Computational simulation of hemodynamic-driven growth and remodeling of embryonic atrioventricular valves

Philip R. Buskohl · James T. Jenkins · Jonathan T. Butcher

Abstract Embryonic heart valves develop under continuous and demanding hemodynamic loading. The particular contributions of fluid pressure and shear tractions in valve morphogenesis are difficult to decouple experimentally. To better understand how fluid loads could direct valve formation, we developed a computational model of avian embryonic atrioventricular (AV) valve (cushion) growth and remodeling using experimentally derived parameters for the blood flow and the cushion stiffness. Through an iterative scheme, we first solved the fluid loads on the axisymmetric AV canal and cushion model geometry. We then applied the fluid loads to the cushion and integrated the evolution equations to determine the growth and remodeling. After a set time of growth, we updated the fluid domain to reflect the change in cushion geometry and resolved for the fluid forces. The rate of growth and remodeling was assumed to be a function of the difference between the current stress and an isotropic homeostatic stress state. The magnitude of the homeostatic stress modulated the rate of volume addition during the evolution. We found that the pressure distribution on the AV cushion was sufficient to generate leaflet-like elongation in the direction of flow, through inducing tissue resorption on the inflow side of cushion and expansion on the outflow side. Conversely, shear tractions minimally altered tissue volume, but regulated the remodeling of tissue near the cushion surface, particular at the leading edge. Significant shear and circumferential residual stresses developed as the cushion evolved. This model offers insight into how natural and perturbed mechanical environments may direct AV valvulogenesis and provides an initial framework on which to incorporate more mechano-biological details.

Keywords Growth and remodeling · Morphomechanics · Morphogenesis · Cushion · Residual stress · Hemodynamic loads · Mechanical environment

1 Introduction

Atrioventricular valve formation is thought to be regulated by dynamic interactions between molecular and mechanical signaling. The primitive valves (cushions) initiate as gelatinous masses of hyaluronan from the myocardial wall of the heart tube. A layer of endothelial cells line the inner surface of the heart tube, with the outer wall consisting of cardiomyocytes (Gonzalez-Sanchez and Bader 1990). In a highly coordinated process, the endothelial cells lining the cushion invade the underlying matrix and acquire a mesenchymal phenotype [see illustrated reviews (Person et al. 2005; Schroeder et al. 2003; Butcher and Markwald 2007)]. As the cushion matures, these mesenchymal cells remodel the matrix directing a transition from hyaluronan to collagen-based matrix and a transition from globular to planar morphology (Kruithof et al. 2007; Hinton et al. 2006). Significant advances have been made in identifying the key molecular signals needed for this initiation and maturation (Butcher and Markwald 2007; Eisenberg and Markwald 1995; Person et al. 2005);
yet, little is known about the role of mechanical signaling in cushion development. The hemodynamic environment of the embryonic cushion rapidly increases in pressure over development, resulting in an exponential increase in cardiac output and heightened wall shear stresses (Hu and Clark 1989; Yalcin et al. 2011). Concomitant with this increase in mechanical load, the AV cushions elongate to form thin, fibrous leaflets with increased extracellular matrix (ECM) proteins and greater mechanical stiffness (Buskohl et al. 2012; Butcher et al. 2007; Kruijshof et al. 2007).

These findings motivate the hypothesis that hemodynamic forces direct valve morphology and stimulate the turnover and remodeling of the internal valve constituents. Surgical manipulations of heart development have demonstrated that alteration of hemodynamic flows result in altered cardiac morphology (Hogers et al. 1997; Vermot et al. 2009), which correlates with differences in local shear stress profiles (Hove et al. 2003; Groenendijk et al. 2005), pressure (Sedmera et al. 2003), and myocardial activity (Bartman et al. 2004). It is not yet known whether pressure gradients or wall shear stress could drive AV valve morphogenesis, but directly uncoupling the effects of pressure and shear tractions are impossible to do in vivo. Without this understanding, prediction of AV cushion morphology in altered hemodynamic environments is limited.

Computational approaches to the study of the mechanical regulation of morphogenesis are an attractive alternative to address these issues of coupled loading and predictability. Numerical models have provided insights into the fluid dynamics of the embryonic heart, such as the transition of peristaltic to pulsatile flow (Taber et al. 2007) and the distribution of normal and shear forces in AV canal (Biechler et al. 2010; Miller 2011). Recent gains in fluorescent and ultrasound imaging have enhanced these computational studies by providing critical information on the magnitude and temporal nature of in vivo hemodynamic loads (Forouhar et al. 2006; Hove et al. 2003; Yalcin et al. 2011). Previous stress-driven growth models have qualitatively captured the morphology of several developmental phenomena such as invagination (Munoz et al. 2010), gastrulation (Taber 2008, 2009), cardiac looping (Ramasubramanian et al. 2008), and ventricle growth (Lin and Taber 1995). Stress-based growth laws assume that tissue morphology is a direct response to the current stress state or to the difference in current stress from a homeostatic stress state. This is in contrast to growth models phrased in terms of strain or strain energy, with corresponding homeostatic states assumed as functions of these quantities (Cowin and Buskirk 1979). Experimental evidence in plants and embryos supports stress as the mechanical criterion to which living organisms respond (Belousov and Luchinskaia 1995; Belousov and Grabovsky 2006). Stress-based evolution equations for growth also arise naturally when the entropy inequality is employed (Ambrosi and Guillou 2007; Garikipati et al. 2004), further supporting this form of growth law.

The objective of this study was to develop and implement a computational framework incorporating both fluid–structure interaction and growth mechanics to identify mechanical mechanisms sufficient to reproduce valve-like morphology. Physiological fluid flow parameters and cushion material properties were utilized. The results indicate that fluid pressure directs spatially dependant volume addition and removal resulting in valve elongation. Shear tractions do not significantly alter volume, but instead stimulate tissue distortion, particularly near the cushion surface. Growth and remodeling induces residual stresses that may significantly alter (or guide) cushion formation over time. This model provides an initial framework of mechanically induced valve development on which further biological detail may be incorporated.

2 Methods

2.1 Kinematics

Consider a stress-free body in the reference configuration at \( t = 0 \), denoted as the initial configuration \( \beta_0 \) in Fig. 1. The body undergoes a combined elastic–inelastic deformation from the initial to current configuration (\( \beta \)) defined by the mapping \( x = X(X, \beta) \). The observable, total deformation, \( F = \frac{dx}{dX} \), includes components of growth, remodeling, and elastic deformation. We assume \( F \) can be expressed as a multiplicative decomposition of the elastic components and growth and remodeling (inelastic) components as done in several preceding works (Rodriguez et al. 1994; Lubarda and Hoger 2002; Ramasubramanian and Taber 2008). The total deformation is thereby defined as the product of the inelastic, \( \mathcal{F} \), and the elastic, \( f \), deformations.

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F = f \mathcal{F}
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