Published in final edited form as:

J Mech Behav Biomed Mater. 2016 July ; 60: 515–524. doi:10.1016/j.jmbbm.2016.03.007.

Artery Buckling Analysis using a Two-Layered Wall Model with Collagen Dispersion

Mohammad Mottahedi¹ and Hai-Chao Han¹

¹Department of Mechanical Engineering, University of Texas at San Antonio, USA

Abstract

Artery buckling has been proposed as a possible cause for artery tortuosity associated with various vascular diseases. Since microstructure of arterial wall changes with aging and diseases, it is essential to establish the relationship between microscopic wall structure and artery buckling behavior. The objective of this study was to develop arterial buckling equations to incorporate the two-layered wall structure with dispersed collagen fiber distribution. Seven porcine carotid arteries were tested for buckling to determine their critical buckling pressures at different axial stretch ratios. The mechanical properties of these intact arteries and their intima-media layer were determined via pressurized inflation test. Collagen alignment was measured from histological sections and modeled by a modified von-Mises distribution. Buckling equations were developed accordingly using microstructure-motivated strain energy function. Our results demonstrated that collagen fibers disperse around two mean orientations symmetrically to the circumferential direction ($39.02^\circ \pm 3.04$) in the adventitia layer; while aligning closely in the circumferential direction ($2.06^\circ \pm 3.88$) in the media layer. The microstructure based two-layered model with collagen fiber dispersion described the buckling behavior of arteries well with the model predicted critical pressures match well with the experimental measurement. Parametric studies showed that with increasing fiber dispersion parameter, the predicted critical buckling pressure increases. These results validate the microstructure-based model equations for artery buckling and set a base for further studies to predict the stability of arteries due to microstructural changes associated with vascular diseases and aging.

Graphical abstract

Address Correspondence to: Dr. Hai-Chao Han, Department of Mechanical Engineering, The University of Texas at San Antonio, San Antonio, TX 78249, Tel: (210) 458-4952, Fax: (210) 458-6504, ; Email: haichao.han@utsa.edu

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Tortuosity; Mechanical instability; critical buckling pressure; two-layered artery wall; collagen fiber dispersion

1. Introduction

Tortuous arteries and veins, frequently seen in elderly, are associated with aging, hypertension, degenerative vascular disease and atherosclerosis (Del Corso et al., 1998; Han, 2012; Jackson et al., 2005; Nichols and O'Rourke, 1998; Pancera et al., 2000; Weibel and Fields, 1965). In recent studies, artery buckling (loss of mechanical stability) has been proposed as a possible mechanism for the development of vessel tortuosity (Han, 2012; Han et al., 2013; Zhang et al., 2014). Since microstructure of arterial wall changes with aging and diseases, it is essential to establish the relationship between microscopic wall structure and artery buckling behavior to better understand artery buckling and tortuosity in vascular disease.

Arterial walls are non-homogenous with three-layered structure: intima, media, and adventitia. While initial mechanical analysis of arterial wall often simplified the arterial wall as a single layer of uniform wall, current studies often take into account the multi-layered structure of the arterial wall (Fung, 1993; Humphrey, 2002). Though intima with endothelium and base membrane has its distinct function, it is a very thin layer and mechanical often combined with the intima for mechanical analysis. Thus the arterial wall is often divided into two layers for mechanical analysis: Intima-media layer and the adventitia layer with distinct material properties (Bellini et al., 2014; Rachev, 1997; Ren, 2012; Wang et al., 2006; Yu et al., 1993). However, previous artery buckling analyses were limited to single-layered uniform arterial wall assumption (Han, 2009; Rachev, 2009).

The mechanical behavior of arteries depends upon their microstructure, including collagen fiber alignment in the arterial wall (Fung, 1993; Humphrey, 2002; Qi et al., 2015). Microstructurally motivated constitutive equations have been established to model arterial wall behavior under various conditions (Baek et al., 2007; Holzapfel et al., 2000). We have recently demonstrated that collagen alignment affects artery critical buckling pressure using a four-fiber model (Liu et al., 2014). However, our previous models assumed perfectly aligned collagen fibers and homogenous artery wall properties (Liu et al., 2014). Canham and colleagues showed that in contrast to media layer, collagen fiber orientation was

dispersed in intima and adventitia layers (Canham et al., 1989). The idealized perfectly aligned two fiber family model, though well captures the feature of collagen alignment in the media, it is limited in capturing the dispersed distribution of collagen fibers in the adventitia (Gasser et al., 2006; Ren, 2012). An improved model with dispersed collagen fiber distribution is needed to better capture the actual wall structure. To this end, a hyperelastic strain energy function proposed by Gasser et al (Gasser et al., 2006) based on generalized structured tensor to characterizes the dispersed collagen distribution could be employed for representing anisotropic behavior of the arterial wall.

The objective of this study was to develop and validate artery buckling equation using a two-layered microstructure based arterial wall model that incorporates collagen orientation dispersion obtained from experimental measurement. The developed artery buckling model can be used in future work to determine the effect of microstructural changes in arterial wall due to aging and disease.

2. Material and Methods

Common carotid arteries were harvested from farm pigs (about 100 kg B.W.) post mortem at a local abattoir with the approval from the Texas Department of State Health Service. The arteries were transported to our laboratory in ice-cold phosphate buffer saline (PBS) and prepared for mechanical testing (Hayman et al., 2013; Lee et al., 2012).

