Late sodium current inhibitors to prevent disease progression in hypertrophic cardiomyopathy

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Current therapies for hypertrophic cardiomyopathy (HCM) are unable to prevent disease progression and reduce the risk of lethal arrhythmias in patients, as they reduce symptoms and do not target the molecular and cellular mechanisms of cardiac remodeling and dysfunction occurring in the hearts of HCM patients. Moreover, no drugs are available to stop or delay the development of cardiac phenotype in young carriers of mutations associated with HCM, identified in family screening programs prior to disease onset. The lack of translational mechanistic studies limited the development of mechanism-driven pharmacological options to treat HCM.

In the last 8 years, we have extensively characterized the cellular and subcellular abnormalities occurring in the hearts of HCM patients, by studying cardiomyocytes and trabeculae isolated from cardiac samples of HCM patients who underwent surgical myectomy. The increase of late Na+-current (INaL), by causing intracellular Ca2+-overload, plays a major role in determining diastolic dysfunction and arrhythmogeneicity in HCM myocardium Ranolazine, a non-selective INaL inhibitor, as well as the selective INaL-blocker GS-967 shortened action potentials, reduced cellular arrhythmias, lowered intracellular Ca2+ and ameliorated diastolic function in human HCM myocardium. Following these results, a randomized placebo-controlled study with ranolazine in HCM patients has been performed, which conformed the antiarrhythmic potential of INaL inhibition.

To establish whether long-term inhibition of INaL affects cardiac remodeling and disease onset/progression, we used a validated transgenic mouse line carrying the HCM-linked R92Q mutation of the Troponin-T gene. R92Q mice received an oral lifelong treatment with ranolazine and werecompared with age-matched vehicle-treated animals. Ranolazine treatment prevented the development of HCM-related cardiac phenotype, including LV hypertrophy, diastolic dysfunction, LV fibrosis and the propensity towards ventricular arrhythmias. The beneficial effect of long term INaL inhibition was mediated by a sustained reduction of intracellular Ca2+ and of the activity of Calmodulin Kinase-II. We conclude that pharmacological inhibitors of INaL are promising candidates for an early preventive therapy in young subjects carrying high-risk HCM-related mutations.