Modeling of elastic lamina buckling coupled with smooth muscle layer deformation in the aortic media: technique for readily implementing residual stresses

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Abstract

In vivo aortic wall thickening is a mechanical adaptation to the prolonged increase in intravascular pressure resulting from hypertension, which is mainly regulated by primary components of the aortic media, the elastic lamina (EL) and the smooth muscle-rich layer (SML). This study built a simplified finite element (FE) model of the aortic medial wall comprising the EL and SML, and simulated EL undulation or buckling at a no-load condition, i.e., (in the in vitro) unloaded state, by releasing a set of compressive prestresses initially given to the EL. Using the design of experiments approach (Graeco–Latin square method), we identified specific mechanical boundary conditions to computationally reconstruct EL buckling in the circumferential direction of the aorta. Additionally, it was shown that EL waviness almost vanished when ~20% strain (mimicking a circumferential stretch due to intravascular pressure) was applied to the buckled FE model obtained in the in vitro unloaded state. This feature is beneficial for numerical modeling of the detailed aortic wall structure, because the entire process is computationally efficient and can be readily implemented in a commercially available FE solver. Although further study is required, our findings will help clarify the roles of the EL and SML in the aortic wall and promote the understanding of the mechanisms of the medial tissue stress response. In addition, we expect this modeling technique to serve as a useful tool in the future for interpreting stress distribution relevant to vascular physiology at normal and pathological states.

Keywords: Elastic lamina (EL), Smooth muscle-rich layer (SML), Buckling, Waviness, Residual stress, Aortic media

1. Introduction

Uncontrolled hypertension is a primary risk factor for diverse cardiovascular diseases and remains responsible for significant morbidity and mortality, causing approximately 30% of the deaths worldwide (World Health Organization, 2018). Therefore, it is critically important to understand the mechanisms underlying the development of hypertension or a hypertensive aorta. Various mathematically robust, physically relevant theoretical models of arterial tissue have been developed (Latorre and Humphrey, 2018; Heusinkveld et al., 2018; Rachev and Shazly, 2019) to investigate this intricate pathophysiological phenomenon and detect or assess the clinical symptoms of hypertension in the early stage. In recent years, even patient-specific, finite element (FE) models with a detailed geometry are readily available (Mousavi and Avril, 2017; Liu et al., 2019a). However, it is still difficult to define the initial reference configuration of the aortic wall, because such biological materials or soft tissues are constantly exposed to a complex, inhomogeneous loading environment, while being mechanically balanced under physiological conditions or the in vivo state.

The aortic wall has a composite structure and comprises three distinct layers: the intima, media, and adventitia. Of these, the aortic media is a major component of the aortic wall. It mainly contains lamellar units, including an elastic
lamina (EL), a smooth muscle-rich layer (SML), intracellular stress fibers (SFs), and collagen fibers. Although arranged to support loads preferentially in the circumferential direction, collagen fibers are coiled even at mean physiological pressure (O’Connell et al., 2008), implying that they are not the primary factor for the structural deformation of the aortic wall in vivo. As shown in Fig. 1, adjacent ELs have an SML in between, and it is estimated that both the EL and SML retain residual stresses on the order of ±1–10 kPa at a no-load condition or in the in vitro unloaded state (Matsumoto et al., 2004a; Breslavsky and Amabili, 2018; Liu et al., 2019b). Physiologically, the EL and SML are circumferentially and axially or longitudinally subjected to mechanical stretch in vivo. In contrast, it is theoretically predicted that the EL is slightly compressed and the SML is correspondingly elongated in the in vitro unloaded state in order to mutually maintain a mechanical balance between them (Fig. 2). Histological examination of excised specimens of the aortic wall shows that most of the EL in the circumferential (X) direction is wavy, indicating that the EL is compressed and buckled in the in vitro unloaded state, while, in response, the SML is slightly stretched (Matsumoto et al., 2004b). Therefore, considering residual stress in the aortic media is an important step toward developing a realistic computational aorta FE model. Indeed, Chuong and Fung (1986), who conducted a theoretical analysis on residual stresses in rabbit thoracic arteries, revealed that even a small residual stress at the unloaded state contributes significantly toward reducing the high-stress concentration on the inner wall at the loaded state.

