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Computed Numerical Analysis of the Biomechanical Effects on Coronary Atherogenesis Using Human Hemodynamic and Dimensional Variables

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The objectives of this investigation were to evaluate biomechanical factors in the atherosclerotic process using human in vivo hemodynamic parameters and computed numerical simulation qualitatively and quantitatively. The three-dimensional spatial patterns of steady and pulsatile flows in the left coronary artery were simulated, using a finite volume method. Coronary angiogram and Doppler ultrasound measurement of the proximal left coronary flow velocity were performed in humans. Inlet wave velocity distribution obtained from in vivo data of the intravascular Doppler study allowed for input of in vitro numerical simulation. Hemodynamic variables, such as flow velocity, pressure and shear stress of the left anterior descending coronary bifurcation site were calculated. We found that there were spatial fluctuation of flow-velocity and recirculation areas at the curved outer wall of the left anterior descending coronary artery, which were due to the differences of flow-velocity and shear stress, especially during the deceleration phase of pulsatile flow. This study suggests that rheologic properties may be a part of the atherogenic process in the coronary bifurcated and curved areas.

Key Words: Numerical analysis, pulsatile blood flow, hemodynamic changes, flow velocity, shear stress

One of the major causes of death in the Western world is ischemic heart disease due to atherosclerosis of the coronary artery. Various kinds of systemic risk factors to the arterial wall are intermingled in complex cascades of interactions, such as the environmental, genetic and biologic risk factors for atherogenesis and progression of atherosclerosis (Ross, 1990; Fuster *et al.* 1992; Loree *et al.* 1992; Ross, 1993; Beriiner *et al.* 1995). Although many systemic risk factors predispose to its development, atherosclerosis preferentially affects certain regions of the circulation (Stary *et al.* 1992; 1994; 1995). This suggests that the lesion-prone areas may be at least in part due to biomechanical-related factors. Furthermore, intraluminal hemodynamics, such as flow velocity, pressure changes, and wall shear stress have been suggested as other risk factors for the development of coronary atherosclerosis (Friedman *et al.* 1983; Zarins *et al.* 1983; Ku *et al.* 1985; Nerem, 1992; MacIsaac *et al.* 1993).

There is a lack of information regarding the spatial three-dimensional distribution of intraluminal

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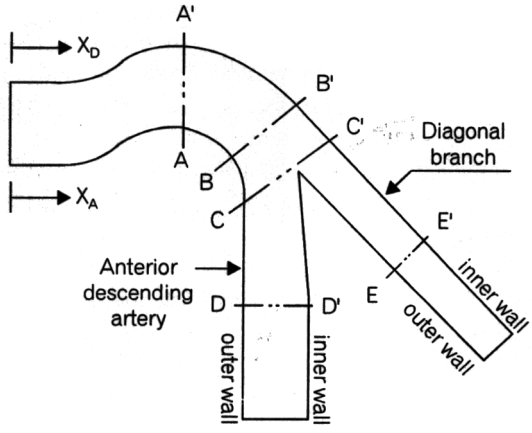
hemodynamics of the coronary vascular tree. This is due to the technical difficulties in characterizing and quantitating microenvironmental hemodynamics. Also, the exact rheologic effect to the atherogensis and progression of atherosclerosis have not been completely understood. Computed numerical simulation of the human coronary model, using a finite volume method will be important in understanding biomechanical pathophysiology of atherosclerosis and its complications. By this technique, it is possible to apply human in vivo data and to quantitate the local hemodynamic variables.

This study was aimed at defining uneven geometric distribution of the hemodynamic variables presented in the same coronary arterial tree, and to evaluate the biomechanical effects on atherogenesis, using human data and computer simulation. To accomplish these aims we visualized and quantitated geometrical patterns of hemodynamic variables of the human left coronary artery model and compared the rheologic properties of steady flow with pulsatile flow for validation of the physiologic condition.

