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Multi-scale modeling of the lamellar unit of arterial media

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Research Article

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Abstract: The heterogeneity of the lamellar unit (LU) of arterial media plays an important role in the biomechanics of artery. Current two-component (fibrous component and a homogenous matrix) constitutive model is inappropriate for capturing the micro-structural variations in the LU, such as contraction/relaxation of vascular smooth muscle cells (VSMCs), fragmentation of the elastin layer, and deposition/disruption of the collagen network. In this work, we developed a representative volume element (RVE) model with detailed micro-configurations, *i.e.*, VSMCs at various phenotypes, collagen fibers, and elastin laminate embedded in the ground substance. The fiber architecture was generated based on its volume fraction and orientations. Our multi-scale model demonstrated the relation between the arterial expansion and the micro-structural variation of the lamellar unit. The obtained uniaxial response of the LU was validated against the published experimental data. The load sharing capacity of fibrous component and VSMCs of the LU were obtained. We found that the VSMC could take 30% of the circumferential load when contracted until the collagen fibers were recruited, while this value was less than 2% for the relaxed VSMC. In addition, the contribution of collagen fibers at low stretch levels was negligible but became predominant when straightened in high stretches. Moreover, aging effects by collagen deposition was modeled to estimate the arterial stiffening. It was revealed that the aortic stiffness is mainly controlled by collagen fibers, instead of VSMCs. Our findings could shed some light about the contribution of VSMCs in arterial stiffness which has been under debate in recent years.

Keywords: VSMC; ECM; artery; aorta; RVE; stiffening; multi-scale modeling

1 Introduction

Cardiovascular disease accounts for 17.3 million deaths globally and one of every four deaths in the United States each year [1]. Increased arterial stiffness, also referred to as, arterial stiffening, is the biomarker for many diseases, including heart failure, myocardial infarction, stroke, vascular dementia, and chronic kidney disease [2]. Arterial stiffening is also considered as one of the pathophysiological mechanisms contributing to the development of hypertension [3].

The stiffness of the arterial wall is strongly dependent on the structure and integrity of its lamellar units (LU) (*i.e.*, vascular smooth muscle cells [VSMCs] encompassed by elastic lamellae and interposed with a collagen fiber network) [4]. Collagen deposition and elastin breakdown in the extra cellular matrix (ECM) has been widely acknowledged as the predominant mechanism of arterial stiffening [5]. However, it was also reported that ECM adaptions were not consistently observed in hypertensive arteries [6]. In some cases, clinical hypertension measurements detected a reduction in vascular collagen content [7]. This might be associated with the mechanical contribution of the VSMCs [8], while controversy also exists regarding this [9].

The VSMCs' relaxation can potentially occur in concert with an increase, a decrease, or no change in vascular wall stiffness [10]. It has been hypothesized that VSMCs' relaxation softened arterial stiffness by reducing tension generated by the VSMCs themselves. On the other hand, VSMCs' relaxation could increase the arterial stiffness by engaging stiff collagen fibers. Moreover, it was observed that the total arterial stiffness was directly related to the VSMCs' stiffness [11]. It was demonstrated that the adaptation of a hypertensive artery was caused by the phenotype changes in VSMCs, from contractile to synthetic, which led to more collagen fibers. In the synthetic phe-

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notype, the stiffness of VSMCs was lower than that of the contractile phenotype, while the total arterial stiffness was higher [3]. This inverse relation between the VSMCs' stiffness and the arterial wall was based on the VSMC phenotypes. Although the arterial stiffening has been well documented in human and animal models, the contribution of the VSMCs to mechanics of the LU unit has not been quantified yet. This was attributed to the complexity of the LU micro-structure, nonlinear properties of the fibrous network, and interaction between the VSMCs and ECM [12].

Several structurally motivated constitutive models for the arterial wall have been recently developed [13–17]. Nakamachi *et al.* created a multi-scale model in which a two-layer aorta was considered with the LU modeled by a representative volume element (RVE) consisting of a VSMC embedded in a homogenous ECM [18]. They illustrated the stresses and strains of the VSMC under tension; however, the heterogeneity of the fibrous part of the LU, the waviness of collagen fibers, and the constituent's volume fractions, were neglected.

