Published in final edited form as:

J Biomech Eng. 2009 November ; 131(11): 114502. doi:10.1115/1.4000085.

Increase in Opening Angle in Hypertension off-loads the Intimal Stress: A Simulation Study

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Abstract

The stress distribution in the vessel wall has important bearing on vascular function including intima, media and adventitia. The residual strain in the vessel wall has been thought to largely normalize the transmural stress distribution with slightly higher values at the intima. In hypertension, the compensatory increase in opening angle is thought to maintain a uniform stress distribution. We have recently shown that the circumferential stress at adventitia may exceed that at intima at physiological loading due to large opening angle (OA) in normal porcine coronary arteries. The objective of this study was to show that increases in opening angle subsequent hypertension can further shift the stress from the intima to the adventitia. The change of stress distribution during acute hypertension was calculated using available data on the changes of vessel geometry, material property and internal pressure during the hypertension. It was found that the increase of OA following acute hypertension offloads the stress from intima to adventitia, therefore relieves some of the stress increase in the intimal layer induced by the sudden pressure increase. This has important implications for hypertension where it may shift the excessive stress from the inner layer to the outer layer. This may be a protective mechanism for the intima layer in hypertension.

Keywords

Opening angle; Strain; Intima; Adventitia; Remodeling

INTRODUCTION

The stress distribution in the vessel wall has important bearing on vascular function in health and disease. We have recently shown that a larger opening angle (OA) can shift the circumferential stress from the intima-media to the adventitia layer (12). The simulation of transmural wall stress was based on measurements of strain and material properties of coronary arteries in reference to the zero-stress state. A one-layer model with material constants of the intact vessel was used to calculate the circumferential stress distribution. A sensitivity analysis using both a one layer model and a two-layer model (intima-media and adventitia layers) was carried out to study the effect of the OA on the circumferential stress

distribution and average circumferential stress. An important new hypothesis emerged that the circumferential stress at the adventitia may exceed that at the intima at physiological loading due to the larger OA in the porcine coronary artery. This hypothesis has important implications for growth and remodeling where an increase in opening angle may shift excessive stress from the inner layer to the outer layer.

Fung and colleagues [1–3] have previously shown that the OA is a sensitive index of the non-uniformity of growth and remodeling. In hypertension, the inner layer outgrows the outer layer and hence the vessel sector bends outward (OA increases) rapidly after the onset of hypertension [2–5]. Based on these observations, we hypothesized that the rapid increase in OA following acute hypertension may serve to off-load the intima (endothelium) of excess stress. To verify this hypothesis, we used previously published data on the aorta following hypertension by aortic constriction [3]. We show that the stress distribution factor (ratio of outer-to-inner stress) increases in the two days post hypertension due to the increase in OA. This mechanical protective mechanism underscores the importance of the rapid changes of the OA or the zero-stress state post hypertension.

METHODS

The effect of changes in the OA on the stress distribution in the vessel wall post acute hypertension was studied. To calculate the stress distribution in the vessel wall, material constants of the blood vessel, intramural pressure and the geometry of the zero-stress state; i.e., the inner and outer circumferences and the wall area in the zero-stress state, are needed. Liu and Fung [3] studied the time course of change of pressure and zero-stress state of aorta post constriction. Since material constants of the rat aorta for the three-dimensional Fung model are not available, the material constants of the rabbit carotid artery [6] were used: $C=22.4\text{kPa}$, $b_1=1.0672$, $b_2=0.4775$, $b_3=0.0499$, $b_4=0.0903$, $b_5=0.0585$, $b_6=0.0042$. The material parameters were assumed to remain unchanged since only acute remodeling (within two days) was considered. The change of OA after the banding was measured by Liu and Fung [3], whereas the changes of three parameters: inner-surface circumference; outer-surface circumference and area of the vessel segment were not directly recorded. The vessel wall area A can be derived from two measured quantities: wall thickness H and wall thickness-to-radius ratio H/R_i . Measurements at the 4% L, which is the distance of the aortic segment to the heart divided by the total length of aorta, were chosen. The wall thickness of each vessel was normalized to the respective body weight in the original study. Here, we assume the average weight in the subsequent calculation so the normalizing factor is 1. The following equation describes the relation between the wall thickness, thickness-to-radius ratio and wall area in the no-load state as:

