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Original Article

Hemodynamic Effects on Atherosclerosis-Prone Coronary Artery: Wall Shear Stress / Rate Distribution and Impedance Phase Angle in Coronary and Aortic Circulation

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The objective of the present study was to evaluate the hemodynamic characteristics of an atherosclerosis-prone coronary artery compared to the aorta. We describe three-dimensional spatial patterns of wall shear stress (WSS) according to the impedance phase angle in pulsatile coronary and aorta models using *in vivo* hemodynamic parameters and computed numerical simulations both qualitatively and quantitatively. Angiography of coronary arteries and aortas were done to obtain a standard model of vascular geometry. Simultaneously to the physiologic studies, flow-velocity and pressure profiles from *in vivo* data of the intravascular Doppler and pressure wire studies allowed us to include *in vitro* numerical simulations. Hemodynamic variables, such as flow-velocity, pressure and WSS in the coronary and aorta models were calculated taking into account the effects of vessel compliance and phase angle between pressure and flow waveforms. We found that there were spatial fluctuations of WSS and in the recirculation areas at the curved outer wall surface of the coronary artery. The mean WSS of the calculated negative phase angle increased in the coronary artery model over that in the aorta model and the phase angle effect was most prominent on the calculated amplitude of WSS of the coronary artery. This study suggests that the rheologic property of coronary circulation, such as the fluctuation of WSS/WSR induces several hemodynamic characteristics. A separation of flow-velocity, a difference in phase between pressure conductance and blood flow and prominent temporal and/or spatial oscillatory fluctuations of the shear forces as a function of pulsatile flow might be important factors in atherogenesis and progression of atherosclerosis.

Key Words: Coronary artery, shear stress/rate, and phase angle

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INTRODUCTION

Atherosclerosis and its clinical manifestations such as cardiovascular, cerebrovascular, and peripheral vascular insufficiency are major causes of morbidity and mortality. Various kinds of systemic risk factors affecting the arterial wall are intermingled in complex cascades of interactions, such as environmental, genetic and biologic risk factors that cause atherogenesis and progression to atherosclerosis.[1-4] Although many systemic risk factors predispose to its development, atherosclerosis preferentially affected certain regions of the circulation.[5] 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 (WSS) have been

suggested to be additional risk factors for the development of coronary atherosclerosis.[6-8]

Recently, the rheologic effects to the atherogensis and progression of atherosclerosis have been studied.[9,10] There is presently little information about the spatial three-dimensional distribution of hemodynamics in the coronary microcirculation and rheologic characteristics between different arteries with comparative data. This is due to technical difficulties in characterizing and quantifying microenvironmental hemodynamics. In this report we could computed and quantified the hemodynamic variables by a numerical simulation method using human *in vivo* data under the physiologic pulsatile conditions in the coronary artery and the abdominal aorta model. We hypothesized that there might be an uneven geometric distribution of WSS between the coronary and aortic circulation. The effect of different impedance phase angles between both arteries might accentuate the fluctuation of WSS in atherogenesis and the progression of atherosclerosis of coronary circulation. To accomplish these goals, we visualized and quantified the geometrical patterns of WSS in the human artery models, and compared the rheologic properties of the coronary with the aortic circulation in order to delineate the influence of the phasic difference (phase angle) of the coronary and aortic circulation on the WSS.

MATERIALS AND METHODS

Coronary artery and abdominal aorta model

To evaluate the hemodynamic variables in human coronary and aortic models, the basic models were deduced from their measurements of *in vivo* left coronary artery and abdominal aorta at iliac bifurcation level using angiography. Angiography was performed by a femoral approach according to standard techniques. The subjects used in the study were having nonspecific chest pain, who had a completely normal coronary angiograhy, and had no any other atherogenic risk factors. There were 14 subjects in total having a mean age of 57 $\pm$ 7.5 years. Ten subjects were male.

