Optimizing CPVT Therapy in Calsequestrin-mutant Mice

Guy Katz¹, Efrat Kurtzwald¹,², Edith Hochhauser², Yeleno Chepurko², Eyal Porat², Asher Shainberg³, Jonathan Seidman⁴, Michael Eldar¹, Michael Arad¹

¹Leviev Heart Center, Sheba Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Hashomer, ²Felsenstein Medical Research Center, Cardiac Research Lab, Sackler School of Medicine, Tel Aviv University, Tel Aviv, ³Department of Life Sciences, Bar Ilan University, Israel, ⁴Department of Genetics, Harvard Medical School, Boston, USA

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a lethal human arrhythmia provoked by physical or emotional stress and mediated by spontaneous Ca²⁺ release and delayed after-depolarizations. Beta-adrenergic blockers are the therapy of choice for human CPVT, but achieve complete arrhythmia control in <50% of cases. Using a murine model of recessively-inherited CPVT caused by either a D307H mutation (CASQ2D307H) or CASQ2 knock-out (CASQ2⁻⁻), we conducted a pharmacological screen to optimize the therapy for CPVT.

Heart rhythm telemetry was obtained in awake animals at rest, during treadmill exercise and after intra-peritoneal (IP) injection of epinephrine [0.5μg/g]. The protocol was repeated after IP injection of different anti-arrhythmic agents. The primary end-point was the ability to induce CPVT, defined as VT recorded in an animal during any one of the stress protocol stages.

Adult CASQ2 mutant mice suffered from complex ventricular arrhythmia at rest and developed bidirectional and polymorphic VT on exertion. Class I antiarrhythmic agents (procainamide, lidocaine, flecaïnide) were ineffective in controlling arrhythmia. Propranolol and sotalol attenuated arrhythmia at rest but failed to prevent CPVT during sympathetic stimulation. The calcium channel blocker verapamil showed a dose-dependent and genotype-dependent protection against CPVT. Verapamil was more effective than the dihydropyridine L-type Ca²⁺ channel blocker nifedipine, and its activity was markedly enhanced when combined with propranolol.

We conclude that verapamil is the drug of choice in CASQ2 mice. Beta-adrenergic blockers have little benefit in murine CPVT but markedly enhance the effects of verapamil. L-type Ca²⁺ channel blockade is only one of the mechanisms participating in CPVT suppression.