Impact of the Cross-Sectional Geometry of the Post-Deployment Coronary Stent on In-Stent Neointimal Hyperplasia

— An Intravascular Ultrasound Study —

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To establish the relationship between the cross-sectional geometry of the post-deployment stent and the degree of in-stent neointimal hyperplasia (INH), intravascular ultrasound (IVUS) was used to examine cross-sections of the coronary arteries from 23 patients with coronary stents 6 months after implantation. Stent cross-sectional area (Sa) and stent perimeter (Sp) from 200 stent cross-sections, and the stent radius (Sr) and thickness of INH (Id) of 2,880 radial axes, were measured, and the mean degree of roundness (Rd) of stent cross-section was calculated for each stent as $Rd = 4 \text{ Sa} / \text{Sp}^2$. The degree of deformity (Df) of the stent cross-section was also calculated by comparing it with a hypothetical circle (the area of this hypothetical circle was equal to the Sa): $Df = \text{Sr} / R$, where R is the radius of the hypothetical circle. The area of INH was significantly larger in the $Rd < 0.87$ group ($n = 84$) than in the $Rd \geq 0.87$ group ($n = 116$) (3.83 ± 1.26 vs $3.16 \pm 1.32 \text{ mm}^2$, $p < 0.0005$). There were significant differences in the thickness of INH among the 3 groups classified by the value of Df ($Df < 0.95$: $n = 425$, $0.21 \pm 0.12 \text{ mm}$; $0.95 \leq Df < 1.05$: $n = 2008$, $0.29 \pm 0.15 \text{ mm}$; $Df \geq 1.05$: $n = 447$, $0.34 \pm 0.15 \text{ mm}$, overall $p < 0.0001$). These data suggest that in-stent neointimal proliferation is more likely to occur in stented coronary arteries with a more oval than rounded cross-section, and particularly within the more pronounced and curved portion of the oval. (Circ J 2002; 66: 489–493)

Key Words: Intravascular ultrasound; Neointimal hyperplasia; Stent

In-stent neointimal hyperplasia (INH) is the main cause of restenosis after stenting¹ and several mechanisms have been proposed as determinants of the degree of in-stent neointimal proliferation: the amount of residual plaque burden;² the degree of rupture or dissection of the vessel wall after balloon dilation;³ the aggressiveness of the stent implantation technique;⁴ the degree of overexpansion or oversizing of the balloon;^{5,6} multiple stents;⁷ high acute gain;^{7,8} high inflation pressure;^{7,9} length of the stenosis;⁷ small reference diameter;⁷ small stent size;^{10,11} and stent design.^{12–14} Among these reports, Garasic et al documented the effect of local stent geometry on INH in rabbit arteries;¹³ but there are no reports on the role of local stent geometry in intimal hyperplasia in human coronary arteries in vivo.

Intravascular ultrasound (IVUS) can visualize INH in vivo, so it was used in the present study to examine the relationship between the cross-sectional geometry of the post-deployment coronary stent and the degree of INH.

Methods

Patient Selection

Twenty-three patients (13 men, 10 women; 63 ± 10 years old, range, 31–79 years) with coronary stents (13 Multilink, 10 GFX stents) were selected and underwent follow-up cardiac catheterization at approximately 6 months (mean, 6.5 ± 1.1 months) after stent implantation between 1997 and 2000. Exclusion criteria included a stented left main coronary artery, extreme tortuosity of the lesions, additional cardiac events during the 6 months since implantation, lesions with calcification of more than a 90° arc, lesions with poor IVUS image quality because of significant dropout, artifact and/or non-uniform rotational distortion, lesions wedged with a IVUS catheter. All stents had been deployed with an expanded balloon pressure of 10 atm.

The study was approved by the Institutional Review Board of Clinical Research of Yamaguchi University. All patients gave informed written consent before IVUS imaging.

