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Investigating the Mechanical Response to Stress in Coronary Arteries

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Abstract

This work focuses on establishing a computational and theoretical framework for using COMSOL Multiphysics in modeling arterial wall dynamics in order to better understand arterial tissue biomechanics. A physically accurate, three layered, axial-symmetric cross section of a coronary artery was considered. The composite material found in the three layers of the artery wall were defined using experimental data from studies done on human coronary arteries. This research primarily investigated the mechanical response of arteries to different levels of stress due to internal blood pressure and the contractile activity which is produced by the vascular smooth muscle (VSM), found in the medial layer of the artery wall. Our model simulates distinctive changes in each layer due to the stresses induced by hypertension and coronary artery spasms. This research also looks into the effects of intimal wall thickening on the overall stress distribution of the artery wall. VSM is very little understood and there have been no models, to the authors knowledge, that incorporate VSM and intimal dynamics in a human based model. Thus, this study elucidates the relationship between blood pressure and VSM by analyzing the stress distributions and the corresponding structural changes produced.

1 Introduction

Biological processes are by nature very complex with many forces that determine their behavior. The field of mathematical physiology can be very useful in analyzing and predicting biological dynamics. This in turn can deepen the underlying understanding of these processes and often provides information on how to better treat and diagnose many different diseases. This is done by creating models that can capture the dynamics of biological processes, and then performing analyses which can describe the behavior of the system. In this investigation, the biological process under consideration is arterial wall dynamics in humans.

An artery is an elastic blood vessel that transports blood away from the heart. Understanding the structure of an artery is key to accurately depicting its dynamics in a model. The artery wall consists of three layers. The outermost layer is the tunica adventitia which is composed of connective tissue as well as collagen and elastic fibers, allowing for the stretching of arteries.

The tunica media is the middle layer and is composed of vascular smooth muscle (VSM) and elastic fibers. The VSM is what causes arterial tone and thus directly influences the stress and strain distribution of the arterial wall through changes in diameter and thickness [5]. The influence of this smooth muscle on the dynamics of blood flow and artery constriction is not well understood as it behaves differently than most other muscle tissues. Very little has been done to fully understand its behavior and functions although it plays a key role in many health related processes. What is different about the VSM is that it contains cells that sense changes in pressure and so responds with a myogenic response. This response causes an outward pushing force that attempts to prevent changes in shape. Therefore, under stress, it actually pushes outward rather than becoming compressed.

The third innermost layer is the tunica intima which is composed mostly of collagen fibers, and shows the most distinctive structural changes with age and disease [4]. This layer is often not included in investigations of arterial wall dynamics mostly because previous studies use data from animals which have an intima but its a single layer of cells and thus does not contribute to the mechanical response. This layer is important to study for its material changes the most as humans age and so will likely have a strong effect on the overall stress distribution of the system.

The intent of this research is to develop a model of the arterial wall dynamics in human coronary arteries. The model will include muscle constriction in the medial layer [5] as well as mechanical properties and structure developed from studies done on human arteries [4]. The model is then used to study the stress distribution on the arterial wall and to understand the structural changes that are induced by different mechanical properties such as stiffness and blood pressure.

2 Methods

2.1 Geometry

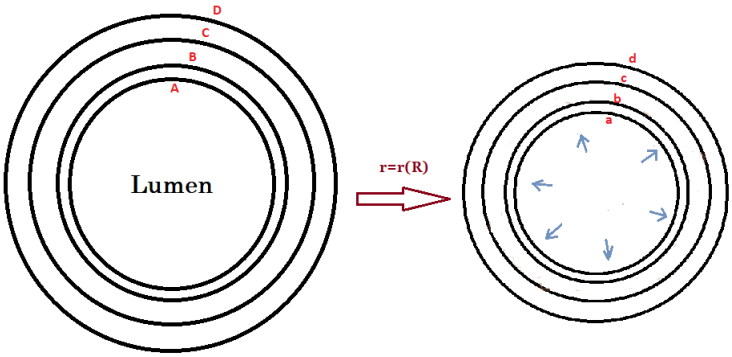


Figure 1: Cross-section of artery layers before and after deformation.