2.1 Experimental Measurements

Inflation test of intact arteries: To determine the stress-strain relationship of intact porcine arteries, the axial extension and radial inflation were measured in a group of seven porcine carotid arteries under internal lumen pressure (Lee et al., 2012). Our previous studies using similar sample sizes ($n=5$ to 7) were able to detect difference in vascular wall components and functions (Hayman et al., 2013; Lee et al., 2012; Zhang et al., 2014). Each artery was mounted horizontally onto a cannula at one end and tied to a luer stopper at the other end. The luer stopper closed the end but allowed for free axial movement. The cannula was connected to a pressure meter and syringe pump filled with PBS solution. The artery was preconditioned by slowly inflating the artery to a pressure of 300 mmHg and then deflating for 5 to 6 cycles to obtain reproducible mechanical data. After preconditioning, the artery was slowly inflated while the outer diameter and length were photographed. These vessel dimensions were then measured from digital images taken during the inflation test. The outer diameter was obtained by averaging several measurements along the vessel and vessel length were measured along the central line of the vessel. The initial lumen diameter and wall thickness were measured from the ring segments cutting from both ends of the vessel and averaged.

Buckling test: The arteries were stretched to the given levels of stretch ratios (1.0–1.7), with both ends tied to the fixed cannulae and pressurized with PBS solution under steady flow until large deflections were achieved. The steady flow was generated using a peristaltic pump and a pulse dampener dome (Cole-Parmer) in the flow loop (Liu and Han, 2012). The critical buckling pressure was determined as the pressure when the deflection at mid-point of

the artery reached 0.5 mm which can be reliably measured and consistent with previous measurements (Lee et al., 2012).

Inflation test of intima-media layer: After completing the buckling test on each intact artery, the adventitia layer was carefully dissected. Then, the remaining intima-media (IM) layer was tested using the same pressurized inflation test protocol described above to obtain the mechanical properties of the intima-media layer.

No-load and zero-stress state: To obtain the no-load opening angle of the intact artery, rings were cut off from proximal and distal ends of the arteries and photographed under no-load condition. The rings were cut open radially and left in PBS solution for over 10 min to release the residual strain and photographed (Lee et al., 2012). The same process was repeated after removing the adventitia layer to measure the opening angle of the intima-media layer.

Histology: The ring samples collected after the mechanical testing were fixed in 10% formalin overnight and subsequently transferred to 70% ethanol. The samples were pressured and embedded in paraffin blocks. Sections of 5 mm thickness were cut in the longitudinal direction (θ -z plane) to capture the fiber orientation. Sections were treated with Picrosirius Red staining to visualize the collagen fiber and then imaged with the bright field microscope with 10x objective with 3 representative images being taken from each slide. Six sections across the adventitia thickness were analyzed and averaged.

2.2 Image analysis and determination of collagen distribution

The image analysis processing was performed using Scikit-Image (van der Walt et al., 2014) package in Python programming environment and is illustrated in Figure 1. After performing a white balance to ensure same level of brightness, the images were converted to grayscale. Otsu's method was used to reduce the gray level image to a binary image to distinguish the collagen fibers from the ground tissue (Otsu, 1979). Morphological opening and closing operation were performed to remove imperfection from the images. The opening process opens the gaps between connected collagen bundles. The closing operation was performed to fill the small holes in images which will result in cleaner images for further image processing (Burger and Burge, 2008; Soille, 2000). The fiber bundle orientation was measured by calculating the centroid and second order central moments of the collection of points which describes a connected region. The orientation is described by the angle between circumferential direction and the major axis that runs through widest part of the region (Burger and Burge, 2009; Haralick and Shapiro, 1992; Jähne, 2005; Stojmenovic and Nayak, 2007; van der Walt et al., 2014).

2.3 Model equations

Arteries are modeled as two-layered cylinder with the intima-media (IM) layer and the adventitia (A) layer, each modeled as fiber-reinforced composite in which collagen fibers are embedded in non-collagenous ground matrix which is presented as an incompressible isotropic neo-Hookean model (Baek et al., 2007; Holzapfel et al., 2000). Based on the circumferential symmetry of the vessels, we assumed that there were two fiber families

aligned symmetrically from the axial direction, each aligned with dispersion described by the fiber distribution model proposed by Gasser et al, (Gasser et al., 2006). Accordingly, the strain energy density functions are given by

$$\psi_j = \frac{c_j}{2} (I_1 - 3) + \frac{b_{1j}}{b_{2j}} \left[e^{b_{2j} [\kappa_j I_1 + (1-3\kappa_j) I_4 - 1]^2} - 1 \right] \quad j=IM, A \quad (1)$$

where b_{1j} , b_{2j} , and c_j are positive material constants, (b_{2j} are dimensionless; c_j and b_{1j} have the same unit as stress). $I_1 = \text{tr}(F^T F) = \lambda_z^2 + \lambda_\theta^2 + \lambda_r^2$ is the first invariant and $I_4 = \lambda_z^2 \sin^2(\alpha_{0j}) + \lambda_\theta^2 \cos^2(\alpha_{0j})$ is a measure of stretch in the fiber direction with λ_z , λ_θ and λ_r being the stretch ratios in the axial, circumferential and radial directions, respectively. α_{0j} is the mean angle between the fiber families and circumferential direction of the artery. κ_j is the dispersion parameter ranges between $[0, \frac{1}{3}]$ with $\kappa_j=0$ for fully aligned fibers and $\kappa_j=1/3$ for evenly distributed fibers (Gasser et al., 2006). The model becomes the same as the two-fiber model when $\kappa_j=0$ (Gasser et al., 2006; Holzapfel et al., 2000).