For the computed simulation calculation, we measured each arterial diameter using a quantitative coronary assessment (QCA) method. And we also performed intracoronary two-dimensional ultrasound to measure the phasic vessel wall area and the luminal areas as well as using Doppler ultrasound measurements of the coronary flow-velocity at the proximal and distal regions of interest in the coronary artery. During coronary angiography, both the aortic and coronary pressures were simultaneously measured using a guiding catheter and Pressure Wire^{TM}, and a 0.014 inch guide wire-mounted pressure sensor (Radi Medical Systems AB, Uppsala, Sweden), respectively. During aortography, aortic pressure tracing were gated by electrocardiogram. Finally, we measured the aortic flow velocity in the distal abdominal aorta by using a Doppler ultrasound 3.5MHz transducer (Cardiometrics, Mountainview, CA, USA).

Flow-velocity of coronary circulation in intravascular Doppler studies demonstrated a diastolic dominance and a peak velocity in the early diastolic phase. The half level of diastolic peak velocity was defined as the point between the acceleration and deceleration of both sides of the velocity-time integral. Otherwise, the flow-velocity of aortic circulation demonstrated a systolic dominance and a peak velocity in the systolic phase. The half level of systolic peak velocity was defined as being the point of the acceleration and deceleration between both sides of velocity-time integral. *In vivo* hemodynamic data of coronary and aortic circulation allowed us to obtain a numerical simulation and to demonstrate the geometrical patterns of WSS (Fig. 1, Table 1).

Rheological properties of blood and numerical analysis

To define the geometrical shear distribution in the vascular models, a non-Newtonian fluid model was adopted as being a constitutive equation that represents the apparent viscosity of blood as a function of shear rate. Among various constitutive equations, the Carreau model of following equation was used to specify the shear rate versus the apparent viscosity relationship[11,12]; shear rate, dv/dr, and the rate that the axial velocity rises as

Table 1. Hemodynamic Variables in a Condition of Pulsatile/non-neutonian Fluid

	Abdominal Aorta	LAD
Diameter(cm)	1.5	0.3
Qmean(cm^3/sec)	15.55	1.413
Qamp(cm^3/sec)	2.0 Qmean	1.0 Qmean
T (sec)	0.75	0.75
Re(Reynolds number)	400	182
a(Womersley parameter)	12	2.39
Diff. Diameter/ diameter	3%	5%
U (viscosity, CP)	3.45	3.45
Density(g/cm^3)	1.045	1.045
Phase angle	-45°	-111°
mean WSS($dyne/cm^2$)	1.806 + 10.72	19.42 + 20.53
mean WSR(1/sec)	49.86 + 281.4	542.8 + 587.3

one moves from the vessel wall toward the center.

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

This velocity gradient causes a shear stress (τ) on the endothelium, parallel to the blood flow and proportional to the viscosity (η), $\tau=\eta\cdot dv/dr$

For effective numerical analysis of hemodynamics, we used a finite volume method, adapted from the Rhie-Chow algorithm,[13] and was computed by the CFX 4 package program (AEA technology, Harwell, UK) in SUN SPARC station 20 (Sun korea Co., Seoul, Korea). The governing equations are analyzed using a non-staggered grid system. In a non-staggered grid system, the velocity components in the equations are calculated for the same points that coincide with the grids points of the pressure units. The fully implicit scheme is used to solve the physiologic flow problem, where the time step is set to be 0.01second. Following the visually determined geometric characterization of the flow-velocity vector, the distribution of WSS was calculated for the coronary and aortic models using the governing equations (Table 1).

The following continuity equation and the Navier-Stokes equation was used as the governing equations for the numerical analysis,[11,12] where, ρ, u, p, η and i, j were the density, velocity vector, pressure, apparent viscosity, and tensor indexes, respectively.