The initial geometry of the artery, before any deformative processes take effect, is given by

$$A \leq R \leq B, \quad B \leq R \leq C, \quad C \leq R \leq D, \quad 0 \leq \Theta \leq 2\pi, \tag{1}$$

where A, B, C, and D, are positive constants that define the length of the inner radius, intima layer, media layer, adventitia layer, and outer radius respectively. This can be seen in Figure 1. The lumen is space within these layers where blood passes through. The variables R and Θ are cylindrical coordinates where R is the radius and Θ is the angle. The deformation of the artery is described by

$$r = r(R), \quad \theta = \Theta, \tag{2}$$

where θ still goes from 0 to 2π, but now $r(A) = a$, $r(B) = b$, $r(C) = c$, and $r(D) = d$. This deformation is caused by a combination of the stresses due to the internal blood pressure and the stress from the constriction

in the medial layer where elastic deformation gradient is given by

$$\mathrm{F} = \begin{pmatrix} \frac{dr}{dR} & 0 \\ 0 & \frac{r}{R} \end{pmatrix} = \begin{pmatrix} \lambda_r & 0 \\ 0 & \lambda_\theta \end{pmatrix} \tag{3}$$

in cylindrical coordinates, where λ_r and λ_θ are the stretches and are defined as the ratio between the deformed length and initial length of a material line.

To enforce incompressibility, the determinant of the elastic deformation gradient, where F is defined above, is set to:

$$\det \mathrm{F} = 1. \tag{4}$$

Taking the determinant of this gives the definition of the stretches in the radial and circumferential directions, $\lambda_r = 1/\lambda_\theta = R/r$. Using equation (3), this then produces the equation

$$\frac{dr}{dR} = \frac{R}{r} \tag{5}$$

allowing the use of separation of variables to find that the deformation $r(R)$ is given by

$$r = (a^2 + R^2 - A^2)^{1/2}, \tag{6}$$

where a and A can be replaced with b and B, c and C, d and D to produce four equations that map the non-deformed geometry to the deformed.

The relationship between stress (T) and stretch, where stress is the force intensity, is given by the constitutive laws. An extension of Hooke's Law for nonlinear materials gives

$$T_{rr} = \lambda_r \frac{\partial W}{\partial \lambda_r} - p, \quad \text{and} \quad T_{\theta\theta} = \lambda_\theta \frac{\partial W}{\partial \lambda_\theta} - p \tag{7}$$

as definitions for the radial and circumferential stresses. The strain energy function, W which is the stored energy due to deformation, in this case is given by Equation(8) below and describes the mechanical properties of the wall material. Note that longitudinal stress is not considered as this model only describes a cross section of an artery.

2.2 Model

The software COMSOL Multiphysics was used to develop and simulate a mathematical model of an artery wall.

This study developed a model that is a time independent, cross section of an artery wall, so only the radial and circumferential directions are considered throughout the paper. The processes included were the internal pressure perpendicular to the artery wall caused by blood pressure, and the VSM constriction in the middle layer. Arterial tissue can be assumed to be incompressible because it is composed mostly of water and so its area must be conserved as it changes geometry. The model tries to enforce this incompresibility by choosing a large value for the bulk modulus, κ, although with enough contraction of the VSM the material can become compressible in the simulation. The artery can also undergo large deformations due to its hyperelastic, nonlinear material and is additionally anisotropic, meaning that the deformation is different when measured in different directions due to the specific orientations of the collagen fibers [4]. While some studies have considered mechanical models that include muscle constriction, these studies did not include the anisotropic behavior and other properties of arterial tissue that are now known [5, 6, 7, 8]. All of these characteristics were included in the formulation of the model as well as realistic parameter values, seen in Table 1, that were found from a study done on human coronary arteries by Holzafel [4].