The strain energy expression can be rewritten in terms of Green strain E_z , E_θ , and E_r as:

$$\psi_j = c_j (E_z + E_\theta + E_r) + \frac{b_{1j}}{b_{2j}} \left[e^{b_{2j} [2\kappa_j (E_z + E_\theta + E_r) + 2(1-3\kappa_j)(E_z \sin^2(\alpha_{0j}) + E_\theta \cos^2(\alpha_{0j}))]^2} - 1 \right], \quad j=IM, A \quad (2)$$

We assumed that an artery has an opening angle Φ_0 (Φ_0^A , Φ_0^{IM} for the adventitia and intima-media layers, respectively). At zero stress state, the inner radius, middle radius (where the media and adventitia divide), outer radius and length of the artery are defined by R_i , R_m , R_e and L , respectively. Similarly the inner radius, middle radius, outer radius, and length at deformed state under internal pressure P are r_i , r_m , r_e and l , respectively. By integrating the equilibrium equation along the radius, the lumen pressure and axial force can be found from the following equations (see Appendix):

$$P = \int_{r_i}^{r_m} \left(\lambda_\theta^2 \frac{\partial \psi_{IM}}{\partial E_\theta} - \lambda_r^2 \frac{\partial \psi_{IM}}{\partial E_r} \right) \frac{dr}{r} + \int_{r_m}^{r_e} \left(\lambda_\theta^2 \frac{\partial \psi_A}{\partial E_\theta} - \lambda_r^2 \frac{\partial \psi_A}{\partial E_r} \right) \frac{dr}{r} \quad (3)$$

$$N = \pi \int_{r_i}^{r_m} \left(2\lambda_z^2 \frac{\partial \psi_{IM}}{\partial E_z} - \lambda_\theta^2 \frac{\partial \psi_{IM}}{\partial E_\theta} - \lambda_r^2 \frac{\partial \psi_{IM}}{\partial E_r} \right) r dr + \pi \int_{r_m}^{r_e} \left(2\lambda_z^2 \frac{\partial \psi_A}{\partial E_z} - \lambda_\theta^2 \frac{\partial \psi_A}{\partial E_\theta} - \lambda_r^2 \frac{\partial \psi_A}{\partial E_r} \right) r dr \quad (4)$$

The critical buckling equation was derived based on the approach previously as (Lee et al., 2012)

$$P_{cr} = \left[\frac{N + \left(\frac{n\pi}{l_e} \right)^2 H}{\pi r_i^2} \right] \quad (5)$$

Where l_e is the equivalent length of the artery which is equal to half the original length for the artery with both end fixed, and H is defined by:

$$H = \pi \int_{r_i}^{r_m} \left(J_{z,IM} - \frac{1}{3} J_{\theta,IM} \right) r^3 dr + \frac{\pi r^3}{3} \int_{r_i}^{r_m} J_{\theta,IM} dr + \pi \int_{r_m}^{r_e} \left(J_{z,A} - \frac{1}{3} J_{\theta,A} \right) r^3 dr + \frac{\pi r^3}{3} \int_{r_m}^{r_e} J_{\theta,A} dr \quad (6)$$

Where $J_{\theta,j}$ and $J_{z,j}$ ($j=IM, A$) are determined by

$$J_{z,j} = 2c_j + b_{1j} e^{b_{2j} I_{g,j}^2} \left(8I_{g,j} [\kappa_j + (1-3\kappa_j) \sin^2(\alpha_{0j})] + (1+2E_z)(8+16b_{2j} I_{g,j}^2) [\kappa_j + (1-3\kappa_j) \sin^2(\alpha_{0j})]^2 - (1+2E_r)(8+16b_{2j} I_{g,j}^2) \kappa_j [\kappa_j + (1-3\kappa_j) \sin^2(\alpha_{0j})] \right) \quad (7)$$

$$J_{\theta,j} = b_{1j} e^{b_{2j} I_{g,j}^2} (8+16b_{2j} I_{g,j}^2) [\kappa_j + (1-3\kappa_j) \sin^2(\alpha_{0j})] ((1+2E_\theta) [\kappa_j + (1-3\kappa_j) \cos^2(\alpha_{0j})] - (1+2E_r) \kappa_j), \quad (8)$$

With $I_{g,j} = \kappa_j I_1 + (1-3\kappa_j) I_4 - 1 = 2\kappa_j (E_z + E_\theta + E_r) + 2(1-3\kappa_j) (E_2 \sin^2(\alpha_{0j}) + E_\theta \cos^2(\alpha_{0j}))$; $j=IM, A$.

A brief description of derivation of these equations is given in the Appendix. The model equation for one-layered model can be given similarly by changing the integral from lumen to outer radius and assuming the uniform material properties across the wall (Lee et al., 2012; Liu et al., 2014).

