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Hemodynamic Analysis of Coronary Circulation in Angulated Coronary Stenosis Following Stenting

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The present study in angulated coronary stenosis used human *in vivo* hemodynamic parameters and computed simulation, both qualitatively and qualitatively, to evaluate the influence of flow velocity and wall shear stress (WSS) on coronary atherosclerosis, the changes of hemodynamic indices following coronary stenting, and their effect on evolving in-stent restenosis.

Initial and follow-up coronary angiographies in patients with angulated coronary stenosis were performed (n=60). The optimal degree of coronary stenting for angulated coronary stenosis had two models, the less than 50% angle changed group (model 1, n=33) and the more than 50% angle changed group (model 2, n=27). This angle change was based on the percentage change of vascular angle between pre- and post-intracoronary stenting. The flow-velocity wave obtained from *in vivo* intracoronary Doppler study data was used for *in vitro* numerical simulation. Spatial and temporal patterns of the flow-velocity vector and recirculation area were drawn throughout the selected segment of coronary models. WSS of pre- and post-intracoronary stenting was calculated from three-dimensional computer simulation.

As results, follow-up coronary angiogram demonstrated significant difference in the percentage of diameter stenosis between the two groups (group 1: 40.3 $\pm$ 30.2 vs. group 2: 25.5 $\pm$ 22.5%, $p<0.05$). Negative shear area on 3D simulation, which is consistent with the re-circulation area of flow vector, was noted on the inner wall of the post-stenotic area before stenting. The negative WSS disappeared after stenting. High spatial and temporal WSS before stenting fell within the range of physiologic WSS after stenting. This finding was more prominent in model 2 ($p<0.01$).

The present study suggests that hemodynamic forces exerted by pulsatile coronary circulation, termed WSS, might affect the evolution of atherosclerosis within the angulated vascular curvature. Moreover, geometric characteristics, such as the angular difference between pre- and post- intracoronary stenting might define optimal rheologic properties for vascular repair after stenting.

Key Words: Wall shear stress, in-stent restenosis, hemodynamic analysis, angulated coronary stenosis

INTRODUCTION

The advantages of intracoronary stent over balloon angioplasty include larger acute gains in luminal diameter, and better long-term patency and clinical outcomes.[1,2] Nevertheless, stents provoke greater absolute, late luminal loss than balloon angioplasty[3,4] and carry the additional risk of thrombosis.[5] In addition, in-stent restenosis has become a current major problem to be solved by

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the interventional cardiologist. Since there are many patient- or lesion-related variables for predicting in-stent restenosis, such as diabetes, unstable angina, reference vessel diameter, final minimum lumen diameter, diameter stenosis, vessel size and lesion length,[6] better understanding of the biomechanical and biological contributors to in-stent restenosis is important.

Intimal hyperplasia, which is the main contributor of in-stent restenosis, results from cellular response to vascular injury. The acute cellular response mainly comes from strut-imposed- vascular damage, which dictates the extent of intimal thickening in experimental animals.[7,8] Furthermore, as stent deployment transfixes the artery in a permanently altered shape, the transitions in diameter, contour, and changes of flow pattern may influence vascular repair and restenosis.[9] Recently, Garasic et al.[10] reported that immediate post-deployment, luminal geometry determines neointimal thickness independently. When it comes to investigating in-stent restenosis there are not only biological but also biomechanical factors to be considered. We hypothesized that restenosis of mechanically revascularized coronary arteries by stent may be related in part to abnormalities of disturbed local blood flow and shear stress.

To test the hypothesis that geometrical change of coronary artery after stenting affects restenosis according to the rheologic properties, such as flow velocity and wall shear stress (WSS), we analyzed the influence of these two properties before and after stenting using human *in vivo* hemodynamic parameters and *in vitro* numerical analysis of coronary circulation qualitatively and qualitatively. We also evaluated the clinical results of patients treated with stenting in angulated coronary stenosis.

MATERIALS AND METHODS

Coronary angiography and stenting in angulated coronary stenosis

Coronary angiography was performed by the femoral approach according to standard techniques. The coronary lesions with angulated stenosis (diameter stenosis > 70%) were selected for coronary balloon angioplasty and stenting. Six-month follow up coronary angiography to evaluate restenosis was performed (n=60). Each arterial diameter was measured by quantitative coronary assessment (QCA) for the percentage of diameter stenosis. For the delineation of angulated coronary stenosis, the angular measurements were performed using the serial images of angiography taken at a different angle. The highest angulation in the stenotic lesion at the most longitudinal axis for that artery was chosen for pre-intracoronary, stenting angulations. After stenting and six-month follow up coronary angiogram, the corresponding image taken with the same view was used for the measurement of post-intracoronary stenting angulation.

