Superimposed tissue formation in human aortic valve disease: differences between stenotic and regurgitant valves

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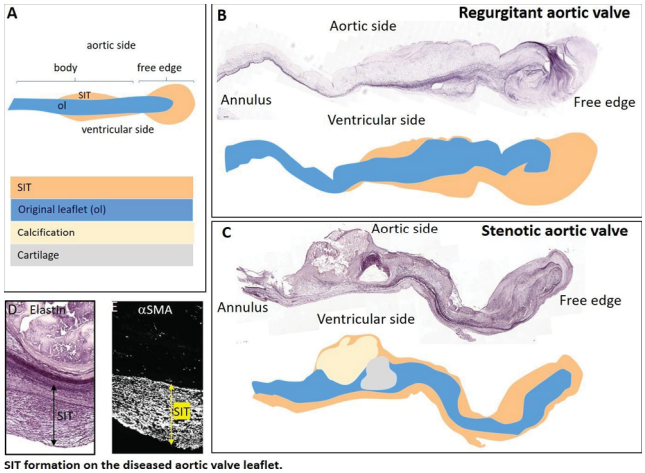
Introduction: The formation of superimposed tissue (SIT), a layer on top of the original valve leaflet, has been described in patients with mitral regurgitation, as a major contributor of valve thickening and probably secondary to increased valve mechanical stress. However, little is known whether SIT formation also occurs in aortic valve disease. Both in the case of aortic stenosis or aortic regurgitation, the aortic valve (AV) is subjected to increased mechanical stresses, although different in type, extent and location.

Purpose: To characterize SIT formation in aortic stenosis and regurgitation.

Methods: Human diseased AV leaflets (n=31) were obtained from patients undergoing aortic valve replacement because of aortic stenosis (n=17) or aortic regurgitation (n=14). Histological analysis was performed and elastin staining was used to distinguish the SIT from the original leaflet. Alpha-smooth muscle actin (SMA) staining was performed to identify myofibroblasts and Masson's Trichrome staining to identify collagen fibres.

Results: In both regurgitant leaflets (RL) and stenotic leaflets (SL) SIT was found at both the ventricular and aortic side (94% of SL, 93% of RL) and could reach up to 50% of total leaflet thickness (Fig. A-C). Although the average SIT thickness did not differ between SL and RL (0.30 mm, standard error of the mean (SEM): ±0.04 for SL vs 0.38 mm, SEM: ±0.05 for RL; p=0.61), the distribution of SIT differed. The SIT at the free edge of the aortic valve was significantly thicker in the RL (0.39 mm, SEM: ±0.06 for SL vs 0.88 mm, SEM: ± 0.07 for RL; $p<0.0001$), whereas the SIT at the aortic side of the body part was thicker in the SL (0.099 mm, SEM: ±0.023 for SL vs 0.033 mm, SEM: ± 0.021 for RL; $p<0.05$). Although the SIT comprised of various compositions of extracellular matrix, the overall collagen content was higher in SIT of the SL (212 a.u., SEM: ±4.37 for SL vs 169 a.u., SEM: ±4.06 for RL; $p<0.0001$). Myofibroblasts were predominantly observed in the SIT as compared to the original leaflet in SL and RL (Fig. D,E; myofibroblast-positive area: 11.6%, SEM: ±3.1 for SIT vs 1.2%, SEM: ±0.3 for original leaflet; $p<0.001$). The density of myofibroblast in the SIT of the body part of the aortic leaflet, however, was higher in the SL (myofibroblast-positive area: 15.5%, SEM: ±2.0 for SL vs 4.1%, SEM: ±1.3 for RL; $p<0.01$), whereas the density of myofibroblast in the SIT of the free edge was higher in the RL (myofibroblast-positive area: 15.3%, SEM: ±3.7 for SL vs 4.0%, SEM: ±1.4 for RL; $p<0.001$).

Conclusions: Both in aortic stenosis and aortic regurgitation, the AV is characterized by SIT formation but with difference in distribution and composition. These observations suggest the involvement of hemodynamic and mechanical stresses in the regulation of SIT formation of the AV. Understanding the formation of SIT might provide new insights in pathology of AV disease.



SIT formation on the diseased aortic valve leaflet.