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

Arterial and fluid model for calculating wall shear according to phase angle

In human arteries, pressure and flow (impedance phase angle) waves are not in phase due to the presence of wave reflection from distal arteries and arterial elasticity.[14,15] The impedance phase angle, which determines the phasic relationship between the wall pulsation and flow rate in the vascular circulation, may be expected to influence the local fluid mechanics near the pulsating wall.[16] In order to delineate the influence of the phasic difference (phase angle) of the coronary and aortic circulation on the WSS, elastic straight artery models for the coronary artery as well as the aorta were simulated under typical flow conditions of the two arteries.

To isolate the effect of the phase angle, flow waveform and wall motion waveforms were assumed to be sinusoidal as shown in equation (1) and (2). The wall motion waveform (movement of the vessel radius in the radial direction) was assumed to have a phase difference phi with respect to the flow.

$$Q(t) = Qmean + Qamp\ \sin(wt\text{-}phi) \quad (1)$$
$$R(t) = Rmean + Ramp\ \sin(wt) \quad (2)$$

The phase angle between the blood flow and wall motion at typical flow conditions for coronary arteries was calculated by phase difference between each first harmonic of the Fourier series by analyzing the wall motion (the inversed flipped wave form of the pressure wave) and flow wave forms from a normative human data. The

phase angle for the abdominal aorta was adopted from the study of Merillon JP et al.[16]

The axisymmetric artery was modeled using a 260 × 40 grid. Blood viscosity was modeled using a modified Powell-Erying non-Newtonian model.[17] A no-slip condition was postulated at the vessel wall since the wall expands and contracts in a wall-normal direction. We assumed the phase of the wall motion to be the same in the entire model because of the rapid speed of the pressure wave (long wave length assumption). This is the same assumption used in the perturbation solution by Tarbell JM et al.[14,15]

A numerical analysis was performed for five periods (0.0-4.5 sec) to eliminate transient effects and a 0.005 sec time increment was employed to solve this problem. The solutions converged after the third and fourth period. We assumed that the wall shear rate (WSR) and the WSS can be also represented by the mean, amplitude and phase angles as in equation (3) and (4). Each parameter was calculated from the least square approximation of the solution in the sinusoidal form.

$$WSR(t) = WSR + WSR \sin(wt\text{-}phi1) \quad (3)$$

$$WSS(t) = WSS + WSS \sin(wt\text{-}phi2) \quad (4)$$

RESULTS

1. Flow velocity and WSS profiles at the coronary artery (Fig. 2)

The flow-velocity of coronary circulation in our *in vivo* intravascular Doppler study demonstrated a diastolic dominance and a peak velocity in the early diastolic phase. Contrary to flow-velocity, coronary pressure tracing had demonstrated systolic dominance and peak pressure in the systolic phase during the *in vivo* pressure wire study. The waveform of the coronary pressure was identical to that of aortic pressure (Fig. 1a). The velocity profiles of the diastolic acceleration and deceleration phases were represented as a pulsatile waveform of coronary circulation (Fig. 1 and 2). Compared to the acceleration phase in which there was no flow reversal on the curved area of the left coronary artery (Fig. 2a). The deceleration phase of coronary circulation demonstrated that the recirculation zone in the curved area was accentuated (Fig. 2b).

The distributions of WSS of coronary circulation were different between those in the acceleration phase and those in the deceleration phase. Geometrical analysis of WSS during deceleration phase showed that the highest value at the inner WSS, the lowest value at the outer wall. The most highly separated value of WSS in the anterior descending artery was more prominent during the deceleration phase.

2. Flow velocity and WSS profiles at the abdominal aorta (Fig. 3)

Contrary to the coronary circulation, the flow-velocity of the aortic circulation in our *in vivo* Intravascular Doppler study demonstrated a systolic dominance and a peak velocity in the systolic phase. Aortic pressure tracings demonstrated a systolic dominance and a peak pressure in the systolic phase in the *in vivo* Pressure Wire

