JOURNAL OF THE MECHANICAL BEHAVIOR OF BIOMEDICAL MATERIALS 54 (2016) 244–258

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/jmbbm

Research Paper

On intrinsic stress fiber contractile forces in semilunar heart valve interstitial cells using a continuum mixture model

*Yusuke Sakamoto, Rachel M. Buchanan, Michael S. Sacks**

Center for Cardiovascular Simulation, Institute for Computational Engineering and Sciences, Department of Biomedical Engineering, The University of Texas at Austin, 201 East 24th Street, POB 5.236, 1 University Station C0200, Austin, TX 78712, USA

ARTICLE INFO

Article history:
Received 24 July 2015
Received in revised form
21 September 2015
Accepted 22 September 2015
Available online 11 November 2015

Keywords:
Valve interstitial cell
Finite element method
Active contraction
Alpha-SMA stress fibers
Heart valves
Micropipette aspiration
Atomic force microscopy

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. However, it remains unknown how expression and contraction of the α-SMA fibers, which vary among different VIC types, contribute to the overall VIC mechanical responses, including the nucleus and cytoskeleton contributions. In the present study, we developed 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. Moreover, we examined the respective mechanical responses of aortic and pulmonary VICs (AVICs and PVICs, respectively), which are known to have different levels of α-SMA expression levels and contractile behaviors. To calibrate the model, we simulated the combined mechanical responses of VICs in both micropipette aspiration (MA) and atomic force microscopy (AFM) experiments. These two states were chosen as the VICs were under significantly different mechanical loading conditions and activation states, with the α-SMA fibers inactivated in the MA studies while fully activated in the AFM studies. We also used the AFM to study the mechanical property of the nucleus. Our model predicted that the substantial differences found in stiffening of the AVIC compared to the PVICs was due to a 9 to 16 times stronger *intrinsic* AVIC α-SMA stress fiber contractile force. Model validation was done by simulating a traction force microscopy experiment to estimate the forces the VICs exert on the underlying substrate, and found good agreement with reported traction force microscopy results. Further, estimated nuclear stiffness for both AVICs and PVICs were similar and comparable to the literature, and were both unaffected by VIC activation level. These results suggest

*Corresponding author. Tel.: +1 512 232 7773.
E-mail address: msacks@ices.utexas.edu (M.S. Sacks).

http://dx.doi.org/10.1016/j.jmbbm.2015.09.027

substantial functional differences between AVICs and PVICs 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.

1. Introduction

Heart valves are specialized cardiac structures that ensure unidirectional blood flow (Sacks et al., 2009; Sacks et al., 2009). Heart valves undergo approximately 40 million cycles per year, with a total of at least 3 billion times over an average lifetime (Schoen, 2008). According to the American Heart Association, valvular heart disease resulted in 21,824 deaths directly and was a contributing factor in 45,062 deaths in the US in 2008 (Roger et al., 2012). Thus, it is essential to understand the heart valve pathophysiology and to develop means to mitigate its effects using intervention approaches that range from pharmaceutics to surgical interventions. While surgical interventions remain the gold standard, new therapeutic approaches that are based on an understanding of valve pathophysiology could potentially allow for novel approaches aimed at minimizing the onset and progression of valve disease.

Valvular interstitial cells (VICs) are located throughout heart valve leaflet tissues of all four heart valves. Studies of normal and pathological heart valves have demonstrated that VICs play critical roles in the maintenance of heart valve tissues and the onset and progression of heart valve disease (Sacks et al., 2009; Schoen, 2008). Heart valve leaflets experience dynamic and complex mechanical stress states over the cardiac cycle, including surface shear stress due to blood flow, flexure (opening and closing), and high in-plane tension (closed valve). The resulting forces are translated to the VICs through the complex micromechanical interactions with the extra cellular matrix (ECM) such as collagen stretch with reorientation and fiber compaction. VICs thus interact with the ECM in highly stress-dependent manner in a valve tissue (Sacks et al., 2009; Schoen, 2008; Mendelson, 2006). Recently, the stiffness of mitral heart valve VICs (MVICs) within leaflet tissues under controlled biaxial loading were estimated using finite element simulations (Lee and Sacks, 2014). This study found that while the MVIC effective stiffness was quite similar within each of the four leaflet layers, MVICs experienced significantly different mechanical deformations resulting from differing layer microstructures. We speculated that this may induce the MVICs to respond in a layer-specific manner despite their similar phenotypic state, as evidenced by similar stiffnesses.

Such speculations are built on the knowledge that VICs respond to their biomechanical cues by upregulating ECM protein synthesis and the development of a highly contractile cytoskeleton via α-smooth muscle actin (α-SMA) fibers. Activated VICs continuously maintain valvular ECM by synthesizing ECM and remodel collagen and other ECM components using matrix degrading enzymes (Sacks et al., 2009; Butcher et al., 2008), all to maintain heart valve tissue homeostasis. After completion of remodeling and repair, the activated VICs are thought to revert back an inactivated state (Schoen, 2008; Rabkin-Aikawa et al., 2004) or are removed by apoptosis (Liu et al., 2007). However, excessive and persisting environmental changes cause the improper regulations of VICs, and a clinically significant valve pathology may result (Sacks et al., 2009). The VICs in a diseased state cause the continuous force generation and excessive ECM production, resulting in pathological fibrosis, scarring, and fibrocontractile disease (Schoen, 2008; Walker et al., 2004). Thus, it is important to investigate where the contractile activities of the differentiated VICs are generated.

In recent years, the mechanical properties of VICs have been investigated using various experimental techniques, such as micropipette aspiration (MA) (Merryman et al., 2006, 2009; Wyss et al., 2012), collagen-gel contraction (Merryman et al., 2007), and atomic force microscopy (AFM) (Merryman et al., 2007). In these studies, VICs were isolated from the different heart valve leaflet tissues and suspended in an aqueous solution (MA), seeded on a 2D flat substrates (AFM), or seeded on collagen gels. The studies of the VICs and myofibroblasts in general suggest that the expression of α-SMA into the stress fibers upregulates the contraction and stiffness (Clement et al., 2005; Hinz et al., 2001, 2007, 2012; Wang et al., 2006; Wang and Lin, 2007), with the disruption of α-SMA incorporation abolishes the contractile activity (Clement et al., 2005; Chaponnier et al., 1995; Hinz et al., 2002). The properties of VICs have been also studied within the 3D hydrogels with varying material properties (Gould and Anseth, 2013; Benton et al., 2009) or under mechanical loading conditions (Gould et al., 2012). These studies indicate that cell-matrix interactions such as cell adhesion, stiffness of the matrix, and mechanical cues due to different loading conditions influence the activation states of the VICs.

To integrate these various and complex behaviors, we need to develop a computational model of VICs that is capable of capturing a wide range of activation states and the effects of the surrounding micro-environment. Currently, linear elastic models have been widely used to interpret the experimental data of the MA and AFM experiments, such as Theret's model for MA (Sato et al., 1990) and Hertz model for AFM (Mathur et al., 2001; Afrin et al., 2005). While these models can capture some of the important trends in the stiffness values of the VICs (Merryman et al., 2006, 2007), more advanced models are necessary to study the complex physiology of the internal cell mechanics. For example, the stiffness values of the VICs measured by AFM are about 10–100 times larger than the ones measured by MA. It is likely that during MA experiments, VICs are suspended in a liquid