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Investigating the role of smooth muscle cells in large elastic arteries: A finite element analysis

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HIGHLIGHTS

- The influence of intracellular calcium on the biomechanics of arteries is studied.
- FE implementation and model verification are provided using isometric contraction/relaxation.
- Arterial rings are loaded with pressure wave and intracellular calcium functions.

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ABSTRACT

Physiological loading in large elastic arteries is considered to be mainly carried by the passive components of the media but it is not known how much the contraction of the smooth muscle cells is actually involved in the load carrying. Smooth muscle contraction is considered to occur in a relatively slow time domain but the contraction is able to produce significant tension. In the present work the role of smooth muscle contraction in large elastic arteries is investigated by analyzing how changes in the intracellular calcium, and thereby the active tone of smooth muscle cells, influence the deformation and stress behavior; different intracellular calcium functions and medial wall thicknesses with cycling internal pressure are studied. In particular, a recently proposed mechanochemical model (Murtada et al., 2012. J. Theor. Biol. 297, 176–186), which links intracellular calcium with mechanical contraction and an anisotropic model representing the elastin/collagen composite, was implemented into a 3D finite element framework. Details of the implementation procedure are described and a verification of the model implementation is provided by means of the isometric contraction/relaxation analysis of a medial strip at optimal muscle length. In addition, numerically obtained pressure–radius relationships of arterial rings modeled with one and two layers are analyzed with different geometries and at different calcium levels; a comparison with the Laplace equation is provided. Finally, a two-layer arterial ring is loaded with a realistic pressure wave and with various intracellular calcium functions (different amplitudes and mean values) and medial wall thicknesses; residual stresses are considered. The finite element results show that changes in the calcium amplitudes hardly have an influence on the current inner ring radius and the circumferential stress. However, an increase in the mean intracellular calcium value and the medial wall thickness leads to a clear influence on the deformation and the stress behavior.

1. Introduction

One of the main functions of smooth muscle cells is to regulate size and wall tension of hollow organs through contraction/relaxation. Smooth muscle cells are located in the medial layer of an artery and they play a significant role in maintaining the mechanical strength in the wall and in regulating the blood pressure. During a cardiac cycle, the resulting blood pressure and flow depend on the arterial wall stiffness which may be divided into an active and a passive part. The passive part in the arterial wall is governed by the passive components such as elastin and collagen that are found in the medial and adventitial layers. The active part is related to the contraction/relaxation of smooth muscle cells located in the medial layer. Smooth muscle contraction/relaxation is regulated by phosphorylation of the myosin motors associated to the smooth muscle contractile units. The myosin phosphorylation is mainly regulated by the phosphorylating myosin light-chain kinase (MLCK) and the dephosphorylating

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myosin light-chain phosphatase (MLCP). MLCK activity is regulated by intracellular calcium $[Ca^{2+}]_i$ through a calcium–calmodulin complex while different calcium sensitizing pathways regulate the activity of MLCP. By varying the MLCK and MLCP activities the active stiffness of the smooth muscle cells can be adjusted. The arterial wall stiffness also depends on the structure and the morphology of the wall.

Smooth muscles can be categorized into two subtypes namely phasic (faster) and tonic (slower) but they are generally considered as a 'slow muscle type' (the fastest smooth muscle type has a slower velocity of shortening than the slowest striated muscle type) (Fisher, 2010). The tonic (slow) smooth muscle cells located in the large elastic arteries reach steady-state force during isometric contraction in minutes and how this influences the arterial wall during a cardiac cycle, where the load cycle is within a second, is not so well-known. To better understand the role of smooth muscle contraction in larger arteries, it is an important issue to investigate how vascular smooth muscle reacts and affects its surrounding for different levels of active tone.

The pressure–radius relationship of arteries with different levels of activation can be studied by using Laplace's equation. However, in many cases this is an approximation that is accurate and only valid when the mean radius is much larger than the wall thickness, due to the negligence of any radial stresses. For larger arteries, where the mean radius–wall thickness ratio is smaller, the use of Laplace's law is not accurate and an alternative approach to analyze the underlying mechanochemical process is necessary. The finite element method (FEM) is very useful to study complex boundary-value problems and it can surpass the limitations of Laplace's law. However, the approach requires a material description of the arterial wall that can be implemented into a finite element (FE) analysis program.