Patient grouping and coronary artery models

To evaluate the hemodynamic variables in human coronary models, the basic models were adopted from the measurement of *in vivo*, left coronary, artery angiography (Fig. 1). For computed simulation, arterial diameter was measured by QCA. *In vivo* hemodynamic data of coronary flow were used for the numerical simulation, with Doppler ultrasound measured by using a 3.5 MHz transducer (Cardiometrics, Mountainview, California, USA) and pressure wire with a 0.014 inch, guide wire- mounted, pressure sensor (Radi Medical Systems AB, Uppsala, Sweden). This arrangement allowed measurement of coronary flow-velocity and pressure at proximal and distal regions of interest of the coronary artery (Fig. 2). According to the percentage change of vascular angle between pre- and post-intracoronary stenting, the patients were divided into two groups: group 1 (n=33) and model 1, < 50% angle changed; group 2 (n=27) and model 2, > 50% angle changed (Table 1).

Rheological properties of blood and numerical analysis

To define the geometric shear distribution in the vascular models, a non-Newtonian fluid was adopted as the constitutive equation that represents the apparent viscosity of blood as a func-

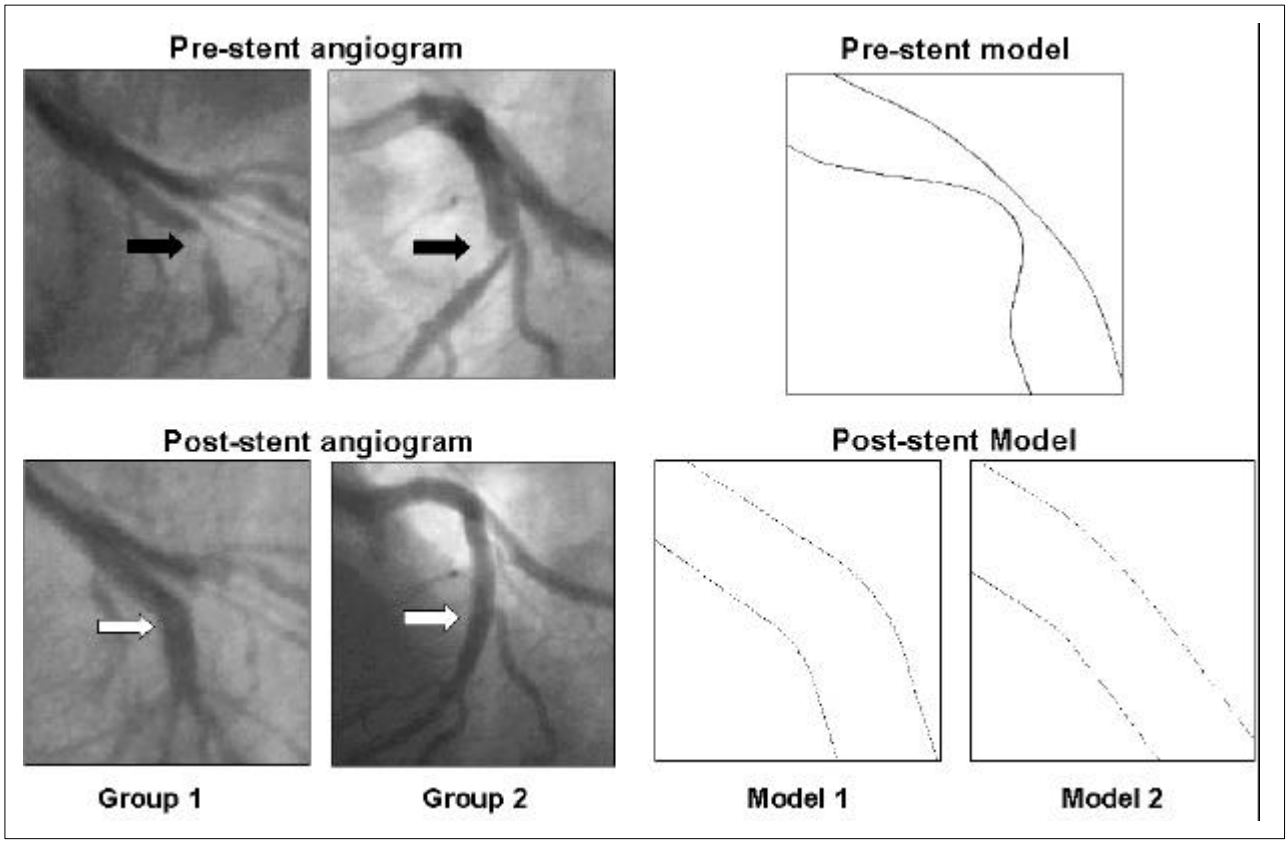


Fig. 1. Coronary groups and computerized schematic models before and after stenting, based on images of the human left anterior descending artery (Closed arrow: pre-stent stenosis; open arrow: post-stent). Subjects and models were grouped by percentage angle change (group and model 1, <50%; group and model 2, >50%)

tion of shear rate. Among various constitutive equations, the Carreau model of the following equation was used to specify the relationship between shear rate and apparent viscosity,[11,12] and the shear rate, dv/dr, which is the rate that the axial velocity rises as one moves from the vessel wall toward the center.