In this work, a multi-scale model has been developed to characterize the load sharing capacity of the VSMC in the LU and the corresponding aortic wall deformation. An RVE model was constructed by considering the architecture of collagen fibers based on their volume fraction and distribution, and the nonlinear response in tension. The obtained mechanical response of the RVE was imported to a macro-scale model of the three-layer aortic wall (*i.e.*, intima, media, and adventitia) to capture its deformation under the physiological blood pressure. The contribution of VSMCs to load sharing of the artery was then characterized at various stretch levels and cellular contraction states. Moreover, the effects of aging through deposition of collagen fibers and fragmentation of elastin fibers could be studied. The developed model allowed us to incorporate the micro-structural variation of the LU induced by aging and the resulting changes in aortic mechanical behavior.

2 Materials and methods

2.1 Micro-mechanical modeling

A 3D RVE was constructed to capture the biomechanical response of a single lamellar unit. The average lamella thickness of 1.5 μm and an interlamellar (IL) spacing of 10 μm were adopted [19]. We exploited the LU symmetry in the circumferential and radial directions and considered a VSMC embedded in the ECM. The volume fraction of elastin fibers within the lamella has been estimated as 85% [20]. The orientation histogram revealed that planar dispersion of the elastin and collagen fibers is in the longitudinal-circumferential plane (Figure 1). This allows us to treat lamella as a homogenous solid section attached to the interlamellar space (Figure 2). The volume fractions and geometric dimensions of each component of LU are listed in Table 1. The contracted VSMC is approximately eight times stiffer than its relaxed state. The VSMC could be defined as either relaxed or contracted condition by adopting the relevant elastic modulus.

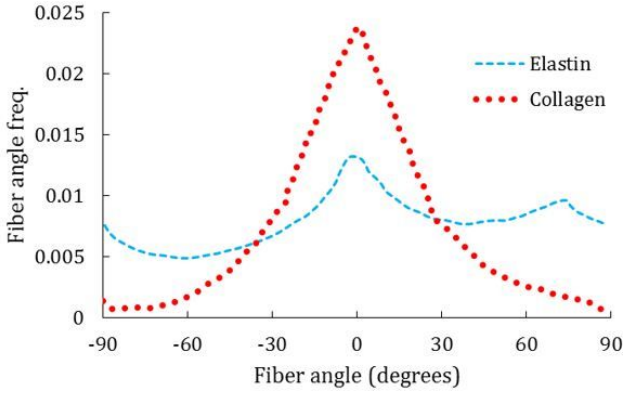

Figure 1: Distribution of collagen and elastin in LU; Angle of 0o means circumferential direction and 90o is along the length of artery [20]

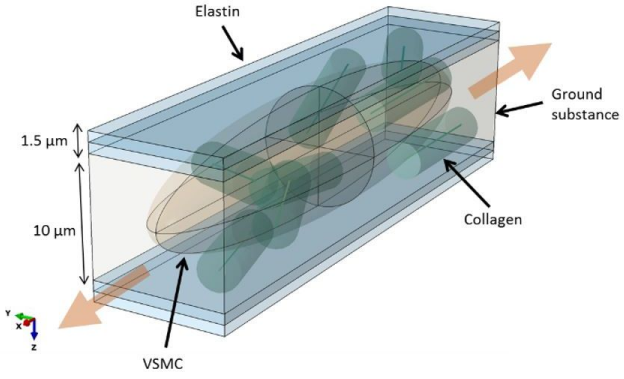

Figure 2: The developed RVE model of lamellar unit (LU)

For collagen fibers, a bilinear constitutive response was adopted to capture the effect of the fiber waviness [23]:

$$\sigma = \begin{cases} 0 & , \lambda < \lambda_{Collagen} \\ E_{Collagen}\left(\lambda - \lambda_{Collagen}\right) & , \lambda \geq \lambda_{Collagen} \end{cases} \quad (1)$$

where λ is the current stretch ratio of fibers, $\lambda_{Collagen}$ is the recruitment stretch criteria, and $E_{Collagen}$ is the elastic

Table 1: The volume fraction and geometry of RVE constituents

Component	Volume fraction (%) [11]	Geometry (Units are in μm)
VSMC	47	Major radius = 20 [19] Minor radius = 4.5
Elastin laminate	13	Thickness = 1.5 [21]
Collagen fiber	12	Diameter = 3 [22] Length = 9
Ground substance	28	Length × Width × Height = 10 × 10 × 40