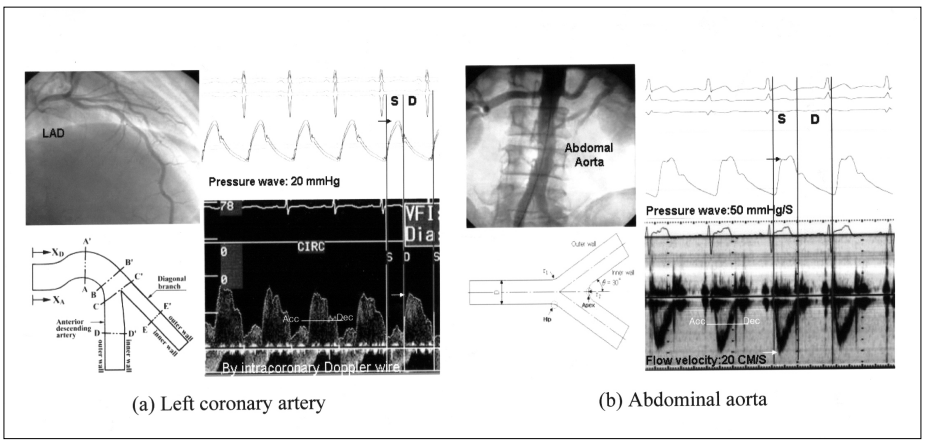

Fig. 1. Coronary model (a, left lower) and aortic model (b, left lower) based on the images of human left anterior descending (LAD) artery and abdominal aorta with a pressure tracing and Doppler flow-velocity study. Acc: acceleation phase, Dec: deceleration phase.

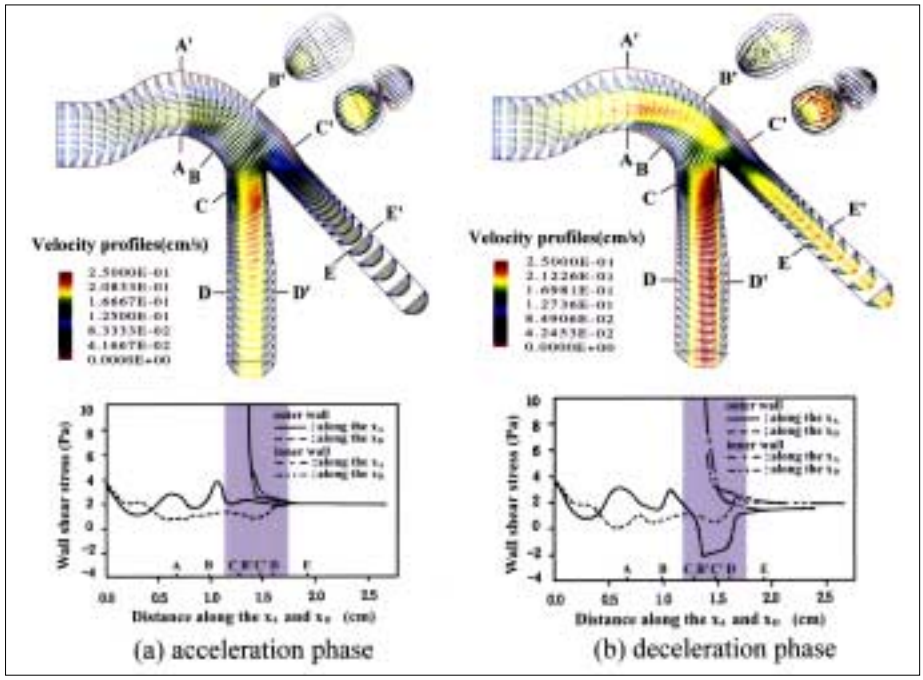

Fig. 2. The velocity vectors (upper) and distribution of wall shear stress (lower) of the coronary model. Prominent abrupt changes in velocity and wall shear stress at the outer wall around the branched site are noted.