$$h = h_{\infty} + (h_0 - h_{\infty})[1 + l^2 g^2]^{\frac{a-1}{2}}$$

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 the hemodynamics, we used a finite volume method, adapted from the Rhie-Chow algorithm,[13] computed with CFX 4 package program (AEA technology, Harwell, UK) on a SUN SPARC station 20 (Sun Korea Co., Seoul, Korea).

The following continuity equation and Navier-Stokes equation were used as 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.

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

Statistical analysis

Results are expressed as mean ± SD unless otherwise stated. The main statistical analysis of clinical characteristics and angiographic follow up results at 6-month coronary angiography were analyzed by t-test and ANOVA. Comparing of WSS before and after stenting between the two models was performed by paired and unpaired t-test.

RESULTS

Clinical and angiographic results of the patients treated with stenting in angulated coronary stenosis

Sixty cases of patients with angulated coronary stenosis were enrolled in this study. Initial clinical characteristics and angiographic findings were not statistically different between the two groups (Table 1, 2). Angiographic data before stenting revealed no statistical difference between the two groups in stent diameter, stent length, minimal luminal diameter (MLD), reference diameter, percentage diameter stenosis, and lesion length. However, vascular angulation after stenting was statistically smaller in group 2 (14.7 ± 13.80) than in group 1 (32.9 ± 19.30)(Table 2).

Percentage diameter stenosis at 6-month follow up coronary angiography revealed that group 2 had lower percentage restenosis (25.5 ± 22.5%) than group 1 (40.3 ± 30.2%)(Fig. 3).

Table 1. Clinical Characteristics of Both Angulated Stent Groups

	Group 1 (n=33)	Group 2 (n=27)	*p*
Age	58.5 ± 9.9	59.9 ± 10.9	NS
Male (%)	18 (54.5)	18 (66.7)	NS
LAD/LCX/RCA (%)	19/5/9(57.6/15.2/27.3)	13/7/7(48.1/25.9/25.9)	NS
Risk factors (%)			
Diabetes M.	7 (24.1)	4 (16.0)	NS
Hypertension	14 (48.3)	12 (48.0)	NS
Hyperlipidemia	11 (37.9)	5 (20.0)	NS
Smoking	13 (39.4)	10 (37.0)	NS

LAD, left anterior descending artery; LCX, left circumplex artery; RCA, right coronary artery.
Data are presented as mean SD or patient numbers and percentages in parentheses.

Table 2. Initial Angiographic Characteristics

	Group 1 (n=33)	Group 2 (n=27)	*p*
Stent data			
Stent diameter(mm)	3.2 ± 0.4	3.1 ± 0.4	NS
Stent length(mm)	23.0 ± 6.6	20.9 ± 6.7	NS
Quantitative coronary angiographic data			
MLD prestent	0.7 ± 0.3	0.7 ± 0.2	NS
poststent(mm)	3.0 ± 0.3	3.0 ± 0.5	NS
Reference diameter(mm)	3.1 ± 0.3	3.0 ± 0.5	NS
%DS prestent	78.1 ± 9.3	78.7 ± 8.7	NS
poststent	3.8 ± 4.8	3.2 ± 5.0	NS
Lesion length(mm)	14.5 ± 7.3	13.2 ± 4.1	NS
Vessel angulation (o)			
Vessel angle prestent	43.3 ± 22.5	34.3 ± 22.0	NS
poststent	32.9 ± 19.3	14.7 ± 13.8	<0.001
Changes in angle	10.4 ± 7.0	22.3 ± 13.7	<0.001

MLD, minimal lesion diameter; DS, diameter stenosis.
Data are presented as mean SD or patient numbers and percentages in parentheses.

