Ranolazine reduces electro-mechanical dysfunction in trangenic mouse models of hypertrophic cardiomyopathy

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Introduction: Hypertrophic cardiomyopathy (HCM) is the most common inherited disease of the heart (1/500). It is frequently associated with reduced exercise capacity related to diastolic dysfunction and an increased risk of fatal ventricular arrhythmias. To date, HCM still lacks specific pharmacological therapies, capable of improving exercise tolerance and reducing arrhythmic burden. Our previous work[1] highlighted the possible role of ranolazine in reducing myocardial dysfunction in cardiomyocaytes from the hearts of HCM patients. However, pharmacological studies on human samples are made difficult by the scarce availability of material. The use of animal models of HCM can overcome these limitations.

Objectives: We aim at characterizing the functional abnormalities occurring at the level of single cardiomyocytes and intact myocardium in transgenic mice carrying the HCM-associated R92Q mutation of the troponin T (TnT) gene. Further, we will test the effectiveness of ranolazine in reducing the electro-mechanical dysfunction of mutant mouse myocardium.

Results: R92Q TnT mutant mice are able to replicate all the cellular phenotype of human HCM[1], comprising prolonged action potentials, slower rate of Ca^{2+} transient decay, elevated diastolic Ca^{2+} and resting tension. Moreover, cardiomyocytes from TnT mutant mice showed an increased frequency of arrhythmogenic spontaneous Ca^{2+} releases in the presence of β-adrenergic stimulation (isoproterenol 100nM), leading to isolated premature contractions or trains of spontaneous beats in intact trabeculae. Ranolazine, used at 10 μM, hastens Ca^{2+} transient kinetics and reduces diastolic Ca^{2+}, ameliorating myocardial relaxation in samples from TnT mutant mice. Further, it reduces the rate of spontaneous Ca^{2+} waves under isoproterenol admistration in cardiomyocytes from HCM mice, nearly abolishing the occurrence of spontaneous beats in intact trabeculae.

Conclusions: Transgenic mutant mice carrying the R92Q TnT mutation are a good model for testing drugs for the treatment of HCM. Ranolazine proved extremely effective in ameliorating myocardial dysfunction in these mice, suggesting its potential role for the reduction of arrhythmias and diastolic dysfunction in HCM.

References:

1. Coppini R, Ferrantini C, Yao L, Fan P, Del Lungo M, Stillitano F, Sartiani L, Tosi B, Suffredini S, Tesi C, Yacoub M, Olivotto I, Belardinelli L, Poggesi C, Cerbai E, Mugelli A. Late sodium current inhibition reverses electromechanical dysfunction in human hypertrophic cardiomyopathy. *Circulation*. 2013;127:575-584