HUMAN HYPERTROPHIC CARDIOMYOPATHY: FROM ELECTROPHYSIOLOGICAL INSIGHTS TO PHARMACOLOGICAL STRATEGIES

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Hypertrophic cardiomyopathy (HCM) is the commonest genetic cardiac disease, with a prevalence of 1/500. It is caused by over 1400 different mutations, mainly involving the genes coding for sarcomere proteins. The main pathological features of HCM are left ventricular hypertrophy, diastolic dysfunction and the increased ventricular arrhythmogenesis. Predicting the risk of heart failure and lethal arrhythmias is the most challenging clinical task for HCM patient management. Moreover, there are no disease-modifying therapies that can prevent disease progression or sudden arrhythmic death in HCM patients. In the last years, cell and animal models and translational studies that have been employed to get insight into the mechanism underlying HCM structural, mechanical and electrophysiological abnormalities, eventually leading to lethal arrhythmias. Preclinical tests of novel or existing drugs in these models are essential for a deeper understanding of HCM pathophysiology and for obtaining meaningful information on novel treatments, in order to improve patient risk stratification and therapeutic management. Guideline-directed therapy of HCM includes non-selective drugs such as disopyramide, non-dihydropyridine calcium channel blockers, or β-adrenergic receptor blockers, mainly used in patients with symptomatic obstruction of the outflow tract. Based on preclinical studies, drugs acting on potential HCM-specific targets were tested in patients. Despite the huge efforts, none of these studies was able to change clinical practice for HCM patients: in recent years, novel compounds have been developed addressing myocardial hypercontractility and altered energetics in a direct manner, through allosteric inhibition of myosin. Hopefully, the impact of these targeted interventions will alter the natural history of the disease in the near future.
During the last 15 years, we have studied the electrical and mechanical properties of cardiomyocytes and intact trabeculae isolated from cardiac samples of over 70 HCM patents with symptomatic outflow obstruction who underwent surgical myectomy. With this approach, we have identified the fundamental ion channel and Ca-handling alterations of HCM myocardium, and tested the effects of a number of traditional and innovative compounds. More recently, we have validated cardiomyocytes differentiated from patient specific induced pluripotent stem cells as a representative model of human HCM, to be used for future drug screening attempts. Finally, computational approaches were developed to help tailoring therapy on the needs of each patient.