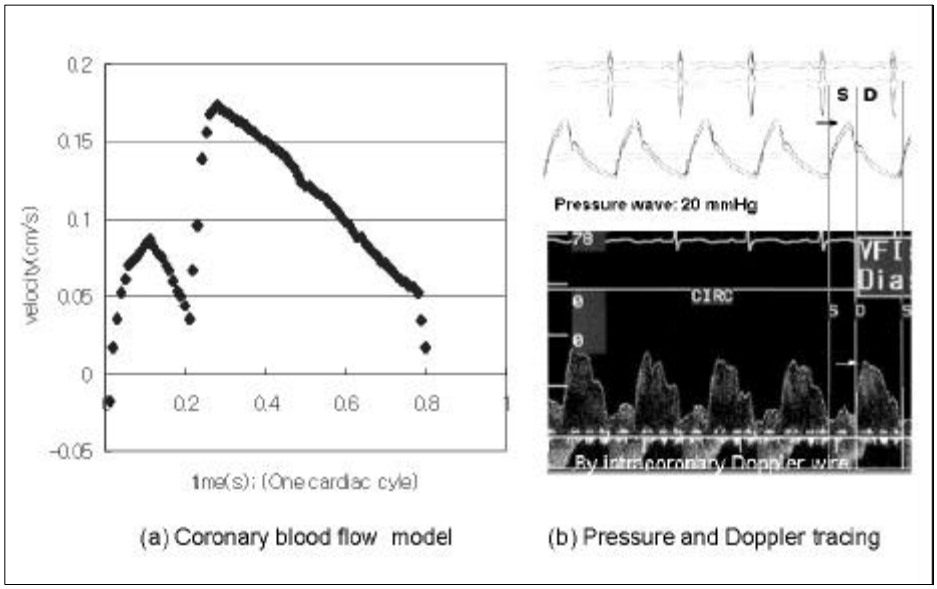


Fig. 2. Physiologic waveform of pulsatile coronary blood flow-velocity model(a) adopted from normal human coronary pressure and Doppler study(b).

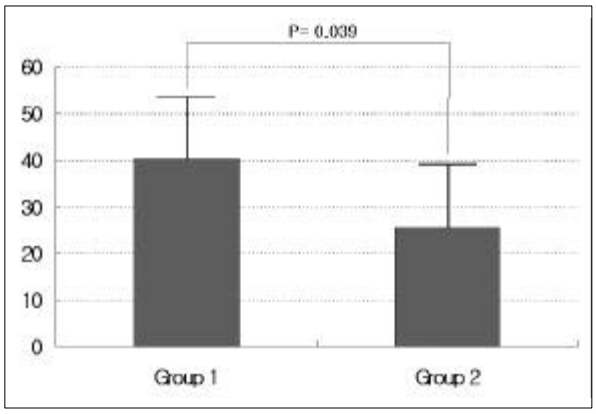


Fig. 3. Percentage diameter restenosis in 6-month follow up coronary angiography revealed that group 2 had significantly lower percentage of in-stent restenosis than group 1 (p=0.039).

Flow-velocity vector change in both coronary artery models before and after stenting

The flow-velocity vector of pre-intracoronary stenting revealed a very high flow velocity toward the outer wall of the artery due to critical coronary stenosis, as well as flow separation, flow recirculation and flow attachment phenomena in the inner wall (Fig. 4a). Both post- intracoronary stenting models revealed reduced peak flow velocity and a complete absence of flow recirculation in the same coronary artery. This finding was prominent in model 2 ($p<0.01$) (Fig. 4b, 4c)

Comparison of wall shear stress (WSS) profiles between both coronary artery models before and after stenting

The 3D spatial and temporal WSS distribution according to distance, i.e. from inlet to outlet of the stenotic region, and according to time, i.e. from systolic to diastolic phase, revealed that peak WSS developed in the early diastolic phase. A negative shear area was also noted around the just distal area of the highest shear, which is consistent with the recirculation area in the inner wall. In the outer wall before stenting, there was also very high shear area similar to the inner wall but with no negative shear area (Fig. 5 and 6a).

The mean and standard deviation of WSS before and after stenting, according to the two modes, were drawn on the same chart on each wall (Fig. 6 and 7). Post-intracoronary stenting WSS showed a markedly reduced peak WSS, as much as one twentieth the pre-intracoronary stenting WSS in the inner and outer walls, as well as nonexistent negative shear area in the inner wall (Fig. 6b and 6c). The wide variation of WSS with respect to time and distance, indicating various fluctuations of WSS, or oscillatory WSS, was always observed in the pre-intracoronary stenting model. However, the variety of WSS was markedly diminished in the post-intracoronary

