Structural Remodeling of a bovine carotid artery in response to flow overload

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Introduction

As a living biological tissue, the blood vessel maintains a homeostatic stress state by responding to changes in its local chemo-mechanical environment with tissue growth and/or resorption. The structural and mechanical remodeling in response to flow overload has been studied in the rat's femoral artery [**I**].The goal of this study is to extend the analysis of the flow overload remodeling process to larger animals and to quantify the structural remodeling with morphometric changes in the *zero-stress* configuration. Five porcine carotid arteries were subject to an increase in internal blood flow for varying length's of time (1(x3) and 2(x2) weeks). Three normal carotid arteries were excised and used for control data. By ligating and removing one carotid artery from the pig, thereby forcing an approximate step increased in blood flow is through the remaining intact carotid artery. The flow overloaded (FO) carotid artery is then ligated and excised after it has been allowed to remodel. By surgically re-routing the internal blood flow, there is no effect of local operative trauma to the FO prior to, and during the course of the remodeling process. The strains were computed through the thickness of the *no-load* wall configuration. Volumetric blood flow rate measurements were used to approximate *in-vivo* shear stresses. The opening angles were also calculated for varying points through the remodeling process.

No-load and zero-stress configurations

Residual strains (and corresponding residual stresses) exist in the unloaded configuration of blood vessels [II III]. Although a complete description for the development and mechanisms of residual strains in biological tissue is far from complete, it is well accepted that residual strains develop due to nonuniform tissue growth and resorption. It is also known that, the existence of circumferential residual strains in blood vessels homogenizes the stress field through the vessel wall at physiologic pressures [IV].

The blood vessel is considered to be an incompressible thick-walled circular cylindrical tube. Axial residual strains are observed by a significant reduction in segment length upon excision and are computed directly from the *in-vivo* and *ex-vivo* segment lengths. Arterial rings were then cut everywhere perpendicular to the axial direction. In the so-called *no-load* state, inner and outer radii measurements were optically measured using SigmaScan Pro [V] image analysis system. Following a single radial cut, the arterial sector springs into an open sector. The open sectors were let stand in saline at room temperature for thirty minutes to relieve all residual stresses, thereby attaining equilibrium in the so-called *zero-stress* configuration. The thickness, inner and outer arc lengths were optically measured.

An approximate method for the quantification of the residual strains in an arterial segment, originally proposed by Chuong and Fung (1986), has been implemented. The *no-load* configuration is approximated as a circular cylindrical segment and the *zero-stress* configuration is approximated and an open circular sector of constant thickness. These geometries are illustrated as Figure 1. Mathematically, the *zero-stress* configuration is defined by the inner and outer radii, and the opening angle, respectively denoted $R_i, R_o, \text{ and } \alpha$. These quantities are related to the measured thickness and inner and outer arc lengths, T $L_i \text{ and } L_o$, of the open sector by the following relations:

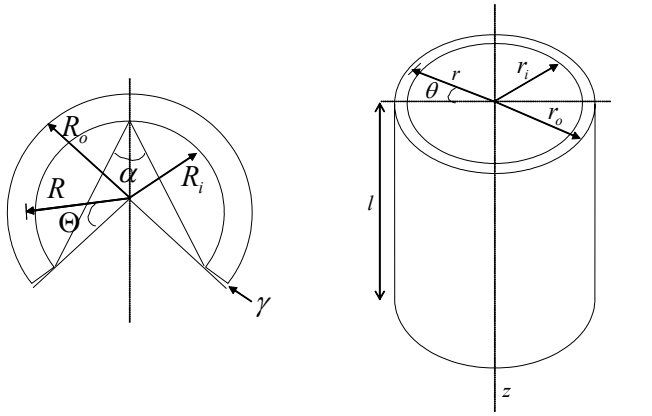


Figure 1: (a) Arterial section in the *zero-stress* configuration ($r\theta$ - plane); (b) Arterial section in the *no-load* configuration.

$$R_i = \frac{T}{L_o/L_i - 1}; \quad R_o = \frac{TL_o}{L_o - L_i};$$

$$\alpha = \pi - \frac{L_o - L_i}{2T}$$

The geometry of the *no-load* configuration is defined by the inner and outer radii, and the length of the arterial section; respectively denoted $r_i, r_o, \text{ and } l$.