Table 2: Mechanical properties of RVE

Role	Parameter	Fitted value
VSMC	E_{VSMC}	0.0881 MPa (Contracted) [24] 0.0148 MPa (Relaxed) [24]
Elastin laminate	$E_{Elastin}$	0.6 MPa [25]
	$\lambda_{Elastin}$	1
Collagen fiber	$E_{Collagen}$	80 MPa [26]
	$\lambda_{Collagen}$	1.4 [27]
Ground substance	E_{GS}	0.0001 MPa

modulus of the fiber. Collagen fibers with $\lambda < \lambda_{Collagen}$ do not sustain any loading. The bundle of collagen fibers had a diameter of 3 μm [22]. Table 2 summarizes the mechanical properties adopted in our RVE configuration.

The RVE was subjected to a circumferential stretch of $\lambda = 1.5$. The obtained stress-strain response of LU was then imported into the macro-mechanical model described below.

2.2 Macro-mechanical modeling

A model of the aortic cross section with its three-layer structure (*i.e.*, intima, media, and adventitia) was developed as shown in Figure 3. Current computational models of the multi-layer artery were summarized in Table 3. These layer-specific artery models were used for estimating the residual strain, unloaded configuration, and stress state in the arterial wall. Considering the axial symmetry of the aorta, only ¼ of the cross section was modeled. The inner diameter of the aorta was 25 mm with a thickness of 1.5 mm. Following the mesh sensitivity analyses, the model was discretized with 1608 CPS4R elements. The cyclic internal pressure profile mimicking the physiological blood load was applied.

The hyperelastic behaviors of the intima and adventitia layers were adopted from the published experimental data [38], which were fitted using the reduced polynomial constitutive equation:

$$U = \sum_{i,j=1}^{3} C_{ij}(I_1 - 3)^i(I_2 - 3)^j \tag{2}$$

where, I_1 and I_2 are the first and second invariants of the Cauchy-Green tensor. The fitted material coefficients C_{ij} are listed in Table 4. While for the media layer, we extracted the mechanical response from the aforementioned RVE model, validated against the uniaxial test data of the media layer (Figure 4). Our micro-scale simulation captured the hyperelastic behavior of the media layer. The media stiffness varies on the level of blood pressure. At higher blood pressure, it stiffened sharply due to the engagement of collagen fibers in load bearing. The difference between the simulation and experiment could be attributed to the forced separation of the media layer from adventitia/intima layers [37].

Table 3: A summary of computational models of arterial walls, and the applied material properties

Conducted research	Geometry and deformation type	Number of layers	Material properties
Von Maltzahn *et al.* [28]	Cylinder (axisym.)	2	Isotropic, anisotropic
Chuong *et al.* [29]	Cylinder (axisym.)	1	Isotropic
Delfino *et al.* [30]	Bilateral, bifurcated	1	Isotropic
Holzapfel *et al.* [31]	Cylinder (axisym.)	2	Orthotropic
Taber and Humphery [32]	Cylinder (axisym.)	2	Orthotropic
Ohayon *et al.* [33]	2D FE model	2	Isotropic
Holzapfel and Ogden [34]	Cylinder (axisym.)	3	Isotropic
Sommer and Holzapfel [35]	Cylinder (axisym.)	2	Isotropic or Orthotropic
Kural *et al.* [36]	3D (FSI)	1	Transversely isotropic
Monir *et al.* [37]	Ring-like FE model	3	Isotropic