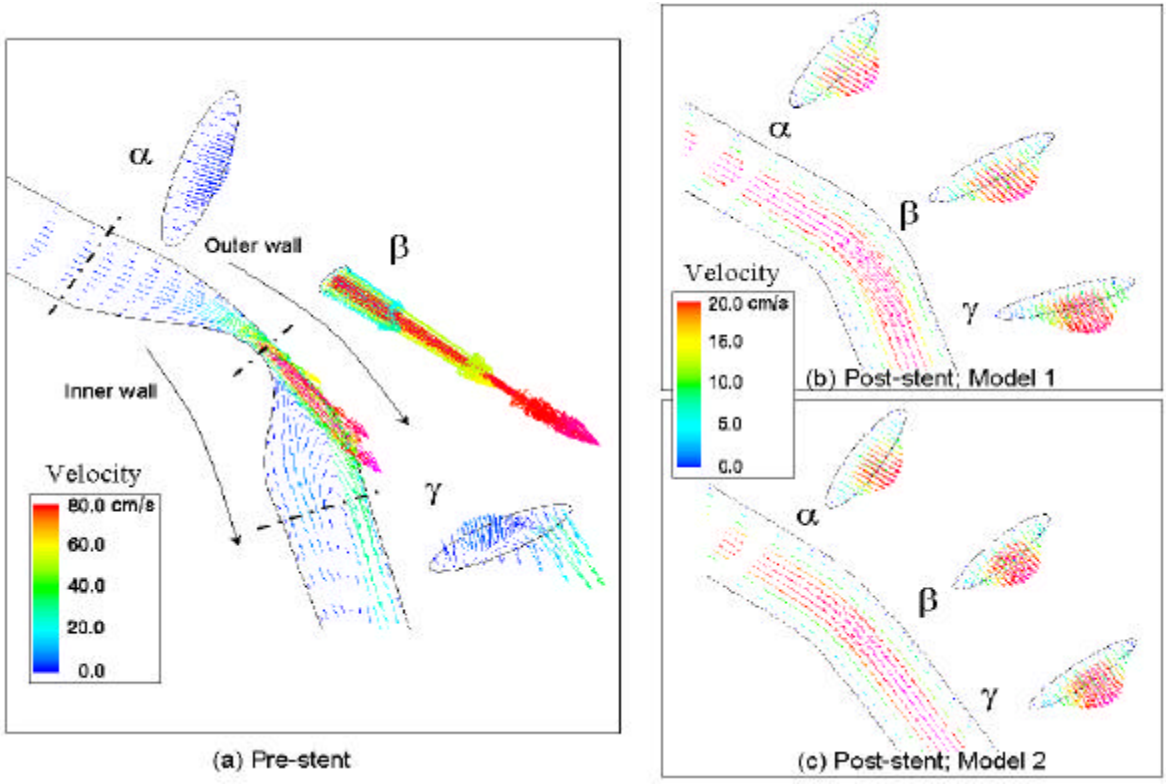


Fig. 4. Calculated flow-velocity vectors in pre- and post-intracoronary stenting models. The flow-velocity vectors revealed a very high flow velocity toward the outer wall of the artery due to critical coronary stenosis (β), as well as flow separation, flow recirculation and flow attachment phenomena at the post-stenosed site (γ) in the inner wall of the pre-stenting model (a). The peak flow velocity was reduced and flow recirculation was absent in both post-intracoronary stenting models (b, c). This finding was more prominent in model 2.