2.3 Determination of model parameters

2.3.1 Determination of collagen dispersion parameter κ —In order to determine the dispersion parameter κ , we assumed that the collagen fibers were distributed according to a π -periodic von Mises distribution (Gasser et al., 2006; Wang et al., 2014). The standard π -periodic von Mises distribution was modified to:

$$\bar{\rho}(\theta) = \frac{e^{[b(\cos(\theta-\mu))]} }{2\pi I_0(b)} \quad (9)$$

Where θ denotes the angle, b is the concentration parameter, μ is the principal fiber orientation, and I_0 is the modified Bessel function of the first kind of zeroth order. The normalization equation is

$$\int_0^\pi \rho(\theta) \sin \theta d\theta = 2 \quad (10)$$

Since our experimental observation showed that the collagen fibers in adventitia layer are distributed around two distinct mean orientation, a weighted mixture of two von Mises distribution function

$$\rho_{mix} = w\rho_1(\theta) + (1-w)\rho_2(\theta) \quad (11)$$

was fitted to the fiber angle data (and also normalized using equation Eq. (10)) to determine four parameters b_1, μ_1, b_2, μ_2 using maximum likelihood estimation (MLE). Where the w being the mixing weight with $w > 0$.

The dispersion parameter was calculated by numerical integration and represents the fiber distribution in an integral sense as described previously (Gasser et al., 2006):

$$\kappa = \frac{1}{4} \int_0^\pi \rho(\theta) \sin^3(\theta) \theta d\theta \quad (12)$$

2.3.2 Determining Material Constants of individual layers—The material constants c_j , b_{1j} , b_{2j} for the intima-media layer and adventitia layer were determined by fitting the experimental data using least square fitting to minimize the square of the differences of lumen pressure P and axial force N between theoretical values and experimental data:

$$\delta^2 = \sum_{i=1}^n \left[\left(\frac{P_t - P_{exp}}{P_{exp}} \right)_i^2 + \left(\frac{N_t - N_{exp}}{N_{exp}} \right)_i^2 \right] \quad (13)$$

Where n is the number of experimentally measured data point during the inflation test.

The fitting was done in two steps to determine all the parameters for both intima-media and adventitia layers. First, the constants for the intima-media layer were determined by fitting inflation testing data of the intima-media layer with lumen pressure P and axial force N given only by the first terms in equations (3) and (4), respectively. Then, the material constants for the adventitia layer was determined by fitting inflation testing data of the intact arteries with lumen pressure P and axial force N given in equations (3) and (4). The constants for the intima-media layer obtained in the first step were used as known input in the second step.

3. Results

3.1 Collagen alignment and dispersion

By fitting collagen fiber distribution data with modified von Mises distribution given in equations (9) to (12), we found that two dominant fiber families in the adventitia layer while only a single fiber family closely aligned along circumferential direction in media layer (Figures 2 & 3). Table 1 presents the fiber orientation and dispersion parameter for the intima-media and adventitia layers of 7 porcine carotid arteries. Note that the dispersion parameter for the adventitia layer is the mean value of the two distinct dispersion parameters obtained for each existing dominant fiber family.

The initial dimensions and opening angle of the arteries measured are summarized in Table 2. The middle radius (diameter) obtained from histology are also listed in Table 2.

3.2 Constitutive Parameters

The constitutive parameters c_j , b_{1j} , b_{2j} obtained are given in Table 3. With these parameters, the circumferential and axial stretch versus pressure plots match well with experimental data (Figure 4). The material properties for the one-layered arterial wall model were calculated by using dispersion parameter obtained for adventitia layer since adventitia is the dominating layer for collagen fiber distribution.

3.3 Critical buckling pressures

Critical buckling pressures estimated at different axial stretch ratios (1.0–1.7) using the two-layered arterial wall model with fiber depression are comparable to the experimental data (Figure 5). In general the critical buckling pressure estimated using the one-layered arterial wall model was high than the critical buckling pressure estimated using the two-layered model. E.g. the predicted critical buckling pressure at a stretch ratio of 1.6 using one-layered and two-layered models was 18.29 ± 3.57 kPa and 13.14 ± 1.73 kPa, respectively, compared to 15.67 ± 3.53 kPa obtained from experimental measurements. The estimated critical buckling pressures obtained using both the two-layered and one-layered models correlated strongly with the experimental measurements (with $R^2 = 0.88 \pm 0.09$ and 0.89 ± 0.07 , respectively).

3.4 Effect of dispersion parameter on critical buckling pressure

To illustrate the effect of collagen fiber dispersion, experimental data were re-analyzed using the two-layered model with the fiber dispersion set to zero ($\kappa = 0$). Our results showed that the critical buckling pressure estimated by the two-layered model with fiber dispersion set to zero was lower than the two-layered model with dispersed collagen fiber (see Figure 5). Further parametric studies showed that the critical buckling pressure increases with increasing dispersion parameter κ in the range of $[0, \frac{1}{3}]$ in the adventitia layer while other material parameters were kept unchanged (Figure 6). This behavior was explained by previous studies which shown that larger dispersion will increase the stiffness and reduces the dependence of the response on the mean orientation of the families of collagen fiber (Gasser et al., 2006).

3.5 Effect of mean fiber angle in adventitia on the critical buckling pressure

To investigate the effect of mean fiber angle on critical buckling pressure, a parametric study was performed with increasing the fiber angle in adventitia while all other parameters remained the constant. The results indicate that with alignment of collagen fibers toward axial direction the critical buckling pressure increases (Figure 7). This trend agrees with the trend observed in a 4-fiber model reported in our previous study (Liu et al., 2014).

4. Discussion

In this study we determined the dispersed collagen fiber distribution in porcine carotid arteries and established the artery buckling equations using the two-layered, structurally motivated, fiber reinforced arterial wall model. Critical buckling pressure was estimated at axial stretch ratios from the sub-physiological to hyper-physiological range. The model estimated buckling pressure demonstrated a reasonable increasing trend with respect to increasing axial stretch ratio as compared to experimental measurements.