To incorporate the material properties of a human coronary artery a strain energy density function, W, was defined. This function captures the nonlinear (i.e. the more it is stretched, the stiffer it becomes) and anisotropic behavior of the tissue. It was also used to incorporate active stress, or muscle constriction into

the middle layer of the wall in the model. The passive strain energy function, which defines the material without active stress, was experimentally found by Holzafel and is given by,

$$W = \mu(\lambda_r^2 + \lambda_\theta^2 - 2) + \frac{k_1}{k_2}(\exp(k_2[(1-\rho)(\lambda_r^2 + \lambda_\theta^2 - 2)^2 + \rho(\lambda_\theta \cos^2\phi + \sin^2\phi - 1)^2])) \tag{8}$$

where λ_θ is the circumferential stretch and λ_r is radial stretch, μ is the shear modulus, or the measure of the stiffness of the layer, ϕ is the angle between the fibers that compose the layers, reflecting the anisotropic nature of the tissue. This can be seen in Figure 2. The parameter values found in this equation vary from layer to layer and can be found in Table 1.

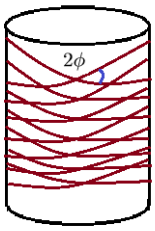


Figure 2: Fiber directions, shows anisotropic material with ϕ being the angle between fibers.

There are many proposed formulations for including active stress in models of the artery wall[5,6,9]. The one considered in this project was developed by Rachev [5] and was derived from experimental data. This stress function was included in the medial layer's mechanical properties and is defined as

$$T_{\theta\theta a} = S(-1.777\lambda_\theta^3 + 4.96\lambda_\theta^2 - 2.48\lambda_\theta). \tag{9}$$

Here S is the measure of contractile activity, or tone, in the medial layer. It represents the maximum stress per unit deformed area. It is measured in Pascals, just as stress is, with $S = 50$ kPa being a normal level of muscular tone, according to Rachev. It is important to note that Rachev formulated this model using data found in animals so it is not clear how different values of S would correspond to human levels of contractile activity.

Figure 3 shows the active stress as a function of stretch as formulated by Rachev. This figure simply shows that as the stretch in the circumferential direction increases, so does the stress. It accounts for the length-tension relationship. Notice that when the stretch is 1, meaning that there is no deformation, there still is some residual active stress, which would account for normal muscle tone. When there is no active stress, the artery is in compression, with a stretch value between 0.6 and 0.7. This indicates that the active stress helps prevent compression, or a deformation in shape.

Table 1: Parameter values

Layer	μ	k_1	k_2	ϕ	ρ
adventitia	7.56	38.57	85.03	67.0	0.55
media	1.27	21.60	8.21	20.61	0.25
intima	27.90	263.66	170.88	60.3	0.51

μ (kPa), k_1 (kPa), k_2 (dimensionless), ϕ (degrees), ρ (dimensionless).

The first steps in developing the model was to validate simpler models developed in COMSOL by comparing the results to ones formulated in Matlab. The first model developed was one layered with simple neohookean material properties which was then validated by Matlab. This was done with progressively

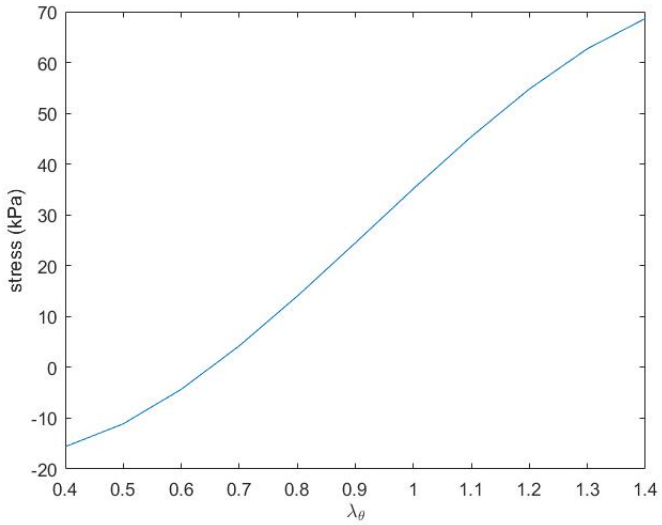


Figure 3: Active stress versus circumfrential stress as defined by Equation 9.

complex models, moving to two layers, incorporating active stress and the appropriate material properties. This is shown in Figure 4. With well founded confidence in COMSOL, a three layer model was created that incorporated active stress and the anisotropic material defined in Eq. 1 and 2 as well as the parameter values found in Table 1.