IVUS Imaging

Follow-up IVUS images were obtained with a 3.2 or 2.6Fr short monorail imaging catheter (30 MHz Ultracross® and/or 40 MHz Discovery® or Atlantis®/Boston Scientific, Natick, MA, USA). Therapeutic anticoagulation was achieved with 5,000 IU heparin iv. Intracoronary isosorbide dinitrate (1.0 mg) was administered just before IVUS imaging. The transducer was then advanced as distally as possible, after

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Fig 1. Measurement of index of local cross-sectional stent deformity (Df). Each stent cross-section was divided by 36 radial axes 10 degrees apart around the center of gravity (G) of the stent area. Stent radius (Sr) and the thickness of INH were measured for each radial axis. The Df of the stent strut is calculated and compared with a hypothetical circle the area of which was equal to the stent area. $Df = Sr/R$, where R is the radius of the hypothetical circle. INH, in-stent neointimal hyperplasia.

which it was automatically pulled back by a motorized pullback system at a speed of 0.5 or 1.0 mm/s. All IVUS images were recorded continuously on S-VHS videotape for subsequent offline data analysis. Each stent was divided along its length into 10 equal segments and an IVUS cross-sectional image was obtained for each segment. Each cross-sectional IVUS image was digitized as a 640×480 pixel image on a Macintosh computer.

Geometric Analysis of IVUS Images

Public-domain software (NIH image) was used to planimeter the IVUS images. Stent cross-sectional area (Sa) and stent perimeter (Sp) were first obtained from the 10 cross-sections for each stent. The degree of roundness (Rd) of each stent cross-section was calculated as $Rd = 4 \cdot Sa / Sp^2$. When $Rd = 1$, the shape of the cross-section is a perfect circle. When $Rd < 1$, the shape becomes more elliptical. For comparing the degree of INH, cross-sections were divided into 2 groups determined by the mean value of Rd (Group 1: $Rd < 0.87$, $n = 84$; Group 2: $Rd \geq 0.87$, $n = 116$). The area of INH was calculated as stent area minus lumen area. In this analysis, it was hypothesized that stent area and its geometry did not change during the follow-up period.

Furthermore, to evaluate a more localized relationship between stent cross-sectional geometry and INH, 4 equidistant stent cross-sectional images, but not those from the stent ends, were first selected. Each of these images was divided by 36 radial axes 10 degrees apart around the cen-

Fig 2. Comparison of the area of in-stent neointimal hyperplasia (INH) between Group 1 ($Rd < 0.87$) and Group 2 ($Rd \geq 0.87$). Rd, degree of roundness of stent cross-section.

ter of gravity for the stent area. Stent radius (Sr) and the thickness of INH were measured for each radial axis. Then, we calculated the degree of deformity (Df) of the stent strut compared with a hypothetical circle (the area of this hypothetical circle was equal to the Sa): $Df = Sr/R$, where R is the radius of the hypothetical circle (Fig 1). When $Df > 1$, the corresponding stent portion lies outside the circumference of the hypothetical circle, and has a higher degree of curvature. When $Df < 1$, the stent portion lies inside the circumference of the hypothetical circle, and has a lower degree of curvature. All portions of stent examined curved in the same direction as the circumference of the hypothetical circle: none was concave in relation to the center of gravity. Sectors were divided into 3 groups determined by the value of Df to compare the degree of INH thickness (Group A, $Df < 0.95$; Group B, $0.95 \leq Df < 1.05$; Group C, $Df \geq 1.05$). The values 0.95 and 1.05 corresponded to the values of mean minus SD and mean plus SD, respectively (Group A: $n = 425$; Group B: $n = 2008$; Group C: $n = 447$; total 2,880 sectors).

In these analyses, the portions from the edge of the stent were all excluded because of the possible influence of tissue damage of the nonstented area by the intervention. Any portions examined were at least 1 mm away from the edge.

Statistical Analysis

Values are expressed as mean $\pm$ SD. Continuous variables were compared by analysis of variance with post-hoc Scheffe's analysis. Categorical variables were compared using χ^2 analysis. A p value of less than 0.05 was considered significant.