The effect of residual strain

The outer diameter of the intact vessel was measured after it was stretched to its physiologic axial stretch and pressurized to 100mmHg. The inner diameter was determined from the assumption of material incompressibility, (i.e. $\det \mathbf{F} = 1$). In a similar analysis procedure introduced by Chuong and Fung (1986), the following relations were used to map a through the thickness radial position ($R_i \le R \le R_o$) in the *zero-stress* (or reference) configuration ($R \le \Theta \le Z$) to its corresponding through the thickness radial position ($r_i \le r \le r_o$) in the *no-load* (p_i=0), and then loaded (internally pressurized to p_i=100mmHg) configuration (r, θ, z),

$$r = \sqrt{\left(R^2 - R_i^2\right)\frac{\pi - \alpha}{\pi} + r_i^2}; \quad \theta = \frac{\pi}{(\pi - \alpha)}\Theta$$

The principle stretch ratios for polar cylindrical coordinate systems are given as the diagonals of the deformation tensor **F**,

$$\mathbf{F} = diag\left[\frac{R(\pi - \alpha)}{\pi \lambda_z r}, \frac{\pi r}{(\pi - \alpha)R}, \lambda_z\right] = diag\left[\lambda_r, \lambda_\theta, \lambda_z\right]$$

The distribution of residual strains through the thickness of the *no-load* configuration is quantified in the form of Green's strain. Green's strain tensor, **E** is defined below,

$$\mathbf{E} = \frac{1}{2}\left(\mathbf{F}^T\mathbf{F} - \mathbf{I}\right) \equiv \frac{1}{2}\left(diag\left[\lambda_r{}^2 - 1, \quad \lambda_\theta{}^2 - 1, \quad \lambda_z{}^2 - 1\right]\right)$$

Trends from the present data analysis is consistent with to conclusions reached in previous studies [II IV]; that the existence of circumferential residual strains (i.e. when $\alpha \neq 0$) effectively homogenize the distribution of circumferential strain through the vessel wall at physiologic loading conditions. For the specific case of a positive opening angle, α, the tissue at the inner wall (r_i) is under compressive residual strain while the tissue at the outer wall (r_o) is under tensile residual strain. A stress-free configuration (i.e. the *zero-stress* state) is attained when the arterial ring springs into an open sector when a radial cut is made. The magnitude and distributions of residual strains at the *no-load* state are unique to each vessel, the analysis of a control carotid artery (0 weeks remodel time) is presented as Figure 2.

The remodeling process

The approximate step increase in internal blood flow can be translated into an increase in wall shear stress felt by the inner vessel wall; calculated with Poiseuille's law,

$$\tau = 4\eta Q / \pi r_i^3$$

Q being the volumetric blood flow rate, the radius of the vessel's inner wall (r_i) is approximated as the *ex-vivo* measurement at an internal pressure of 100 mmHg, and η is the fluid (blood) viscosity. The viscosity of blood can be assumed constant, the shear rate is calculated by normalizing the shear stress with respect to viscosity, $\gamma = \tau / \eta$. Newtonian laminar flow in a rigid circular cylinder is thus assumed. Kamiya and Togawa [VI] were among the first to report a canine carotid vessel's response to flow overload with an increased inner and outer radial dimension. Following a chronic increase in flow (i.e. inner wall shear stress), the vessel reactively dilates to return and maintain normal levels of inner wall shear stresses [VI VII]. In the present study, the surgical procedure induces an average volumetric blood flow rate of 300 +/-25 ml/min, inducing an increase of 125 +/-25 ml/min from the normal blood flow rate of 175 +/-25 ml/min. A corresponding increase in *ex-vivo* diameters at the physiologic pressure of 100mmHg returned wall shear rates within 27.7% and 12.8% of normal levels for the respective one and two week OCA specimen groups. The reader is referred to Figure 3 for shear rate calculations as a function of total remodeled time (i.e. the time between the approx. step inc rease in flow to excision).