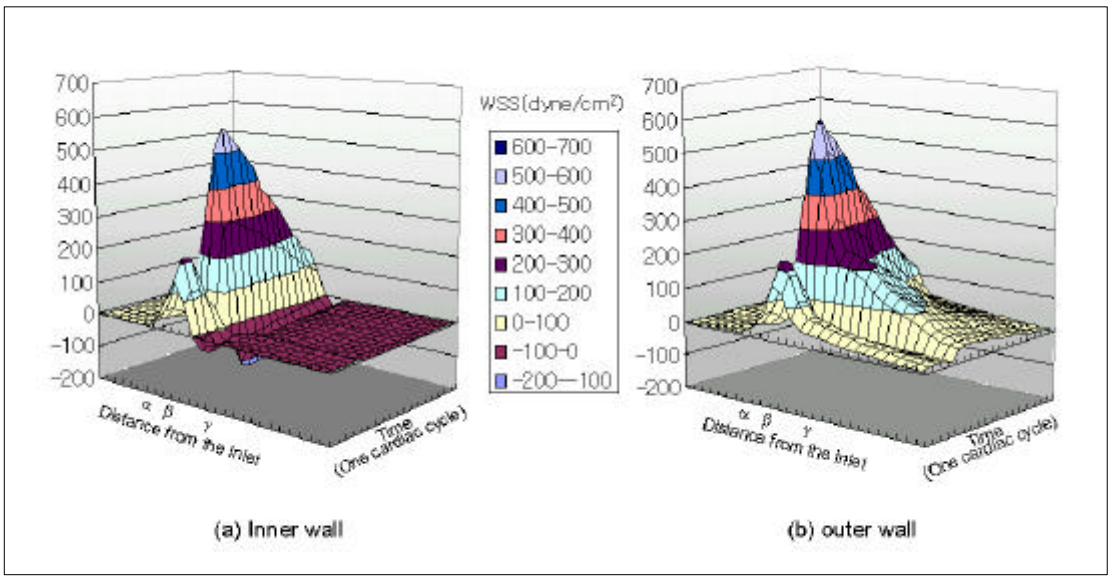
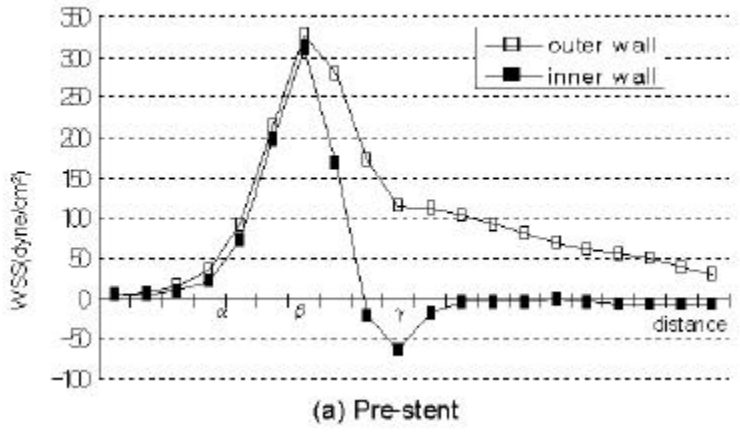


Fig. 5. 3D shear stress distribution curves in the inner and outer walls of the pre-intracoronary stenting model according to time and distance. Peak shear stress occurred in the early diastolic phase and negative shear area just distal to the highest shear, findings which are consistent with the recirculation area in the inner wall. In the outer wall before stenting, there was also a very high shear area similar to that of the inner wall but no negative shear area.



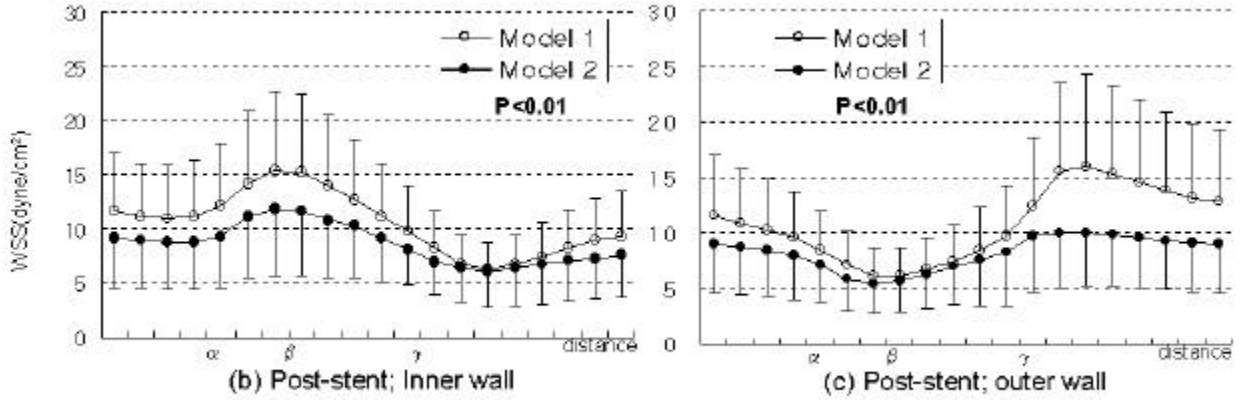


Fig. 6. Shear stress distribution curves in the inner and outer walls of pre- (a) and post-intracoronary stenting (b, c) models according to distance. Post-intracoronary stenting WSS distribution curves (b, c) showed markedly reduced peak shear stress in both inner and outer walls and absent negative shear area in the inner wall, along with negative shear in the pre-stent inner wall. This finding was more prominent in model 2. The WSS waveform in model 2 revealed a much smaller amplitude variation, i.e. oscillatory WSS, than in model 1 ($p<0.01$) along the coronary artery wall.

stenting model. Furthermore, the WSS waveform in model 2 revealed a much smaller variation of its amplitude than in model 1 ($p<0.01$), along the coronary artery wall and with respect to time (Fig. 6b, 6c, 7b, 7c).

