The protective effects of GRK5 gene removal in stress induced cardiomyopathy

Authors:
M De Rosa¹, B Trimarco¹, G Iaccarino², M Ciccarelli², ¹Federico II University of Naples - Naples - Italy, ²University of Salerno - Salerno - Italy,

Topic(s):
Basic Science - Cardiac Diseases: Cardiomyopathies

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S36

Background: Cathecolamines-Stress Induced Cardiomyopathy (SIC) is an acquired cardiopathy in which acute dysregulation of adrenergic system induces a pattern of regional contractile abnormalities, typically located at the apex. G protein coupled receptor 5 (GRK5) is a ser/thr kinase involved in regulation of the beta adrenergic receptors (βARs) signaling and cardiac function. Recently, L41Q polymorphism of GRK5 has been described as a risk factor for the development of SIC probably due to its effect on kinase ability to desensitize βARs in response to adrenergic system activation.

Purpose: We want to evaluate GRK5 involvement in SIC physiopathology and whether GRK5 gene removal could exert a protective effect on SIC-regional contractile abnormalities.

Methods: In our study, we reproduced SIC in 20 weeks old mice by intraperitoneal injection of high dose of Isoproterenol (ISO, 300 mg/Kg), a non-selective beta adrenergic agonist, and evaluated the effects on cardiac contractility by echocardiography (Vevo 770) in mice with gene deletion of GRK5 (GRK5KO) and C57BL/6J (WT), used as controls. For this purpose, we evaluated ejection fraction (EF) and Fractional wall thickening (FWT), defined as the ratio between wall thickness in systole and diastole at basal condition and in response to ISO. FWT was calculated in 18 different cardiac segments. Results are presented as variation of EF and FWT (ΔEF% and ΔFWT) versus basal. Furthermore, we collected heart samples from the base and the apex of all mice and measured protein levels of GRKs on plasma membranes by Western Blot as a marker of beta adrenergic signaling activation.

Results: In WT group after 2 hours from ISO injection we observed a 25% ± 2% for ΔEF, while the analysis of ΔFWT evidenced an alteration of the contractile response in 14/18 cardiac segments. In GRK5KO group after 2 hours from ISO injection we observed an higher increase of the EF versus WT (52% ± 4%) while the analysis of ΔFWT evidenced an alteration of the contractile response in only 9/18 cardiac segments. Noteworthy, difference between WT and GRK5KO in ΔFWT is mainly evident in the apical segments (WT:6/6 vs GRK5KO 3/6). Furthermore, Western blot analysis revealed a different distribution of GRKs in the myocardium between the base and the apex.

Conclusions: This data confirm the role played by the βARs signaling in mediating SIC. The protective effects on myocardial stunning played by GRK5 removal suggest that this kinase is involved in ISO induced SIC through its role on desensitization and downregulation of βARs. Moreover, the variability in cardiac segment contractility in response to ISO could be related to a different distribution of GRKs and/or βARs in the myocardium.