

### **C107. Molecular Mechanisms Underlying The Early Onset Of Bicuspid Aortic Valve Stenosis**

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**OBJECTIVES:** Bicuspid aortic valve stenosis develops 1 to 2 decades earlier than non-bicuspid aortic stenosis. We tested the hypothesis that alterations in the expression of genes may contribute to this early remodeling in patients with bicuspid aortic stenosis.

**METHODS:** Immunohistochemistry was performed on 38 stenotic valves (bicuspid, n=17, and non-bicuspid, n=21) obtained at the time of aortic valve replacement. Quantification of inflammation and angiogenesis was performed using double-labeled immunohistochemistry for macrophage/T cell infiltration (CD68+CD3), and neovessel content (CD34), respectively. Total RNA was isolated from 12 randomly selected stenotic valves (bicuspid, n=6 and non-bicuspid, n=6). The gene expression of angiogenic growth factor VEGF, angiogenic inhibitor chondromodulin-I (ChM-I), and NOTCH1 were measured by real time-PCR.

**RESULTS:** The total number of macrophage/T cell infiltration ( $55 \pm 8.4$  Vs  $19 \pm 2.2$ ;  $P=0.001$ ), and the total number of neovessels ( $33 \pm 2.9$  Vs  $17 \pm 1.6$ ;  $P=0.0001$ ) were increased in bicuspid aortic stenosis. The gene expression of VEGF was upregulated ( $0.0711 \pm 0.0242$  Vs  $0.0157 \pm 0.003$ ;  $p=0.03$ ), while that of ChM-I was downregulated ( $0.00089 \pm 0.0002$  Vs  $0.0051 \pm 0.0021$ ;  $p=0.03$ ) in bicuspid aortic stenosis. Furthermore, the expression of NOTCH1 was decreased ( $0.0046 \pm 0.0011$  Vs  $0.0167 \pm 0.0029$ ;  $p=0.04$ ) in bicuspid aortic stenosis when compared to non-bicuspid aortic stenosis.

**CONCLUSIONS:** The increased neovessel content in bicuspid aortic stenosis correlated with increased expression of VEGF and decreased expression of ChM-I. Alterations in NOTCH1 expression may contribute to early onset in bicuspid aortic stenosis supporting its known role in calcification. Understanding the molecular signaling of these genes may help to modify therapeutic interventions that may slow progression in patients with bicuspid aortic stenosis.