The role of calcification biomarkers in the formation of aortic stenosis

Y. Sibagatullina[1], M. Pugina[2], I. Voronkina[3], E. Zhiduleva[1], P. Evstigneeva[3], M. Gordeev[1], P. Murtazalieva[1], A. Malashicheva[1], D. Semenova[4], O. Moiseeva[1], O. Irtyuga[1]

[1]Almazov National Medical Research Centre, Saint Petersburg, Russian Federation; [2]Clinical interdistrict hospital of Vsevolozhsk, Vsevolozhsk, Russian Federation; [3]Institute of Experimental Medicine, Saint Petersburg, Russian Federation; [4]Institute of Cytology RAS, Saint Petersburg, Russian Federation

Funding Acknowledgement: Type of funding sources: None.

Background: The main mechanism of aortic valve (AV) calcification is not yet known. One of the possibility pathway responsible for AV calcification (AVC) includes osteoprotegerin (OPG), receptor activator of nuclear factor kappa-B ligand (RANKL) – the parts of the RANKL-RANK-OPG system and fetuin-A: cysteine protease inhibitors.

Aim: Evaluation of OPG, sRANKL, fetuin-A in blood serum and tissues in patients with varying severity of aortic stenosis (AS) to establish potential methods of estimation AVC depending on the presence of congenital heart disease: bicuspid AV (BAV) or its absence.

Materials and methods: The study involved 285 patients with AS (59.06±6.95 years, m:f – 1.1:1): 163 with (BAV) and 122 with tricuspid AV (TAV). The control group 53 patients (48.31±9.04 years, m:f-1:1) without valvular pathology, connective tissue dysplasia and coronary heart disease. ECHO (Vivid 7, GE, USA) was performed in all patients. The expression of OPG, RANKL, fetuin-A in homogenates of aortic valve were determined by immunoblotting. Serum concentration of OPG, RANKL, fetuin were performed in all pts by enzyme-linked immunosorbent assay.

Results: In the control group the concentration of fetuin-A in the blood serum was significantly higher than in TAV and BAV subgroups (446.66 [293.63; 619.19] vs 319.9 [239.6; 400.2] vs 315.6 [245.6; 385.6] pmol/l, p=0.0000001). In all groups of patients with AS an increased level of sRANKL in the blood serum was revealed compared to the control group (TAV=0.39 [0.25; 0.53] vs BAV=0.38 [0.21; 0.55] vs control group 0.31 [0.18; 0.44] pmol/l; $p<0.005$). OPG level in serum was increased in patients with TAV: 8.1 [4.3; 11.9] pmol/l compared to BAV: 6.8 [3.9; 9.7] pmol/l, p=0.003, as well as the control group: 6.15 [3.41; 8.89] pmol/L, p=0.001. RANKL expression in AV tissue was significantly lower in patients in the control group: 2119,06 [1990.94; 2554.11] as compared with AS pts: 4273.03 [2887.620; 4956], p=0.001, and in subgroups with TAV: 4273.08 [2887.620; 5285], p=0.002 or BAV: 4272.99 [2884.430; 4847], $p<0.01$. In addition, a positive correlation of moderate strength was found between the RANKL in the blood serum and the expression of RANKL in the AV tissue in patients with BAV (r=0.357, p=0.04). OPG expression in the AV tissue was higher in patients in the control group: 3949,953 [1931.88; 6447.67], while significant only in comparison with the BAV subgroup: 2599.28 [1066.38; 4132.18], p=0.02. A positive correlation of moderate strength was found between the OPG in the blood serum and the expression of OPG in the AV tissue in TAV subgroup (r=0.423, p=0.03).

Conclusion: Different pathogenic mechanisms of AV calcification are accompanied by an increase in various markers of the OPG / RANK / RANKL system: in patients with TAV calcification marker is OPG, in patients with BAV it is RANKL.