DISCUSSION

The present study has extended our understanding of the hemodynamic characteristics of pulsatile flow-velocity and WSS conditions to significant coronary atherosclerotic stenosis, as well as in mechanical revascularization with intracoronary stenting following our previous report on the hemodynamic characteristics in normal physiologic coronary and aortic circulation.[12,14] Furthermore, we visualized and quantified the geometrical patterns of hemodynamic variables in two angulated coronary stenosis models before and after intracoronary stenting, and compared the rheologic properties of the two models to evaluate in-stent restenosis by *in vitro* computerized simulation using the *in vivo* hemodynamic data.

In 6-month follow up coronary angiograms, group 2 had a lower percentage of in-stent restenosis than group 1, which suggests an inverse correlation between straightened angle and in-stent restenosis rate. This finding supported the hypothesis that changes of patterns in flow- velocity and WSS conditions around the stenotic lesion, which were induced by geometrical changes, might affect in-stent restenosis. The flow- velocity vector model of pre-intracoronary stenting revealed a very high flow velocity toward the outer wall of the artery due to critical coronary stenosis, as well as flow separation, flow recirculation and flow attachment phenomena in the inner wall. Negative shear area on 3-D simulation, which is consistent with the re-circulation area on the flow vector pattern, was noted on the inner wall

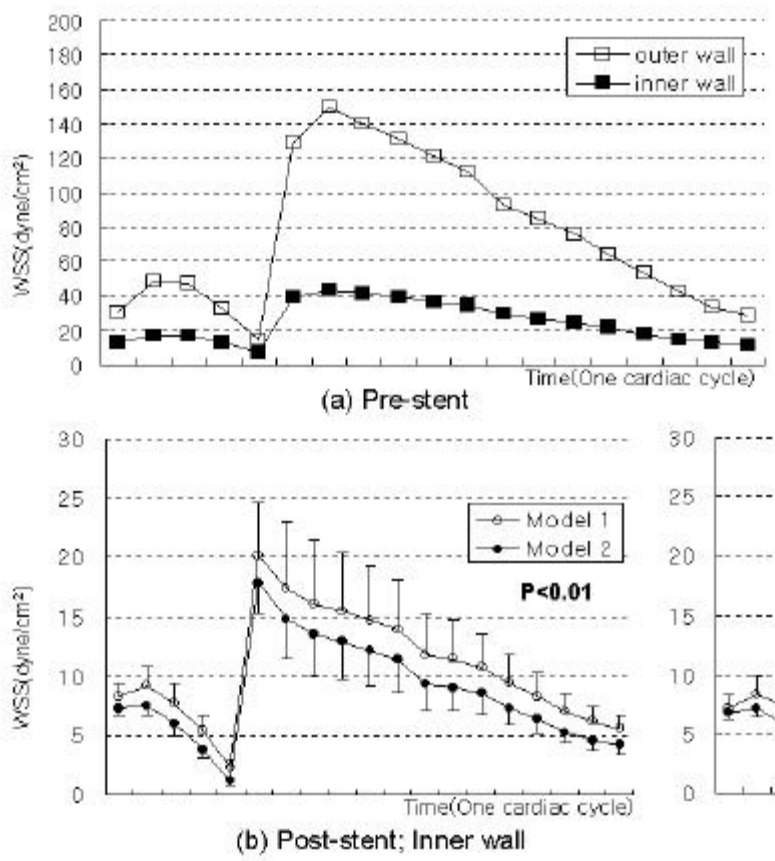


Fig. 7. Shear stress distribution curves in the inner and outer walls of pre- (a) and post-intracoronary stenting (b, c) models according to time during one cardiac cycle. Distribution of post-intracoronary stenting WSS (b, c) showed markedly reduced peak shear stress in both inner and outer walls. This finding was more prominent in model 2. The WSS waveform in model 2 revealed a much smaller variation of its amplitude, i.e. oscillatory WSS, than in model 1 ($p < 0.01$) during one cardiac cycle.

of the post-stenotic area before stenting; a finding more prominent than for non- stenotic normal coronary artery.[12,14] Moreover, this negative shear area disappeared after intracoronary stenting. The WSS after stenting was markedly reduced, to as little as one twentieth of that before stenting. The amplitude of WSS fluctuation in model 1 of post-intracoronary stenting was significantly larger than that in model 2. The six-month in-stent restenosis was higher in group 1, which represented model 1. The present study suggests that hemodynamic forces exerted by flowing blood, termed WSS, might affect the evolution and progression of atherosclerosis within the angulated vascular curvature. Furthermore, this study demonstrated that the effect of geometric characteristics, such as the angular difference between pre- and post-intracoronary stenting, on vascular repair might vary according to the hemodynamic conditions or rheologic properties.