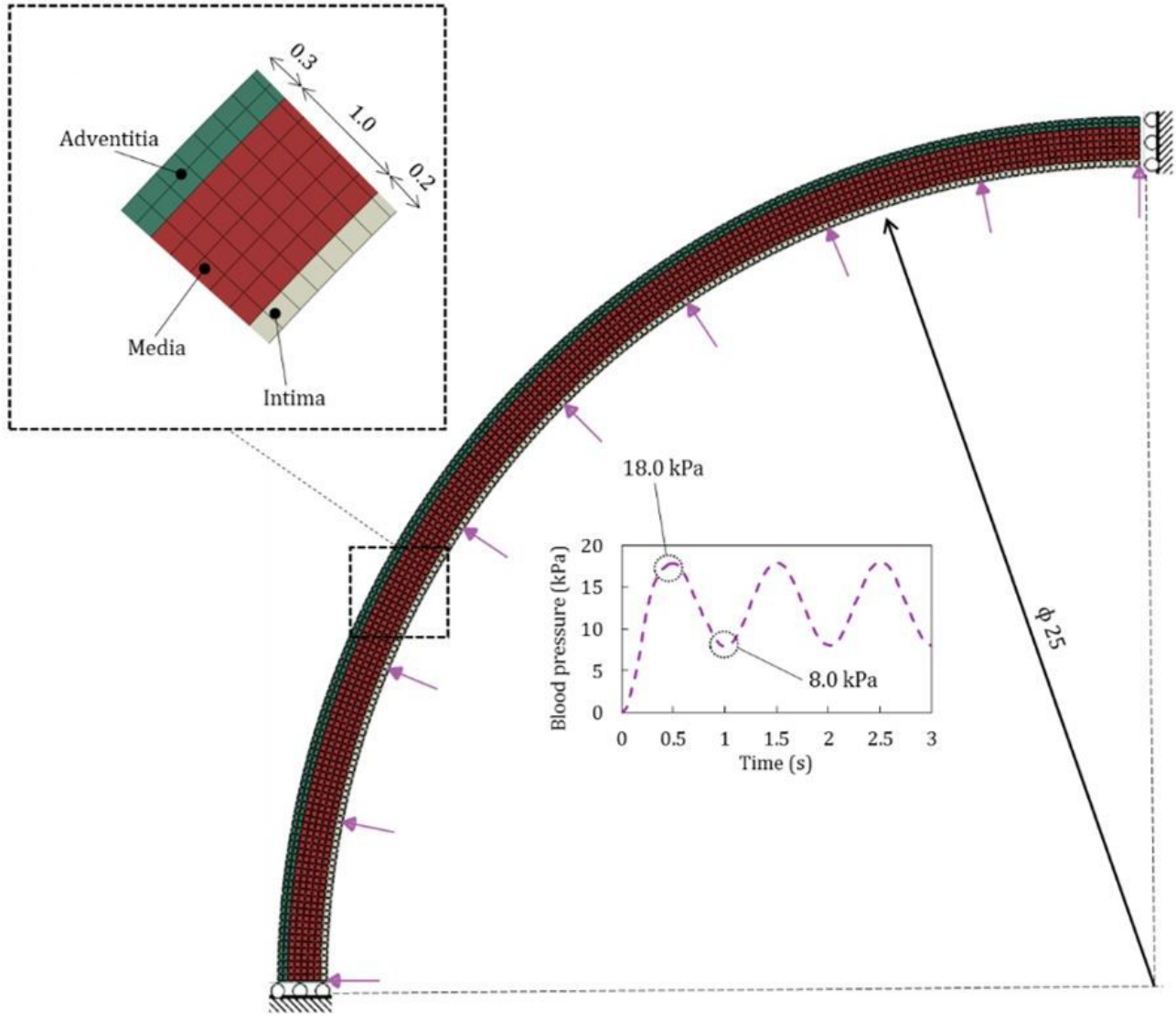

Figure 3: Finite element model of the human aorta, dimensions (unit: mm) and loading condition

Table 4: Material coefficients of both adventitia and intima layers

Layer	Coefficient
Adventitia	$C_{10} = -1.1373$
	$C_{01} = 1.206$
	$C_{20} = 6.5364$
	$C_{11} = -17.819$
	$C_{02} = 12.870$
Intima	$C_{10} = -0.7699$
	$C_{01} = 0.8235$
	$C_{20} = 2.623$
	$C_{11} = -7.5097$
	$C_{02} = 5.8136$

