Life-Long Treatment with Late Sodium Current Blocker Prevents Myocardial Dysfunction and Remodeling in a Mouse Model of Hypertrophic Cardiomyopathy

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Hypertrophyc cardiomiopathy (HCM) is the most frequent hereditary form of cardiac pathology and the main cause of sudden death among young individuals. Current pharmacological treatments are limited and ineffective to prevent phenotype development and adverse cardiac remodeling that occur during disease progression. Ranolazine, a late Na+current blocker, proved to reduce arrhythmogenicity and improved relaxation in cardiomyocytes and trabeculae from HCM patients (Coppini et al., Circulation 2013). Using a transgenic mouse model carrying the HCM-associated R92Q mutation in theTNNT2gene, we previously showed that acute in vitro treatment with ranolazine is capable to reverse some electromechanical alterations, including the prolonged kinetics of Ca2+transients, the higher diastolic [Ca2+] and the increased frequency of arrhythmogenic spontaneous activity. Here we employed the same mouse model to assess whether long-term oral treatment with ranolazine since birth is capable to prevent the HCM phenotype and the associated myocardial remodeling. We compared WT, R92Q-untreated and R92Q-treated 1-year old mice. In vivo, echocardiographic measurements showed that the R92Q-treated hearts lacked the left ventricular hypertrophy, hypercontractility and diastolic dysfunction found in the R92Q-untreated mice. Gadolinium-contrast magnetic resonance showed that the intramyocardial fibrosis of the R92Q-untreated hearts was largely reduced by treatment. Moreover, ranolazine prevented the development of the functional changes observed in cardiomyocytes from R92Q mice (prolongation of Ca2+ transients, increased rate of spontaneous Ca2+ release). Mechanical experiments in intact left and right ventricular trabeculae confirmed the alterations we had previously reported in R92Q-untreated mice compared to WT and showed that those alterations were mostly reversed by ranolazine treatment. In the R92Q-treated preparations the inotropic response to isoproterenol was preserved and the occurrence of spontaneous activity was markedly reduced to valuescomparable to those found in WT trabeculae. Finally, ranolazine treatment prevented the hypertrophy-related changes in the expression of several genes, such as ATP2a2, KV4.3, KChip2, BNP, ANP and TGFβ associated with the functional and morphological remodeling of cardiac tissue. In conclusion, the life-long administration of ranolazine is effective to reduce disease progression and to prevent the development of pathological phenotype in R92Q mutant mice. We conclude that ranolazine may be a promising candidate drug to prevent disease development and progression in young subjects carrying high-risk HCM mutations.