SIRT1ACTIVITY AND DIFFERENT HEART FAILURE PHENOTYPES

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Introduction: Although remarkable progress has been made in medical treatment over the last few years, heart failure (HF) still remains one of the leading causes of morbidity and mortality worldwide. HF is a complex clinical syndrome with diverse risk factors and aetiologies, different underlying pathophysiology and large phenotypic heterogeneity. The management of HF is predominantly guided by objective assessments of left ventricular ejection fraction (LVEF), which has been shown to be predictive of adverse outcomes even in the absence of symptoms. In 2016, the Task Force for the diagnosis and treatment of Acute and Chronic Heart Failure of the European Society of Cardiology introduced a new category of HF with mid-range ejection fraction (EF between 40% and 49%, HFmrEF) as a distinct phenotype. The structural and functional characteristics, as well as clinical outcomes and biomarker profiles of patients with HFmrEF are, in general, intermediate between those of patients with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). However, there is still a large gap in evidence regarding detailed hemodynamic characteristics, follow-up and optimal therapeutic options for these subjects. Indeed, from a therapeutic point of view, HFmrEF represents a "grey area". Consequently, there is an urgent need to identify new biomarkers and pharmacological targets helpful to choose the best therapy according to the different HF phenotypes. From a molecular point of view, the NAD^+-dependent deacetylase Sirtuin 1(SIRT1) has been proposed as a crucial player in maintaining cardiovascular homeostasis via modulation of compensatory mechanisms to contrast deleterious effects of ischemia reperfusion injury. Increased SIRT1protein levels have been shown in patients with a history of myocardial infarction or coronary artery disease. Our previous results showed that a cardiac rehabilitation in HFpEF patients induced SIRT1activity with consequent anti-oxidative and anti-senescent effects. The main aim of this study was to measure SIRT1activity in peripheral blood mononuclear cells (PBMCs) from patients with chronic HF and to evaluate the association between Sirt1activity and clinical parameters characterizing the different HF phenotypes.

Materials and methods: Patients with chronic HF were consecutively enrolled to the Cardiology Unit at University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno. All patients underwent to physical examination, ECG, echocardiography, 6-min walking test and cardiopulmonary exercise testing. Demographic, clinical and functional data were recorded on a case report form. SIRT1activity was measured in nuclear extracts isolated by PBMCs using a specific SIRT1fluorimetric assay.

Results: Ninety-nine patients with chronic HF (66M, 33F; mean age 62.6±9.4) and twenty-nine age-matched healthy volunteers were consecutively included in the study. On the basis of LVEF values, patients were distinguished in three groups: Heart Failure with preserved Ejection Fraction (HFpEF; n=23), Heart failure with mid-range Ejection Fraction (HFmrEF; n=23), and Heart Failure with reduced Ejection Fraction (HFrEF; n=24). The HFpEF subjects showed significant lower SIRT1activity values than both HFmrEF and HFrEF ($p<0.0001$), without any difference when compared to controls. This finding was confirmed by multivariate linear regression analysis, using as dependent variable the EF. In particular, after correction for confounding factors, the best predictors of EF were represented by SIRT1activity. After stratification by HF groups, in the HFmrEF and HFrEF groups a very strong correlation was found, while in subjects with preserved EF this correlation was not found.

Conclusion: These preliminary findings suggest a possible role of SIRT1as marker of severity and progression of cardiac contraction dysfunction mainly in HF patients with reduced and mildly reduced ejection fraction.