Correlation between Spatial Differences in Action Potential Duration and Myocardial Dysfunction in Transgenic LQT2 Rabbits

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Introduction: Enhanced dispersion of action potential duration (APD) due to heterogeneous prolongation of cardiac repolarization is a major contributor to Long-QT syndrome (LQTS)-related arrhythmias [1]. Recently, transmural differences in contraction duration – e.g. a transmural mechanical dispersion - have been detected in LQTS patients [2]. However, the relationship between electrical and mechanical dispersion - such as a potential spatial correlation between regional differences in duration of repolarization and impairment of diastolic function – remains to be elucidated. Using in vivo tissue phase mapping MRI (TPM) [3,4], we have assessed the relationship between electrical and mechanical dispersion in transgenic LQT2 rabbits.

Methods: We have generated transgenic LQT2 rabbits over-expressing dominant-negative loss-of-function pore mutants of the α-subunits of the current I Kr through the potassium channel (hERG-G628S), influencing the repolarization [5]. Transgenic LQTS rabbits show a marked global QT- and APD-prolongation due to an elimination of I Kr in LQT2 rabbit cardiomyocytes – moreover, they have a pronounced dispersion of repolarisation in the LV and RV [6] (see Fig. 1). TPM in adult female transgenic LQT2 rabbits (n=10) and wild type littermate controls (LMC, n=9) under ketamine/xylazine anesthesia was performed on a 1.5T Avanto MR-system (Siemens) with a 12-channel head coil. A black blood Cine gradient echo sequence with prospective ECG-gating was used for TPM data acquisition during free breathing with 3-directional velocity encoding (venc=10cm/s, venc=through-plane=15cm/s). Three slices in short axis view (basal, mid, apiical) were acquired with a spatial resolution of 1.0×1.2 mm (slice thickness 4 mm, 4 averages) and a temporal resolution of 7.6 ms. Global and regional systolic / diastolic radial and longitudinal velocities (Vr, Vz, see Fig 2) were assessed in the LV (AHA 16-segment model). The same rabbits’ hearts were subsequently Langendorff-perfused and subjected to ex vivo epicardial monophasic action potential measurements to assess APD in the corresponding segments. Unpaired t-test were used for statistical analysis (*p<0.05; **p<0.01; ***p<0.001), Pearson’s test to calculate correlations.

Results:
• APD was significantly longer in LQT2 than in LMC rabbits in all segments of the LV and spatial APD dispersion was significantly greater in LQT2 rabbits (Fig. 3).
• Peak systolic Vr significantly reduced in base and apex, peak diastolic Vr in all slices (Fig. 5). No significant differences could be observed for Vz (not shown).
• Peak systolic Vr was reduced in all segments in LQT2 as compared to LMC rabbits, mostly pronounced in the anteroseptal segments (Fig. 4, upper graphs).
• Peak diastolic Vr was reduced in most segments in LQT2 as compared to LMC rabbits, mostly pronounced in the lateral wall (Fig. 4 lower graphs). Peak diastolic Vr in basal LV segments correlated with spatial differences of APD (Vr_dia, CC 0.38, p=0.016).
• Peak diastolic Vz was significantly reduced in the anterior wall in LQT2 as compared to LMC in LV base, mid, and apex (not shown). Peak diastolic Vz in basal LV segments correlated with spatial differences of APD (Vz_dia, CC 0.47, p=0.002).

Discussion: Prolongation of cardiac repolarization and increased dispersion of APD lead to a globally and regionally impaired systolic and diastolic function in transgenic LQT2 rabbits. Moreover, regional APDs correlate with regional peak diastolic velocities indicating that Long-QT syndrome is not purely an electrical but rather an electromechanical disorder. To date, long-QT syndrome is mainly considered an “electrical” disorder, in which the overall QTc duration [7] as well as the extent of QT dispersion are known risk factors for arrhythmias and therapeutic efficacy [8]. The fact that regional differences in APD correlate with regional differences in diastolic dysfunction might open new approaches in treating LQTS patients: in the future, it might be possible to use phase contrast MRI to non-invasively assess mechanical dysfunction in LQTS patients and consecutively use these data to deduce electrical dispersion thereby assessing the arrhythmogenic risk. Since potassium currents and action potentials of rabbits are similar to those of humans, it is likely that rabbits better mimic the human phenotype of diseases with electrical and mechanical impairment than mice.

References:

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