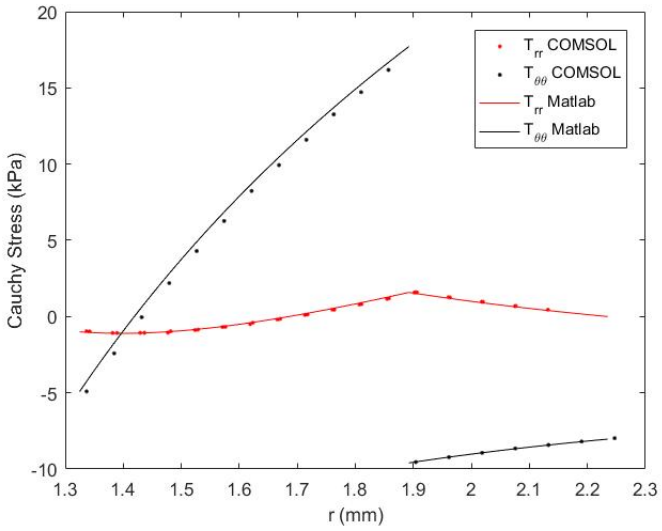


Figure 4: Model Validation graph for two layer with active stress.

3 Results

Various plots were produced in order to investigate the behavior of the model with an emphasis on understanding how the muscle contraction in the medial layer affects the overall stress distribution of the solution.

For all plots two internal pressure cases are considered, $P = 13.33$ kPa which indicates normal blood pressure and a systolic reading of 100 mmHg, and $P = 21$ kPa, which is the case of hypertensive blood pressure and a systolic reading of 158 mmHg.

Figures 5 and 6 show the circumferential stress in the different layers, for the normal and hypertension cases, respectively. Various S values are included to see how the stress distribution changes as VSM undergoes stronger contraction. Note that COMSOL has plotted the curves continuously although in truth they are discontinuous as the different layers have different material properties. A negative stress value means that the layer is under compression. A positive stress value indicates that the layer is in tension. The first curve on the left shows the intima under compression. The medial layer is clearly under tension, and the adventitia layer is not particularly affected by the stresses. There is little difference between the two graphs in terms of magnitude of stress, and the values of compression in the intima for higher S values are also very similar. The only differences between these two graphs are that for higher blood pressure, larger S values are required for the intima to eventually become compressed and for low S values, the intima is in tension.

To the right of Figures 5 and 6 are intensity plots for circumferential Cauchy stress with a lower level of active stress for the two blood pressure cases. They show that the overall stress dynamics is effected by a higher internal pressure. Specifically, only the medial layer appears to have a significant amount of stress for normotensive blood pressure, while in the hypertensive case there is a higher level of stress in the medial layer as well as significant stresses in the intima layer. It is interesting to note that the stress is almost constant in each layer for the normotensive and hypertensive cases, the total amount of stress the artery endures does not change significantly.

Figures 7 and 8 show the circumferential stretch as a function of radius. The stretch is a measure of deformation and is defined as the ratio between the deformed length and the original length. Thus, a stretch value of 1 would mean there is no deformation, greater than 1 would mean the material expanded and less than 1 would indicate a contraction of the material. These two graphs show that for low enough S values, such as $S = 75$ kPa, the artery is in tension due to the internal pressure. At higher S values however, the artery then becomes compressed. There is more tension in the hypertensive case but the maximum compression is still around 16% for both.

