Combined use of transgenic LQT2, LQT5 and LQT2-5 rabbit models with decreased repolarization reserve as novel tool for pro-arrhythmia research

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Background: Reliable prediction of in vivo pro-arrhythmic effects associated with ion channel-blocking properties of novel drugs remains elusive. Thus, there is an unmet need for new animal models with better predictive value.

Purpose: For this aim, different transgenic LQTS rabbit models with impaired repolarization reserve were generated (LQT2, HERG-G628S, loss of IKr; LQT5, KCNE1-G52R, decreased IKs; double-transgenic LQT2–5, loss of IKr/decreased IKs).

Methods: In vivo telemetric ECG (QTc, QTi (QT observed/QT expected)) and ex vivo monophasic action potential measurements in Langendorff-perfused hearts (action potential duration (APD75), triangulation (APD90-APD30), and spatial dispersion of repolarization (APDmax-APDmin)) were performed to assess the effects of several K^+ channel blockers on cardiac repolarization in wild type (WT), transgenic LQT2, LQT5, and LQT2–5 rabbits.

Results: At baseline, QTc (ms) was similar in LQT5 (135.3±5) as in WT (137.2±6) but was significantly prolonged in LQT2 and LQT2–5 rabbit models (162.9±11 and 167.9±15; $p<0.05$ vs. WT). Slight IKr-blockade by low dose dofetilide (0.02mg/kg, im) prolonged QT in vivo only in LQT5 (QTi (%), 104.5±3.5, $p<0.05$ vs. baseline) but not in WT, nor in LQT2 and LQT2–5 rabbits that lack IKr. IK1-blocker BaCl2 (0.3mg/kg, im) prolonged QT in all groups (QTi (%), WT 105.7±3.3, LQT5 104.9±4.1, LQT2 110.8±4.8, LQT2–5 104.9±2.6; $p<0.05$ vs. baseline). Ex vivo,

IKr-blocker dofetilide (1nM) prolonged APD75 in all groups (changes (ms), WT +8.5±2.7, LQT5 +6.0±2.7, LQT2–5 +12.4±3.2; all $p<0.05$ vs. baseline) - except for LQT2 lacking IKr. APD75 prolongation induced by IKs-blocker HMR-1556 (100nM) was more pronounced in LQT2–5 as in WT or LQT5 (changes (ms), LQT2–5 +9.8±5.3 vs. WT +6.0±2.3 or LQT5 +5.5±2.8). IK1-blocker BaCl2 (10μM) or combined IK1/IKs-blockade by BaCl2+HMR prolonged APD75 significantly more in LQT2 and LQT2–5 than in WT (changes (ms), BaCl2: LQT2 +30.0±5, LQT2–5 +27.2±4 vs. WT +17.7±7; BaCl2+HMR: LQT2 +39.6±10, LQT2–5 +31.0±8 vs. WT +18.6±3; all $p<0.05$). Importantly, triangulation of APD was also more pronounced upon IK1-blockade or combined IK1/IKs-blockade in LQT2 and LQT2–5 than in WT (BaCl2: LQT2 +24.5±7, LQT2–5 +24.2±8 vs. WT +13.9±6; BaCl2+HMR: LQT2 +34.6±10, LQT2–5 +28.0±5 vs. WT +16.7±3; all $p<0.05$). Spatial dispersion of repolarization was increased significantly by BaCl2+HMR only in LQT2 (change +7.4±4.4 ms; $p<0.05$ vs. baseline) but in none of the other genotypes.

Conclusion: LQT2 and LQT2–5 rabbit models with pronounced reduction of repolarization reserve are very sensitive to K^+ channel blockers demonstrating not only QT prolongation but also increased APD triangulation and dispersion. The combined use of different transgenic LQTS rabbit models with different extents in reduction of repolarization reserve may provide further insights into pro-arrhythmic mechanisms of K^+ channel blocking drugs.