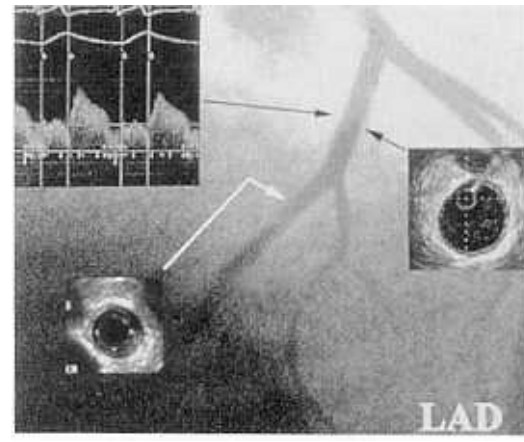
MATERIALS AND METHODS

Coronary artery bifurcation model

To evaluate the hemodynamic variables in a human coronary model, the basic coronary model was adopted from a human angiogram of the left coronary artery. Left coronary angiogram was performed by the femoral approach according to standard techniques. For computed simulation, the measured left anterior descending coronary artery (LAD) diameter using a quantitative coronary assessment (QCA) was calculated as a reference diameter. This area was bifurcated and curved on the coronary angiogram. Several investigators (Grottum *et al.* 1983; Nerem, 1992; Stary *et al.* 1992; MacIsaac *et al.* 1993; Falk *et al.* 1995) have shown that bifurcated and curved areas have a high prevalence of early atherosclerotic lesions. We also performed the promising new techniques involving intracoronary two-dimensional ultrasound for measuring the vessel wall area, luminal area and vessel wall thickness as well as Doppler ultrasound measurement for coronary flow velocity at the proximal and distal region of interest in the coronary artery. This basic model allowed for input of in vivo hemodynamic data and the vascular structural parameters. The left coronary artery bifurcation model is shown in Fig. 1. The symbols X_A and X_D



(a) Left coronary artery model



(b) Left coronary angiogram(LAO view)

Fig. 1. Left coronary artery model for numerical analysis (a) and LAO view of normal human left anterior descending coronary artery (LAD) angiogram (b) with Doppler and intravascular ultrasonographic study. Each parameter is denoted as follows; X_A: Distance along the anterior descending artery, X_D: Distance along the diagonal branch, A-A': Initial mid-portion of LAD, B-B': Curved portion before bifurcation, C-C': The portion of bifurcation apex, D-D' & E-E': Mid-portion of each branch after bifurcation.

in Fig. 1 represent distances along the walls of the left anterior descending artery and the diagonal branch, respectively.

The angle of the left anterior descending artery and the diagonal branch was set to 45°, diameter ratios of the former and the latter to the reference diameter were set to 0.75 and 0.5, respectively, and the diameter of left main coronary artery was set to 5 mm.

The inlet flow velocity waveform of the pulsatile coronary blood flow, physiologic coronary blood flow, is represented in Fig. 2, obtained from in vivo intravascular Doppler ultrasonic flow data.

Rheological properties of blood

To account for the non-Newtonian viscosity of blood, we had to adopt a constitutive equation that represented the apparent viscosity of blood as a function of shear rate. Because of viscosity, the blood velocity at the vessel wall must be zero. The rate at which the axial velocity rises as one moves from the vessel wall toward the center is termed the shear rate, *dv/dr*. This velocity gradient causes a shear stress (τ) on the endothelium, parallel to the blood flow and proprotional to the viscosity (η), $\tau = \eta \cdot dv/dr$. Among various constitutive equations, the Carreau model of the following equation was used to specify the shear rate versus the apparent viscosity relationship (Patankar, 1980).

$$\eta = \eta_\infty + (\eta_0 - \eta_\infty)\,[1 + \lambda^2 \gamma^2]^{\frac{q-1}{2}}$$

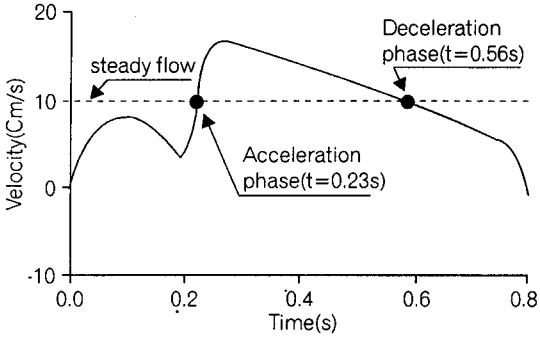


Fig. 2. Physiologic waveform of pulsatile coronary blood flow

where γ denotes the shear rate. η_∞ and η_0 are the apparent viscosity at infinite shear rate and zero shear rate, respectively. λ and q represent the characteristic time and index of this model, respectively.