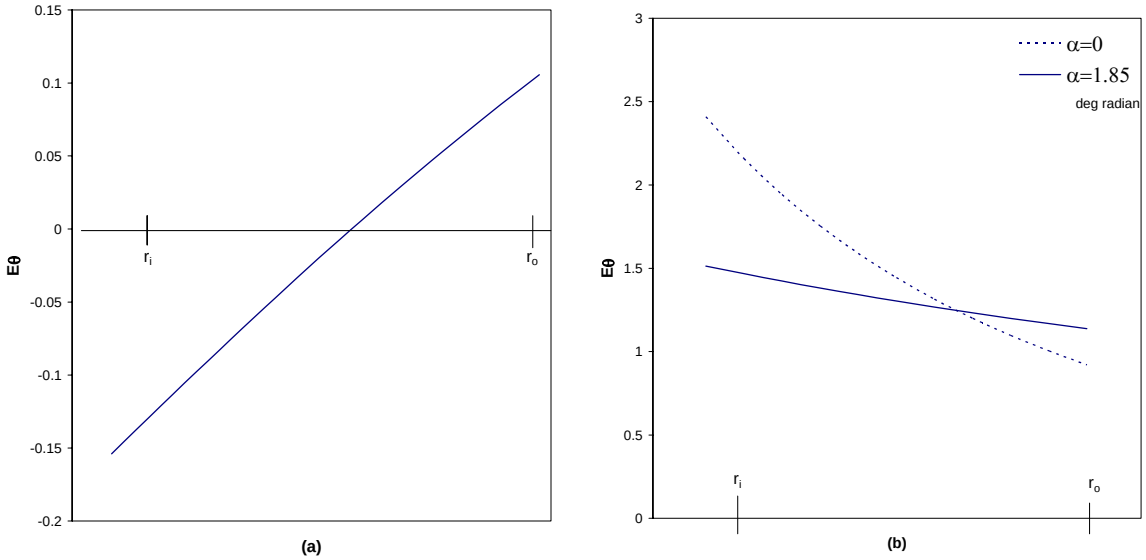


Figure 2 (a): Circumferential Green's Strain distributions for the no-load (0 mmHg), and (b): physiologic (λz=1.5 and pi=100 mmHg) configurations with and without residual strain. Residual strains are shown to homogenize the transmural strain gradient at physiologic loading conditions.

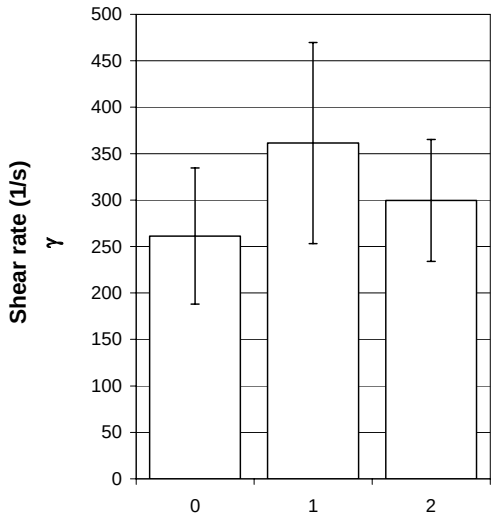


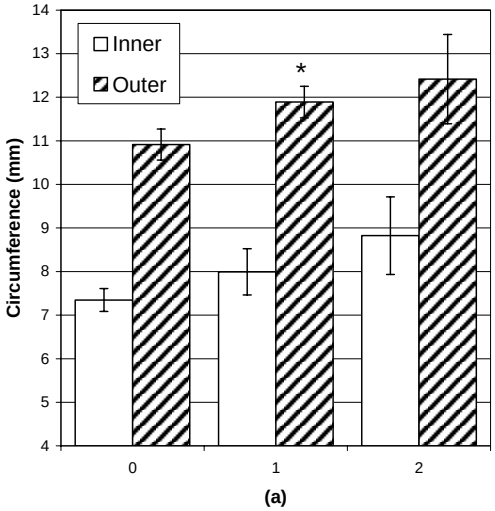
Figure 3

Table 1

FO (weeks)	γ (1/s)	SD
0	261.3	73.2
1	361.4	108.3
2	299.7	65.6

Figure 3: Shear rate at the inner wall surface of FO. Normal shear rate is recovered after two weeks of flow overload.

Morphometric changes also as a function of total remodeled time have been presented in Figures 4 and 5 for each OCA and control specimen. Corresponding data values are tabulated as Tables 2 – 5.