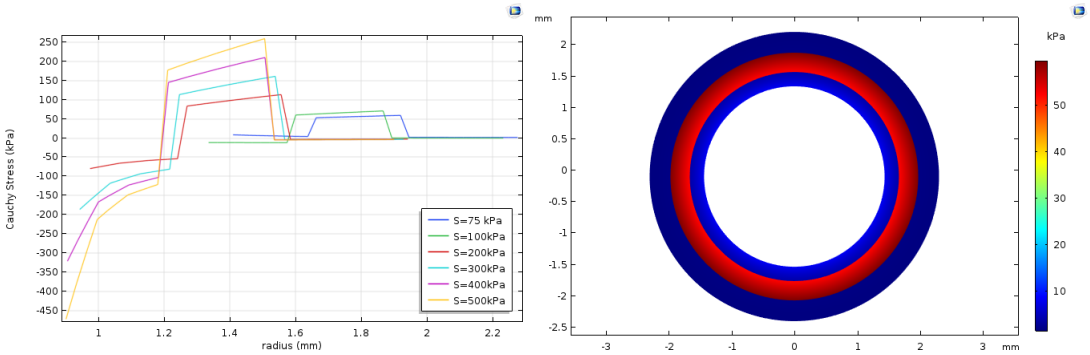
Figure 9 features the radius at the four interfaces – inner, intima-media, media-adventitia, and outer radii – as a function of contractile activity. This shows the artery's deformation as the contractile activity increases. At higher S values the incompressiblity does seem to break down but nonetheless, these graphs indicate that as the contractile activity increases, the radii become increasingly small. Note that although the radii become smaller, the area should not change meaning that the walls compensate for the smaller radii by becoming thicker.

Figures 10 and 11 show the varying distribution of circumferential stress as the stiffness (μ_i) of the intima layer changes. A normal intima layer stiffness is around 27.9 kPa. Note that both of these figures have a fixed S value of 75 kPa. The normotensive case does show some change in the stress distribution for as the intima stiffens, the overall radius becomes slowly compressed, but this is a very minimal effect. In the hypertensive case seen in Figure 11, the intima layer experiences a large amount of tension and the radius value does not change greatly.

The plots seen in Figure 12 show the variations in the stress distribution as the parameter k_{1_i} is varied in the intima. The parameters k_{1_i} and k_{2_i} both contribute to the stiffness of the artery in addition to μ_i. It is thus interesting to note that k_{1_i}, and k_{2_i}, the latter of which is not included as it is essentially the same graph the graph of k_{1_i}, changes very little about the stress distribution in the artery. The hypertensive case shows a small amount of compression for higher k_{1_i} values.

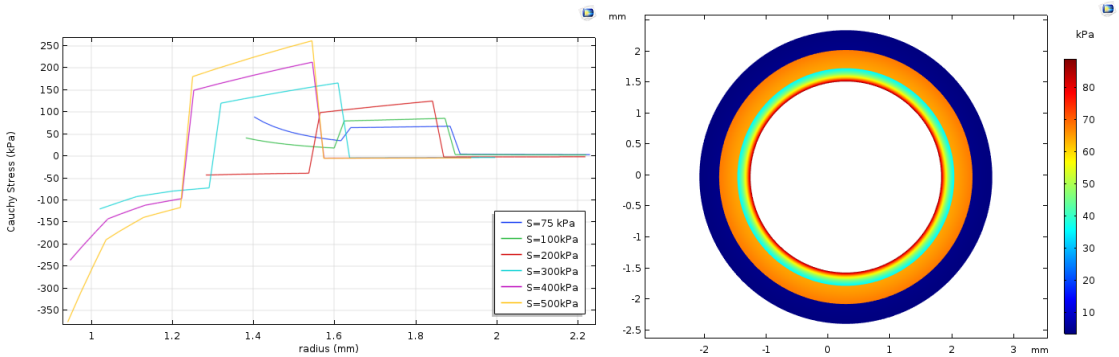
4 Discussion

Figures 5 and 6 clearly show the myogenic response characteristic of VSM. The greater the contractile activity, the stronger the myogenic response is. This makes sense as the myogenic response is a process whose purpose is to ensure optimal mechanical function. The VSM will be in tension or contraction in order to resist deformation. When in tension, as is seen in the graphs, it is called the Bayliss effect. It attempts



(a) (b)

Figure 5: (a) Circumferential Stress versus radius for various S values with regular blood pressure. ($P = 13.33$ kPa), (b) Intensity plot of circumferential Cauchy stress for $S = 75$ kPa and $P = 13.33$ kPa.