$$A=\pi(R_o^2 - R_i^2)=\pi(H^2+2R_iH)=\pi H^2\left(1+\frac{2}{H/R_i}\right) \quad [1]$$

where H is wall thickness, R_o is inner diameter, R_i is inner diameter, and H/R_i is wall thickness-to-radius ratio. Once wall area A is determined, $C_o^2 - C_i^2$ can be determined by:

$$OA=180 - \frac{44(C_o^2 - C_i^2)}{A\pi} \quad [2]$$

The change of C_o or C_i was not directly measured in the study. We assume that the outer circumference C_o does not change during the first two days of hypertension and calculated the change of C_i . There is evidence for this assumption as the studies by Fridez et al. [7] and

Fung et al. [2] found the inner layers thicken more in the acute phase of hypertension. Once the zero-stress state change is determined from the inner and outer circumferences and the wall area, it can be combined with material constants and pressure data to calculate the outer diameter and strains as described below.

Based on the equation of equilibrium and boundary conditions on the inner and external surfaces and the incompressibility assumption (for the one layer model), the outer diameter of the deformed vessel may be determined by solving the integral equation as described by Fung [6]:

$$p_i = \int_{r_e}^{r_i} C \{ (1+2E_r) [b_6 E_\theta + b_5 E_z + b_3 E_r] - (1+2E_\theta) [b_1 E_\theta + b_4 E_z + b_6 E_r] \} e^Q \frac{dr}{r} \quad [3]$$

where p_i is the internal pressure of 100 mmHg. Once the outer diameter is determined, the strains of the vessel can be determined based on the incompressibility condition. Finally, the stress distribution can be calculated as described in references 6 and 8. The circumferential stress at the inner and outer boundary of the vessel wall was taken as an index for the stress in the intima and adventitia layer, respectively.

RESULTS AND DISCUSSION

Figure 1 shows the change of inner-to-outer circumference ratio and stress distribution during the first two days of hypertension. Figure 1A shows the inner circumference outgrows the outer circumference. Hence, the vessel sector bends outward and the OA increases. The fraction (%) of stress in the intima and adventitia during the progression of hypertension is shown in Figures 1B and 1C with and without remodeling of the OA, respectively. It is clear that the consideration of changes in OA shifts the stress to the adventitia (Fig. 1B as compared to Fig. 1C).

It has been found that OA increases rapidly (within hours) during the initial stage of hypertension [2–5]. Remodeling in the zero-stress state can be attributed to changes in inner circumference, outer circumference and wall area. It can be seen from Figure 1A that the inner layer elongates faster than the outer layer in the zero-stress state, which leads to the increase in the OA. Figure 1B shows the off loading from the intima layer to the adventitia layer in comparison to Figure 1C that does not take into account changes in OA. Because most of the pressure increase during the first two days occurs within the initial 15 minutes [3] and the OA does not change in the case of Figure 1C, the stress distribution is solely dependent on the pressure. Hence, the stress distribution does not change significantly thereafter. The offload of the stress to the outside layer is consistent with a sensitivity analysis and previous experimental data which show an increase of OA increases the stress distribution factor (12).

The stress distribution in acute hypertension was simulated with rat aorta data from Liu and Fung [3]. The material constants of rat aorta are not available, however, and hence the material constants of rabbit carotid artery were used [6]. Since the structure and mechanical properties of rat aorta may differ from those of rabbit carotid artery; this approximation may introduce error in absolute strain and stress values. However, material properties will not affect the trend of stress distribution change, i.e., the change of the ratio of the circumferential outer-to-inner layer stress. This statement was validated in simulations with different sets of material parameters.