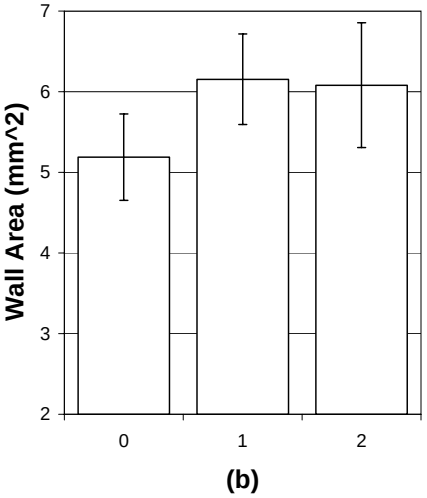


Figure 4: Morpohometric changes in the *no-load* configuration. (a): inner and outer circumferential lengths. (b): wall area.

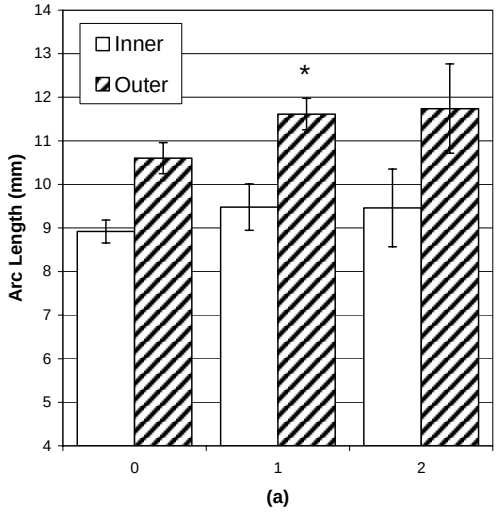
* $p \leq 0.05$

Table 2

FO (weeks)	$2\pi r_i$ (mm)	SD	$2\pi r_o$ (mm)	SD
0	7.35	0.26	10.92	0.36
1	7.99	0.53	11.89	0.36
2	8.82	0.89	12.42	1.02

Table 3

FO (weeks)	Wall Area (mm^2)	SD
0	5.1891	0.5353
1	6.1543	0.5601
2	6.0808	0.7738



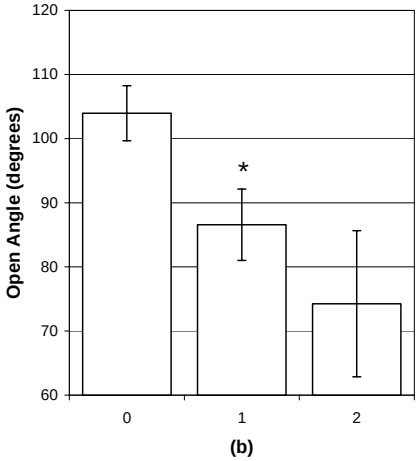


Figure 5: Morpohometric changes in the *zero-stress* configuration. (a): inner and outer arc lengths. (b): Opening angle, α.

* $p \leq 0.05$

Table 4

FO (weeks)	L_i (mm)	SD	L_o (mm)	SD
0	8.92	0.30	10.60	0.21
1	9.48	0.61	11.61	0.39
2	9.46	0.46	11.74	0.74

Table 5

FO (weeks)	Open Angle (degrees)	SD
0	104.0	4.3
1	86.6	5.6
2	74.3	11.4

Discussion

The bovine carotid artery has been found to respond to changes in its mechanical environment (i.e. increases in flow-induced shear strains) with increases in inner and outer radial dimension and decreases in opening angle. Consistent with previous flow overload experimental findings, Figure 4 demonstrates an increase in inner and outer circumference, and wall area for the *no-load* configuration. The effect of increases in the inner radii on the maintenance of normal wall shear stresses is seen directly by Poiseuille's law. The opening angle (α) has also been used as a key indicator of a vessel's residual strains. If residual strains are not considered (i.e. α=0), an obscure strain concentration at the inner wall of an *in-vivo* vessel is predicted and due to the highly non-linear, often times exponential material law, the existence of residual strains have been found to homogenize an even more abrupt stress concentration at the *in-vivo* vessel wall [VIII]. The incorporation of residual strains in the presented calculations, effectively homogenized the transmural strain gradient, Figure 2. Further studies, such as those that include active material properties [IX] and the effect of axial pre-stretch, have shown further homogenize the strain gradient [X]. A reduction in α is observed through the flow overload process and is therefore, indicative of non uniform tissue growth and resporption in response to an increase in flo w-indcued shear stresses at the vessel's inner wall. The degree of open angle, Figure 5(b), decreased following flow overload which, can be explained by Fung's [VIII] hypothesis of nonuniform tissue growth. Specifically, since the inner and outer arch lengths demonstrated non-uniform tissue growth, Figure 5(a).

