THE ROLE OF BLOOD FLOW IN THE LOCALIZATION OF VASCULAR DISEASES: SPECULATION-BASED COMPUTER SIMULATION

S. Wada *, Y. Feng*, T. Yamaguchi* and T. Karino**

* Department of Bioengineering and Robotics, Tohoku University, Sendai, Japan
** Research Institute for Electronic Science, Hokkaido University, Sapporo, Japan

shigeo@pfsl.mech.tohoku.ac.jp

Abstract: In order to find out the role of blood flow in the localization of vascular diseases, computational studies based on various hypotheses were carried out. The computational analysis of mass transport of lipoproteins in blood flow in the artery showed that the concentration of lipoproteins is locally elevated on the vessel wall at low wall shear region due to the permeable nature of the blood vessel. From this simulation we derived a hypothesis that the localization of atherosclerosis results from the hypercholesterolemic environment generated by the flow-dependent concentration polarization of lipoproteins. The computer simulation of the development of vascular diseases based on the high or low wall shear stress hypothesis showed the importance of the change in the geometry of the blood vessel to investigate the relationship between the hemodynamics and the localization of the vascular disease. These computational approaches lead new speculation and provide us insight into the localization mechanism of vascular diseases.

Introduction

A lot of experimental observations indicate that hemodynamic factors are involved in the localized pathogenesis of vascular diseases such as intimal hyperplasia, atherosclerosis and aneurysm in the arterial system [1]. However, the precise mechanism has not been elucidated yet. Blood flow induces mass transfer between flowing blood and arterial wall [2] as well as mechanical stimulation which causes various biological responses of vascular cells [3]. Thus, it has been speculated that the mechanical role of blood flow is related to the localization of vascular diseases. In order to verify this speculation, we have carried out computer simulation of blood flow and mass transfer in arteries based on various hypotheses. In this paper, recent results obtained by our speculation-based analyses are described.

Flow-Dependent Concentration Polarization of LDL

Due to particular semi-permeable nature of arterial wall to plasma, the permeability coefficient to macromolecule is one or two orders smaller than that of the water. This difference could cause concentration polarization of low density lipoprotein (LDL) on the surface of arterial wall [4]. Since the elevation of the LDL level promotes the accumulation of cholesterol within the intima [5], it is suspected that flow-dependent concentration polarization of LDL creates a favorable condition for the genesis and development of atherosclerosis and intimal hyperplasia. In order to evaluate the degree of concentration polarization of LDL in arteries, we have calculated LDL transport from flowing blood to arterial wall in various anatomical models of the artery.

Mass Transport Model

Steady state mass transport of lipoproteins in the flowing blood is described by

$$\mathbf{u}\cdot\nabla C - D\nabla^2 C = 0 \tag{1}$$

where C is the concentration of LDL, D is the diffusivity of LDL. The velocity of blood flow, **u**, is obtained by the governing equations of blood flow, which is the continuity and Navier-Stokes equations;

$$\nabla\cdot\mathbf{u} = 0 \tag{2}$$

$$\rho\left(\mathbf{u}\cdot\nabla\right)\mathbf{u} = -\nabla P + \mu\nabla^2\mathbf{u} \tag{3}$$

where P is blood pressure, ρ and μ are the density and viscosity of blood, respectively. The filtration property of the arterial wall is expressed by the boundary conditions at the wall of blood flow

$$u_n = V_w \tag{4}$$

and mass transport

$$C_w V_w - D\frac{\partial C}{\partial n} = KC_w \tag{5}$$

where V_w is the water filtration velocity, C_w is the surface concentration of LDL, n is a coordinate normal to the wall, and K is the overall mass transfer coefficient of LDL at the vessel wall. Eq. (4) shows the mass balance among the amount of LDL being carried to the wall by the filtration flow, diffusing back to the mainstream, and passing through the wall.

Equations (1)-(3) were solved with a Galerkin-finite element method with streamline upwind technique [6]. The solution domain was divided into linear brick elements in order for blood flow analysis. For the calculation of mass transfer, to reduce the computational cost and increase the accuracy of the calculation, the solution domain was limited to near the wall where

ISSN: 1727-1983

concentration polarization of LDL occurs, and the selected region was sub-divided into smaller elements.

Case Study I: Multiple-Curved Artery

Firstly we investigated the mass transport of LDL in the human right coronary artery with multiple bend [7]. The geometry of the artery was obtained by tracing the outline of the transparent artery which was previously used in flow study [8]. To make the calculation as simple as possible, it was assumed that the vessel was structurally symmetric with respect to its common median plane, and the cross-sections were circular at any location along the entire vessel segment.

