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Short communication

A strain-based finite element model for calcification progression in aortic valves

Amirhossein Arzani [a,*], Mohammad R.K. Mofrad [b]

[a] Mechanical Engineering Department, Northern Arizona University, Flagstaff, AZ, USA
[b] Bioengineering Department, University of California, Berkeley, CA, USA

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ABSTRACT

Calcific aortic valve disease (CAVD) is a serious disease affecting the aging population. A complex interaction between biochemicals, cells, and mechanical cues affects CAVD initiation and progression. In this study, motivated by the progression of calcification in regions of high strain, we developed a finite element method (FEM) based spatial calcification progression model. Several cardiac cycles of transient structural FEM simulations were simulated. After each simulation cycle, calcium deposition was placed in regions of high circumferential strain. Our results show the radial expansion of calcification as spokes starting from the attachment region, agreeing very well with the reported clinical data.

1. Introduction

Calcific aortic valve disease (CAVD) is the major form of aortic stenosis (Otto et al., 1997), where stiffening of the valve leaflets obstructs blood flow from the left ventricle into the systemic circulation. The initiation and progression of CAVD involve various interrelated mechanobiological processes spanning multiple scales (Pawade et al., 2015). Hemodynamics phenomena play an important role in normal aortic valve function and CAVD (Sacks and Yoganathan, 2007; Balachandran et al., 2011; Gould et al., 2013; Ayoub et al., 2016). Wall shear stress exerted on the valvular endothelial cells (ECs) influences the inflammatory processes in CAVD as well as the signaling between the ECs and the valvular interstitial cells (VICs). Mechanical strains sensed by the VICs are believed to promote VIC differentiation to a calcific phenotype (Fisher et al., 2013).

Calcification is more likely to occur on the aortic side of the valve (Otto et al., 1994; Weinberg et al., 2010; Yip and Simmons, 2011), which has been attributed to the disturbed hemodynamics (Weinberg et al., 2010; Ge and Sotiropoulos, 2010) and the structural distinctions (Neufeld et al., 2014). Although progress has been made in modeling the aortic valve biomechanics, modeling CAVD progression has not received much attention. Previous biomechanical aortic valve calcification progression models have either obtained calcification progression from medical imaging data (Halevi et al., 2015), used pre-assumed simple growth laws (Weinberg et al., 2009), or have not reported the calcification growth patterns (Katayama et al., 2013).

Herein, we propose a calcification model based on the observation that mechanical strain promotes calcification in aortic valves (Balachandran et al., 2010; Hutcheson et al., 2012; Fisher et al., 2013; Hsu et al., 2016). We propose an algorithm to model the long-term evolution of calcification based on the mechanical strain on the aortic side of the valve. CAVD initiation and progression involve a complex interplay between various biochemicals, cells, and biomechanical factors (Arzani et al., 2017). In the current study, motivated by the known self-perpetuating process of calcification (Pawade et al., 2015), we simulate the spatial calcification growth patterns based on the mechanical strain obtained from a finite element model.

2. Methods

2.1. Finite element method (FEM)

The idealized aortic valve geometrical model used in prior studies (Weinberg and Mofrad, 2007; Weinberg et al., 2009) was used in this study. The model included the valve leaflet with varying thickness, the aortic root and sinus, and the ascending aorta (Fig. 1). We assumed perfect symmetry of the valve to reduce the computational domain to one-sixth of the valve, similar to previous studies (Weinberg and Mofrad, 2007; Weinberg et al., 2009; Joda et al., 2016). This is a favorable assumption because several cycles of simulation need to be performed. The model was discretized into 192k second order tetrahedral elements with higher

* Corresponding author.
E-mail address: amir.arzani@nau.edu (A. Arzani).

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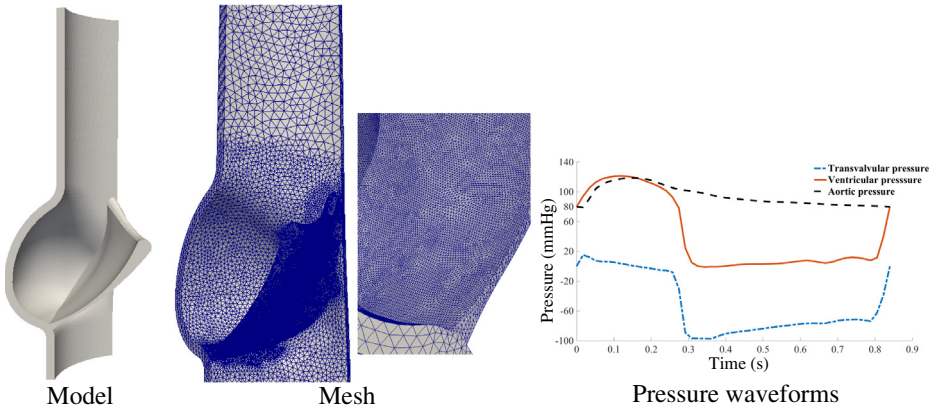

Fig. 1. The computational domain and mesh used in the finite element calculations. The pressure waveforms shown were obtained from Levick (2010) and used as the boundary conditions.

resolution in the leaflet and attachment region (Fig. 1). The mesh was constructed using SimVascular (Updegrove et al., 2017). A mesh independence study using third order elements was performed to verify the results.