Recently, residual stress has been effectively implemented in sophisticated computational models based on a complex constitutive law in order to realize intrinsic aortic behavior (Mousavi and Avril, 2017; Breslavsky and Amabili, 2018; Liu et al., 2019b). However, it is technically difficult to obtain reasonable and reliable mechanical parameters in physical experiments because aortic tissue is a soft material and is not easy to handle, even in vitro, i.e., soft biological tissue can be easily deformed when a small amount of load is applied. It is known that mechanically, the homeostatic stress distribution is retained in the aortic wall in vivo (Fung, 1993) because residual stress homogenizes the circumferential stress across the transmural aortic wall under physiological conditions. Therefore, such residual stress might lead to optimal load-bearing performance, which would maintain a constant circumferential stress of the aortic media by mediating a vascular dilatation-induced stress concentration on the inner wall; this highlights the importance of understanding and incorporating residual stress in numerical models. In that sense, computational reconstruction of EL–SML mechanical interaction in unloaded and loaded states is indispensable for realistic FE aortic modeling.

In our preceding work (Tamura and Kato, 2018), we successfully represented EL buckling in the circumferential (X) direction in the in vitro unloaded state by combining a simplified medial FE model and the design of experiments (DOE) approach developed by Taguchi (1987), and identified three significant mechanical factors (design parameters): circumferential prestress initially given to the EL (Pre-X), EL–SML internodal gap or interconnecting distance between EL and SML in the circumferential direction (Dis X), and the thickness of EL in the radial direction of the aortic wall. As illustrated in Fig. 1, however, we reconstructed EL buckling by allowing its separation from and penetration into the SML, indicating that the EL might not sufficiently buckle when the EL and SML are tightly connected (e.g., Dis X = 10 μm). In reality, though, the SML would also deform in conjunction with the EL in the in vitro unloaded state and demonstrate circumferential undulation as the EL waviness numerically obtained.

Hence, this study primarily aimed to reconstruct the phenomenon of EL buckling, even at a small internodal gap (Dis X = 10 μm), and to identify effective mechanical factors realizing EL–SML coupled deformation in the in vitro unloaded state. In addition, to assess the validity of our modeling approach, we focused on structural deformation of the EL in vitro and in vivo states by applying stretch equivalent to the intravascular pressure.
2. Methods
2.1 Computational model

The aortic medial lamellar unit was considered as a part of the tubular structure mainly comprising two components (Fig. 1), the EL and the SML. We disregarded an active smooth muscle response, which is a pragmatic simplification to characterize the actual biomechanical behavior of the aortic wall. However, the mechanical properties of passive components are essential to realize EL buckling in the \textit{in vitro} unloaded state. We built an original unit FE model using HyperMesh 2017 (Altair Engineering, Inc., Troy, MI, USA) that consisted of the EL, SML, and SFs, in which two SMLs with a 20-μm height (Matsumoto et al., 2004b) were sandwiched between three ELs, assuming that the SML is mechanically isotropic and nearly-incompressible (Fig. 3a). The strain energy function used for the SML ($\Psi_1$) was given by the following equation:

\[ \Psi_1 = A (I_1 - 3) + B (I_2 - 3) \]  

\[ E = 6 (A + B) \]  

where $I_1$ and $I_2$ are the first and second invariants of the right Cauchy–Green strain tensor, and $A$ and $B$ are coefficients...
of the SML (default values: $A = 17.3$ and $B = 0.2$ (kPa), corresponding to Young’s modulus ($E$) of 100 kPa). We conducted a preliminary one-solid element simulation in compression and extension, and a unique combination of $A$ and $B$ was identified using the least-squares method with the constraint of Eq. (2) based on a nominal stress–strain curve (linear response). The original unit model was then modified, as shown in Fig. 3b. The EL was divided into four in the Y (axial) direction of the aortic wall, while each SML was divided into two and three layers in the Y (axial) and Z (radial) directions, respectively. In addition, the EL and SML were circumferentially connected by shared nodes at an even interval (Dis $X = 10 \mu m$) and also axially or longitudinally connected by shared nodes at the even interval (Dis $Y = 10 \mu m$). Unfortunately, specific mechanical data on the internodal gap between the EL and SML are not currently available. However, it has been reported that the volume of a single medial smooth muscle cell (SMC) contained in the rat abdominal aorta is 1,630 $\mu m^3$ (O’Connell et al., 2008). If it is assumed that an SMC is cuboid with a square undersurface, an internodal gap between the EL and SML can be estimated as Dis $X = $ Dis $Y = -9$ (µm). Hence, we connected the EL and SML with the even interval of 10 µm along the circumferential and axial directions, respectively. Adjacent layers of EL were obliquely connected by a set of one-dimensional SF elements in the radial direction of the aortic wall, of which angle was assigned as 53° relative to the circumferential (X) direction, with Young’s modulus of 1 MPa (Deguchi et al., 2006). The available number of nodes was limited in this unit FE model, so we adjusted a cross-sectional area of each SF element to be 100-fold of a regular SF with a 0.3 µm diameter. Consequently, SF elements occupied ~21% volume of the unit FE model.