Figure 1 shows the distribution of wall shear stress induced by blood flowing through the vessel model of a human coronary artery with multiple bends. Reynolds number at the inlet was assumed to be 500. It was found that reverse flow occurs at the downstream of the bend where the wall shear stress becomes relatively low. Figure 2 shows the distribution of LDL concentration at the luminal surface of the vessel. The calculation was conducted by assuming the filtration velocity of water at the vessel wall, V_w = 4×10^{-6} cm/sec, the overall mass transfer coefficient of LDL at the arterial wall, K = 2×10^{-8} cm/sec, and the diffusivity of LDL, D = 5×10^{-8} cm^2/sec. The surface concentration of LDL is locally elevated by 35% at the inner wall of the curved segment

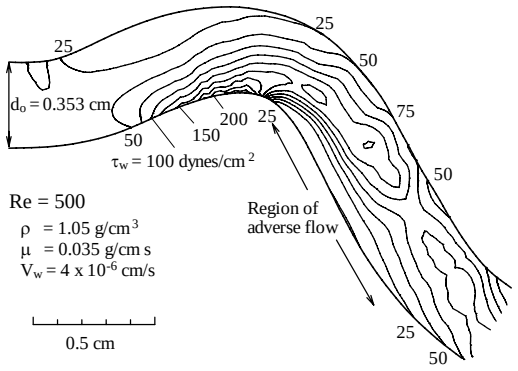

Figure 1: Wall shear stress distribution of steady blood flow in multiple bend artery at Re = 500.

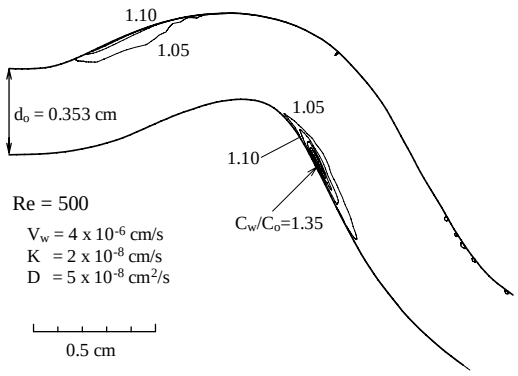

Figure 2: LDL concentration at the luminal surface of the multiple bend artery.

where the wall shear stress is relatively low. This corresponds to the location of wall thickening observed in transparent artery [8].

Case Study II: Anastomosed Artery

Next, to investigate the effect of locally disturbed flows on the distribution of surface concentration of LDL in end-to-end anastomosed arteries, we constructed two anatomically realistic models from the photographs of the transparent arteries with and without a moderate stenosis and carried out computer simulations of blood flow and LDL transport in these arteries [9].

Figure 3 shows the flow pattern and the distribution of surface LDL concentration in the anastomosed artery containing a moderate stenosis. Due to the semi-permeable nature of the arterial wall, concentration polarization of LDL certainly occurs at the luminal surface of the blood vessel, creating regions of high and low surface concentration of LDL in the anastomosed

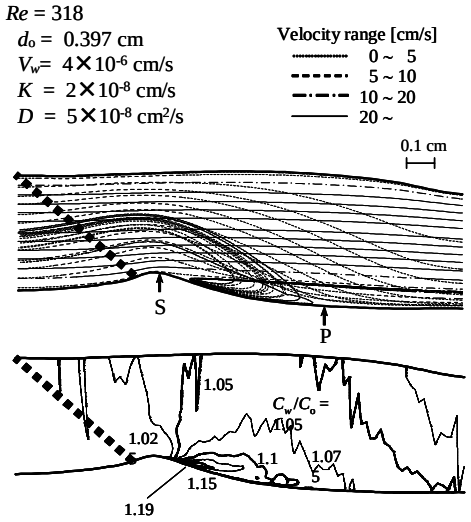

Figure 3: Flow patterns and surface concentration of LDL in the anastomosed artery with a moderate stenosis

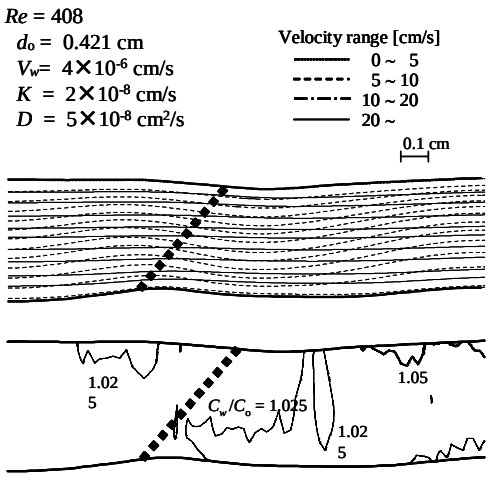

Figure 4: Flow patterns and surface concentration of LDL in the anastomosed artery without stenosis.