Results

Patient Profiles

Of the 23 patients selected, 14 (61%) had a history of myocardial infarction, and 9 (13%) had angina pectoris, and there were associated coronary risk factors: diabetes mellitus, 10 patients (43%); hypertension, 13 patients (57%); hyperlipidemia; 15 patients (65%). Stents were deployed in 12 left anterior-descending arteries, 4 left circumflex arteries, and 7 right coronary arteries. Patients were medicated with aspirin ($n = 22$, 96%), ticlopidine ($n = 17$, 74%), cilostazol ($n = 2$, 9%), tranilast ($n = 2$, 9%), probucol ($n = 1$, 4%), angiotensin converting enzyme inhibitors ($n = 14$, 61%) and angiotensin-receptor blockers ($n = 1$, 4%). The mean nominal size of stent deployed was 3.1 ± 0.3 mm.

Fig 3. Relationship between in-stent neointimal hyperplasia (INH) and Rd (degree of roundness of stent cross-section).

Overall Stent Cross-Sectional Geometry and Neointimal Hyperplasia

Total vessel, stent, lumen and INH areas at a follow up were 14.9 ± 2.6 , 7.4 ± 2.1 , 4.3 ± 1.7 , and $3.1 \pm 1.2 \text{ mm}^2$, respectively.

The average Rd of the stent cross-sections for all patients was 0.87 ± 0.05 . The INH area of Group 1 ($Rd < 0.87$, $n=84$) was significantly larger than that of Group 2 ($Rd \geq 0.87$, $n=116$) (3.83 ± 1.26 vs $3.16 \pm 1.32 \text{ mm}^2$, $p < 0.005$) (Fig 2). The INH area was inversely correlated with Rd ($p < 0.005$, $r = -0.21$) (Fig 3). There was no difference in either stent area or vessel area between the 2 groups. The average Rd of the lumen cross-sections was 0.93 ± 0.03 , which was significantly larger than that of the stent cross-sections ($p < 0.0001$).

Local Stent Cross-Sectional Geometry and Neointimal Hyperplasia

Fig 4 shows representative examples of the coronary INH typically observed in the more pronounced portions of elliptical stent cross-sections.

There were significant differences in the thickness of INH among the 3 groups classified by Df (Table 1, Fig 5). A portion with a higher value of Df was associated with a greater thickness of INH. Post hoc analysis showed significant differences in INH thickness between any pairs in the 3 groups. There were also significant differences in Sr (Fig 1) among the 3 groups: it was greatest in Group C, and smallest in Group A. The plaque was significantly thicker in Group A than in the other groups (Table 1). The INH thickness significantly correlated with Df ($p < 0.0001$, $r = 0.31$) (Fig 6).

Discussion

This study shows that the cross-sectional geometry of

Fig 4. Representative example of asymmetric in-stent neointimal hyperplasia (INH) in an oval stent cross-section. The more curved portion of the stent has a greater degree of INH than the flat portion.

the post-deployment coronary stent is an important determinant of INH. In-stent neointimal proliferation is more likely to occur within the stented area of a coronary artery with a more oval cross-section, particularly within the more pronounced and curved portions of the stent. Although the long-term clinical outcome of each patient was not examined in the present study, the findings may prove useful for understanding the mechanism of in-stent restenosis.

A major determinant of INH is the degree of vascular injury, which in turn depends on the type of plaque^{2,3,7} the type of stent^{7,10,12-14} and the aggressiveness of the coronary intervention⁴⁻⁹. Therefore, it is reasonable to expect that an asymmetrical stent cross-section is associated with asymmetrical distribution of the vascular injury along the cross-sectional vascular perimeter, which leads to non-uniform neointimal hyperplasia.

Garasic et al demonstrated in rabbit iliac artery that immediate post-deployment stent luminal geometry determines neointimal thickness, which may be useful for predicting patterns of intimal growth for novel stent designs.¹³

Table 1 Study Groups Classified by the Degree of Deformity (Df)

	Group A (Df < 0.95) (n=425)	Group B (0.95 ≤ Df < 1.05) (n=2,008)	Group C (Df ≥ 1.05) (n=447)
INH thickness (mm)	$0.21 \pm 0.12^{*†}$	0.29 ± 0.15	$0.34 \pm 0.15^{**}$
Stent radius (mm)	$1.34 \pm 0.16^{*†}$	1.43 ± 0.19	$1.55 \pm 0.18^{**}$
Plaque thickness (mm)	$1.25 \pm 0.47^{*†}$	1.10 ± 0.49	1.06 ± 0.49

INH, in-stent neointimal hyperplasia. * $p < 0.0001$ vs Group B, † $p < 0.0001$ vs Group C, ** $p < 0.0001$ vs Group B.