The EL was modeled as a shell element with a 3-µm thickness (O’Connell et al., 2008; Clark et al., 2015) using a linear elastic material with Young’s modulus of 600 kPa (Fung, 1993) and Poisson’s ratio of 0.45, while the SML was modeled as a solid element using a Mooney–Rivlin hyperelastic material with Young’s modulus of 50–100 kPa (Matsumoto et al., 2004b; Nagayama and Matsumoto, 2004) and Poisson’s ratio of 0.490–0.499 because we assumed that the aortic media is almost incompressible. Overall, each layer of EL and SML contained 160 shell and 120 solid elements, respectively, and a mechanically “strict” constraint because of short internodal gaps (Dis $X$ and Dis $Y$) was compensated or mediated by the modified fine mesh. Material properties assigned for the unit FE model are summarized in Table 1.

In our preceding work (Tamura and Kato, 2018), we revealed that a prestress initially given to EL, Pre-$X$, and an internodal gap between EL and SML, Dis $X$, are dominant factors for representing circumferential EL buckling in the in vitro unloaded state. Since the longitudinal layer of the aortic medial wall is a stack of unit FE models along the aortic axis, a longitudinal prestress given to the EL, Pre-$Y$, would be potentially another dominant factor for reconstructing EL buckling in the in vitro unloaded state. Therefore, we selected Pre-$X$ and Pre-$Y$, initially given to the EL in circumferential and axial directions, as well as Young’s modulus and Poisson’s ratio, assigned for the SML, as design variables. We conducted 16 simulations using the integrated FE model (10-unit structures axially connected in series, as shown in Fig. 3c) based on the Graeco–Latin square method, in which the experimental units are originally grouped in three different ways (Miyakawa, 2000). The Graeco–Latin square method is one of the typical DOE approaches applicable for any size or number of factors and levels employed in experimental units within the range of $N = 3, 4,$ and 5. Table 2 summarizes a combination of design variables, 4 factors and 4 levels ($N = 4$), selected here. Previously (Tamura and Kato, 2018 and 2019), we also found that a compressive prestress that was much greater than 100 kPa (|Pre-$X| > 120$ kPa) should be applied to the EL at the initial reference configuration when the EL and SML were tightly connected, i.e., Dis $X = 10 \mu m$. Thus, as illustrated in the theoretical model (Fig. 2), compressive prestresses ranging from −250 to −175 kPa were only given to each integration point of the EL at the initial reference configuration and were subsequently released, leaving a compressive residual stress with the EL in the in vitro unloaded state. In contrast, as a response, the SML was slightly stretched to maintain a mechanical balance with the buckled EL. Hence, 10-unit models connected serially resulted in a slight elongation along the aortic axis, which was within the range of 10% strain ($n = 16$), while the resultant tensile strain in the circumferential direction was also <10% at the unloaded state. Thus, although the axial length of the aorta is almost constant in in vivo conditions, we did not apply any boundary constraints to the model in the X and Y directions.

Figure 4 shows the definitions of the EL waviness, $W_{EL}$, and the corresponding SML value, $W_{SML}$, obtained in the in vitro unloaded state. $W_{EL}$ was defined as the ratio of an entire deformed EL length, $L_{SML}$, and a straight line connecting both ends, $L$, in the in vitro unloaded state; see Eq. (3). Similarly, $W_{SML}$ was defined as the ratio of an entire deformed SML length, $L_{SML}$, and a straight line connecting both ends, $L$, in the in vitro unloaded state; see Eq. (4). To avoid site-specific variabilities, both $W_{EL}$ and $W_{SML}$ were obtained at the middle layers of the integrated FE model and
averaged. To identify the predominantly influential factors contributing to the initiation of EL buckling, we further conducted an analysis of variance on $W_{EL}$ and $W_{SML}$ for the cases simulated here ($n = 16$). In particular, we computed $F$-values for each selected design variable. By comparing the computed $F$-values and those listed in the $F$-distribution table, we successfully identified the effective design variables among the preselected parameters, i.e., Pre-X, Pre-Y, Young’s modulus, and Poisson’s ratio. Note that statistical significance was considered when $P < 0.05$. It must also be noted that a mesh convergence analysis was performed to confirm that the number of elements contained in the current model was sufficient to successfully and reliably represent EL buckling at the unloaded state with a reasonable CPU time. All simulations were performed using a commercially available explicit finite element solver, LS-DYNA 971 R10.0.0 (Livermore Software Technology Corp., Livermore, CA, USA).

