# Exercise Training Improves Cardiac Function of Calsequestrin Deficient Mice Suffering from Catecholamine Dependent Polymorphic Ventricular Tachycardia (CPVT)

E Kurtzwald [1,2], E Hochhauser [2], G Katz [1], Y Cheporko [2], A Shainberg [3], JG Seidman [4], M Eldar [1], E Porat [2], Arad M [1]

*[1] Heart Institute, Sheba Medical Center, Tel Hashomer, Ramat Gan, [2] Cardiac Research, Laboratory, FMRC, Sackler Medical School, Tel Aviv University, Tel Aviv, [3] Bar-Ilan University, Ramat Gan, Israel, [4] Harvard Medical School, Boston, USA*

CPVT is a lethal ventricular arrhythmia evoked by physical or emotional stress. Recessively inherited CPVT is caused by either missense or null-allele mutations in the cardiac calsequestrin (CASQ2) gene. Defects in CASQ2 causing protein deficiency impair $Ca^{2+}$ uptake to the sarcoplasmic reticulum and $Ca^{2+}$-dependent inhibition of ryanodine channels, leading to diastolic $Ca^{2+}$ leak, after-depolarizations and arrhythmia.

To examine the effect of exercise training on left ventricular remodeling and arrhythmia, CASQ2 knockout ($CASQ^{\Delta E9}$) mice and wild-type controls underwent echocardiography and heart rhythm telemetry before and after 6 weeks training protocol using treadmill exercise.

Left ventricular fractional shortening was impaired in $CASQ^{\Delta E9}$ (35±3% vs 41±8% in controls, $p<0.05$) but improved after training (44±5% and 51±3 in $CASQ^{\Delta E9}$ and control mice, respectively, p=NS). The exercise tolerance was 16±1 min in $CASQ^{\Delta E9}$ mice vs 29±2 min in controls, $p<0.01$, but improved in trained animals (26±2 vs 30±3 min, respectively, p=NS). CPVT prevalence in mutant mice was 67% at rest and 100% at stress. Exercise training did not change the arrhythmia prevalence but decreased CPVT severity at rest and the number of ventricular beats during exercise ($p<0.05$). The hearts of $CASQ^{\Delta E9}$ mice had an increased basal expression of the A and B-type natriuretic peptide genes which were markedly decreased after training (tested by RT-PCR). Although connexin 43 protein levels remained the same, the β1 adrenoreceptor tended to decrease in exercise-trained hearts (Western blot). We conclude that in $CASQ^{\Delta E9}$ mice, exercise training is beneficial and could offer a strategy for prophylactic and therapeutic interventions.