ISSN: 1727-1983

artery depending on the degree of flow disturbances caused by the presence of a stenosis. As evident from this figure, surface concentration of LDL is locally elevated by more than 10% in a restricted region distal to the stenosis where recirculation zone is formed, while in other regions it increased by only 5 % or less. The highest value of C_w/C_o which is found just downstream of the apex of the stenosis is 1.19, and the location well corresponded well to the site where intimal thickening develops preferentially.

Figure 4 shows the results for the anastomosed artery without stenosis in which no recirculation zone is formed. It is found that the surface concentration of LDL increases slightly (2.5% from the value at the inlet) in the region distal to the anastomotic junction, but there is no particular region where surface concentration of LDL is locally elevated in this vessel.

These two case studies based on the anatomically realistic model of coronary artery and anastomosed artery indicate that flow-dependent concentration polarization of LDL plays an important role in the localized pathogenesis and development of atherosclerosis and anastomotic intimal hyperplasia in the human arterial system by locally elevating the surface concentration of LDL.

WSS-Dependent Progression of Vascular Diseases

To investigate the effects of wall shear stress (WSS) on the localized development of various cardiovascular diseases such as atherosclerosis, intimal hyperplasia and aneurysm, we have carried out a computer simulation which follows up the geometrical change of the vessel accompanied with the progression of the diseases induced by WSS.

Case Study I: Thickening of the Vessel Wall Induced by Low WSS

Based on the fact that atherosclerosis is likely to occur at a low wall shear stress region in the artery [10], it was assumed that the vessel wall thickens inward at the location where flow induced WSS is less than a threshold value, τ_{th}. In this simulation, the amount of thickening of the wall during a certain period which corresponds to a computational step is given by

$$\delta = \begin{cases} C\left(\tau_{th} - \tau\right)/\tau_{th} & \text{for } \tau \le \tau_{th} \\ 0 & \text{for } \tau > \tau_{th} \end{cases} \qquad (6)$$

where τ is the wall shear stress obtained by the flow calculation in the artery, and C is a coefficient.

Computer simulations were conducted by repeating the calculation of blood flow, evaluation of wall shear stress, and change in the geometry of the vessel by thickening of the wall. A new geometry of the vessel was obtained each step by moving the nodal points on the wall by δ in the direction normal to the lumen. Then the solution domain was re-meshed for the new geometry. This process was repeated until a stable geometry of the vessel was obtained. The values of τ_{th}

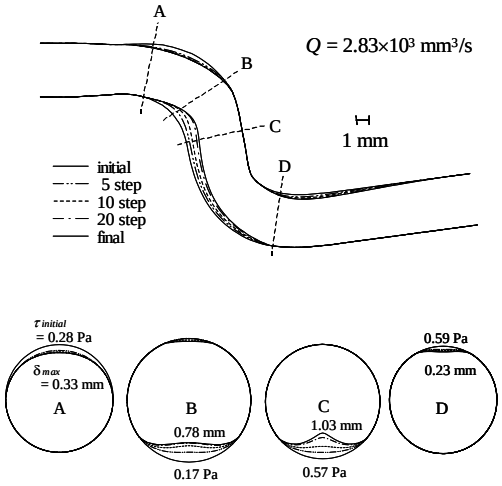

Figure 5: Time course of the thickening of vessel wall and the change in the geometry of the arterial model with a multiple bend induced by low wall shear stress.

and C were chosen to be 1.2 Pa and 100 μm, respectively [11].

Calculations were carried out for blood flowing at a physiological flow rate of 2.83×10^3 mm^3/sec in the human coronary artery model shown in the previous section. The Reynolds number defined at the entrance was 250. A stable geometry of the vessel was obtained in 40 steps.

Figure 5 shows the progress in the thickening of the vessel wall from the initial state to the final stable state. It is found that wall thickness increases nonlinearly with computational steps, indicating that change in geometry affects the new development of the wall thickening. The wall is most thickened around the common median plane at the inner wall of the hind half of the bend (C), where the wall is relatively low at the initial state.