(a) (b)

Figure 6: (a) Circumferential Stress versus radius for various S values with hypertensive blood pressure. ($P = 21$ kPa), (b) Intensity plot of circumferential Cauchy stress for $S = 75$ kPa and $P = 21$ kPa.

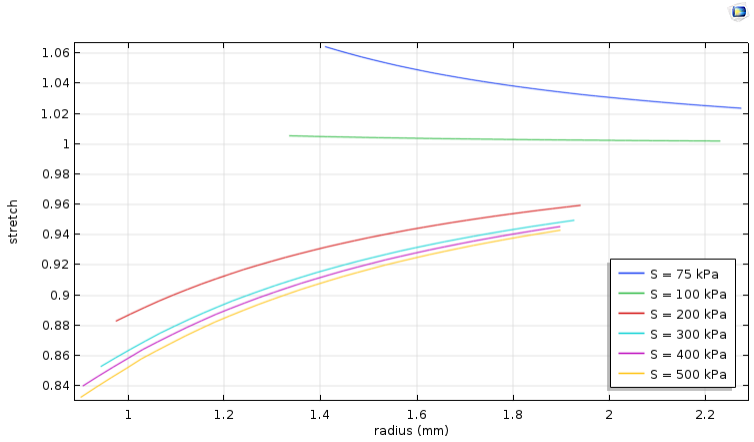


Figure 7: Circumferential Stretch versus radius for various S values with regular blood pressure.

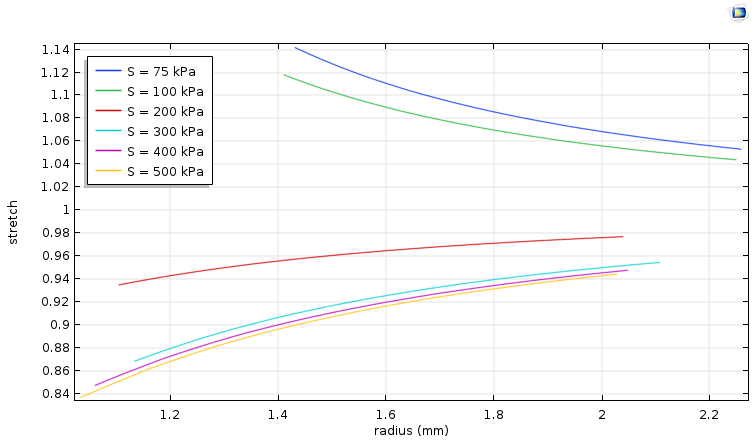
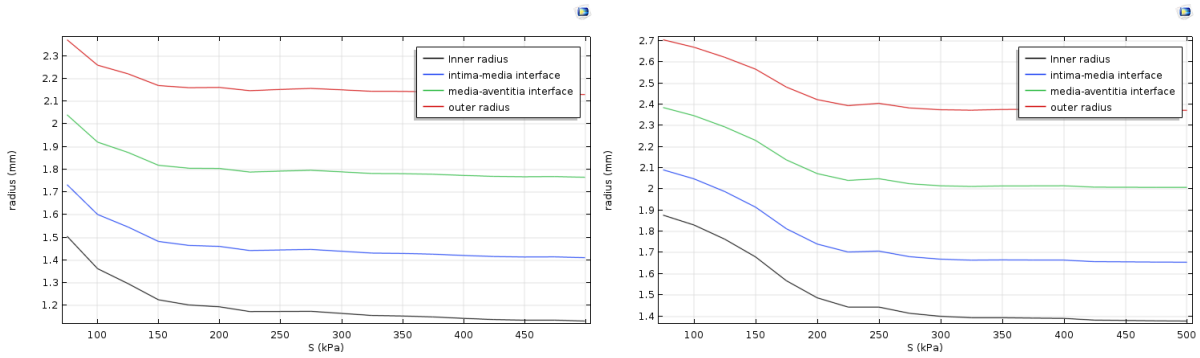


Figure 8: Circumferential Stretch versus radius for various S values with hypertensive blood pressure.