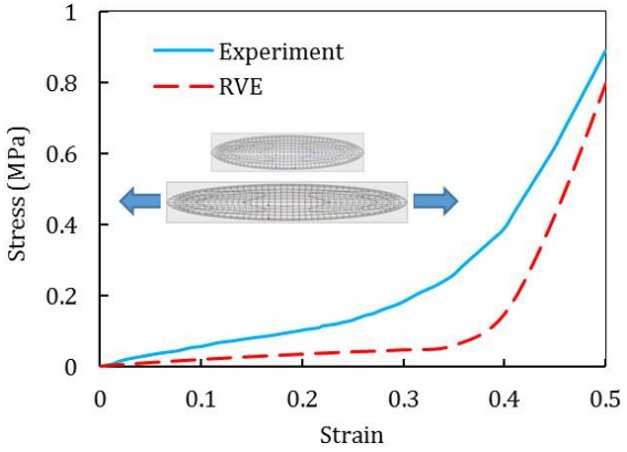

Figure 4: Stress-strain response of the media layer

3 Results and discussions

The developed micro-scale model of the lamellar unit of the human aortic media has incorporated the detailed structural features of the ECM directly. It could recapitulate the circumferential constitutive response of the media layer. The load shared by VSMCs was calculated by integrating all nodal forces along the loading direction. Figure 5 illustrates the load sharing capacity of the ECM and VSMC in the LU subjected to the uniaxial tension. It is clear that the VSMCs at lower stretch levels exhibited a larger contribution in load sharing. However, at larger stretch levels, collagen fibers came into play and took more loads, which muted the contribution of the VSMCs.

In the case of the contracted VSMCs, load sharing of 30% was detected at normal tension levels, while this value decreased to 1.5% in hypertensive conditions (tensile strain of 40% and higher). In contrast, the relaxed VSMCs did not play a significant role in LU stiffness and could not take more than 6% of the tensile load. These values could be altered with respect to the LU micro-structure and the volume fraction of its constituents. It has been reported that VSMCs' static stiffness varies according to their position in the arterial tree. Based on the confocal images of the VSMC shape and actin stress-fiber orientation, VSMCs from arteries with fewer elastic fibers (such as femoral and renal arteries) are considered to be stiffer compared with the thoracic aorta VSMCs [11].

To quantify the effect of fiber fragmentation due to aging effects, a range of fiber loss from 10% to 50% was considered. The corresponding equivalent stiffness of the LU was computed for each case. Figure 6 depicts the loss of stiffness (*i.e.*, the relative difference between current stiffness and the initial one) versus the fragmentation of elastin or collagen fibers. It is clear that at low pressure levels (*i.e.*, tensile strain is less than 40%), the elastin loss decreased the stiffness considerably. Specifically, 50% fragmentation of the elastin layer caused 75% loss of stiffness. However, collagen fiber loss showed its dominant influence in high pressure levels (*i.e.*, tensile strain is more than 40%), when collagen fibers were straightened. Our results have demonstrated that the contribution of fibers to the total stiffness of the LU. Moreover, it has been reported that during the process of arterial aging, and after the loss of the fibrous part of the LU, VSMCs produce more collagen fibers as a remedy to the lack of elastin fibers. However, our results suggest that deposition of wavy collagen fibers cannot contribute to arterial stiffness at normal tension conditions. Our results are consistent with the paradigm shift of age-related arterial stiffness. The age-related arterial stiffening has shifted from elastin/collagen content to cell-ECM interactions and VSMC tone as the principal determinants of arterial wall stiffness [39]. On the other side, it has been reported that the environmental changes caused by aging was associated with the switch from a contractile phenotype to a synthetic phenotype of VSMCs. The latter phenotype is characterized by reduced expression of contractile proteins meaning lower stiffness. Therefore, in this condition, the lack of arterial stiffness is addressed by the thickening of the arterial wall and geometric remodeling.

Differentiated phenotypes (contractile) of VSMCs can be evaluated by morphology studies from which VSMCs are spindle-shaped. In this study, we derived the variation of the VSMCs' section-area for different levels of tension, as shown in Figure 7. Dinardo *et al.* [11] measured the major axis/minor axis ratio of VSMCs located in different arterial beds. This parameter was counted as an indicator of the cell elongation and then interpreted as the contraction level of VSMCs. They observed that VSMCs from femoral and coronary arteries were more elongated than that of

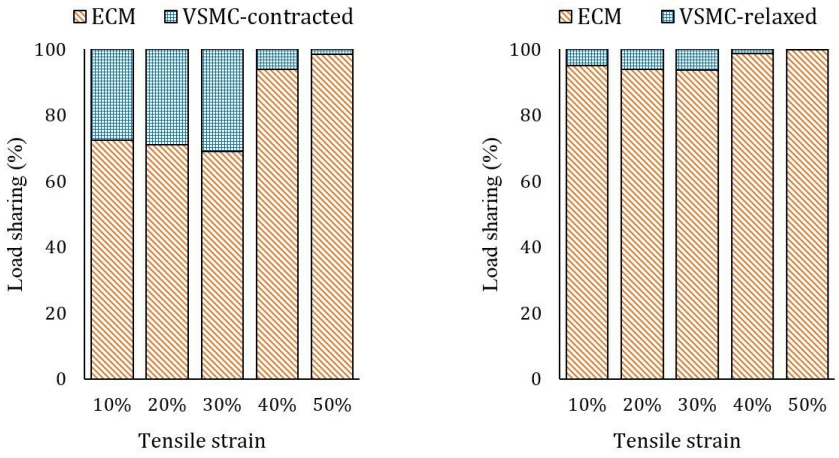

Figure 5: The contribution of VSMC and ECM in load sharing in a healthy carotid aorta LU