Fig. 3 Schematic of a set of unit and integrated FE models of the simplified aortic media (unit: $\mu$m). Each unit FE model has a 10 $\mu$m depth in the axial (Y) direction. (a) The EL–SML coupled interaction was not realized in the original unit model due to the paucity of degree of freedom in deformation. (b) The EL was divided into four layers in the Y direction, while the SML was divided into two and three layers in the Y and Z directions, respectively. (c) The EL and SML were circumferentially and axially connected in the integrated FE model at the even interval, 10 $\mu$m. EL, elastic lamina; SML, smooth muscle layer.
Fig. 4 Definition of EL waviness ($W_{EL}$) and the corresponding SML value ($W_{SML}$) obtained in the in vitro unloaded state after releasing given prestresses. EL, elastic lamina; SML, smooth muscle layer.

$$W_{EL} = \frac{L_{EL}}{L} \quad (3)$$

$$W_{SML} = \frac{L_{SML}}{L} \quad (4)$$

Table 1 Material properties assigned for each component of the aortic media.

| Component         | Element type | Young's modulus (kPa) | Poisson’s ratio |
|-------------------|--------------|-----------------------|-----------------|
| Elastic lamina (EL) | Shell        | 600                   | 0.45            |
| Smooth muscle layer (SML) | Solid      | 50–100                | 0.490–0.499     |
| Stress fiber (SF)   | Bar          | 1000                  | N/A             |

Young’s modulus of SML is obtained by scaling to a default set of values, $A = 17.3$ and $B = 0.2$ (kPa). The EL and SML are circumferentially and axially or longitudinally connected in the integrated FE model at the even interval of 10 µm. EL, elastic lamina; SML, smooth muscle layer.

Table 2 Allocation of selected design variables based on the Graeco–Latin square method ($n = 16$).

| Case ID | Pre-X (kPa) | Pre-Y (kPa) | Young’s modulus (kPa) | Poisson’s ratio |
|---------|-------------|-------------|-----------------------|-----------------|
| 1       | −250        | −250        | 50                    | 0.490           |
| 2       | −250        | −225        | 67                    | 0.496           |
| 3       | −250        | −200        | 83                    | 0.499           |
| 4       | −250        | −175        | 100                   | 0.493           |
| 5       | −225        | −250        | 67                    | 0.493           |
| 6       | −225        | −225        | 50                    | 0.499           |
| 7       | −225        | −200        | 100                   | 0.496           |
| 8       | −225        | −175        | 83                    | 0.490           |
| 9       | −200        | −250        | 83                    | 0.496           |
| 10      | −200        | −225        | 100                   | 0.490           |
| 11      | −200        | −200        | 50                    | 0.493           |
| 12      | −200        | −175        | 67                    | 0.499           |
| 13      | −175        | −250        | 100                   | 0.499           |
| 14      | −175        | −225        | 83                    | 0.493           |
| 15      | −175        | −200        | 67                    | 0.490           |
| 16      | −175        | −175        | 50                    | 0.496           |

Pre-X and Pre-Y are a set of prestresses applied to the EL in the circumferential (X) and axial or longitudinal (Y) directions, respectively. Young’s modulus and Poisson’s ratio are values assigned for the SML. EL, elastic lamina; SML, smooth muscle layer.
2.2 Effect of collagen fibers

To investigate an EL–SML coupled interaction during stretching, we designed an additional analysis based on a series of DOE simulations (n = 16). In a subsequent simulation series, the SML was modified by virtually embedding collagen fibers in a hyperelastic (Mooney–Rivlin) material along the circumferential (X) direction, and uniaxial stretch was applied to the integrated FE model from the in vitro unloaded state with the buckled EL to the in vivo circumferentially elongated state under physiological conditions. In this case, A and B, given in Eq. (5), were set as default values to 17.3 and 0.2 kPa, respectively, with Young’s modulus of 100 kPa. Figure 5 shows the nominal stress–strain (σ–ε) relationships of embedded collagen fibers, which work effectively at critical stretch level $\lambda^* = 1.3, 1.4, or 1.5$, and transversely isotropic material responses due to uniaxial stretch, because collagen fibers are dominant load bearers against the stretch at high strain, i.e., $\varepsilon = 30\%$–$50\%$ (Lillie et al., 2012; Clark et al., 2015; Thunes et al., 2016 and 2018). Material constants regulating the anisotropic behavior of the SML in the aortic media were described by the strain energy function ($\Psi_2$) as follows:

$$\Psi_2 = A (I_1 - 3) + B (I_2 - 3) + F(\lambda) + 1/2 K [\ln (J)]^2 \quad (5)$$

$$\dot{\lambda} = 1 + \varepsilon \quad (6)$$

$$J = \det F \quad (7)$$

where $K$ is the effective bulk modulus, 100 MPa; $\dot{\lambda}$ and $J$ are the stretch along the fiber direction and the volume ratio, respectively, as given in Eqs. (6) and (7) (Quapp and Weiss, 1998) in which $F$ is the deformation tensor. This material model was originally developed to represent the medial collateral ligament of the human knee, in which it was assumed that the collagen fibers were responsible for the transverse isotropy of the ligament and that the ground matrix was incompressible and isotropic. Because the SML of an aorta primarily contributes to its contraction and relaxation, we assumed that the collagen fibers embedded in the aortic media are aligned along the circumferential direction, indicating that the medial wall can be similarly regarded as a transversely isotropic material. The derivatives of the fiber term $F$ were defined to capture the mechanical behavior of crimped collagen. For simplicity, we assumed that collagen fibers do not work under $\lambda^*$, as given in Eqs. (8) and (9), which corresponded to 1.3–1.5 here.

$$\frac{\partial F}{\partial \lambda} = 0 \quad \dot{\lambda} \times \lambda^* \quad (8)$$

$$\frac{\partial F}{\partial \lambda} = \frac{1}{\dot{\lambda}} (C\lambda + D) \quad \lambda \geq \lambda^* \quad (9)$$

Again, we performed a preliminary one-solid element simulation to determine $C = 1300 \text{ kPa}$, and $D$ was automatically determined by LS-DYNA so that the fibers would behave almost linearly once they were straightened past a critical stretch level, $\lambda^*(Rachev and Shazly, 2019)$.

Under normal physiological conditions, the blood pressure varies between 80 and 120 mmHg, corresponding to a $\sim 100 \text{ kPa}$ stretch in the circumferential (X) direction of the aortic media. Hence, we applied a uniaxial stretch equivalent to 100 kPa load per unit area to a group of nodes belonging to the lateral surfaces of the EL and SML of the integrated FE model along its circumferential (X) direction to replicate the mechanical kinematics of the EL during stretch such that EL waviness would resultantly vanish or disappear under physiological conditions. Pre-X and Pre-Y were given constant values of $-225$ and $-200 \text{ kPa}$, respectively. In this simulation setup, a cross-sectional force was also obtained for the SML at the middle portion of the integrated model (Fig. 6) and the nominal stress was computed by dividing its cross-sectional force in the circumferential (X) direction by the SML’s initial cross-sectional area. Further, the nominal strain during stretch was obtained on the basis of $L$ in the in vitro unloaded state; i.e., when EL was buckled and self-equilibrated with slightly extended SML, a macroscopic strain was defined as zero ($\varepsilon = 0\%$).
3. Results

3.1 Reconstruction of EL buckling in vitro

In line with the proposed theoretical model of the EL–SML coupled interaction (Fig. 2), the partial stresses borne by the compressed EL and the consequently extended SML were self-equilibrated in the in vitro unloaded state. Figures 7 and 8 show changes in $W_{EL}$ and $W_{SML}$ as a function of design variables selected here. Pre-$X$ was significantly correlated with EL buckling initiation in the in vitro unloaded state ($P < 0.0001$ vs. $W_{EL}$, $P < 0.05$ vs. $W_{SML}$). $W_{EL}$ and $W_{SML}$ increased when a higher compressive prestress was circumferentially given to the initial reference configuration. Similarly, Pre-$Y$ was also significantly correlated with EL buckling initiation ($P < 0.001$), and $W_{EL}$ and $W_{SML}$ decreased because of Poisson’s effect when a higher compressive prestress was given in the axial direction. When Pre-$X$ is increased, $L_{EL}$ and $L_{SML}$ increased, resulting in an increase in $W_{EL}$ and $W_{SML}$. In contrast, when Pre-$Y$ is increased, $L_{EL}$ and $L_{SML}$ decreased, resulting in a decrease in $W_{EL}$ and $W_{SML}$, as given in Eqs. (3) and (4). However, while Young’s modulus of SML was a significant contributor to $W_{EL}$ ($P < 0.001$), Poisson’s ratio assigned for the SML was not a significant factor in reconstructing EL buckling in the in vitro unloaded state. Moreover, we obtained a reasonable residual stress value of the SML, $3.06 \pm 0.84$ kPa (mean ± SD), in the in vitro unloaded state in a series of DOE simulations ($n = 16$).
Fig. 7 Changes in EL waviness ($W_{EL}$) represented as a function of selected design variables ($n = 16$). Pre-X and Pre-Y are prestresses given to the EL in the circumferential and axial or longitudinal directions, respectively. Young’s modulus and Poisson’s ratio are values assigned for the SML ($^*P < 0.05$, $^**P < 0.001$ for Pre-X; $^***P < 0.0001$ for Pre-Y and Young’s modulus). EL, elastic lamina; SML, smooth muscle layer.

