Blockade Prevents Catecholaminergic Polymorphic Ventricular Tachycardia in CASQ2-Mutant Mice

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Spontaneous calcium release evoking delayed after-depolarizations is responsible for CPVT, a lethal ventricular arrhythmia provoked by exercise or emotional stress. We have generated a murine model of recessively-inherited CPVT caused by either a D307H mutation (CASQ2D307H) or CASQ2 knock-out (CASQ2Δ/Δ). Beta-adrenergic blockers are the therapy of choice but often fail to achieve complete arrhythmia (suppression or eradication) in humans and are ineffective in mouse CPVT. Calcium channel blockers are effective in mice>humans. In the current study we studied the effects of agents modulating the autonomic nervous system on CPVT in mice. Heart telemetry device was implanted for continues ECG recording at rest, during treadmill exercise and after epinephrine injection (0.1 mg/kg I.P). Beta-blockers, propranolol and metoprolol attenuated the arrhythmia at rest but failed to prevent CPVT on stress. Pharmacological attempt of sympathetic denervation by reserpine or parasympathetic activation by neostigmine failed in controlling the arrhythmia. The alpha-blocker phentolamine (50 μg/g) reduced CPVT prevalence from 83% to 0% in CASQ2Δ/Δ mice (n=6, $p<0.01$). Likewise, a combined alpha and beta adrenergic blocker labetalol was very effective against CPVT in mice. Gene expression analysis by RNAseq revealed that the alpha adreno-receptor 1a ADRA1a is expressed x2 higher in the CASQ2 mutant mice compared to the WT (n=5/group, $p<0.001$). We conclude that alpha sympathetic blocking agents have high efficacy against CPVT in mice and when combined with β blockade, may provide a new approach for treatment of CPVT in human patients.