Figure 6 shows the relationship between the wall shear stress in the initial state and the thickness of the wall in the final state at various locations in the artery.

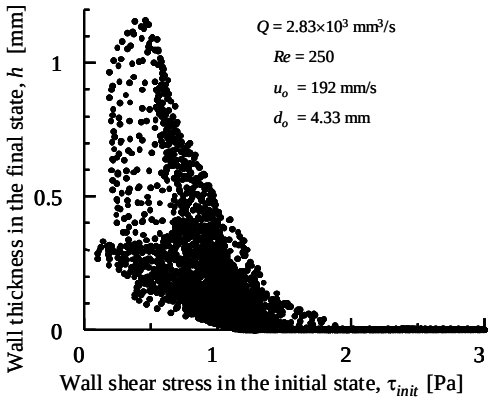

Figure 6: Relationship between WSS in the initial state and the wall thickness in the final sate.

ISSN: 1727-1983

It is found that thickening occurs even at the sites where wall shear stress is larger than the threshold value in the initial state because change in the geometry of blood vessel creates a new site of low wall shear stress. There is a tendency that the wall thickens at the site of low wall shear stress in the initial state. However, lower wall shear stress in the initial state does not always generate thicker wall. This indicates that the final thickness of the wall is determined by not only the value of wall shear stress in the initial state but also the flow patterns affected by the change in geometry of the blood vessel.

Case Study II: Development of Aneurysm Induced by High WSS

In contrast to the localized pathogenesis of atherosclerosis, intracranial aneurysm is likely to occur at sites where WSS are relatively high [12]. To express the local expansion of blood vessel in the development of aneurysm, we made a hypothesis that the high local wall shear stress leads to degeneration of the arterial wall [13] and the Young's modulus of the wall decreases at a constant rate when the local WSS is above a threshold value, τ_{th};

$$E' = E / k \quad \text{for} \quad \tau > \tau_{th} \tag{7}$$

where E' and E are the new and old Young's modulus and k is the degeneration ratio. Under this hypothesis, we have simulated the formation and development of intracranial aneurysms in various artery models by repeating blood flow analysis and structural analysis of the vessel. That is, starting from an initial geometry and material properties of the elastic artery, the following procedure was repeated; calculate the deformation of the artery at a physiological blood pressure, calculate the blood flow in the deformed artery, and change the local Young's modulus of the wall depending on the WSS obtained from the flow calculation.

Figure 7 shows the change in the shape and WSS distribution of a curved artery at simulation step 1, 5, 10, 15, 20 and 25. This simulation was carried out for blood flow at Re = 165 in the artery curved at 90 degree with an inner and outer diameter of 2.7 mm and 2.2 mm, respectively. The initial Young's modulus of the wall is uniformly 2.0 MPa. The threshold value of the WSS and the degeneration ratio were chosen at τ_{th} = 5.0 Pa and k = 1.5, respectively.

Initially, high WSS in the curved part leads to an increase of the vessel diameter in a wide range. The high WSS region is not observed at the same site in each step. Small fluctuations of the shape occur inside the bulged regions creating high and low WSS, and it leads to further increase in the height of the bulge. With progression of the aneurysm, the inside of the bleb is dominated by low WSS and the development of aneurysm gradually settles down. At step 25, the maximum radius of the artery at the aneurysm increases to about 2.1 times of the initial radius. This simulation suggests a possible mechanism of the progression of aneurysm that a small deformation in the arterial wall

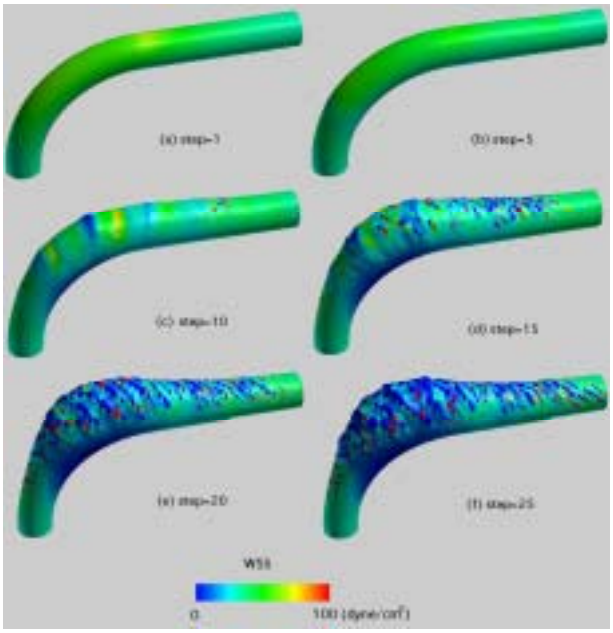

Figure 7: Progression of aneurysm of the curved model. The color map indicates WSS value. The aneurysm develops both in the height and width direction.

can cause the re-distribution of the WSS, which in turn causes the degeneration of the wall and leads to more deformation of the wall. This process repeats and finally forms the aneurysm.