Fig. 8 Changes in SML waviness ($W_{SML}$) represented as a function of selected design variables ($n = 16$). Pre-X and Pre-Y are prestresses given to the EL in the circumferential and axial or longitudinal directions, respectively. Young’s modulus and Poisson’s ratio are values assigned for the SML ($^*P < 0.05$ for Pre-X). EL, elastic lamina; SML, smooth muscle layer.
3.2 EL–SML coupled interaction during stretch

Figures 9a and b illustrate the contour plots of normal (X) stress at the initial and EL buckled configurations, respectively. At the initial reference state, EL shows compression (blue) because Pre-X was only given to the EL along the circumferential (X) direction. However, at the unloaded state (ε = 0%), the EL with compressive residual stress and the SML with tensile residual stress were self-equilibrated, while X-stress of the top, middle, and bottom layers of SML was mechanically mediated (green) by mixing the EL’s compressive (blue) and SML’s tensile (red) residual stresses. Figures 9c and d illustrate the contour plots under loaded conditions with collagen fibers, i.e., λ' = 1.5. At 10% tensile strain, compressive residual stress partly remained in the EL, of which waviness drastically reduced to W_{EL} = 1.02, while the EL and SML almost evenly bore the tensile load (green) at the physiological state (ε = 30%). Particularly, EL waviness (W_{EL}) vanished, W_{EL} < 1.01, at ~20% strain on the basis of the in vitro unloaded state (0% strain) as shown in Fig. 10a. In addition, when collagen fibers were not considered, the resultant strain far exceeded the target value of 30%–50% strain under physiological conditions and reached ~90% when 100 kPa load per unit area was applied. In contrast, when collagen fibers were considered, they bore the load of 60–80 kPa in tension at the in vivo state, while the resultant strain was relatively reasonable (30%–50%), which gradually shifted toward the right as λ' changed from 1.3 to 1.5. Note that residual stress of SML resulted in ~15 kPa at 0% strain in the in vitro unloaded state (Fig. 10b).

Fig. 9 Contour plots of normal (X) stress obtained at (a) the initial reference configuration and (b) the in vitro unloaded state, (c) 10% strain and (d) the in vivo loaded state (30% strain) with λ' = 1.5. EL and SML were self-equilibrated at the in vitro no-load condition. EL, elastic lamina; SML, smooth muscle layer.

Fig. 10 Relationships between (a) EL waviness and the applied macroscopic strain and (b) nominal SML stress and the applied macroscopic strain. A red dashed line represents the mechanical response without collagen fibers. Each “×” indicates the resultant strain obtained under physiological conditions, that is, 100 kPa stretch applied in the circumferential (X) direction. Zero strain (ε = 0%) is defined by a self-equilibrated configuration at the unloaded state. EL, elastic lamina; SML, smooth muscle layer.
4. Discussion

