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Effects of sacubitril/valsartan in an experimental model of aging-related heart failure

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The majority of elderly patients with heart failure 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. Aging itself may contribute independently to deterioration of diastolic function. A recent trial has demonstrated the efficacy of sacubitril/valsartan in reducing mortality and morbidity in patients with HF with reduced EF.

Material and Methods: 18-month-old female Fischer 344 rats were treated with oral administration of either sacubitril/valsartan (60 mg/kg/die, 1:1 ratio) or valsartan alone (30 mg/kg/die) for 12 weeks. 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, and before sacrifice. Cardiac tissue was used for molecular biology and histochemistry assays.

Results and Conclusions: Systolic function remained unaltered in all experimental groups. Tail-cuff analysis indicated a comparable decrease in blood pressure between treatments. Hypertrophy also showed a significant reduction with both treatments. On the contrary, myocardial function analysis demonstrated that no treatment was efficacy on diastolic dysfunction. The lack of improvement of cardiac function could be attributed to the inability of the treatments to counteract the accumulation of fibrotic tissue in the left ventricle, which, in turn, is attributable to the failure to reduce the inflammatory process and oxidative stress, and to the inability to modulate angiotensin II pathway. Our results evidenced that both sacubitril/valsartan and valsartan treatment was able to improve diastolic function and pro-fibrotic remodeling, partly due to a lack of effect on classical and non-classical pathways of angiotensin II.

Biography

Donato Cappetta graduated in Pharmaceutical Chemistry and Technology at University of Naples “Federico II”. After receiving his doctorate in Pharmacology at Second University of Naples focusing on the role of cardiac progenitor cells in myocardial regeneration, he joined a stem cell laboratory at Brigham and Women’s Hospital in Boston. Back in Naples, Donato carried out, with his current research group, studies on characterizing molecular and cellular aspects involved in drug cardiotoxicity, and onset and progression of heart failure.

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