A novelty of this paper is the inclusion of two-layered model as compared to all previous buckling analyses that were based on homogenous 1-layered model (Han, 2009; Lee et al., 2012; Rachev, 2009). Our previous study demonstrated that the four-fiber reinforced arterial wall model overestimated the critical pressure of arteries compared to the Fung model, especially in the high axial stretch ratio range (Liu et al., 2014). The critical pressures predicted by the two-layered model were lower than the critical buckling predicted by the

one-layered model in five of the seven arteries tested. Compared to the one-layered arterial model, the two-layered model was slightly better in predicting the critical buckling pressure as compared to experimental measurement (It is better in three arteries while being the same for the other four arteries, see Figure 5). Though the mechanism for the improvement is not clear and need further study, we suspect that it may be related to the better representation of the transmural variation of stress and stiffness.

Another novelty is the inclusion of experimentally measured fiber dispersion in the model. This improves our previous four fiber model by incorporating the actual fiber dispersion measured from the arteries. The parametric studies showed that critical buckling pressure increased with increasing dispersion parameter probably due to the increase in stiffness in the axial direction, since our previous model and simulations showed that the critical pressure is more affected by the longitudinal stiffness since the buckling is a bending deformation in the axial direction (Han, 2009; Lee et al., 2012). Compared to the model without collagen dispersion ($\kappa=0$, which is equivalent to a two-fiber model), the model incorporate fiber dispersion slightly better predict the critical pressure.

Though the microstructure-based constitutive models have been widely used, most reports used fitting of load-deformation (or stress-strain curve) data to determine material constants and very few reports of using experimental measurement of collagen microstructure, especially for dispersion parameter κ (Avril et al., 2013; Badel et al., 2013; Wan et al., 2012; Wang et al., 2014). The material parameters obtained in this paper will also be useful for computational simulations of arterial wall.

One limitation in this work is that for the determination of material constants, we did not perform sensitivity study and we assumed that the possibility of over-parameterization is low for two reasons: first, our experimental data demonstrated the two peak distribution and the dispersion model was a two-fiber family based model as shown by equation (11). Our previous work using a four-fiber family has demonstrated that the two diagonal fiber families played a dominating role and the other two (circumferential and axial) families are negligible (Liu et al., 2014). So by using the two fiber family based model, we have eliminated unnecessary parameters. Second, the strain energy function employed has been shown to be effective in describe arterial wall behavior in previous studies (Gasser et al., 2006; Wang et al., 2014).

Since our previous work has demonstrated the effect of surrounding tissue matrix (Han, 2009), here we excluded the surrounding tissue for simplicity and clarity in illustrated the relationship between collagen fiber distribution and critical buckling pressure and also for comparison with our previous 4-fiber model (Liu et al., 2014) in order to illustrate the effect of including experimentally measured dispersion parameter κ . Since surrounding tissue will be an add-on effect, we expect the inclusion of surrounding tissue will not change the trend and conclusion of the current model results. The effect of surrounding tissue can be incorporated into future work for in vivo animal studies or clinical patient studies. Another limitation of our model is that we ignored the effect of muscles contraction which has shown a significant effect on the critical buckling pressure (Hayman et al., 2013) and needs further study. While limitations exist, the use of the two-layered model with dispersed collagen fiber

provides an approach better link arterial mechanical stability to specific structural changes in the media and/or adventitia layers as well as to microstructural changes under pathological conditions due to aging, atherosclerosis and arterial degenerative diseases. Furthermore, our previous work has demonstrated elastin degradation in arteries reduces the critical buckling pressure (Lee et al., 2012; Luetkemeyer et al., 2015). Combined, these studies demonstrated arterial mechanical stability is linked to the extracellular matrix of the arterial wall.

In conclusion, we expanded the artery buckling model by incorporating the experimental measurement of microstructure of the arterial wall. The new model allows us to link the microstructure (two-layered wall, collagen fiber distribution) with the buckling behavior of arteries.

Acknowledgments

This work was supported by grant R01HL095852 and partially supported by HHSN 268201000036C (N01-HV-00244) for the San Antonio Cardiovascular Proteomics Center, both from the National Institutes of Health and grant 11229202 from National Natural Science Foundation of China. We thank Drs. Qin Liu, Yangming Xiao, and Andrew Voorhees, and Ms. Aida Nasirian for their help in this study.