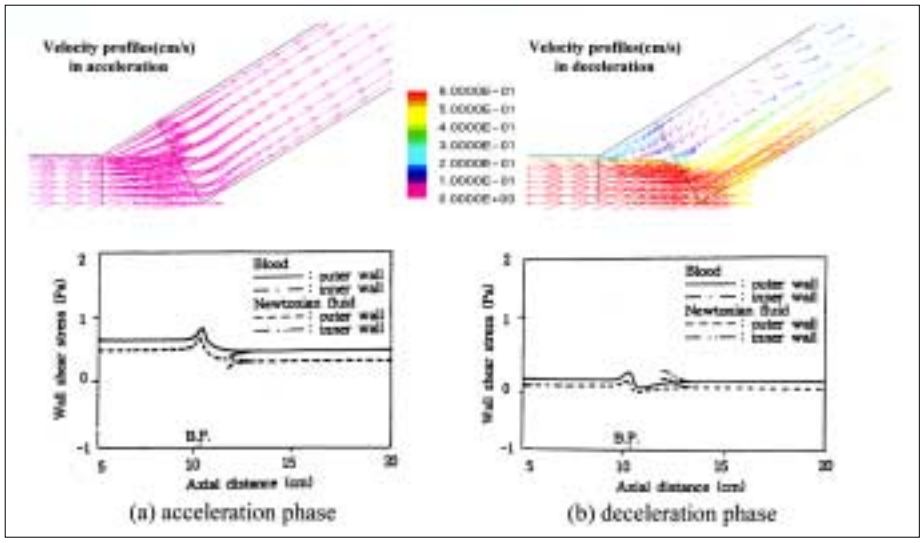

Fig. 3. The velocity vectors (upper) and distribution of wall shear stress(lower) of the aortic model in physiologic pulsatile flow. Skewed changes of velocity, and separated and reversed wall shear stress at outer wall around the branched site are noted.

study (Fig. 1b). Compared with the results in coronary artery data, skewed changes of velocity were noted. It makes a flow reversal at the outer wall of the bifurcation branch during the deceleration phase (upper panels). The separated and reversed wall shear stress at the outer wall around the branched site was noted (lower panels).

The distributions of WSS during pulsatile flow were reversed between the inner and outer walls at the bifurcated branch according to the acceleration and deceleration phase (lower panels). However, the WSS during the cardiac cycle was not obviously different from that in the coronary model (Fig. 2).

3. Comparison of wall shear stresses (WSS) and rates (WSR) between coronary and aortic circulation as a phase angle (Fig. 4)

The calculated phase angle between the blood flow and wall motion on the basis of typical flow conditions for the abdominal and coronary arteries was shown to be as much as -111° for the coronary artery while it was -45° for typical abdo-

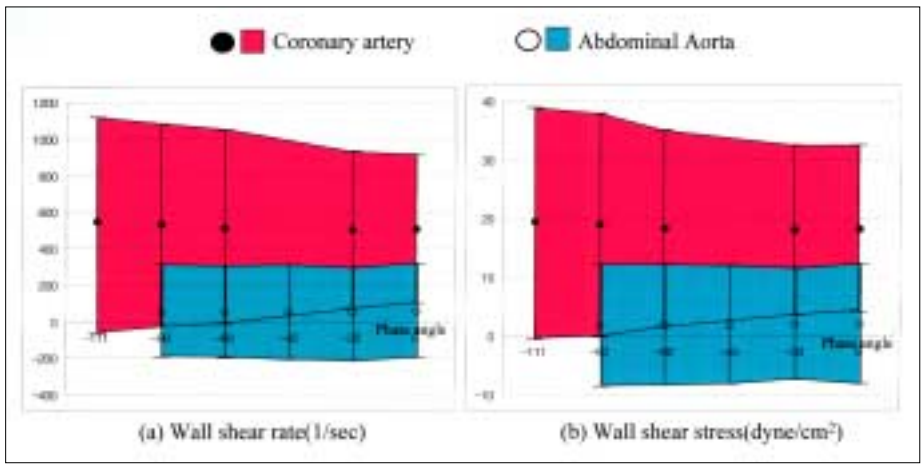

Fig. 4. Influence of phase angle on the wall shear stresses for the coronary artery and abdominal aorta. The mean wall shear rate (WSR) and wall shear stress (WSS) of the coronary artery was more than 10 times higher than that of the abdominal aorta while the amplitude of WSR and WSS was double the results of the abdominal aorta.

minal aortas.

