**Association of endothelial NO-synthase gene polymorphism with the left ventricle diastolic dysfunction and pulmonary hypertension in patients with heart failure and preserved ejection fraction.**

K.M. Amosova1, K.I. Cherniaieva1, Yu.V. Rudenko1, L.V. Natrus1, A.B. Bezrodny1.

**1- Bogomolets’ National Medical University, Kyiv**

**Introduction**. Pulmonary hypertension (PH) develops in 50-80% of patients with left-sided heart failure (HF), regardless to the left ventricle (LV) ejection fraction (EF) and worsens the prognosis of HF. The development of PH is associated with the pulmonary arteries remodeling, due to endothelial dysfunction (ED). ED is a result of the disbalance between vasodilating properties of nitrogen oxide (NO), which depends on endothelial NO-synthase activity, and vasoconstriction due to endothelin-1. It is likely that genetic polymorphisms of eNOS affect the severity of the LV diastolic dysfunction (DD) and the elastic properties of systemic arteries in patients with HFpEF.

**Purpose of the study.** To determine polymorphisms of the nitric oxide synthase gene -786T>C rs 2070744 and the association of the corresponding genotypes with the severity of LV DD, PH and elastic properties of the arteries in patients with arterial hypertension (AH) and HFpEF.

**Materials and methods.** We included 69 patients (pts) with AH and HFpEF (31 women (41.9%) and 33 men (58.1%)), aged 67.4 ± 10.2 years; II-III FC NYHA, hemodynamically stable. All patients underwent general clinical and routine instrumental and laboratory examination, the level of NT - proBNP was determined; transthoracic Doppler echocardiography was performed; LV myocardium mass index (LVMI), E/A and E/e' ratio, pulmonary capillary wedge pressure (PCWP) and transpulmonary gradient (TPG) were calculated; applanation tonometry was performed; arterial elastance (Ea), ventricular elastance (Ees) and their ratio (Ea/Es) were also calculated; 6-minute walk test (6MWT) and a cuff test were performed. Genotyping for NOS 3 was performed by PCR in real-time. Genomic DNA samples were isolated from stabilized blood. Patients were divided into 3 groups, according to genotype.

**Results and discussion**. “Wild” homozygous TT genotype was found in 34 pts (49.3%, TT group), heterozygous TC genotype – in 21 pts (30.4%, TC group) and “mutant” homozygous CC genotype – in 14 pts (20.3%, CC group). The groups did not differ in gender (men 19 or 55.9%, 12 or 60% and 11 or 61.1%, p <0.05) and average age (67.1 ± 8.9, 65.4 ± 10.6 and 64.9 ± 10.3 years p> 0.05), and in prevalence of comorbidities. The worst result of 6MWT was in the CC group compared with TT and TC (371.8 ± 77.7, 385.7 ± 85.4 and 314.3 ± 69.1, p <0.05), as well as higher NT-proBNP level (668.1 ± 317.8, 636.9 ± 433.2 and 806.9 ± 369.7, p <0.05), greater LVMI (187.4 ± 37.1, 182.2 ± 25.7 and 195.2 ± 28.5, p <0.05). There was markedly more pronounced DD LV in the CC group compared with TT and TC, according to average e' (5 ± 1.7, 5.3 ± 0.8 and 4.7 ± 0.6, p <0.05) and E/e '(14.5 ± 1.3, 15.1 ± 1.5 and 15.9 ± 2.1, p <0.05). SPAP was the highest in the CC group (50 ± 19.9 compared to 39.6 ± 10.3 in the TT group and 40 ± 19.2 in the TC group, p <0.05), as well as PCWP and TPG (p <0.05). Patients of the CC group had worse elastic properties of arteries according to AIx75 (p <0.001) and PWVc-f (p <0.05), with a decrease in SAC (by 38.2% and 29% compared to TT and TC (p<0.05) and an increase in Ea, respectively, by 21% and 9% (p <0.05). According to the cuff test in patients of the CC group, compared with those in the TT and TC groups, worse EDVD, respectively by 19.8% and 17.3% (p <0.05) was revealed.

**Conclusions.** Compared to other polymorphisms, the CC genotype of the NOS3 rs 2070744 gene is associated with greater severity of DD LV, LH and impaired LV diastolic function and elastic properties of systemic arteries, according to pulse wave analysis in patients with AH and HFpEF. Taking to account that NO -deficiency plays one of the main role in the HFpEF development, the increase in its production with the participation of NO-synthase is one of the therapeutic goals in the treatment of HFpEF.