The disturbance of laminar blood flow can be encountered with the endothelial cell, and as a result, the cells can be chronically exposed to shear forces with cyclical variation in direction.[15] It was reported that the recirculation area with low shear area might contribute to the atherogenesis and progression of atherosclerosis.[12,14,16] In the present study the above mentioned flow disturbances occurred prominently in the coronary stenosis model at the curved inner wall just after stenosis. Therefore, atherosclerosis might be initiated and progress on the inner wall of a curve due to low flow-velocity, flow separation, flow recirculation and low shear stress in the micro-environmental milieu. This frictional force exerted by flow disturbances at the vascular endothelium has been also implicated in the vascular remodeling after percutaneous transluminal balloon angioplasty or coronary stenting.[17] This insight has provided the basis for the rational design of coronary arterial bypass surgery.[18]

Since there are many variables in the prediction

of in-stent restenosis, we would like to investigate the effect of biomechanical factors on restenosis. The endothelial lining has a dynamically mutable interface, which is local 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.[19,20] 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 times of hemodynamic transition such as percutaneous transluminal coronary angioplasty or stenting.[19] Laminar shear stress stimulates expression of tissue plasminogen activator and reduces secretion of plasminogen activator inhibitor type-1. Importantly, endothelial cells exposed to turbulent flow failed to show increases in thrombomodulin and tissue plasminogen activator, which indicates a prothrombotic condition.[21,22] During the first several hours after stenting, when thrombosis occurs predominantly, if sustained, disturbed shear stress in the stented region exists, it might stimulate more thrombosis. In which case, as platelets in the thrombus secrete various growth factors the increasing proliferation will lead to in-stent restenosis. The present study demonstrated that significant temporal and spatial shear fluctuation in post-intracoronary stenting status still remained in model 1, which represented group 1, and that there was a higher percentage of diameter stenosis at follow-up angiography. This result may indicate the adverse effect of remaining shear fluctuation on th healing process after stenting. Therefore, we might assume that if there are distinct biomechanical factors involved in the progression of atherosclerosis or in-stent restenosis, such as low shear or temporal disturbed shear fluctuation, there will be more cellular proliferation during the early healing period in the stented coronary vasculature.

WSS affects various biological cascades, and it may be critical for endothelial cell survival.[15] Davies et al. demonstrated increased endothelial cell turn over in areas that experience turbulent shear stress condition, suggesting compromised endothelial cell integrity under these conditions.[23] It has been also reported that the lack of shear stress triggers apoptosis in endothelial cells.[24] Mechanically, physiological levels of shear stress interfere with numerous steps of the endothelial cell apoptotic cascade. Sustained physiological levels of shear stress activate the P13K/Akt pathway in an integrin-dependent fashion, thereby mimicking the signaling pathways used by specific endothelial cell growth factors such as VEGF or Ang-1.[25] Under low shear stress condition, endothelial cells on the border of a wound edge failed to maintain contact with neighboring cells and were oriented randomly. Further, cells spread and migrated into wound sites more slowly.[26] Charles et al also reported that the temporal shear gradient stimulates endothelial cell proliferation, based on their experimental result.[27]

Therefore, we suggest that vascular endothelial cells might be influenced by local shear stress conditions during the re-endothelialization period after PTCA or stenting. With the stented coronary artery having disturbed and shear fluctuation due to its geometric alteration, complete endothelialization might be delayed by the presence/formation of dysfunctional endothelial cells. This results in the subendothelium being exposed for a longer time to various growth factors and cytokines, causing more intimal hyperplasia. In our study, although the post- stented shear stress of both inner and outer walls in both models was around the lower margin of physiologic shear stress level, the less straightened model 1 had a significant amount of temporal and spatial WSS fluctuation. Meanwhile, the WSS variation in model 2 was significantly smaller than in model 1 in physiologic WSS range. Therefore, the lower percentage diameter stenosis in group 2, representing model 2, could also be inferred.

This study featured some limitations. As in- stent restenosis occurs with so many factors, it is not possible to confirm that the rheologic properties inside of the stented lesion are mainly responsible for the restenosis. Another limitation is that the straightening effect itself is biologically stressful for mature vessels. We did not evaluate the biologic consequences of this effect *in vivo*. We merely

suggested a physiologic role for hemodynamic variables after geometric change by applying rheologic analysis methods to clinical data of the vascular healing process after percutaneous coronary intervention with stent. Further biologic studies under various *in vitro* and *in vivo* conditions with larger scale clinical data of in- stent restenosis will be required to confirm our findings.

Finally, these results may be used in coronary intervention to prevent the restenosis of coronary arterial disease and its progression. Future investigation on the biomechanical activation of endothelial cells would be useful in this pathophysiologically relevant area.

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