As listed on table 1, the WSS of a typical abdominal aorta was computed to be 1.81 ± 10.7 dyne/cm^2. It was much higher for the coronary artery which amounted to 19.4 ± 20.5 dyne/cm^2. The mean WSR and WSS of the coronary artery was more than 10 times higher than that of the abdominal aorta while the amplitude of WSR and WSS was double that of the abdominal aorta. These phase angle effect can be observed in figure 4.

The negative phase angle between the wall pulsation and the blood flow increased the mean value of WSS compared to the zero phase angle in the coronary artery model than in the abdominal aorta model (negative phase angle amounting to -111°, incrementing the mean WSS by 7.3%, and incrementing the amplitude of WSS by 24.3% versus the negative phase angle amounting to -45°. The decrement of the mean WSS was 9.6% and the decrement in its amplitude was 1.8%, Fig. 4). The amplitude of WSS changed by 17.0% while the phase angle changed from 0° to -90°. The mean WSS changed only by 4.5% for the same change in the phase angle in the coronary artery. These findings suggested that the phase angle effect was most prominent in the calculated amplitude of WSS for the coronary artery.

DISCUSSION

Previously we reported a study using a coronary artery model.[12] The present study has extended the understanding of hemodynamic characteristics under pulsatile oscillating flow conditions in an atherosclerosis-prone coronary artery compared to an abdominal aorta. We visualized and quantified geometrical patterns of various hemodynamic variables in the left coronary artery and abdominal aorta models, and compared the rheologic properties of the derived data from each with a finite volume method. Under pulsatile oscillating flow conditions, the impedance phase angles of the coronary arteries were quite different from those of the abdominal aorta because arterial elasticity depends upon the vascular tone itself and the myocardial contraction-relaxation during the cardiac cycle. This study suggests that the local rheologic influence of the phasic difference between the wall pulsation and blood flow on the mean WSR and WSS of the coronary artery was more than 10 times higher than that of the abdominal aorta. The amplitude of WSR and WSS was the double that of the abdominal aorta, therefore, they might be the precipitating factors in atherogenesis and the progression of atherosclerosis.

In this study, the flow-velocity of the coronary circulation in the *in vivo* intravascular Doppler study demonstrated a diastolic dominance and a peak velocity in the early diastolic phase. Coronary pressure tracings demonstrated systolic dominance and peak pressures in the systolic phase in the *in vivo* Pressure Wire study. Contrary to the coronary circulation, flow-velocity of the aortic circulation in the *in vivo* intravascular Dop-

pler study demonstrated a systolic dominance and a peak velocity in the systolic phase under the same pressure conditions. The computer simulation study showed a separation of the flow-velocity and recirculation area in the bifurcating branch of both the coronary artery and the abdominal aorta. The separation of flow-velocity was most notable in the coronary model and induced spatial fluctuation of WSS. Furthermore, the coronary artery model showed a different phase angle between flow and pressure, and a much higher oscillatory WSS/WSR than that of the aortic model. The phase angle effect was greatest on the amplitude of WSS for the coronary artery quantitatively. The rheologic properties of coronary circulation such as the fluctuation of WSS/WSR induced several hemodynamic characteristics. The separation flow-velocity, the difference in phase between pressure conductance, and blood flow and prominent temporal and/or spatial oscillatory fluctuation of the shear forces according to pulsatile flow might be the participating factors in atherogenesis and the progression of atherosclerosis.