(a) (b)

Figure 9: (a) Radius versus Contractile Activity, normal blood pressure, (b) Radius versus Contractile Activity, hypertensive case.

to create a uniform distribution of circumferential stress in the arterial wall. Although the media layer is under tension, the intimal layer becomes more and more compressed as S increases. This is likely due to the incompressibility of arteries for as the media expands, it compresses the intima in order to conserve its area. Further analysis needs to be done on this to more deeply understand this effect.

The plots featured in this paper show that the adventitia is nearly stress-free and is not sensitive to the changes in the level of contractile activity. The difference between Figures 5 and 6 as well as in 7 and 8 physically is the internal pressure. It is clear that the geometry of the artery is different for the two cases as seen in the radius values of the x-axis. The hypertensive case shows less compression of the overall artery as the innermost radius decreases less than the regular blood pressure case. This implies that an increased outward internal pressure somewhat cancels out the compressive force of the active stress produced by the VSM. This is, in fact, likely the purpose of VSM which is why there is always some active stress in the artery known as basal tone. If the active stress were not there, the artery would likely be significantly more sensitive to such things as high blood pressure and intimal thickening although further investigation is needed to confirm this by plotting the stresses with no active stress.

Figures 10 and 11 show that the stiffness of the intima layer, as measured by μ_i values does change the overall stress distribution. With age, the intima layer does stiffen so these results could shed light on the effects of aging on the stress dynamics of artery walls. Specifically, higher μ_i values show that there is both

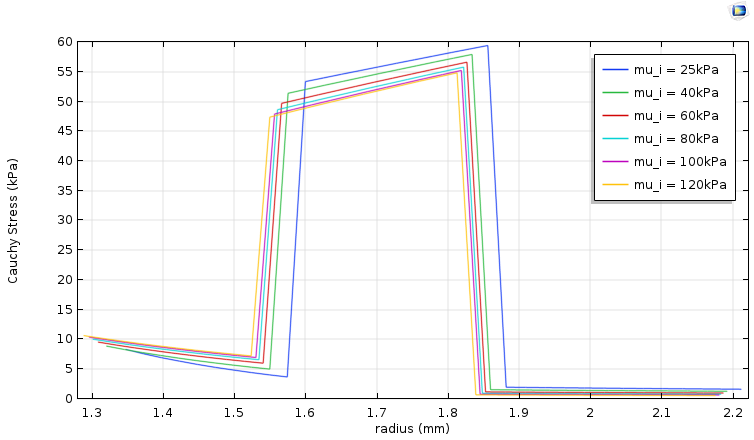


Figure 10: Circumfrential stress versus radius with varying intima layer stiffness's (μ_i) for $P = 13.33$ kPa.

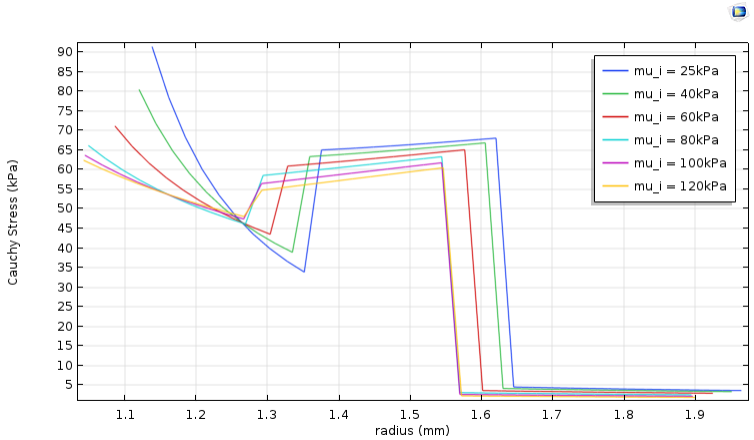
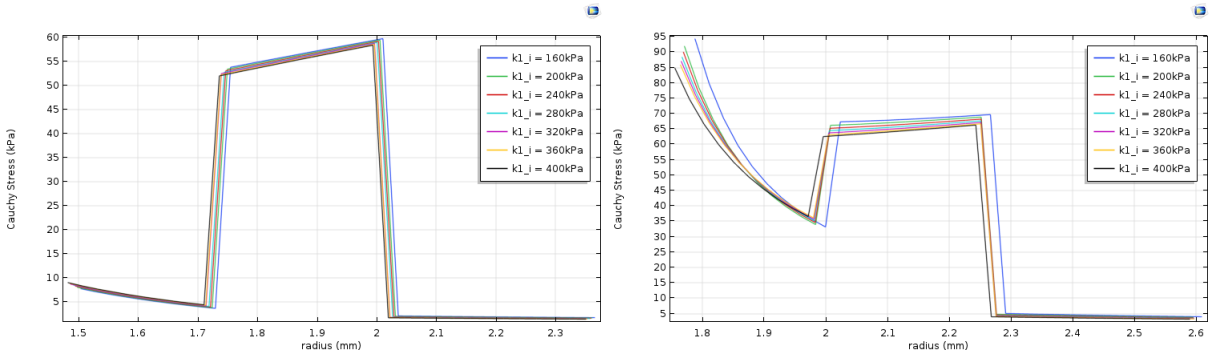


