

 VALVULAR HEART DISEASE

**MYOCARDIAL FIBROSIS IN AORTIC STENOSIS: MOLECULAR MECHANISMS AND AN APPROACH TO ITS NON-INVASIVE ASSESSMENT.**

ACC Poster Contributions  
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**Background:** Myocardial fibrosis promotes ventricular dysfunction and contributes to clinical decline in aortic stenosis (AS). We sought to analyze the expression and pathophysiological consequences of the systems involved in collagen synthesis and degradation within the myocardium of AS patients and its relation with collagen turnover serum markers.

**Methods:** Myocardial samples were obtained in 34 AS patients. Collagen volume fraction (CVF) was determined in red-picrosirius stained samples with an automated image analyzer. The degree of collagen cross-linking was calculated as the ratio between the insoluble and the soluble forms of collagen. Procollagen C-proteinase (PCP), PCP enhancer (PCPE), lysyl-oxidase (LOX), matrix metalloproteinase-1 (MMP-1) and MMP tissue inhibitor-1 (TIMP-1) expression were determined by western blot analyses. Concentrations of carboxy-terminal propeptide of procollagen type I (PICP) and MMP-1/TIMP-1 were measured by ELISA in coronary and peripheral blood samples. Patients were grouped according to tertiles of CVF.

**Results:** PCP, PCPE and LOX expression increased linearly (all  $p < 0.01$ ) with increasing CVF. MMP-1 decreased with increasing CVF ( $p < 0.05$ ). While PCP correlated directly with CVF, LOX expression did it with collagen crosslinking. There were no association between CVF and collagen crosslinking. CVF but not collagen cross-linking was associated with the isovolumic relaxation time, conversely collagen cross-link but not CVF was associated with the constant of left ventricular stiffness.

PICP and MMP-1/TIMP-1 concentrations were higher in coronary sinus than in peripheral blood ( $p < 0.001$ ). PICP serum concentrations increased and MMP-1/TIMP-1 decreased with increasing CVF. Finally, PICP correlated directly with both PCP expression and CVF.

**Conclusions:** Myocardial fibrosis in AS is related with both increased synthesis and reduced collagen degradation within the myocardium. Quantitative and qualitative collagen alterations and its consequences seem to be not related in AS. PICP and MMP-1/TIMP-1 serum concentrations may serve to monitor collagen turnover in this population.