Mechanical Effects of Late Na-Current Blockers in Human Hypertrophic Cardiomyopathy Myocardium

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Diastolic dysfunction and left ventricular outflow tract (LVOT) obstruction are major determinants of symptoms and disability in hypertrophic cardiomyopathy (HCM) patients. Disopyramide (Dis), Ranolazine (Ran) and the novel compound GS-967 are late Na-current blockers with progressively increasing selectivity for late vs. peak Na current. Dis is employed in HCM patients as an agent to relieve obstruction, but the cellular basis of its negative inotropic effect remains unknown. We previously showed that Ran ameliorates the diastolic properties of trabeculae from HCM patients, with no effects on baseline systolic force (Coppini et al, Circulation 2013). Here, we aim to study the effects of late Na-current blockers on diastolic function and contractility of HCM myocardium. Patch-clamp studies and intracellular-Ca2+ recordings were performed in isolated myocytes from myectomy samples of obstructive HCM patients; intact trabeculae were used for mechanical measurements. Dis (5μM) induced similar effects compared to Ran, albeit at 1/10 concentration. Intracellular 10-6M (Iso) significantly reduced isometric twitch tension when applied on top of isoproterenol (10-6M) (Iso+Ran). Contraction kinetics in Iso+Ran were still significantly faster than baseline. The late Na-current blocker GS-967 (1μM) did not reduce baseline twitch force nor accelerated contraction kinetics, highlighting qualitatively similar effects compared to Ran, albeit at 1/10 concentration. Intracellular Ca2+ measurements and patch clamps performed in HCM cardiomyocytes suggest that most of these mechanical effects are mediated by inhibition of the up-regulated INaL via normalization of NCX function and intracellular Ca2+ (Ferrantini et al, Circulation 2013). From the clinical perspective: (i) all the three drugs may reduce diastolic dysfunction by speeding up contraction kinetics; (ii) Ran and GS-967 may reduce septal contractility only at peak exercise, representing a safer option to treat obstruction compared to Dis.

Myocardial Dysfunction in Hypertrophic Cardiomyopathy: Primary Effects of Sarcomeric Mutations Versus Secondary EC-Coupling Remodelling

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In cardiac muscle from HCM patients primary changes in myofilament function, related to the presence of disease-causing mutations in sarcomeric proteins, are always associated with secondary abnormalities due to adverse remodelling of cardiomyocyte EC-coupling (Coppini et al, Circulation 2013). The latter are likely major contributors of the mechanical dysfunction and arrhythmogenicity of HCM human hearts. Here we characterize the changes in sarcomere function and EC-coupling that occur in two HCM mouse models carrying different mutations in the α-subunit of the L-type calcium channel (CtnT, R92Q and E163R). Electrophysiology showed LV hypertrophy, enhanced contractility, diastolic dysfunction and enlarged left atria in both HCM models; the phenotype was more pronounced in the R92Q mice. In E163R ventricular myofibrils, in spite of a significant increase in the rate of the initial isometric slow phase of relaxation, overall relaxation from maximal activation was impaired and prolonged vs WT and R92Q myofibrils that exhibited similar relaxation kinetics. Resting tension was higher in the E163Q compared to WT and R92Q myofibrils. Isometric ATPase both at rest and at maximal Ca2+-activation and the energy cost of tension generation were increased in E163R vs WT and R92Q sinus trabeculae. Myofilament Ca2+-sensitivity was increased in both mutant lines compared to WT; the change was larger in the R92Q preparations. R92Q intact cardiomyocytes and trabeculae compared to WT and E163R preparations showed blunted response to inotropic interventions, reduced amplitude and slower decay of Ca2+-transients with reduced SERCA function. Twitch kinetics were prolonged in both HCM mouse models, despite Ca2+-transient kinetics was faster and SERCA function unchanged in the E163R mice. Intact preparations of both HCM mouse models showed increased probability of arrhythmogenic behavior that increased in response to isoproterenol. The results suggest that similar HCM phenotypes can be generated through different pathogenic pathways. Grant Telethon-GPP13162.