THE EFFICACY OF LATE SODIUM CURRENT BLOCKERS IN HYPERTROPHIC CARDIOMYOPATHY IS DEPENDENT ON GENOTYPE: A STUDY ON TRANSGENIC MOUSE MODELS WITH DIFFERENT MUTATIONS

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Introduction: The late-Na^+ current (I_{NaL}) blocker ranolazine reduced the rate of arrhythmogenic events and improved diastolic function in the myocardium of patients with hypertrophic cardiomyopathy (HCM), via shortening of action potentials and reduction of intracellular Na^+ and Ca^{2+} concentration (Coppini et al. Circulation 2013).

Methods: Here we evaluate the electro-mechanical abnormalities occurring in cardiomyocytes from the hearts of two transgenic HCM mouse models carrying mutations in the troponin-T gene (R92Q and E163R) and test how the two different lines respond to I_{NaL}-blockers. Troponin-T mutations represent a relatively rare condition in the HCM patient population, accounting for about 6-8% of the total amount of cases. However, we noticed that R92Q and E163R mouse models are able to replicate all different clinical phenotypes of human HCM, as marked level of fibrosis and hypertrophic condition and severe diastolic dysfunction (R92Q mice), slight hypertrophy and fibrosis, a slightly reduced diastolic function (E163R model). Moreover, both transgenic models show a high level of arrhythmogenic, spontaneous activity, in terms of premature calcium waves and spontaneous calcium transients. Single cardiomyocytes are obtained through an enzymatic digestion followed by a mechanical dissociation. Then, we realized Patch clamp and Calcium fluorescence experiments on control and pathological mice, evaluating Late sodium current (INaL) density, membrane potential and calcium transient kinetics. For these experiments, cells were treated with ranolazine (10μM) or with the novel selective I_{NaL}-blocker GS-967(0.5μM).

Results: Both INaL blockers used in this study, ranolazine and GS967, improve HCM pathogenic features, as arrhythmogenic activity and diastolic disfunction. Acute administration of ranolazine in preparations from adult R92Q mice lead to hasten Ca^{2+} transients, reduce diastolic Ca^{2+}, reduction of INaL down to the level of that in WT cells, shortening of action potential duration, abolishing of arrhythmic spontaneous activity. Acute administration of ranolazine in E163R samples reduce diastolic $Ca^{2+,}$ abolish arrhythmic spontaneous activity, Ca^{2+} transient kinetics, INaL and APD are not affected. However, these parameters are not modified E163R cardiomyocytes. GS967exerts same effects of ranolazine in both mutant mice preparations, but at a 20 times lower concentration.

Discussion and conclusion: Both INaL blockers used in this study, ranolazine and GS967, can improve HCM pathogenic features, as arrhythmogenic activity and diastolic disfunction, in both transgenic mouse models we used. As in human HCM, the beneficial effects of ranolazine and GS967on R92Q myocardium are likely mediated by the consequences of late sodium current inhibition (blocking Late sodium current, shortening action potential duration, abolition of cellular arrhythmias). In E163R preparations, myocardial arrhythmogenicity is not accompanied by remodeling of ion currents and appear as a consequence of anomalies of RyR2function or increased myofilament Ca^{2+} sensitivity. The beneficial effects of ranolazine and GS967on Ca^{2+} mediated spontaneous activity in E163R myocardium supports the hypothesis that the anti-arrhythmic effect of ranolazine and GS967can be mediated by mechanisms other that INaL inhibition (that is reduction of myofilaments Ca^{2+} sensitivity or pleiotropic effect of ranolazine and GS967on RyR2). These data show that ranolazine and GS967reduce arrhythmogenic activity and improve diastolic function in HCM myocardium but they can exert their full efficacy only in presence of severe Ca^{2+} handling abnormalities, as we can observe in R92Q model. We can consequently conclude that different genetic background influences the response to late sodium current blockers in HCM.