Conclusion

In this paper, the mechanical role of blood flow in the localization of vascular diseases was investigated by computer simulation. The mass transport analysis revealed that the concentration polarization of lipoproteins occurs at the luminal surface of the permeable wall and that the blood flow affects the surface concentration. The computer simulation led to a speculation that the localization of atherosclerosis results from the hypercholesterolemic environment which is generated by the flow-dependent. The developments of wall thickening and local expansion of the artery were also analyzed by including the hypothesis of high and low wall shear stress into the computer simulation. The computer simulation showed the importance of the change in the geometry of blood vessel in the relationship between the hemodynamics and the progression of the vascular diseases. These fact-based and speculation-based computer simulations provide us with a new insight into the localization mechanism of vascular diseases.

References

[1] GLAGOV S., ZARINS C., GIDDENS D. P., KU D. N.(1988): 'Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries', *Arch. Pathol. Lab. Med.*, **112**, pp. 1018-1031.

ISSN: 1727-1983

[2] TARBELL J. M. (2003): 'Mass transport in arteries and the localization of atherosclerosis', *Annu. Rev. Biomed. Eng.*, **5**, pp. 79-118.
[3] NEREM R. M. (1992): 'Vascular fluid mechanics, the arterial wall, and atherosclerosis', *J. Biomech. Eng.*, **114**, pp. 274-282.
[4] WADA S, KARINO T. (1999): 'Theoretical study on flow-dependent concentration polarization of low density lipoproteins at the luminal surface of a straight artery', *Biorheology*, **36**, pp. 207-223.
[5] ROSS R. & HARKER L. (1976): 'Hyperlipidemia and atherosclerosis. Chronic hyperlipidemia initiates and maintains lesions by endothelial cell desquamation and lipid accumulation', *Science*, **193**, pp. 1094-1100.
[6] BROOKS A. N. (1982): 'Streamline upwind/Petrov-Galerkin formulations for convection dominated flows with particular emphasis on the incompressible Navier-Stokes equations', *Comp. Meth. in Appl. Mech. and Eng.*, **32**, pp. 199-259.
[7] WADA S. & KARINO T. (2002): 'Theoretical prediction of low-density lipoproteins concentration at the luminal surface of an artery with a multiple bend', *Ann. Biomed. Eng.*, **30**, pp. 778-791.
[8] ASAKURA T. & KARINO T. (1990): 'Flow patterns and spatial distribution of atherosclerotic lesions in human coronary arteries', *Circ. Res.*, **66**, pp. 1045-1066.
[9] WADA S., KOUJIYA M., KARINO T. (2002): 'Theoretical study of the effect of local flow disturbances on the concentration of low-density lipoproteins at the luminal surface of end-to-end anastomosed vessels', *Med. Biol. Eng. Comput.*, **40**, pp. 576-87.
[10] CARO C.G., FITZ-GERALD J. M., SCHROTER R. C. (1971): 'Atheroma and arterial wall shear. Observation, correlation and proposal of a shear dependent mass transfer mechanism for atherogenesis', *Proc. Roy. Soc. Lond.*, **B177**, pp. 109-159.
[11]WADA S., FUKUZAKI S., KARINO T. (2003): 'Computer simulation of the adaptive changes in vascular geometry caused by the development of atherosclerotic lesions', (in Japanese), *Trans. JSME*, **69A-677**, pp. 62-69.
[12]UJIIE H, LIEPSCH D. W., GOETZ M., YAMAGUCHI R., YONETANI H., TAKAKURA K. (1996): 'Hemodynamic study of the anterior communicating artery', *Stroke*, **27**, pp. 2086-2093.
[13]FENG Y., WADA S., TSUBOTA K., YAMAGUCHI T.(2005): 'The application of computer simulation in the genesis and development of intracranial aneurysms', *Technol. Health. Care.*, **13**, pp. 281-291.

ISSN: 1727-1983