Rheological values of blood are taken as non-Newtonian fluid. Once the local shear rate is calculated, the apparent viscosity of blood can be determined by this equation.

Numerical analysis

For attaining effective numerical analysis of hemodynamics, we used the finite volume method, adapting the Rhie-Chow algorithm (Rhie and Chow, 1983), computed with CFDS-Flow 3D package program (AEA comp., Britain) in SUN SPARC workstation 20 (Sun Micro Systems co., Mountain view, CA, U.S.A). The governing equations are calculated under a non-staggered grid system, in which the velocity components in the equations are calculated for the same points that lie on the pressure grid points. This method simplifies the equations. The fully implicit scheme is used to solve the physiologic flow problem, where the time step is set to be 0.01s. Furthermore, serial cross- sectional studies were undertaken to define a focal flow reversal (recirculation) in the specific coronary flow sites. As described above, we used in vivo flow- velocity of LAD, and after visually determining the geometric characterization of the basic hemodynamic data, then the velocity vector, pressure variations, and wall shear stress distributions were calculated, using the governing equations. And those units were represented as m/sec, mmHg, and Pa, respectively.

Governing equations

The following continuity equation and Navier-Stokes equation were used as governing equations for numerical analysis (Patankar, 1980), where ρ, u, p, η, and i, j were the density, velocity vector, pressure, apparent viscosity, and tensor indexes, respectively.

$$\frac{\partial u_j}{\partial x_j} = 0, \quad \rho\left(\frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j}\right) = -\frac{\partial p}{\partial x_i} + \eta \frac{\partial}{\partial x_j}\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}\right)$$

RESULTS

Flow velocity and pressure profiles at steady state (Fig. 3)

Flow velocity along the inner wall was higher than that along the outer wall in the curved area of the left coronary artery. In serial cross-sectional velocity analysis, abrupt changes of flow velocity and flow reversal (recirculation) showed mainly in the outer curved region of the left coronary artery above the bifurcation area (B). However, this flow reversal and formation of recirculation area disappeared as the flow reached the bifurcation region, where the entrance flow was skewed toward the inner walls of the LAD and the diagonal branch (Fig. 3a).

Flow velocity and pressure profiles at pulsatile blood flow and physiologic coronary flow (Fig. 4, 5)

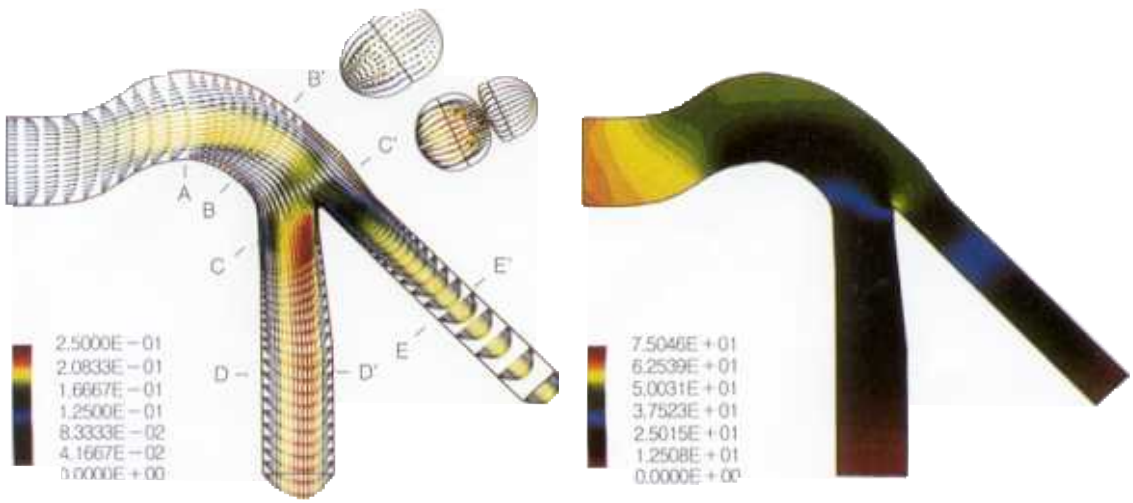
In considering the pulsatile waveform of phasic coronary blood flow, the velocity and pressure profiles of the acceleration and deceleration phase were represented. In the acceleration phase, there was no flow reversal on the curved area of the left coronary artery (B). In the deceleration phase, flow velocity was similar to patterns of the steady state, but the recirculation zone (B) in the curved area was more increased than those of steady flow, compared with their cross-sectional studies. However, there was no definitive abrupt change in the pressure distributions (Fig. 5).

