Prevention of Fatal Arrhythmia in a Catecholaminergic Polymorphic Ventricular Tachycardia Mouse Model Carrying Calsequestrin2 Mutation

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Background Catecholamine-induced polymorphic ventricular tachycardia (CPVT) is a familial syndrome caused by mutations in the ryanodine receptor-2(RyR2) or the calsequestrin-2(CASQ2) genes and characterized by sudden death induced by exercise or emotional stress. Treatment of CPVT patients is limited given that beta-adrenergic blockers were found to be only partially effective and no other agents were broadly tested. Recent studies have shown that CPVT is mediated by increased Ca^{2+} leak through the RyR2 channel. Our aim was to determine whether agents that may inhibit intracellular Ca^{2+} leak can effectively prevent CPVT. **Methods** The efficacy of Ca^{2+} channel blockers, beta-adrenergic blockers and Mg^{2+} were tested using a CPVT mouse model carrying mutation in CASQ2 gene. We assessed the in-vivo prevalence of stress induced arrhythmia at baseline and after short and long-term drug treatment and the drug effect on contractility and Ca^{2+} transient of isolated cardiomyocytes. **Results** All study drugs reduced the frequency of stress induced ventricular arrhythmia in mutant mice. Nevertheless, only Verapamil completely prevented arrhythmia in 80% of the mice. Cardiomyocytes studies indicated that both Mg^{2+} and Verapamil inhibited sarcomere contraction, shortened the Ca^{2+} reuptake period and prolonged the caffeine induced Ca^{2+} transients of mutant cardiomyocytes. Diastolic Ca^{2+} overload and Ca^{2+} oscillations that typically present in stressed mutant myocytes were partially prevented by Mg^{2+} and more effectively by Verapamil. **Conclusion** Verapamil is the most effective agent in preventing ventricular arrhythmia in CPVT mouse model and in modifying the intracellular abnormal calcium handling of mutant cardiomyocytes, probably by inhibiting the intracellular Ca^{2+} leak. Calcium antagonists might have therapeutic value in CPVT and other RyR2 mediated arrhythmias and should be tested in human studies.