References

- Avril S, Badel P, Gabr M, Sutton MA, Lessner SM. Biomechanics of porcine renal arteries and role of axial stretch. *Journal of biomechanical engineering*. 2013; 135:81007. [PubMed: 23722353]
- Badel P, Rohan CP, Avril S. Finite Element simulation of buckling-induced vein tortuosity and influence of the wall constitutive properties. *J Mech Behav Biomed Mater*. 2013; 26:119–126. [PubMed: 23746700]
- Baek S, Gleason RL, Rajagopal KR, Humphrey JD. Theory of small on large: Potential utility in computations of fluid-solid interactions in arteries. *Comput Method Appl M*. 2007; 196:3070–3078.
- Bellini C, Ferruzzi J, Roccabianca S, Di Martino ES, Humphrey JD. A microstructurally motivated model of arterial wall mechanics with mechanobiological implications. *Ann Biomed Eng*. 2014; 42:488–502. [PubMed: 24197802]
- Burger, W.; Burge, MJ. *Digital Image Processing: An Algorithmic Introduction Using Java*. Springer London; New York: 2008.
- Burger, W.; Burge, MJ. *Principles of Digital Image Processing: Core Algorithms*. Springer London; London: 2009.
- Canham PB, Finlay HM, Dixon JG, Boughner DR, Chen A. Measurements from light and polarised light microscopy of human coronary arteries fixed at distending pressure. *Cardiovasc Res*. 1989; 23:973–982. [PubMed: 2611805]
- Del Corso L, Moruzzo D, Conte B, Agelli M, Romanelli AM, Pastine F, Protti M, Pentimone F, Baggiani G. Tortuosity, kinking, and coiling of the carotid artery: expression of atherosclerosis or aging? *Angiology*. 1998; 49:361–371. [PubMed: 9591528]
- Fung, YC. *Biomechanics: Mechanical Properties of Living Tissues*. 2. Springer Verlag; New York: 1993.
- Gasser TC, Ogden RW, Holzapfel GA. Hyperelastic modelling of arterial layers with distributed collagen fibre orientations. *Journal of The Royal Society Interface*. 2006; 3:15–35.
- Han HC. Blood vessel buckling within soft surrounding tissue generates tortuosity. *J Biomech*. 2009; 42:2797–2801. [PubMed: 19758591]
- Han HC. Twisted Blood Vessels: Symptoms, Etiology and Biomechanical Mechanisms. *Journal of Vascular Research*. 2012; 49:185–197. [PubMed: 22433458]
- Han HC, Chesnutt JKW, Garcia JR, Liu Q, Wen Q. Artery Buckling: New Phenotypes, Models, and Applications. *Annals of biomedical engineering*. 2013; 41:1399–1410. [PubMed: 23192265]

- Haralick, RM.; Shapiro, LG. Computer and robot vision. Addison-Wesley Pub. Co; Reading, Mass: 1992.
- Hayman DM, Zhang J, Liu Q, Xiao Y, Han HC. Smooth muscle cell contraction increases the critical buckling pressure of arteries. *Journal of Biomechanics*. 2013; 46:841–844. [PubMed: 23261241]
- Holzapfel GA, Gasser TC, Ogden RW. A new constitutive framework for arterial wall mechanics and a comparative study of material models. *J Elasticity*. 2000; 61:1–48.
- Humphrey, JD. Cardiovascular Solid Mechanics: Cells, Tissues, and Organs. Springer; New York: 2002.
- Jackson ZS, Dajnowiec D, Gotlieb AI, Langille BL. Partial off-loading of longitudinal tension induces arterial tortuosity. *Arterioscler Thromb Vasc Biol*. 2005; 25:957–962. [PubMed: 15746437]
- Jähne, B. Digital image processing. Springer; New York; Berlin: 2005.
- Lee AY, Han B, Lamm SD, Fierro CA, Han HC. Effects of elastin degradation and surrounding matrix support on artery stability. *American Journal of Physiology - Heart and Circulatory Physiology*. 2012; 302:H873–H884. [PubMed: 22159998]
- Liu Q, Han HC. Mechanical buckling of artery under pulsatile pressure. *J Biomech*. 2012; 45:1192–1198. [PubMed: 22356844]
- Liu Q, Wen Q, Mottahedi M, Han HC. Artery buckling analysis using a four-fiber wall model. *Journal of Biomechanics*. 2014; 47:2790–2796. [PubMed: 24972920]
- Luetkemeyer CM, James RH, Devarakonda ST, Le VP, Liu Q, Han HC, Wagenseil JE. Critical buckling pressure in mouse carotid arteries with altered elastic fibers. *Journal of the mechanical behavior of biomedical materials*. 2015; 46:69–82. [PubMed: 25771258]
- Nichols, WW.; O'Rourke, MF. McDonald's Blood Flow in Arteries: Theoretical, Experimental, and Clinical Principles. 4. Vol. Chapter 16. Arnold Publisher; London: 1998.
- Otsu N. A Threshold Selection Method from Gray-Level Histograms. *Systems, Man and Cybernetics, IEEE Transactions on*. 1979; 9:62–66.
- Pancera P, Ribul M, Presciuttini B, Lechi A. Prevalence of carotid artery kinking in 590 consecutive subjects evaluated by Echocolor Doppler. Is there a correlation with arterial hypertension? *J Intern Med*. 2000; 248:7–12. [PubMed: 10947875]
- Qi N, Gao H, Ogden RW, Hill NA, Holzapfel GA, Han HC, Luo X. Investigation of the optimal collagen fibre orientation in human iliac arteries. *Journal of the mechanical behavior of biomedical materials*. 2015; 52:108–119. [PubMed: 26195342]
- Rachev A. Theoretical study of the effect of stress-dependent remodeling on arterial geometry under hypertensive conditions. *J Biomech*. 1997; 30:819–827. [PubMed: 9239567]
- Rachev A. A theoretical study of mechanical stability of arteries. *Journal of biomechanical engineering*. 2009; 131:051006. [PubMed: 19388776]
- Ren JS. Effects of dispersion of fiber orientation on the mechanical property of the arterial wall. *Journal of theoretical biology*. 2012; 301:153–160. [PubMed: 22391392]
- Soille P. Morphological Image Analysis: Principles and Applications. *Sensor Review*. 2000; 20
- Stojmenovic, M.; Nayak, A. Direct Ellipse Fitting and Measuring Based on Shape Boundaries. Springer Berlin Heidelberg; Berlin, Heidelberg: 2007. p. 221–235.
- van der Walt S, Schönberger JL, Nunez-Iglesias J, Boulogne F, Warner JD, Yager N, Gouillart E, Yu T. scikit-image: image processing in Python. *PeerJ*. 2014; 2:e453. [PubMed: 25024921]
- Wan W, Dixon JB, Gleason RL Jr. Constitutive modeling of mouse carotid arteries using experimentally measured microstructural parameters. *Biophys J*. 2012; 102:2916–2925. [PubMed: 22735542]
- Wang C, Garcia M, Lu X, Lanir Y, Kassab GS. Three-dimensional mechanical properties of porcine coronary arteries: a validated two-layer model. 2006
- Wang R, Raykin J, Li H, Gleason RL Jr, Brewster LP. Differential mechanical response and microstructural organization between non-human primate femoral and carotid arteries. *Biomech Model Mechanobiol*. 2014; 13:1041–1051. [PubMed: 24532266]
- Weibel J, Fields WS. TORTUOSITY, COILING, AND KINKING OF THE INTERNAL CAROTID ARTERY. I. ETIOLOGY AND RADIOGRAPHIC ANATOMY. *Neurology*. 1965; 15:7–7. [PubMed: 14257832]