Wall shear stress for steady flow (Fig. 6)

In approaching the bifurcation site, the wall shear stress in the outer wall of the left coronary artery decreased due to the directional change of flow, and finally it showed its lowest value at the branching site of the outer wall (B-C). The wall shear stress at both branching apexes was highest in the inner wall, and then, it decreased gradually.

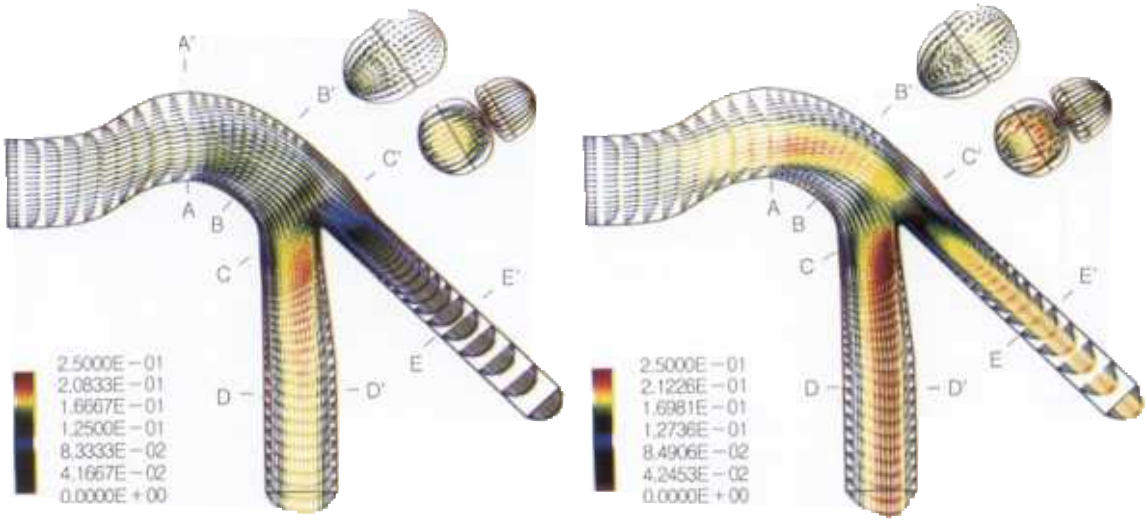
Wall shear stress for pulsatile flow (Fig. 7)

The distributions of wall shear stress in pulsatile flow were different between the acceleration and



