11th World Congress on Computational Mechanics (WCCM XI)
5th European Conference on Computational Mechanics (ECCM V)
6th European Conference on Computational Fluid Dynamics (ECFD VI)
July 20 - 25, 2014, Barcelona, Spain

A COMPUTATIONAL APPROACH FOR IN SITU ESTIMATION OF AORTIC VALVE INTERSTITIAL CELL MECHANICAL STATE FROM TISSUE LEVEL MEASUREMENTS

[*]Rachel M. Buchanan, Robert J. Fagan and Michael S. Sacks

The University of Texas at Austin, 107 W Dean Keeton St. Austin, TX 78712,
rachelbuchanan@utexas.edu

Key Words: *In Situ, Aortic Valve, Biomechanics, Valve Interstitial Cells.*

Mechanical forces are known to regulate aortic valve interstitial cell (AVIC) functional state by modulating their biosynthetic activity, translating to differences in tissue composition and structure and, potentially, to aortic valve (AV) dysfunction. While advances have been made toward the understanding of AVIC behavior ex-situ, the AVIC physical state (specifically stiffness and contractile state) in its native tissue microenvironment remains largely unknown. We hypothesize that deriving the biomechanical state of AVICs in-situ using an inverse modeling approach will reveal more accurate information regarding AVIC adaptations to various stimuli. Such an approach can reveal important changes resulting from pathological state and corresponding pharmaceutical interventions. To achieve this, a novel, integrated numerical/experimental methodology was developed to estimate AVIC mechanobiological state in-situ. Flexural deformations of intact AV leaflet specimens were used to quantify the effects of AVIC stiffness and contraction at the tissue level. In addition to being a relevant deformation mode of the cardiac cycle, flexure is highly sensitive to changes in AVIC mechanics. This is a result of the fact that collagen fibers remain crimped and unloaded during flexure, preventing them from dominating the tissue response. Additionally, flexure probes individual layer effects of AVIC behavior.

As a first step, a bilayer tissue level model was developed that accurately captures the bidirectional flexural response of AV intact layers in a passive state [1] (Fig. 1). Next, this model was extended to incorporate tissue micromorphology in a down-scale framework that simulates AVIC-Extracellular matrix (ECM) interactions as a function of layer location. AVIC size, shape, distribution and orientation were quantified from histological data from all three layers (Fig. 2). A representative volumetric element was optimized statistically for each layer to represent the native 3D structure. The optimized RVE size in each layer defined a single mesh element within the macro model. Cellular inclusions and surrounding ECM were defined as neo-Hookean materials. Micropipette measurements of nonadherant AVIC cell stiffness were used to define the baseline cell stiffness (passive state) in the micro-model. Displacements at the RVE boundaries in the macro-model were applied as boundary conditions to the micro-model. The resulting stress was averaged over the entire RVE and compared to the stress of the homogenized RVE in the macro-model. Due to cell inclusions, the ECM stiffness was increased from the homogenized stiffness predicted in the macro model until the averaged RVE stress in each model was equivalent. The resulting down-scale

AV model introduces a means to estimate changes in effective cell stiffness and contraction in-situ that are otherwise grossly unattainable through experimental approaches alone.

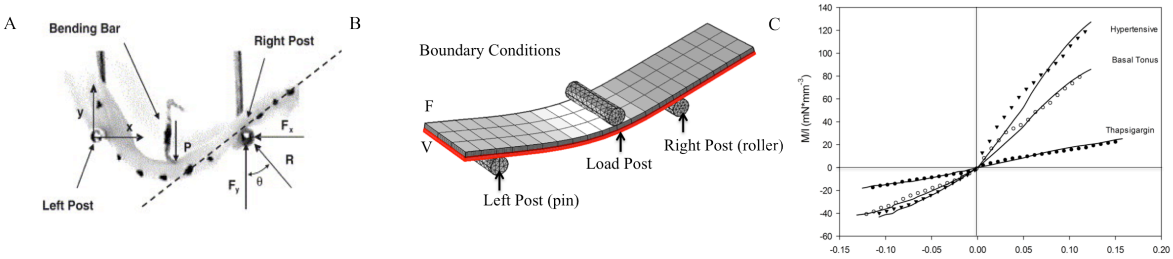

Figure 1. The experimental flexure testing (A) and corresponding macro-scale model (B) of the AV leaflet. The model's predicted M-Δk relationships plotted against experimental measurements (C).

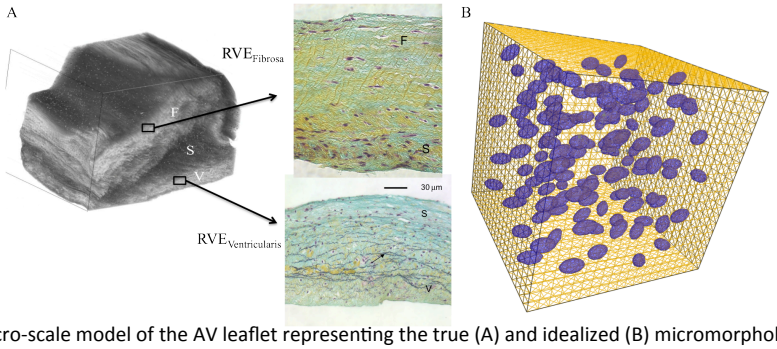

Figure 2. Micro-scale model of the AV leaflet representing the true (A) and idealized (B) micromorphology of the selected RVE.

Experimental flexure data from three different activation states (thapsigargin, basal tonus and hypertensive) were used in conjunction with the model to probe the effects of cell stiffness and contraction on the tissue level response. Parametric studies were performed using the down-scale model by holding the ECM stiffness constant and increasing both cell stiffness and cell contraction until the averaged RVE stress matched that of the macro homogenized stress for various tissue states (Fig. 3). The expected differences between the computed macro and micro stress was attributed to cell stiffness and contractile changes. This numerical/experimental methodology will be used to deduce AVIC properties under various pathophysiological conditions. Statins are a class of clinically administered cholesterol-lowering drugs that also have been shown to inhibit calcification in atherosclerotic coronary arteries and aortic valves. Specifically, statins have demonstrated the ability to regulate AVIC contractile behavior in-vitro and likely reverse the myofibroblast phenotype that dominates sclerotic valves. However, the effects of statins on AVICs in-situ remain unclear. The ability to assess AVIC responses in-situ will lead to further understanding of AVIC-ECM mechanical coupling in response to physiological conditions synonymous with valvular disease.

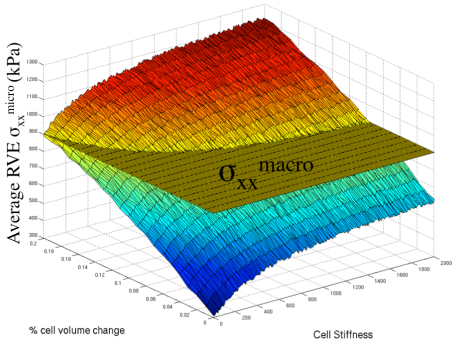

Figure 3. Graphical representation of estimating both cell stiffness and cell contraction effects on the macro-level measured stiffness (σ_{xx}^{Macro}) in the AV leaflet.

REFERENCES

[1] R.M. Buchanan and M.S. Sacks, Interlayer micromechanics of the aortic heart valve leaflet. *Biomech Modeling Mechanobiol.*, pp. 1-14, 2013.