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The Role of Mutant Protein Degradation in Catecholamine Dependent Polymorphic Ventricular Tachycardia (CPVT)

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Humans with recessively inherited CPVT and genetically engineered mice develop arrhythmia, which may arise due to malfunction or degradation of calsequestrin (CASQ2) protein. We investigated the relation between protein level and arrhythmia severity in $CASQ2^{D307H/D307H}$ (KI), compared to $CASQ2^{\Delta/\Delta}$ (KO) and wild type control (C) mice.

CASQ2 expression and Ca^{2+} transients were recorded in cardiomyocytes isolated from hearts of neonatal (7 days) or adult (40 weeks) mice. *In vivo* arrhythmia was studied using heart rhythm telemetry at rest, exercise and after epinephrine injection (0.1 ƒ□g/g IP).

CASQ2 protein was absent in KO heart. Neonatal KI and C hearts expressed similar amounts of CASQ2 protein which were significantly lower (~60%, $p<0.05$)than the level in the adult C. A severe form of spontaneous Ca^{2+} release, Ca^{2+} oscillations , was present in 67% of KO cardiomyocytes but in a significantly lower proportion of either WT or KI cells (15%, $p<0.01$). Heart of adult KI mice expressed only 15% of CASQ2 protein found in C. Cardiomyocytes from adult mutant mice had increased susceptibility to spontaneous Ca^{2+} release (KO: 82%, KI 63% compared to 12% in WT, $p<0.01$). KO cells had more Ca^{2+} oscillations CPVT was comparably prevalent in KO (100%) and KI mice (83%), but arrhythmia was more severe and resistant to therapy in KO. We then treated mice with proteasome inhibitor, bortezomib (B, 1 µg/g IV on days 1, 4, 8, 11) trying to inhibit $CASQ2^{D307H}$ degradation B increased CASQ2 expression in KI hearts by ~50% ($p<0.05$). B-treated KI mice had lower CPVT prevalence during rest and exercise and less abnormal ventricular beats during peak exercise (30% instead of 95%, $p<0.05$). No benefit against arrhythmia was observed in B-treated KO mice or KI mice treated with saline. We conclude that some physiological function is preserved in $CASQ2^{D307H}$ protein. Preventing the degradation of mutant protein should be explored as a possible therapeutic strategy in appropriate CPVT patients.