

CYCLIC TENSION, TRANSFORMING GROWTH FACTOR- β 1, and the AORTIC VALVE MYOFIBROBLAST: A SYNERGISTIC MECHANISM for DEGENERATIVE VALVE DISEASE?

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Phenotypically, the aortic valve interstitial cell (AVIC) is a plastic myofibroblast, appearing contractile and activated in times of development, disease, and remodeling. The precise mechanism of phenotypic modulation is unclear, but it is speculated that both biomechanical and biochemical factors are influential. Therefore, we hypothesized that isolated and combined treatments of cyclic tension and TGF- β 1 would alter the phenotype (smooth muscle α -actin, SMA) and subsequent collagen biosynthesis (via heat shock protein 47, Hsp47) of AVICs in situ. Porcine aortic valve leaflets received 7 and 14 day treatments of 15% cyclic stretch (Tension), 0.5 ng/ml TGF- β 1 (TGF), 15% cyclic stretch and 0.5 ng/ml TGF- β 1 (Tension+TGF), or neither mechanical nor cytokine stimuli (Null). At both 7 and 14 days, SMA (Fig. A) and Hsp47 (Fig. B) quantities were significantly greater ($p < 0.001$) in the Tension+TGF group compared to all other groups. Additionally, Tension alone appeared to maintain SMA and Hsp47 levels that were measured at day 0, while TGF alone elicited an increase in SMA and Hsp47 compared to day 0 levels. Null treatment revealed diminished proteins at both time points. Elevated TGF- β 1 levels, in the presence of cyclic mechanical tension, resulted in synergistic increases of contractile and biosynthetic proteins in AVICs. Since cyclic mechanical stimuli can never be relieved in vivo, the presence of TGF- β 1 from infiltrating macrophages likely results in hyper-contractile and overly biosynthetic AVICs, leading to altered ECM architecture (histology images, bottom), compromised valve function, and may be a possible contributor to degenerative valvular disease.

