Electrical and mechanical effects of late Na-current blockers in human hypertrophic cardiomyopathy myocardium

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In hypertrophic cardiomyopathy (HCM) patients, diastolic dysfunction and left ventricular outflow trait (LVOT) obstruction are major determinants of symptoms and disability, while the increased rate of ventricular arrhythmias raises the risk of Sudden Cardiac Death (SCD)(1)**.** Functional alterations at cardiomyocyte level contribute to such abnormalities: prolonged action potentials due to reduced K^+ currents and increased late Na^+ current (I_{NaL}) underlie arrhythmogenesis, while altered intracellular Ca^{2+} homeostasis causes delayed myocardial relaxation and high diastolic tension(2). Disopyramide (Dis), Ranolazine (Ran) and the novel compound GS-967 are I_{NaL} blockers with progressively increasing selectivity for late vs. peak Na current. Dis is employed in HCM patients as an agent to relieve obstruction(3), 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 by normalizing Ca^{2+} transients in single cardiomyocytes; in addition, Ran reduces cellular arrhythmogenesis by shortening action potential duration (APD)(2). 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-Ca^{2+} recordings were performed in isolated myocytes from myectomy samples of obstructive HCM patients(4); intact trabeculae were used for mechanical measurements. Dis (5μM) reduced twitch tension in a dose dependent manner (EC50: 5.29±1.55μM) and accelerated contraction kinetics in HCM trabeculae; in single cells, Dis shortened APD and led to faster Ca^{2+} transients with markedly reduced amplitude. Ran (10μM), despite no significant effect on the amplitude of baseline contraction, significantly reduced isometric twitch tension when applied on top of isoproterenol 10^{-6}M (Iso+Ran). Contraction kinetics in Iso+Ran were still significantly faster than baseline. In agreement with these findings, Ran applied on top of Iso in single cells led to shorter APD and lower diastolic Ca^{2+}. The I_{NaL} blocker GS-967 (1μM) did not reduce baseline twitch force but accelerated contraction kinetics, highlighting qualitatively similar effects compared to Ran, albeit at 1/10 concentration. Intracellular Ca^{2+} measurements and patch clamp studies performed in HCM cardiomyocytes suggest that most of these mechanical effects are mediated by inhibition of the up-regulated I_{NaL} via normalization of NCX function and intracellular Ca^2 cycling. Interestigly, GS-967 (1μM) shortened APD and reduced the occurrence of early after-depolarizations. From the clinical perspective: (i)all the three drugs, by speeding up contraction kinetics, may reduce diastolic dysfunction; (ii)Ran and GS-967 may reduce septal contractility only at peak exercise, representing a safer option than disopyramide to treat inducible obstruction in patients; (iii)by shortening action potential duration and reducing spontaneous Ca^{2+} fluctuations, all the three drugs may exert a significant antiarrhythmic effect in HCM patients.

REFERENCES:

1. Gersh BJ, Maron BJ, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy... *Circulation.* 2011
2. Coppini R, Ferrantini C et al. Late sodium current inhibition reverses electromechanical dysfunction in human hypertrophic cardiomyopathy. *Circulation.* 2013
3. Sherrid MV, Maron BJ et al.. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *Journal of the American College of Cardiology.* 2005.
4. Coppini R, Ferrantini C et al. Isolation and functional characterization of human ventricular cardiomyocytes from fresh surgical samples. *Journal of visualized experiments : JoVE.*2014.