Future Work

The formative stage of an investigation into the influence of a blood vessel's local mechanical environment on non-uniform tissue growth has been presented. Morphometric data shows promising trends that call for a deeper understanding of the means that govern the flow overload remodeling process. Statistically significant variance has been verified by the Student's t-test ($p \leq 0.05$) for the outer circumference, arc length, and open angle of the 1 week FO specimen group. There are too few data points to determine statistical significance of the 2 week FO specimen group however, the presented data shows a promising trend. In the short term, investigation into changes in the bio- material properties quantified by an appropriate strain-energy function and changes in orientation and composition of the tissues microstructure are to be carried out while, the continuation of studies to include more data points is planned. The presented work has been carried out using axi-symmetric models and no attention has been paid to the effect of perivascular *in-vivo* tethering. A detailed mathematical model that addresses the nonlinearity, anisotropy, and incompressibility of the arterial tissue, and the geometric nonlinearities that are associated with finite deformations is to be implemented for the quantification of strain (and therefore stress) fields for an *in-vivo* vessel subjected to the combined effects of flow-induced wall shear stresses, pressure induced normal stresses, residual strains (and therefore stresses), and perivascular tethering. The proposed biomechanical problem is to be analyzed in a quasi-static, semi-inverse approach since, advances and availability of non-invasive imaging techniques provide means for valuable data collection. A stress-growth law for flow overloaded OCA's is to be formulated by the quantification of the strain and stress distributions at intermittent time-points through the remodeling process; this work should further the understanding of the strain and stress fields in healthy arteries as well.

References

[I] Lu, X.; Zhao, J.B.; Wang, B.R.; Gregersen, H. and Kassab, G.S. (2001): Remodeling of the zero-stress state of femoral arteries in response to flow overload, *Am J Physiol Heart Circ Physiol*, v. 280, H1547-H1559.

[II] Vaishnav R.N.; Vossoughi, J. (1983): Estimation of residual strains in aortic segments. In Biomedical Engineering II: *Recent Developments*. Hall CW (ed.) Pergamon Press, p. 330-333.

[III] Chuong, C.J.; Fung, Y.C. (1983): Three-dimensional stress distribution in arteries, *Journal of Biomechanical Engineering*, vol. 105, p. 268-274.

[IV] Chuong, C.J.; Fung, Y.C. (1986): On the residual stresses in arteries, *Journal of Biomechanical Engineering*, vol. 108, p. 189-192.

[V] SigmaScan Pro 4.0, Jandel Scientific, 1996.

[VI] Kamiya, A.; Togawa, T. (1980): Adaptive regulation of wall shear stress to flow change in the canine carotid artery. *American Journal of Physiology, Heart and Circulatory Physiology*, vol. 239, p. H14-H21.

[VII] Langille, B.L.; O'Donnell, F. (1986): Reductions in Arterial Diameter Produced y Chronic Decreases in Blood Flow are Endothelium-Dependent, Science, *Science,* vol. 231, p.405-7.

[VIII] Fung, Y.C. (1984): *Biomechanics: Motion, Flow, Stess, and Growth*, Springer-Verlag, New York.

[IX] Rachev, A.; Hayashi, K. (1999): Theoretical Study of the Effects of Vascular Smooth Muscle Contraction on Strain and Stress Distributions in Arteries, *Annals of Biomedical Engineering*. vol. 27, p. 459-468.

[X] Zhang, W.; Herrera, C.H.; Atluri, S.N.; Kassab, G. (2003): The Uniform Biaxial Strain Hypothesis. In Press, contact authors for details.