The increase in OA post hypertension stems from the growth of the intimal circumference relative to the adventitia [9–11]. Hassler [9] found that a significant increase in number of

new cells are formed at 6 hours after hypertension and most of the newly formed cells are found in the tunica media and intima layer. Owens and Reidy [11] found a hyperplastic growth of vascular smooth muscle cells three days following induction of acute hypertension. However, the detailed patterns of the changes in the inner circumference, outer circumference and wall area following hypertension and how these changes relate to the structural remodeling of the vessel have not been reported. There is clearly a need for future studies to systematically characterize these changes and to investigate the potential role of changes in OA to protect the intima and hence endothelium.

Acknowledgments

This research is supported in part by the National Institute of Health-National Heart, Lung, and Blood Institute Grant HL-087235 and HL-084529.

References

1. Fung, YC. Biomechanics: Motion, Flow, Stress and Growth. New York: Springer-Verlag; 1990.
2. Fung YC, Liu SQ. Changes of Zero-Stress State of Rat Pulmonary-Arteries in Hypoxic Hypertension. *Journal of Applied Physiology*. 1991; 70(6):2455–2470. [PubMed: 1885439]
3. Liu SQ, Fung YC. Relationship between Hypertension, Hypertrophy, and Opening Angle of Zero-Stress State of the Arteries Following Aortic Constriction. *Journal of Biomechanical Engineering-Transactions of the ASME*. 1989; 111(4):325–335.
4. Fridez P, Makino A, Miyazaki H, et al. Short-Term Biomechanical Adaptation of the Rat Carotid to Acute Hypertension: Contribution of Smooth Muscle. *Annals of Biomedical Engineering*. 2001; 29(1):26–34. [PubMed: 11219505]
5. Fung YC, Liu SQ. Change of Residual Strains in Arteries due to Hypertrophy Caused by Aortic Constriction. *Circulation Research*. 1989; 65(5):1340–1349. [PubMed: 2805247]
6. Chuong CJ, Fung YC. On Residual Stresses in Arteries. *Journal of Biomechanical Engineering-Transactions of the ASME*. 1986; 108:189–192.
7. Fridez P, Zulliger M, Bobard F, Montorzi G, et al. Geometrical, Functional, and Histomorphometric Adaptation of Rat Carotid Artery in Induced Hypertension. *Journal of Biomechanics*. 2003; 36(5): 671–680. [PubMed: 12694997]
8. Humphrey, JD. Cardiovascular Solid Mechanics: Cells, Tissues, and Organs. New York: Springer; 2002.
9. Hassler O. Arterial Cell-Kinetics in Experimental Hypertension. *Virchows Archiv Abteilung A Pathologisue Anatomie*. 1974; 362(4):283–289.
10. Owens GK. Control of Hypertrophic Versus Hyperplastic Growth of Vascular Smooth-Muscle Cells. *American Journal of Physiology*. 1989; 257(6):H1755–H1765. part 2. [PubMed: 2690643]
11. Owens GK, Reidy Ma. Hyperplasic Growth-Response of Vascular Smooth-Muscle Cells Following Induction of Acute Hypertension in Rats by Aortic Coarctation. *Circulation Research*. 1985; 57(5):695–705. [PubMed: 4053303]
12. Wang C, Guo X, Kassab GS. A New Observation on the Transmural Stress Distribution in the Coronary Artery Wall. *J Biomech Eng*. In Press.

Figure 1.

Acute hypertension during the first two days. A) Ratio of inner-to-outer circumferential length in the zero-stress state. B) The fraction (%) of the stress at the intima and adventitia layer taking into account the changes in opening angle. C) The fraction (%) of stress at intima and adventitia layer if there is no change in opening angle. The circumferential stress at inner and outer boundary of the vessel wall was considered as the stress in the intima and adventitia layer, respectively. The fraction value is the ratio of individual layer stress to the sum of stresses in both layers.