Figure 11: Circumfrential stress versus radius with varying intima layer stiffness's (μ_i) for $P = 21$ kPa.

compression of the radius as well as a decrease in tension. As has been seen with previous figures, higher S values create a large compressive stress values and a smaller lumen. Thus, a stiffer artery may exacerbate the amount of compression and thus may predict a smaller lumen at lower stresses. A dramatic decrease in the size of the lumen can prevent blood flow through the artery. Medically, this is called a coronary artery spasm.

A coronary artery spasm (CAS) is a tight constriction in the middle layer of the artery wall that temporarily restricts blood flow to the heart. They are by nature very hard to diagnose and so any insight into their behavior and physical effects on the artery wall is useful. The CAS are represented in this model by high S values although it is unclear what exactly constitutes a CAS in the framework of this model. Nevertheless, the results of this research has provided some insight into how a tight constriction in the artery, such as a CAS, can affect its overall stress distribution. For instance, it can be seen in the figures that the radius of the artery gets smaller with high active stress, and get larger with high blood pressure and a less stiff intima. A smaller inner radius value corresponds to a smaller lumen diameter, and when it is small enough, not enough blood can pass through the artery which would be classified as a CAS. CAS can produce abnormal heart rhythms which can lead to cardiac arrest and sudden death as well as heart attacks when the spasms are severe enough. Due to the short duration of CAS it is very difficult to diagnose as when the arteries are tested they appear normal. It is especially difficult to diagnose postmortem as no distinctive



(a) (b)

Figure 12: (a) Circumferential Stress versus radius for various k_{1_i} with $P = 13.33$ kPa (b) Circumferential Stress versus radius for various k_{1_i} with $P = 21$ kPa.

morphologic markers are clearly known. Recent research has discovered, however, an observed folding of the inner tissue layer of arteries (the tunica intima) during a coronary spasm [1, 2, 3]. The mechanisms behind folding are not understood, but further research in this can be key in diagnosing CAS as well as gaining a better understanding of muscle dynamics within arteries.

This work provides a first glimpse into the dynamics of VSM in human arteries. It is preliminary in nature and there are many more steps to take to furthering this investigation of understanding VSM. Next steps are to isolate the active and passive stress so it is clear which components contribute to what stresses. It is also important to solve the model for no active stress at all and see how different parameter values and internal pressures affect the behavior of the system. The Rachev model for active stress is somewhat limited and it is not clear what S values are reasonable to expect in humans so developing and incorporating a different model of active stress to compare and contrast is important. This model focuses only on a cross section of an artery and is time independent. These provide simplifying assumptions but next steps in developing this model could be to make it three dimensional with a time component.

Building a physically accurate model that includes muscle constriction in the middle layer of the artery wall provides the framework for investigations into different phenomena that involve arterial wall dynamics such as coronary artery spasms, hypertension, and intimal wall thickening. These dynamics are complicated but it is clear from the results that the model conforms to the behavior expected from a biological perspective. It is now possible to delve deeper into an understanding of these processes using this model to ask even more questions and to help elucidate the complicated inner workings of VSM and stress dynamics within coronary arteries.

5 Acknowledgments

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