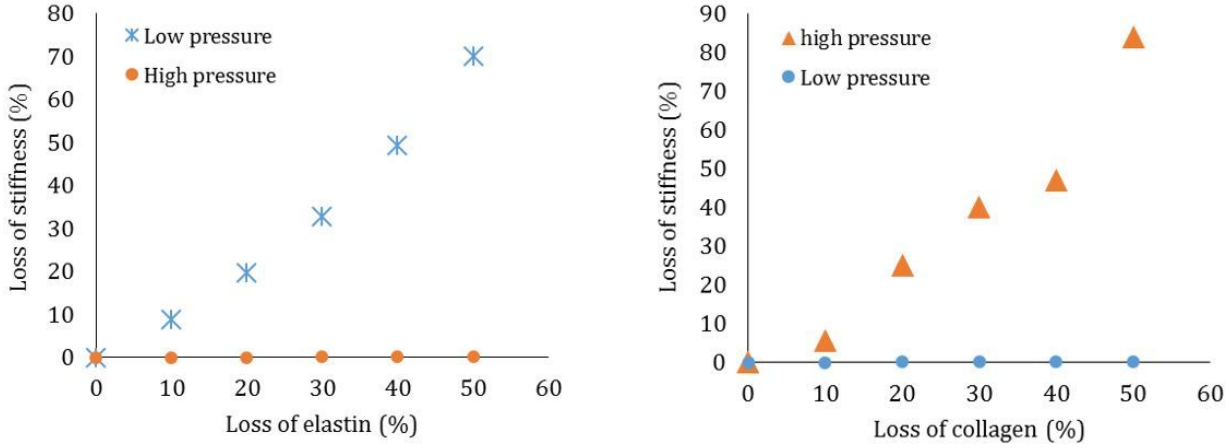

Figure 6: The influence of Collagen disruption and elastin fragmentation on the LU stiffness

other vessels and concluded that the VSMCs from former arteries have higher contraction (static rigidity). On the other hand, they observed that femoral and coronary arteries have the lowest content of elastin and ECM/VSMC ratio. According to our results, the higher volume fraction of VSMC means it had a larger contribution in load sharing and more elongation. These physical variations occurred even if the contractility of VSMCs remained at a fixed value. As we observed, the ratio of the major axis/minor axis and therefore the VSMCs' area was directly related to the tensile strain caused by hemodynamic loads. Moreover, it has been observed that the contraction of 2D cultured VSMCs and the ratio of the major axis/minor axis is inversely related. Therefore, the elongation of VSMCs cannot be an appropriate parameter to detect the contraction level. However, comparing this parameter can provide useful information about the phenotype of the cell and the load sharing of VSMCs.