The aortic wall thickens in response to continued elevations in blood pressure leading to hypertrophy and hyperplasia of the SML, thereby, restoring the mean stress of the circumferential wall toward its normal value (Wolinsky, 1971); this is referred to as mechanical homeostasis. When cardiovascular pressure increases, even a slight residual stress in the artery is known to effectively mitigate a stress concentration induced on its inner wall (Chuong and Fung, 1986). In addition, Matsumoto et al. (1996) suggested that the SML affects transmural residual stresses via changes to its contractile state, which contribute to the regulation and control of stress distribution in the aortic media; such residual stresses are likely to originate from the mechanical interaction between the EL and SML (Matsumoto et al., 2004a and 2004b). Therefore, in the present study, we focused on reconstructing EL buckling at the unloaded state, which is coupled with SML deformation in the medial wall, because this is a first step toward producing a realistic computational representation of the aortic wall with residual stresses. The mechanical heterogeneity of the aortic medial wall results from variation in the mechanical properties of its components (e.g., the EL, SML, and collagen fibers), of which stiffness ranges from ~10 kPa to 1 GPa, causing differences between microscopic and macroscopic deformations. We assumed that an abnormal sign or symptom associated with hypertension could be detected by abnormalities in stress or strain distributions in the aortic media. Thus, it will be necessary to determine the type of heterogeneity that can be considered as part of the normal and healthy condition of the aortic wall to correctly distinguish the difference between normal and abnormal signs. At present, many mathematical models assume a radially homogenized wall, that is, a single layer, because of computational convenience and a lack of data on layer-specific changes in composition and properties. Hence, the novelty of this study was our approach to numerical modeling of the aortic medial wall, considering each component (EL, SML, and SFs), in order to promote an understanding of the mechanism underlying the aortic tissue mechanical response. By introducing a set of prestresses, Pre-X and Pre-Y, we readily and successfully reconstructed EL buckling coupled with SML deformation. To our knowledge, this is the first study to model the aortic media, considering a specific EL–SML interaction.

According to the definition of $W_{EL}$ and $W_{SML}$ (Eqs. (3) and (4)), the larger the $L_{EL}$ or $L_{SML}$ and the smaller the connecting line length of the unit FE model ($L$), the larger the $W_{EL}$ and $W_{SML}$. Therefore, to successfully represent circumferential EL buckling at the no-load condition, i.e., (in the in vitro) unloaded state, we would need a larger [Pre-X] and a smaller [Pre-Y] because such mechanical conditions readily lead to circumferential elongation of the EL coupled with the SML by releasing the stored internal energy corresponding to the amount of initial prestress, which would work as the spring-back of a forcibly compressed spring. In addition, a higher Young’s modulus (> ~80 kPa) would be preferred for reconstructing EL buckling, because a stiffer material property initially assigned for the SML can constrain EL elongation in the circumferential (X) direction when Pre-X is released. However, Poisson’s ratio of SML does not significantly affect EL buckling as long as material incompressibility (0.490–0.499) is maintained in the in vitro unloaded state.

As we have shown in this work, EL buckling can be replicated without its separation from or penetration into the SML by controlling a combination of prestresses, Pre-X and Pre-Y, as well as the SML’s material stiffness. However, immunohistochemically stained images of aortic medial tissue isolated from the porcine aortic wall (Matsumoto et al., 2004b) demonstrate that some of the buckled EL separates from the SML, indicating that completely integrated deformation between the EL and SML is neither necessarily desirable nor realistic. Of another note is that we obtained the reasonable residual stress of the SML (3.06 ± 0.84 kPa; $n = 16$) in the in vitro unloaded state, which is comparable with the estimated value of 1–10 kPa reported earlier (Matsumoto et al. 2004a; Breslavsky and Amabili, 2018; Liu et al., 2019b). In our preceding work (Tamura and Kato, 2018), we found that residual stress of the SML slightly decreases with an increase in the cross-sectional area of interlamellar SFs in the in vitro unloaded state when the assigned SF area is 0.07–7.07 μm² (1–100-fold compared to a regular SF). That is, SFs partly bear the tensile reaction load resulting from the prestressed EL in the in vitro unloaded state. Nevertheless, more than a 100-fold increase in the SF area is ineffective and does not act as a substantial resistant load against stretch because SFs, which were obliquely aligned here, are marginally compressed during shear-like deformation induced by circumferential stretch, replicating various vascular physiological conditions. We revealed it in our preceding work (Tamura and Kato, 2018) by changing the scaling factor from 100-fold (21% volume fraction) to 480-fold, i.e., 100% volume fraction. Therefore, the cross-sectional area of interlamellar SFs employed in this work was fixed and did not provide noticeable mechanical resistance to the applied stretch, either. However, it should be noted that the precise alignment angle of SFs at the initial
reference configuration is not currently available; this might be influential under the highly stretched condition of the hypertensive aorta.