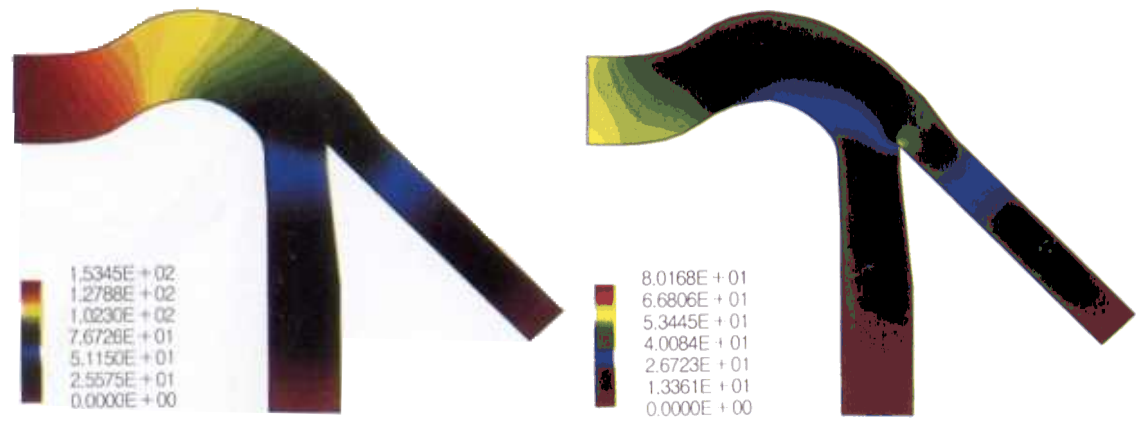
(a) velocity vectors(m/sec) (b) pressure contours(mmHg)

Fig. 3. The velocity vectors (a) and pressure contours (b) of steady blood flow in the left coronary artery model (Reynold's number=100). The results of cross-sectional study are represented adjacent to the velocity vector result of two-dimensional analysis (a). The "→", and "×" shaped vectors represent unidirectional, and bidirectional flow-vectors, respectively. Color legends and numbers represent the calculated value of each velocity and pressure. The numbers are represented as exponential form. Abrupt changes of velocity between axial flow and the outer wall is noted at the outer curved area and proximal portion of the anterior descending artery (B-C). The pressure contour is shown to have no definitive abrupt change, but skewed to the axial flow direction.



(a) acceleration phase (b) deceleraion phase

Fig. 4. The velocity vectors of physiologic blood flow in the left coronary artery model (m/sec). The cross-sectional study was done at the same site of steady flow condition. The "→", and "×" shaped vectors represent unidirectional, and bidirectional flow-vectors, respectively. Color legends and numbers represent the calculated value of velocity in each phase. The numbers are represented as exponential form. Prominent abrupt changes of velocity between axial flow and the outer wall are noted at the outer curved area and proximal portion of the anterior descending artery in deceleration phase (b: B-C), but not in acceleration phase (a).



(a) acceration phase (b) deceleration phase

Fig. 5. The pressure contours of physiologic blood flow in the left coronary artery model (mmHg). Color legends and numbers represent the calculated value of pressure. The numbers are represented as exponential form. It is noted that the pressures of the inlet are 153.45, and 80.16 mmHg in acceleration (a), and deceleration phase (b), respectively. There is no definitive abrupt change, but it is skewed to the axial flow direction in deceleration phase.

deceleration phases. Compared with the steady flow, the wall shear stress during the deceleration phase had a similar pattern compared with that of the steady state. However, the highest value of the inner wall shear stress and the lowest value of the outer wall in the anterior descending artery were more

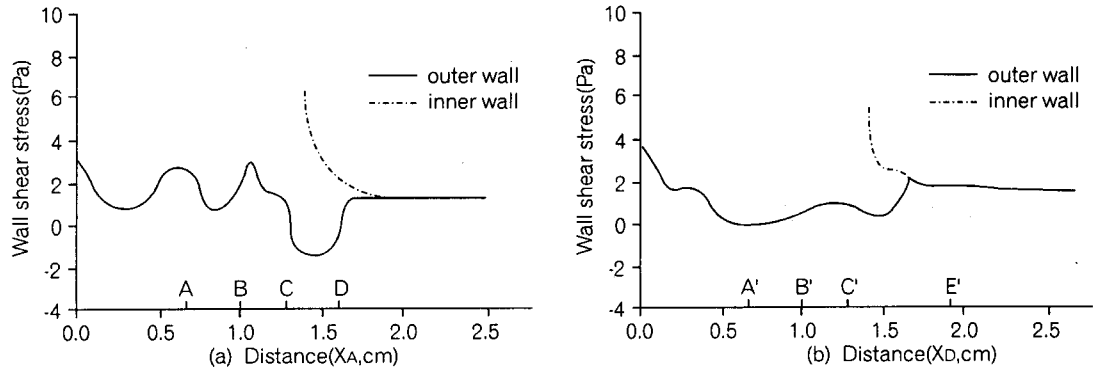


Fig. 6. Distribution of wall shear stress in steady blood flow. It is noted that the wall shear stress of outer wall is varying, initially. Then, it decreases approaching bifurcation, and represents its lowest value at the bifurcation site (B-C), prominent in the outer wall of the anterior descending artery (a). The highest value of wall shear stress is noted at the inner wall of bifurcation apex.