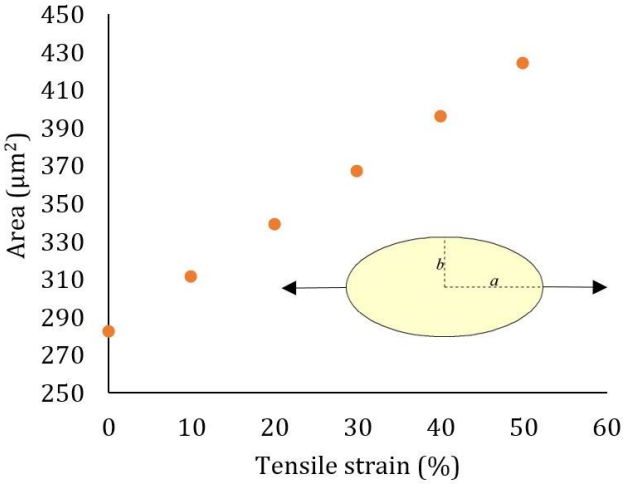

Figure 7: The calculated area of VSMC with respect to the stretch level

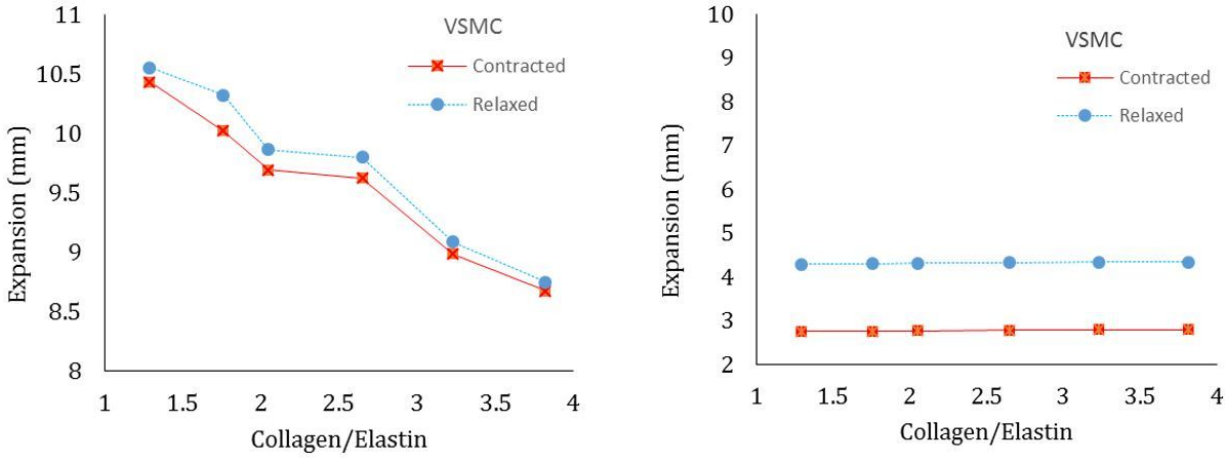

Figure 8: Arterial expansion with respect to the different VSMC status and collagen/elastin ratios; Normal tension (right), hypertension (left)

The aging effects on the aortic expansion were evaluated at various tension levels. Figure 8 shows the recorded expansion of the aorta for various collagen/elastin ratios and each VSMC's status. For higher values of the collagen/elastin ratio the expansion of the aorta decreased drastically. This variation happens by collagen deposition caused by aging. The largest decrease in aortic expansion for high tension levels was 20%, while in normal tension levels the relation of collagen deposition and arterial expansion was insignificant. Hereby, we did not change the volume fraction of elastin. As a result, at a normal tension level the expansion fluctuation is minimal.

Moreover, at a normal tension level the expansion of the aorta was distinguishable for each VSMC status. However, for high pressure levels, the response of contracted and relaxed VSMCs converged. This result showed that in hypertension and where collagen deposition occurs, variation of VSMCs' stiffness cannot change the aortic stiffness and expansion. On the other hand, it could be seen that if material remodeling happens, but the aorta still works under a normal pressure level, VSMCs' contraction/relaxation can considerably affect the arterial dilation. It has been reported that the mechanical phenotype correlates with the composition of ECM and can be modulated by the stretching imposed on VSMCs by blood flow circumferential stress [11]. In this study, we found out that the mechanical variation of VSMCs could be meaningful only in a normal tension level, when aging occurred and more collagen fibers were produced in the ECM.

4 Conclusion

In this work, we have developed a multiscale model to characterize the arterial expansion with respect to the micro-structural variation of the lamellar unit. The micro-scale RVE model was based on the configurations of lamellar unit in the aortic media. The developed model helped us to distinguish the load sharing capacity of fibrous components and VSMCs. Our results showed that the VSMC can take up to 30% of the applied load when contracted. It is known that the relaxed VSMC is around 10 times softer than the contracted one, which affects its contribution in load sharing of the LU. On the other side, the contribution of collagen fibers at low stretch levels was negligible but became predominant when straightened at greater stretch level. The obtained uniaxial response of the LU was validated against the published experimental data. Finally, aging effects by collagen deposition was modeled and aortic dilation was estimated. It was revealed that stiffening of the VSMC when the aorta is exposed to high pressure does not affect the aortic stiffness but is mainly controlled by collagen fibers. Our findings can shed some light about the contribution of VSMCs in arterial stiffness which has been under debate in recent years.

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