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Transgenic LQT5, LQT2 and LQT2-5 rabbit models with decreased repolarization reserve for more reliable prediction of drug induced ventricular arrhythmias

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Topic(s):
Basic Science - Cardiac Diseases: Arrhythmias

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Background: For more reliable prediction of pro-arrhythmic side-effects of novel drug candidates, different transgenic LQTS rabbit models with impaired repolarization reserve were generated by overexpressing loss-of-function mutations of human HERG (HERG-G628S, loss of IKr; LQT2), KCNE (KCNE1-G52R, decreased IKs; LQT5), or both transgenes (LQT2-5) in the heart.

Purpose: The effects of K+ channel blockers on cardiac repolarization and arrhythmia (AR) development were studied in wild type (WT), transgenic LQT5, LQT2, and LQT2-5 rabbits.

Methods: In vivo (QTc, Tpeak-Tend [Tp-e], STVQT) and ex vivo (action potential duration (APD75), triangulation and reverse use-dependence) pro-arrhythmic biomarkers were monitored by ECG and monophasic action potential (MAP) measurements in Langendorff-perfused hearts. Arrhythmia development was provoked ex vivo by low K+ (2.0mM) and IK1-blocker BaCl2 (10µM) (5 minutes).

Results: At baseline, QTc, Tp-e (ms±SEM) and STVQT were similar in LQT5 (144.3±1.2, 30.2±0.7, 2.0±0.1) as in WT (137.0±2.4, 29.8±0.8, 1.9±0.1) but were significantly prolonged in LQT2 and LQT2-5 (LQT2: 161.9±5.8, 40.2±1.3, 2.9±0.1 and LQT2-5: 164.7±3.2, 36.0±1.1, 2.5±0.2; all p<0.05 vs. WT or LQT5). Slight IKr-blockade by dofetilide (0.02mg/kg, iv.) increased STVQT (?±0.7±0.2), prolonged Tp-e (?±2.1±0.5) and QTc (?±7.7±1.9) only in LQT5 (all p<0.05 vs. baseline). IK1-blocker BaCl2 (0.1mg/kg, iv.) prolonged QT and Tp-e more pronouncedly in LQTS animals as in WT (QTc, LQT2: +20.4±3.0, LQT2-5: +24.0±7.4 vs. WT: +10.2±0.9; Tp-e, LQT5: +4.9±1.3, LQT2-5: +6.8±1.7, LQT2-5: +6.0±1.0 vs. WT: +1.5±0.3; all p<0.05) and increased STVQT only in transgenic rabbits (all p<0.05 vs. baseline) but not in WT. Following IKs 'pre'-activation by iv. isoproterenol, QT prolongation by IKs-blocker HMR-1556 (0.1 mg/kg iv.) was more pronounced in WT or LQT2 as in LQT5 or LQT2-5 (QTc, WT: +11.8±1.7 vs. LQT5: +4.1±1.1 or LQT2-5: +16.5±1.8 vs. LQT2-5: +0.2±3.1; all p<0.05), indicating impaired IKs function in LQT5 and LQT2-5. Ex vivo prolongation of APD75, triangulation of APD and reverse use-dependence were more prolonged upon IK1 (10µM BaCl2) or combined IK1/IKs (10µM BaCl2 + 100nM HMR-1556) - blockade in LQT2 and LQT2-5 than in WT. Ultimately, 5 min. perfusion by low K+ (2.0mM) and IK1-blocker BaCl2(10µM) resulted in higher incidence of arrhythmia (VT, LQT5: 50%/2/4 LQT2: 100%/3/3, LQT2-5: 100%/3/3 vs. WT: 0%/0/7; VF, LQT2:67%/2/3, LQT2-5:67%/2/3 vs. WT:0%/0/7), all p<0.05, ?2-test) and longer duration (total AR in %±SEM, LQT5: 57.3±18.4, LQT2: 83.2±8.4, LQT2-5: 82.6±9.0 vs. WT: 16.2±5.9; all p<0.05) in LQTS animals compared to WT.

Conclusion: LQT5 and LQT2 or LQT2-5 rabbits with mild/severe reduction of repolarization reserve are more sensitive to K+-channel blockers as WT animals demonstrating not only more pronounced increase in various pro-arrhythmic biomarkers but also higher incidence, longer duration and more malignant type of arrhythmia development.
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