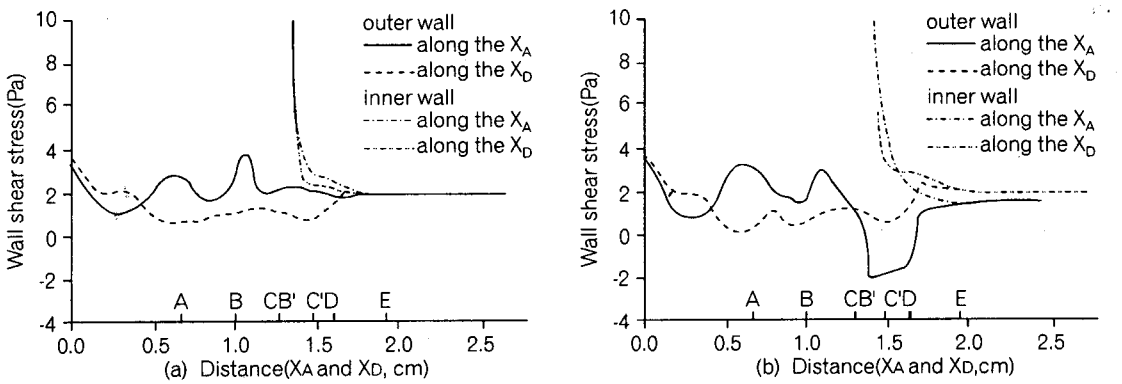


Fig. 7. Distribution of wall shear stress in physiologic pulsatile blood flow. It is noted that the wall shear stress of outer wall is varying, initially. Then, it decreases approaching bifurcation, and represents its lowest value at the bifurcation site (B-C), prominent in the deceleration phase (b) of the outer wall of the anterior descending artery. In acceleration phase (a), there were no definitive abrupt changes in the outer wall from inlet to both branching arteries.

prominent in the deceleration phase than in the steady flow.

DISCUSSION

We visualized and quantitated geometrical patterns of hemodynamic variables of the human left coronary artery model and compared the rheologic properties of steady flow with pulsatile flow (physiologic flow) using a finite volume method. By this technique, it was possible to apply human in vivo data and to quantitate the local hemodynamic variables. In this study, abrupt changes of flow velocity and flow reversal (formation of recirculation) showed in the outer curved region of the left coronary artery around the bifurcation area. In approaching the bifurcation site, the wall shear stress in the outer wall of the left coronary artery decreased due to the directional change of flow, and finally it showed its lowest value at the branching site of the outer wall. The wall shear stress at both branching apexes was highest in the inner wall, and then it decreased gradually. However, the highest value of the inner wall shear stress and the lowest value of the outer

wall in the anterior descending artery were more prominent in the deceleration phase than in the steady flow. This study suggests that temporal and/or spatial fluctuations of the shearing force and flow-velocity variation in the same coronary arterial tree may have some interplay with biomechanical and humoral stimuli in the atherogenesis and progression of atherosclerosis.

