EFFECTS OF SACUBITRIL/VALSARTAN ON DIASTOLIC FUNCTION IN AGING RATS

Donato Cappetta[1], Konrad Urbanek[1], Elena Piegari[1], Loreta Pia Ciuffreda[1], Anna Cozzolino[1], Agostino Micciché[1], Francesco Rossi[1], Antonella De Angelis[1], Liberato Berrino[1]

[1]Department of Experimental Medicine, Section of Pharmacology, University of Campania "Luigi Vanvitelli", Naples - Italy

Introduction: The majority of elderly patients with heart failure (HF) has a preserved ejection fraction (HFpEF) that constitutes a syndrome characterized by frequent hospitalizations and high mortality. Despite the growing social burden of HFpEF, the comprehension of its pathophysiology is incomplete, and treatment remains largely undefined. As recently highlighted, the mechanisms might involve both cardiovascular and non-cardiovascular components, such as left ventricle hypertrophy and remodeling, microvascular dysfunction, hypertension and mitochondrial dysfunction that lead to diastolic abnormalities. Moreover, aging itself may contribute independently to deterioration of diastolic function. A recent trial has demonstrated the efficacy of sacubitril/valsartan, first-in-class angiotensin receptor-neprilysin inhibitor, in reducing mortality and morbidity in patients with HF with reduced EF. Additional studies conducted on elderly patients with HFpEF and diastolic abnormalities are expected in the next years.

Methods: 18-month old female Fischer 344rats were treated with oral administration of sacubitril/valsartan (60 mg/kg/die, 1:1ratio) for 12weeks. Age-matched and 3-month old young animals were administered with vehicle, and served as controls. Tail-cuff method was used to monitor blood pressure weekly. Echocardiography and left ventricle catheterization were employed to assess systolic and diastolic function, at baseline, during the treatment and before sacrifice.

Results: Mean blood pressure resulted increased in aging rats in comparison to young rats. At sacubitril/valsartan treatment completion, we observed a significantly reduction of blood pressure. As documented by pulsed wave Doppler, the decrease of E/A ratio along with increase of E deceleration time and isovolumetric relaxation time evidenced the impairment of diastolic function in aging rats. Sacubitril/valsartan exposure partially ameliorated diastolic performance in old rats. Similarly, hemodynamic analysis indicated alterations of diastolic part of cardiac cycle that were positively affected by sacubitril/valsartan. Both echocardiography and hemodynamics showed normal systolic parameters. To determine the effect of treatment on cardiac hypertrophy, heart weight-to-tibia length ratio was measured. Interestingly, this parameter was significantly reduced in sacubitril/valsartan-treated rats.

Discussion and conclusion: Our preliminary results evidenced a modulation by sacubitril/valsartan of active relaxation and passive diastolic compliance resulted altered in aging rats, although the specific molecular mechanisms are yet to be identified.