Yu Q, Zhou J, Fung YC. Neutral axis location in bending and Young's modulus of different layers of arterial wall. The American journal of physiology. 1993; 265:H52–60. [PubMed: 8342664]
 Zhang J, Liu Q, Han HC. An in vivo rat model of artery buckling for studying wall remodeling. Ann Biomed Eng. 2014; 42:1658–1667. [PubMed: 24793586]

Appendix: Artery buckling equation

For cylindrical arterial wall, the Green strain components are (Humphrey, 2002)

$$E_r = \frac{1}{2} (\lambda_r^2 - 1), \quad E_\theta = \frac{1}{2} (\lambda_\theta^2 - 1), \quad E_z = \frac{1}{2} (\lambda_z^2 - 1) \quad (A1)$$

where λ_r , λ_θ and λ_z are the stretch ratios in the radial, circumferential and axial directions, respectively.

The equation of equilibrium in a cylindrical artery is

$$\frac{\partial \sigma_r}{\partial r} + \frac{\sigma_r - \sigma_\theta}{r} = 0 \quad (A2)$$

with boundary conditions:

$$\sigma_r|_{r=r_i} = -P; \quad \sigma_r|_{r=r_e} = 0; \quad (A3)$$

Where P is the lumen pressure, r_i and r_e are the inner and outer radii.

For two-layered arterial wall, we assume that the two layers divides at a radius of r_m and have strain energy density functions ψ_j ($j=IM, A$ for intima-media and adventitia layers, respectively). The Cauchy stresses in cylindrical coordinates are given by (Humphrey, 2002)

$$\sigma_i^j = \lambda_i^2 \frac{\partial \psi_j}{\partial E_i} + K_j, \quad i=r, \theta, z; j=IM, A \quad (A4)$$

where K_j is the Lagrangian multiplier which enforces incompressibility. By integrating the equation of equilibrium (A2) for radius r in the range of (r_i, r_m) and (r_m, r_e) , respectively, and using boundary conditions (A3), the radial stress component of intima-media and adventitia layers are given by:

$$\sigma_r^{IM} = \int_{r_i}^r \left(\lambda_\theta^2 \frac{\partial \psi_{IM}}{\partial E_\theta} - \lambda_r^2 \frac{\partial \psi_{IM}}{\partial E_r} \right) \frac{dr}{r} - P \quad (A5)$$

$$\sigma_r^A = \int_{r_e}^r \left(\lambda_\theta^2 \frac{\partial \psi_A}{\partial E_\theta} - \lambda_r^2 \frac{\partial \psi_A}{\partial E_r} \right) \frac{dr}{r} \quad (A6)$$

Taking equations A5 & A6 into A4 yields

$$\sigma_z^{IM} = (\lambda_z^2 \frac{\partial \psi_{IM}}{\partial E_z} - \lambda_r^2 \frac{\partial \psi_{IM}}{\partial E_r}) + \int_{r_i}^r \left(\lambda_\theta^2 \frac{\partial \psi_{IM}}{\partial E_\theta} - \lambda_r^2 \frac{\partial \psi_{IM}}{\partial E_r} \right) \frac{dr}{r} - P \quad (A7)$$

$$\sigma_z^A = (\lambda_z^2 \frac{\partial \psi_A}{\partial E_z} - \lambda_r^2 \frac{\partial \psi_A}{\partial E_r}) + \int_{r_e}^r \left(\lambda_\theta^2 \frac{\partial \psi_A}{\partial E_\theta} - \lambda_r^2 \frac{\partial \psi_A}{\partial E_r} \right) \frac{dr}{r} \quad (A8)$$

At the transition from media to adventitia layer $r = r_m$, stress continuity equation is:

$$\sigma_r^{IM}|_{r=r_m} = \sigma_r^A|_{r=r_m}, \quad (A9)$$

Taking equations A5 and A6 into A9 yields the lumen pressure P given by equation (3) in the text and integrating the axial stress σ_z over the cross-sectional area yields the axial force N given by equation (4) in the text (Lee et al., 2012).