A central premise of modern vascular biology is that the endothelial lining is a dynamically mutable interface, locally responsive to various stimuli originating from the circulating blood and/or neighboring cells and tissues, and thus can actively participate in the physiological adaptation or pathophysiological dysfunction of a given region of the vasculature. The localization of early intimal lesions to the lesion-prone areas around arterial branches suggested a role of fluid mechanics in the initiation of atherosclerosis (Barakat *et al.* 1992). And, it was explained that the blood flow had fluid mechanical characteristics of localizing influence (Nerem, 1992). It is suggested that vascular endothelial cells and smooth muscle cells produce several chemotactic cytokines including various kinds of cell adhesion molecules and receptor topography appears to regulate the efficiency of a molecule in initiating adhesion under the flow conditions. The lesion-prone areas, arterial bifurcations and curvatures usually have temporal and/or spatial fluctuations of the shearing force and flow velocity variation in the same in vitro system. Furthermore, considerable progress has been made recently in defining certain of the molecular mechanisms involved, including the identification of positive and negative shear stress responsive elements (SSREs) in the promoters of biomechanically responsive genes and transcription factors that regulate their activation (Konstantinopoulos and McIntire, 1996; Gimbrone *et al.* 1997). Although the hemodynamics do not play a sole role, biomechanical and humoral stimuli in the induction and modulation of adhesion molecule expression in vivo vascular endothelium have some interplay in the formation of early atherosclerotic lesion in the lesion-prone areas. Among various local hemodynamic variables, concepts important to atherogenesis are flow separation, flow reversal and turbulence, and shear stress (MacIsaac *et al.* 1993).

When flowing blood encounters a sudden change in lumen diameter or abruptly branching vessels, stream lines of flow lose attachment to the wall and form a jet. Between the jet and the wall of a stagnant flow region, where the velocity is low, the blood flow may even be reversed from the jet direction to form a recirculation area. MacIsaac *et al.* said that this recirculation area (low shear area) might contribute to the atherogenesis and progression of atherosclerosis (MacIsaac *et al.* 1993). In this study, it was noted that the velocity profiles were skewed toward the inner wall, showing higher velocity along the inner wall region, while spatial fluctuation and variation of flow velocity between the axial flow and the outer wall of a stagnant flow region were noted distinctively at the curved area of the left coronary artery and on the outer wall of the proximal part of the anterior descending artery around the branching site. In approaching the bifurcation site, the wall shear stress in the outer wall of the left coronary artery decreased due to the directional change of flow, and eventually showed its lowest value at the branching site of the outer wall. Conversely, the wall shear stress of the inner wall was highest in the branching apex. Under the physiologic condition, it was reported that the recirculation zone formed by the abrupt change of blood flow might have an important role in early atherosclerosis and that the turbulent transformation of flow occurred more readily in the deceleration phase of pulsatile flow. We also showed that the flow reversal and recirculation region were more prominent in the deceleration phase of pulsatile flow and that the portion of low wall shear stress occurred at the same site as the recirculation area shown in the result taken from flow velocity calculation. These findings were supported by many other studies on low shear stress (Zarins *et al.* 1983; Friedman *et al.* 1986; Nerem, 1992; MacIsaac *et al.* 1993). Also, we found that the wall shear stress in the pulsatile flow was oscillating according to the acceleration or deceleration phase, while it remained constant in steady flow conditions. This correlated with the study of Ku *et al.* which reported that shear stress also contributed to an increased residence time (Ku *et al.* 1985). Furthermore, a fluctuations of the shearing force and flow variation in the same in vitro system were more dependent on the flow field than the pressure force.

In this study, we defined that the sapatial fluctua-

tion of flow-velocity and recirculation areas occurred in the curved outer wall of the left anterior descending coronary artery, which were due to the differences of flow-velocity and shear stress, especially during the deceleration phase of pulsatile flow, using the computer simulation method. As well, we suggest that local rheologic properties may be a part of the atherogenesis in the coronary bifurcated and curved areas.

Finally, these results can be used to understand the pathogenesis of atherosclerosis, and to predict its progression or restenosis in coronary intervention. Moreover, it is expected that these effort can be used in coronary interventions with site specific delivery of the genetic therapy on intimal proliferation to prevent restenosis of coronary arterial disease, and it can be applied to vascular surgical designs in coronary artery bypass graft. The emerging paradigm of biomechanical activation of endothelial cells promises to be a conceptually rich and pathophysiologically relevant area for future investigation. However, we had some limitations in practically applying these results to clinical settings. And there are marked individual variations in vascular structure and hemodynamics. It will be necessary that further experiments be undertaken under various conditions including in vitro and in vivo biologic study. This will be reported in our next study on the role of hemodynamics in advanced stages of atherosclerosis and conditions after interventions such as coronary artery bypass grafting and percutaneous angioplasty.

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