.001).

Results: ECG measurements demonstrate an E4031-induced QT interval prolongation in LMC and more pronouncedly in LQT1 (Fig 1). Global long-axis velocity (Vz) time courses show an E4031-induced significantly increased AMPsys (p<0.010) and shortened TTPsys (p<0.012) as well as a significantly decreased AMPdia (p<0.002) and slightly prolonged TTPdia in LQT1, indicating an increased systolic function and an impaired diastolic relaxation (Base: Fig 2; mid and apex not shown; Fig. 1 second column). These results are confirmed by segmental analysis of V_Z. In E4031-treated LQT1, peak systolic velocities are significantly higher in 16 of 16 segments (seg.) (p<0.05, Fig. 2) and systolic Time-To-Peak are significantly shortened in 8 of 16 seg. (p<0.05, not shown). Moreover, peak diastolic velocities are significantly decreased in 13 of 16 seg. (p<0.05, Fig.4), whereas TTPdia are only prolonged in 2 of 16 seg. (p<0.05, not shown). In contrast, in LMC, E4031 does not affect peak systolic velocities and only slightly affects peak diastolic velocities (4 of 16 seg., p<0.05, Fig. 4) as well as systolic and diastolic Time-To-Peak (2 and 4 of 16 seg., p<0.05, not shown).

Discussion: Similarly as observed in transgenic LQT2 rabbits, IKr-blocking drug E4031 prolongs cardiac repolarization (QT interval) and, importantly, also affects mechanical cardiac function. Due to electro-mechanical coupling, a prolonged cardiac repolarization results in an increased Ca^{2+} influx thus increasing cytoplasmic Ca^{2+} concentration [5]. This increased cytoplasmic Ca^{2+} may increase systolic function – as observed in E4031-treated LQT1 rabbits. Since physical properties of (resting) sarcomeres are related to cytoplasmic Ca^{2+} [6], an increased cytoplasmic Ca^{2+} may additionally result in an impaired diastolic relaxation – as observed in E4031-treated LQT1 rabbits. How this altered electro-mechanical function in LQTS may impact on the development of arrhythmias remains to be elucidated.

Conclusions: TPM enables a comprehensive analysis of global and segmental alterations of mechanical cardiac function in inherited and acquired LQT-syndrome and thus may provide a better understanding of electro-mechanical effects of ion channel blocking drugs.

References:

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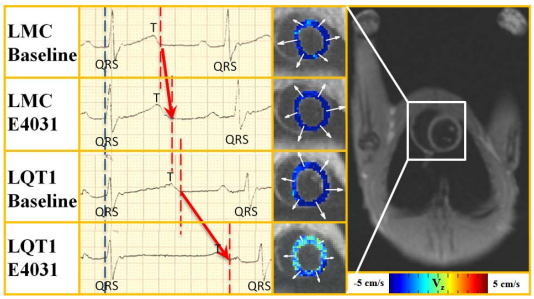

Fig. 1: Representative comparison of ECG (first column) and diastolic peak velocities AMPdia (second column, color-coded, V_z) between LQT1 and LMC before and during E4031-infusion indicating an E4031-induced QT interval prolongation (red arrows) and decreased diastolic peak velocity in LQT1.

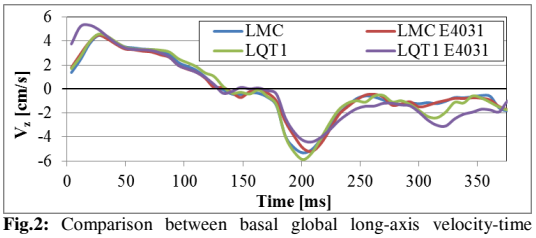

Fig.2: Comparison between basal global long-axis velocity-time courses (V_z) averaged over all rabbits of each group.

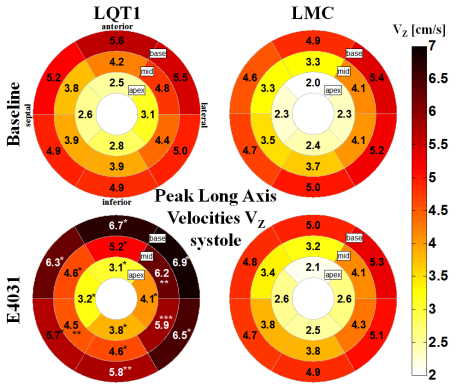

Fig. 3: Segmental systolic long-axis velocities (AMPsys V_Z) for LQT1 (first column) and LMC (second column) before (first row) and during E4031-infusion (second row).

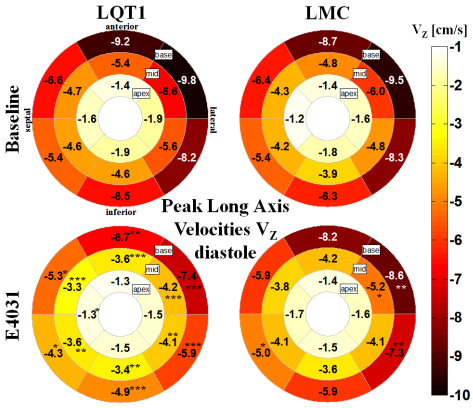

Fig. 4: Segmental diastolic long-axis velocities (AMPdia V_Z) for LQT1 (first column) and LMC (second column) before (first row) and during E4031-infusion (second row).