Of note, the EL and SML are likely to bear the load independently as shown in the contour plots (Fig. 9), i.e., stress distribution is gradually mediated during stretching at the boundary between the EL and SML because the unit model we employed was developed assuming structural inhomogeneity of the aortic medial wall. This was also predicted by Yamada et al. (1999) who conducted a layer-structured FE analysis of arteries by modeling active (SML) and passive (EL and collagen fibers) elements separately. Compared to experimental results obtained with micro- and macroscopic observations on an aortic medial strip subjected to uniaxial stretch (Uno et al., 2010), \( W_{EL} = 1.11 \) we obtained (Fig. 10a) is reasonable in the in vitro unloaded state. The aim of our additional series of simulations was to identify a specific contribution of collagen fibers that would make it possible for the computationally model-predicted \( W_{EL} = \varepsilon \) relationship to match the one experimentally obtained by Uno et al. (2010), most of which was within the range of \( W_{EL} = 1.05–1.15 \) in vitro (\( \varepsilon = 0\% \)). They reported that EL waviness vanished at ~20% strain, which is equivalent to our simulation results. In addition, Lillie et al. (2012) reported that intact aortic ring segments exhibited stress values of 100–400 kPa at \( \varepsilon = 30\%–45\% \) when uniaxial stretch was applied, also supporting the resultant strain, 30%–50%, at 100 kPa stretch obtained in our simulation results. Interestingly, resultant stress value of the SML gradually decreased as \( \varepsilon \) increased (Fig. 10b). This is because more collagen fibers were recruited at smaller \( \varepsilon \) due to stretch, while more compressive residual stress remained in the buckled EL was released as the EL was further elongated. This would mediate resultant tensile stress of SML induced by circumferentially stretching the model. As a consequence, the initially assigned prestresses, Pre-X and Pre-Y, and Young’s modulus of the SML, all significantly affect the mechanical behavior of the EL and SML. These findings are now applied to a ring model replicating the aortic medial wall, and we are trying to computationally reconstruct the mechanical interaction between EL and SML at the in vitro and in vivo states with more realistic boundary conditions (Tamura and Matsumoto, 2020).

This study had a few limitations. First, the Graeco–Latin square method cannot take into account the effects of interaction among the design variables selected here. For example, the effect of Young’s modulus on \( W_{SML} \) was not straightforward (Fig. 8c), probably because of the interaction among the design variables, and requires further investigation. Second, we are also aware that more elaborate models exist describing the influence of collagen fibers (Thunes et al., 2016 and 2018). Nevertheless, we primarily focused on representing EL buckling of the aortic medial wall, because the EL acts physiologically as the predominant load bearer for low intravascular pressure load, while collagen fibers do not experience very large strains (Kamenskiy et al., 2014). Hence, detailed computational modeling of arterial mechanics involved in collagen fibers, the dominant load bearer at high stretch, was beyond the scope of this study. Third, we used a short EL–SML intermodal gap of 10 \( \mu \)m, while the EL and SML might be connected more tightly in the intrinsic aortic media. This issue can be technically overcome by using a more refined or sophisticated FE mesh model, although it will not be computationally cost effective. In fact, our results strongly indicate that EL buckling would be replicated even when the EL and SML are more tightly connected with an intermodal gap less than 10 \( \mu \)m. In addition, it should be noted that we obtained the residual stress for the SML at the unloaded state, 15 kPa, under the assumption that it is a transversely isotropic material (Fig. 10b); this value compares well with a previously estimated value, 10 kPa, obtained by introducing material anisotropy of the SML (Matsumoto et al., 2006), although the validity of the given prestress remains undetermined. Moreover, the accuracy of the computed stress and strain in finite deformation may also be a concern because the EL was assumed to be an elastic material. Nevertheless, Matsumoto et al. (2008) reported that the isolated EL shows a linear mechanical response up to ~90% strain during stretching, suggesting that it can be regarded as a perfect elastic material. Furthermore, buckling occurs within the range of 10% strain, whereas EL deformation is relevant at a maximum of 30%–50% strain, even at the in vivo condition. Thus, although our assumption is likely acceptable, further studies are required to elucidate the mechanism underlying EL buckling coupled with SML deformation along the aortic axis.
5. Conclusion

A series of numerical simulations were conducted using a simplified aortic medial FE model based on the Graeco–Latin square method. We have demonstrated that EL buckling in the in vitro unloaded state can be readily represented by implementing and controlling the prestress initially given to the EL ($|\text{Pre}-X| > |\text{Pre}-Y|$). The SML (Young’s modulus > ~80 kPa) deforms well in conjunction with buckled EL waviness with a small internodal gap of 10 μm, indicating that even if the EL and SML are tightly connected, such EL–SML coupled interaction can be computationally reconstructed using a more refined or sophisticated FE mesh model.

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