A single term Mooney-Rivlin constitutive law, $W_{wall} = c_{wall}(I_1 - 3)$, was assumed for the aortic wall (Weinberg and Mofrad, 2007). The aortic valve was assumed transversely isotropic with the collagen fibers aligned in the circumferential direction using the constitutive law proposed by Humphrey and Yin (1987):

$$W = c\{\exp[c_1(I_1 - 3)] - 1\} + c_0\left\{\exp\left[c_2(\sqrt{I_4} - 1)^2\right] - 1\right\} + \frac{1}{2}\kappa(J-1)^2, \quad (1)$$

where I_1 is the first invariant of the right Cauchy-Green strain tensor ($\mathbf{C}$), J is the Jacobian determinant or volume ratio, $I_4 = \mathbf{C} : \mathbf{a_0} \otimes \mathbf{a_0}$ is the square of the fiber stretch along the circumferential direction ($\mathbf{a_0}$), and κ is a sufficiently large parameter used to impose a nearly incompressible material behavior. The anisotropic term (second term) is only switched on if $I_4 \geqslant 1$. The constant c_{wall} was set to 0.33 MPa. At low strains, this choice recovers the constant material stiffness of 2 MPa used in prior studies (Conti et al., 2010; Sturla et al., 2016; Cao and Sucosky, 2017). The constants in Eq. (1) were fitted to the experimental data of valve leaflets and reported in a prior study (Auricchio et al., 2012). These material constants are given in Table 1. A density of 1100 kg/m^3 was used for the tissues (Conti et al., 2010). The pressure waveforms shown in Fig. 1 obtained from Levick (2010) were applied as boundary conditions. Namely, the transient aortic and ventricular pressure waveforms were applied to the inner aortic wall above and below the valve leaflet, and the transvalvular pressure waveform was applied to the aortic or ventricular side of the valve leaflet, depending on the pressure sign. Only radial expansion was allowed at the ends of the aortic wall. A symmetry boundary condition was applied weakly at the plane of symmetry using the Nitsche method (Freund and Stenberg, 1995; Stenberg, 1995) with a sufficiently large penalty-like parameter. The Cauchy's equation of motion was formulated in the reference configuration (Ogden, 1997) for a nearly incompressible material (Holzapfel et al., 2000) and solved using a second order finite element method implemented in FEniCS (Logg et al., 2012). Time integration was performed using the generalized-α method (Chung and Hulbert, 1993) with sufficiently small time steps to ensure the convergence of the nonlinear Newton solver.

Table 1
The parameters used in the constitutive model (obtained from Auricchio et al. (2012)).

c	c_1	c_0	c_2
0.022 MPa	5.81	0.062 MPa	24.97

2.2. Calcification algorithm

Here we describe the proposed solely strain-based calcification algorithm. Calcification was only allowed for the elements on the aortic side of the valve. A cardiac cycle of simulation was performed to obtain the peak temporal circumferential strain for each element on the aortic side of the valve. To emphasize that our model does not capture the temporal evolution, we will refer to each cardiac cycle as a simulation cycle. The computed strain was projected to the element because in our model calcification occurs element-wise. If the calculated strain was larger than a certain threshold the element calcified. Calcification was modeled by increasing the stiffness of the element. This was done by increasing the material constant (c) in the isotropic term of the constitutive model (first term in Eq. (1)) proportional to the strain and a stiffening factor (see Algorithm 1). We have assumed that calcium deposition does not affect the anisotropic behavior of the leaflet, which is due to the collagen fibers. The simulation cycle was repeated after calcification to obtain the updated peak temporal circumferential strains. This procedure was repeated until no more calcification could happen. That is, either there were no more elements with strains higher than the threshold or the calcifying elements (elements with high strain) had reached a predefined peak stiffness.

The strain threshold for calcification was chosen as 0.05 based on in vitro data (Fisher et al., 2013). Note that a peak strain of 0.05 is within the physiological range of strain, however, under pathological conditions certain biochemicals such as transforming growth factor-β promote myofibroblastic or osteogenic differentiation of VICs, and therefore calcification. Our calcification model is intended to represent such conditions. The maximum stiffness that a calcified element can reach (*MAT_const_max*) is defined to be orders of magnitude larger than the material constant (Wong et al., 2012; Holzapfel et al., 2002; Halevi et al., 2015). In the algorithm, if the updated material constant exceeded this maximum value, the maximum value was used as the new material constant. Algorithm 1 illustrates the details of the calcification algorithm, and Table 2 gives the parameters used in the algorithm.

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