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Title: PUTTING ON THE SQUEEZE – HOW VALVULAR INTERSTITIAL CELLS ADAPT TO THEIR LOCAL MICROENVIRONMENT

Abstract:
Heart valve interstitial cells (VICs) play a critical role in the maintenance and pathophysiology of heart valve tissues. Normally quiescent in the adult, VICs can become activated in periods of growth and disease. When activated, VICs exhibit increased levels of cytokines and extracellular matrix (ECM) synthesis, and upregulated expression and strong contraction of α-smooth muscle actin (α-SMA) fibers. There is increasing evidence that tissue stress-induced MV interstitial cell (MVIC) deformations can have deleterious effects on their biosynthetic states that are potentially related to the reduction of tissue-level maintenance and to subsequent organ-level failure. To better understand the interrelationships between tissue-level loading and cellular responses, we developed the following integrated experimental-computational approach. Since in-vivo cellular deformations are not directly measurable, we quantified the in-situ layer-specific MVIC deformations for each of the four layers under a controlled biaxial tension loading device coupled to multi-photon microscopy. Next, we explored the interrelationship between the MVIC stiffness and deformation to layer-specific tissue mechanical and structural properties using a macro-micro finite element computational model. Experimental results indicated that the MVICs in the fibrosa and ventricularis layers deformed significantly more than those in the atrialis and spongiosa layers, reaching a nucleus aspect ratio of 3.3 under an estimated maximum physiological tension of 150 N/m. The simulated MVIC moduli for the four layers were found to be all within a narrow range of 4.71–5.35 kPa, suggesting that MVIC deformation is primarily controlled by each tissue layer’s respective structure and mechanical behavior rather than the intrinsic MVIC stiffness. This novel result further suggests that while the MVICs may be phenotypically and biomechanically similar throughout the leaflet, they experience layer-specific mechanical stimulatory inputs due to distinct extracellular matrix architecture and mechanical behaviors of the four MV leaflet tissue layers. This also suggests that MVICs may behave in a layer-specific manner in response to mechanical stimuli in both normal and surgically modified MVs. We also present a novel solid-mixture model for VIC biomechanical behavior that incorporated 1) the underlying cytoskeletal network, 2) the oriented α-SMA stress fibers with passive elastic and active contractile responses, 3) a finite deformable elastic nucleus. We implemented the model in a full 3D finite element simulation of a VIC based on known geometry. Current results suggest substantial functional differences between VIC from different valves at the subcellular level. Moreover, this first VIC computational biomechanical model is but a first step in developing a comprehensive, integrated view of the VIC pathophysiology and interactions with the valve ECM micro-environment based on simulation technologies.