When buckling occurs at critical pressure, arteries deform into a sinusoidal shape with small central line deflection u_c and an incremental axial strain, E_z . Using equations A7 and A8, the incremental stress due to incremental axial strain E_z can be expressed as (Lee et al., 2012; Liu et al., 2014):

$$\Delta \sigma_z^{IM} = J_{z,IM} \Delta E_z + \int_{r_i}^r J_{\theta,IM} \Delta E_z \frac{d\xi}{\xi} \quad (A10)$$

$$\Delta \sigma_z^A = J_{z,A} \Delta E_z + \int_{r_e}^r J_{\theta,A} \Delta E_z \frac{d\xi}{\xi} \quad (A11)$$

Where $J_{z,j}$ and $J_{\theta,j}$ ($j=IM, A$) are corresponding to the expressions given in equations (7) and (8). Accordingly, by determining the bending moment of the incremental axial stress across the cross sectional area, the buckling equation can be obtained as given in equation (5) in the text (Lee et al., 2012; Liu et al., 2014).

Highlights

- Artery buckling equation for two-layered wall with collagen fiber dispersion.
- Critical buckling pressure increases nonlinearly with increasing axial stretch.
- An increase in collagen fiber dispersion increases the critical buckling pressure.
- Collagen fibers align towards axial direction increases critical buckling pressure.

Figure 1. Representative microscopic image of adventitia layer stained with Picrosirius red staining (*Top*), and magnified image of the region in the black box converted to binary image (*Middle*) and the image after the opening and closing operations were performed (*Bottom*).

Figure 2.

Representative microscopic image of an adventitia (*Top*) and media (*Bottom*) slides obtained from porcine carotid artery with Picrosirius red staining for analysis and measurement of fiber orientation.

Figure 3.

Histogram of collagen orientation in the adventitia layer of an artery (artery 5). Two distinct fiber families detected corresponding to two peaks. The angle α_0 is the half the distance between the two peaks indicated by two red lines.

Figure 4.

Representative plots of pressure-circumferential stretch ratio at the outer wall (*Left*) and pressure-axial stretch ratio (*Right*) of an intact artery. The initial outer diameter and length of the artery were 6.66 mm and 55 mm. The stretch ratios are the ratios of the deformed diameter and length with respect to their initial values, respectively. The circles represent the experimental data and solid lines are the fitting curves.

Figure 5.

Comparison of critical buckling pressure estimated from the two-layered model (solid line), one-layered wall model (dash line), and two-layered model with depression parameter set to zero (dotted line) with experimental measurements (○).

Figure 6.

The effect of increasing dispersion parameter on critical buckling pressure. The dispersion parameter was increased from 0 to 0.3.

Figure 7.

The effect of adventitia mean fiber angle on critical buckling pressure. The fiber angle was changes while all other parameters were kept unchanged.

Table 1

Fiber orientation and fiber dispersion parameters. The reported mean fiber orientation angles were measured with respect to circumferential direction

	Intima-Media		Adventitia	
	Fiber orientation(degree)	κ_{IM}	Fiber orientation(degree)	κ_A
Artery 1	2.971	0.015	39.570	0.105
Artery 2	-1.646	0.023	47.350	0.113
Artery 3	3.870	0.017	46.580	0.099
Artery 4	4.432	0.017	37.600	0.106
Artery 5	8.264	0.013	38.280	0.100
Artery 6	0.123	0.010	39.230	0.105
Artery 7	3.361	0.016	34.590	0.116
Mean	3.067	0.016	40.605	0.107
$\pm$ SD	2.940	0.004	4.385	0.006

Table 2

Summary of the initial dimensions of the arteries and the opening angle for intact and intima-media.

<i>Artery ID</i>	Length (mm)	Outer Diameter (mm)	Inner Diameter (mm)	Middle Diameter, R_m (mm)	Opening Angle (degrees)	
					Intact	Intima-Media
<i>1</i>	72.79	7.24	4.40	6.58	92.99	196.81
<i>2</i>	37.90	5.58	2.85	5.18	165.08	85.24
<i>3</i>	50.24	6.09	3.08	5.64	147.38	162.34
<i>4</i>	45.19	5.45	2.82	5.07	127.06	125.75
<i>5</i>	53.30	5.43	3.03	5.14	149.66	140.06
<i>6</i>	55.57	5.59	2.74	5.18	124.94	116.12
<i>7</i>	55.09	6.66	3.96	6.29	156.90	72.15
<i>Mean</i>	52.87	6.00	3.27	5.58	137.72	128.35
$\pm SD$	9.99	0.65	0.60	0.57	22.77	39.92

Table 3

Constitutive parameters (c , b_1 , b_2) in equation (1) obtained from experimental data of the intact wall and media.

Artery	Intact			Intima-Media			Adventitia		
	C	b_1	b_2	C_{IM}	b_{1IM}	b_{2IM}	C_A	b_{1A}	b_{2A}
Artery 1	7.5060	6.4040	1.3010	9.4330	1.1800	0.6700	0.0001	1.9602	0.0078
Artery 2	15.6500	3.7440	0.9100	0.0100	7.5680	0.0100	11.3917	98.5136	1.5738
Artery 3	9.0770	2.1830	1.3050	5.8830	0.3170	7.1570	0.0001	11.2688	1.2624
Artery 4	8.1090	0.1290	0.9280	5.2130	0.0060	15.3300	1.2340	5.0125	13.3540
Artery 5	5.7410	0.1040	1.4000	0.0100	0.0100	1.9950	0.7413	50.1036	4.3999
Artery 6	5.4010	1.3160	0.4000	7.7120	0.1000	0.7220	1.3862	1.4929	2.5751
Artery 7	5.2190	1.6700	0.9960	2.0000	0.1600	0.5660	1.1346	0.0123	6.7252