Simulation of mitral valve layer-specific stresses and their relation to interstitial cell deformation under physiological loading

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ABSTRACT

Within each of the four layers of mitral valve (MV) leaflet tissues there resides a heterogeneous population of interstitial cells that maintain the structural integrity of the MV tissue via protein biosynthesis and enzymatic degradation. 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. We first developed a meso-scale structural constitutive model of the MV leaflets, focusing on the contributions of the distinct collagen and elastin fiber networks within each of its four layers. Microstructures were investigated and quantified using second harmonic generation (SHG) imaging microscopy, supported by conventional histology. We then used this information to guide the details of the model, performing parameter estimation using a comprehensive set of mechanical datasets (biaxial tension, equibiaxial strain, uniaxial strain). We evaluated novel model extensions specialized for the mitral valve that explored the potential for angular dependence of collagen fiber recruitment that ensured constant fiber ensemble stress for all orientations. To further validate the meso-scale model, we utilized the model-predicted collagen fiber strains and compared them with extant MV small angle X-ray scattering (SAXS) data to independently estimate the mechanical properties of the collagen fibrils. The model also predicts a consistent effective collagen fiber modulus of 132.5 – 167.3 MPa between all testing modes. The model also shows good predictive capabilities for additional testing protocols under extra-physiological loading. Next, 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.

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