In the present work the mechanochemical model, as proposed by Murtada et al. (2012), is implemented into a three-dimensional framework of the finite element software Abaqus. The implemented model is then verified by comparing FE results of the isometric contraction/relaxation of a medial strip at optimal muscle length with the solution of a 1D problem using Matlab. Next, for certain mechanical loading conditions, the influence of different smooth muscle activations and different medial wall thicknesses on the mechanical response of the wall is studied for a large elastic artery. Smooth muscle activations are regulated by different shapes and magnitudes of $[Ca^{2+}]_i$ transients during the cardiac (pressure) cycle.

2. Background

In the following section, as a brief review, by starting with a description of the cross-bridge kinetics theoretical models for studying smooth muscle contraction in arteries appropriate for implementations into a finite element analysis program are presented.

2.1. Cross-bridge kinetics

Smooth muscle contraction occurs when myosin filaments interact with actin filaments through load-bearing cross-bridges. The myosin is activated by phosphorylation of the regulatory light chain (RLC), located on the myosin, through the MLCK which is triggered by a calcium–calmodulin complex. Hence, an increase in $[Ca^{2+}]_i$ is associated to an increased myosin activation. When activated, the myosin interacts with the actin by attaching, pulling (power-stroke) and detaching, more known as the cross-bridge cycle which leads to sliding of the myosin and actin filaments and thereby causing contraction. Deactivation of the myosin is regulated through dephosphorylation of RLC by MLCP in which the cross-bridges slowly detach and the muscle relaxes. A detailed review of the regulatory pathways for MLCP activity can be found in Somlyo and Somlyo (2003). It was observed that smooth muscle is able to maintain tension even though the phosphorylation of myosin RLC is decreased. This phenomenon is referred to as the 'latch state' of the cross-bridges in which the myosin is deactivated but is still attached to the actin carrying load (Hai and Murphy, 1988). The latch cross-bridge is described as a slowly cycling cross-bridge or as a weaker cross-bridge (Butler et al., 1986). The equilibrium of the fraction of activated and deactivated cross-bridges in the smooth muscle contractile units defines the level of contraction/relaxation.

2.2. Theoretical models – a brief review

Cross-bridges are commonly modeled as elastic springs and three major parameters regulate the active stress during muscle contraction/relaxation: the number of attached load-bearing cross-bridges (activation parameter), the average elastic stiffness of the cross-bridges (material parameter) and the average elastic elongation of the attached cross-bridges (deformation parameter). There are several models available with the aim to simulate the behavior of contracting smooth muscle cells. In this section, the basic features of models, specifically designed for describing active vascular smooth muscle cells within a continuum mechanical framework that are appropriate to be implemented into FE codes, are reviewed.

2.2.1. *Rachev and Hayashi (1999)* and *Zulliger et al. (2004)*

Rachev and Hayashi (1999) proposed a phenomenological model of uniformly distributed vascular smooth muscle cells in the arterial wall, which accounts for two main characteristics of smooth muscle: (i) the capability to generate stress when activated, (ii) the configuration of the contractile proteins in the muscle which is reflected by the stretch. The model describes the active circumferential stress as a function of a contractile activity parameter specified for a certain stimulus, the stretch in the circumferential direction and a normalized function dependent on the circumferential stretch, which account for the active smooth muscle length–tension relationship.

The model was extended by Zulliger et al. (2004) through a three parallel element model (two passive and one active) where the activity parameter is expressed as a function of the different states of the muscle (fully relaxed, maximally contracted and normal tone), and where the active smooth muscle elasticity is extended to a more sophisticated function of the circumferential stretch.

2.2.2. *Schmitz and Böl (2011)* and *Böl et al. (2012)*

Schmitz and Böl (2011) proposed a steady-state model of smooth muscle activation which includes a phenomenological explanation of the active length–tension behavior, similar to the Rachev and Hayashi (1999) model. It also includes a structural description of the smooth muscle layer orientation. The activity parameter in the model was set as constant.

The model was further expanded by Böl et al. (2012) to couple intracellular calcium to the activity parameter in the model through a cross-bridge kinetics model (Hai and Murphy, 1988). The intracellular calcium was described as a field variable and is following Fick's law of diffusion. The coupled model was then used to study the dependence of chemical activation on the contraction of an arterial muscle strip and the chemo-mechanical contraction performance of a carotid artery. Among the reviewed models, this model was the only one that had been implemented into a FE environment at the point of time when this study was conducted.