Advances in modern vascular biology[17] reveal that the endothelial lining of the artery is a dynamically mutable interface, which is locally responsive to various stimuli originating from the circulating blood and/or neighboring cells and tissues. Thus it can actively participate in the process of the physiological adaptation or pathophysiological dysfunction of a given region of the vasculature.[18] In an *in vivo* setting, cell attachment to endothelial wall depends upon the balance between dispersive hydrodynamic forces including WSS, and the adhesive forces generated by the interaction of membrane-bound receptors and their ligands.[9] Biomechanical modulation of endothelial gene expression, in particular the genes encoding positive and negative shear stress responsive elements in the promoters of biomechanically responsive genes and adhesion molecules involved in cell-cell and cell-matrix interactions, may also play an active role at the time of hemodynamic transition.[18] Clearly, biomechanical forces have important implications for endothelial adhesion biology beyond their direct rheologic effects on leukocyte-endothelial interaction, which has been implicated in atherogenesis.[9,18] Xuping B., et al.[19] have shown that temporal gradients in shear stress lead to enhanced and sustained expression of MCP-1 and PDGF-A in HUVEC, whereas the presence of steady laminar shear stress reduces these levels. Both the stimulatory effects of temporal gradients on shear and the inhibitory effects of steady shear on gene expression have been found to be mediated by NO, probably by an activation and inactivation of their transcription factors, NF-kB and egr-1. A potential explanation might be that regional differences in NF-kB signaling preferentially transuded systemic stimuli, that results in the regional coordinate expression of proatherogenic genes. It was reported also that VCAM-1 is expressed in atherosclerosis-predisposed regions even in normocholesterolemic animals. Regardless of the proximal sensing mechanisms, it is clear that the application of mechanical forces, including fluid shear stress, results in the generation of oxidant stress and NF-kB activation.[9] Although the hemodynamics do not play the sole role, biomechanical and humoral stimuli in the induction and modulation of adhesion molecule expression *in vivo* vascular endothelium have interacted to form early atherosclerotic lesions in the lesion-prone areas.[20]

A disturbance of laminar blood flow, with boundary layer separation, flow reversal, secondary flow, and shifting stagnation points can be encountered. As a result, endothelial cells can be chronically exposed to shear forces with cyclical variations in direction. In these situations, the mean shear stress is relatively low.[10] It has been reported that a recirculation area with a low shear area might contribute to the atherogenesis and progression of atherosclerosis, and that helical velocity patterns and disturbance of flow patterns have been associated with oscillatory WSS, which has been implicated in plaque formation. The frictional force exerted by flowing blood at the endothelium of the artery has been repeatedly implicated in the pathogenesis of atherosclerosis and vascular remodeling.[21] In our study, the spatial fluctuation of flow-velocity and recirculation areas occurred in the curved outer wall of the coronary artery and the abdominal aortic bifurcation model. This was due to the differences of flow-velocity and shear stress, especially during the deceleration phase of pulsatile flow. Ap-

proaching the bifurcation site, the WSS in the outer wall of left coronary artery decreased due to the directional change of flow, and showed the lowest value at the branching site of the outer wall. This study suggests that local rheologic properties may contribute to the atherogenesis in bifurcated and curved areas, especially in the coronary artery physiologic situations. These insights have provided a basis for a rational design of promising new therapeutic strategies for managing cardiovascular diseases.[22] The influence of the phasic difference (phase angle) between the wall pulsation and the blood flow on the mean WSR and WSS of the coronary artery was more than 10 times higher than that of the abdominal aorta. The amplitude of WSR and WSS was the double that of the abdominal aorta. The rheologic properties of coronary circulation such as the fluctuation of WSS/WSR induced the separation flow-velocity, the difference in phase between pressure conductance and blood flow and the oscillatory WSS according to pulsatile flow might be the precipitating factors in atherogenesis and the progression of atherosclerosis. Several studies[23,24] also support these findings.

We had some limitations in the practical application of these results to clinical settings. Further experiments under various conditions of *in vitro* and *in vivo* biologic study are necessary. The emerging paradigm of biomechanical activation of endothelial cells promises to be conceptually rich and a pathophysiologically relevant area for future investigation.

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