

### **P18. Calcific Aortic Valve Stenosis: Possible Role Of Tissue Factor In Disease Development**

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**OBJECTIVES:** Aortic valve stenosis (AVS) is an atherosclerotic-like process with active calcification of the leaflets. Tissue factor (TF), the main activator of coagulation, is involved in smooth muscle cell migration and proliferation and may regulate osteopontin function through thrombin generation. We hypothesized that TF might play a role in AVS and evaluated expression and localization of TF and other components of atherosclerosis.

**METHODS:** Calcified aortic valves were obtained from 52 patients (70±1 years; mean transvalvular gradient 55±2 mmHg; mean valve orifice 0.7±0.4 cm<sup>2</sup>) undergoing valve replacement. Cellular and lipid infiltration and protein expression were evaluated by immunohistochemistry. TF, tissue factor pathway inhibitor (TFPI), osteopontin and thrombin antigens were measured by ELISA. TF and alkaline phosphatase (ALP) activity were assessed using chromogenic assays. Transcripts were analyzed by RT-PCR.

**RESULTS:** Immunohistochemistry revealed that TF, TFPI, OSP and thrombin expressions were associated with calcification and lipid deposits in the fibrosa and subendothelial layer at the aortic side of the leaflets. TF, osteopontin and thrombin antigens were overexpressed in calcified regions of the valve (733±7 vs 429±7 pg/mg, 95±2 vs 16±4 pg/mg; 0.49±0.07 vs 0.28±0.04 µg/mg, respectively; p<0.05). By contrast, TFPI antigen was reduced in these regions. Additionally, TF antigen and activity were significantly correlated with ALP activity and osteopontin antigen.

**CONCLUSIONS:** Aortic leaflet TF expression is a new and important feature of AVS. TF colocalizes with calcification and is associated with osteopontin and ALP activity. Since osteopontin function has been shown to be regulated by thrombin cleavage, we hypothesize that TF may be involved in the mineralization process of aortic valves through its trophic properties and the generation of thrombin which subsequently alters osteopontin function.