Fig 5. Comparison of the thickness of the in-stent neointimal hyperplasia (INH) among the 3 groups classified by the value of Df (the degree of local stent deformity). P values are determined using ANOVA.

Fig 6. Relationship between the thickness of the in-stent neointimal hyperplasia (INH) and Df (the degree of local stent deformity).

Fig 7. Hypothesis of the mechanism of asymmetric in-stent neointimal hyperplasia (INH) in an oval stent cross-section. The more curved portion may result in a greater degree of vascular injury. Some mechanism to preserve laminar flow or uniform shear stress distribution may exist for the purpose of restoring luminal circularity when a stent assumes an oval cross-section immediately after deployment. Therefore, the more curved portions of stent cross-section may have a greater degree of INH.

However, Hoffmann et al reported that no effect of stent luminal asymmetry could be observed in determining the frequency of restenosis.¹ The index of asymmetry used in their report was the maximum/minimum dimension ratio, which differs that used by us in this report, and they did not examine the amount of in-stent intimal hyperplasia, rather the rate of restenosis. Our geometrical indices, Rd and Df, better represent the local geometry.

Neointimal hyperplasia is generated by adventitial myofibroblast migration¹⁶ and transformation of smooth muscle cells¹⁷ or monocytes,¹⁸ provoked by the vascular insult during coronary intervention. The difference in the amount of INH among the groups with differing degrees of asymmetry of the post-deployment stent cross-section may be explained by the difference in the degree of vascular injury. When a stent is oval in cross-section, there are 2 distinct sections: the flat portion with a lower degree of Df, and the more curved portion with a greater degree of Df. These sections are formed by the non-uniform expansion of the stent: underexpansion in the flat portion and/or overexpansion for the more curved portion. Wider opening of the stent struts causes markedly larger surface contact and contact stresses between the stent struts.^{13,14} Stent-imposed stress for a vessel of any given size will increase as a function of increasing diameter,¹³ and so it is reasonable to speculate that the more curved portion generates a greater degree of intimal hyperplasia as a consequence of a greater degree of vascular injury.

The group with Df<0.95, which had a smaller degree of INH, had a larger amount of plaque behind the stent, which appears to contradict reports that residual plaque burden is one of the determinants of INH.² It has been documented that the amount of plaque behind the stent is different from that immediately after stent implantation.⁹ Furthermore, the plaque dimension used in the present study was the plaque thickness just behind the portion of interest. The degree of vascular injury is not determined by the thickness of plaque, but rather the amount or volume, or the softness or compliance of the total plaque. In the present study, the greater plaque thickness in the group with the smaller Df might represent low expandability of the plaque that formed the flat portion of the oval stent cross section. Therefore, vascular injury may be less in the flat portion than in the

more curved portion. This low expandability could be associated with calcification, which was not examined in the present study.

Another explanation is possible from the rheological aspects. Our data indicate that the lumen cross-section was rounder than the stent cross-section. The stent cross-section coincides with the lumen cross-section immediately after stent expansion. Restoration of luminal circularity may be driven by local arterial strain or flow characteristics. Local turbulence and/or stagnation of flow dynamics may become a trigger for restoring the lumen to a circular shape for the purpose of optimizing fluid flow characteristics at the blood–tissue interface.^{20–22} Platelet and inflammatory cell adhesion and activation are markedly reduced in the more laminar flow within the lumen of more circular stented vessels. Non-uniform distribution of shear stress may also result in non-uniform neointimal proliferation.²³ Therefore, the more curved portions of the stent may generate a greater degree of in-stent hyperplasia (Fig 7).

Study Limitations

Although radial axes were studied in the order of 3,000, one limitation of the present study was that there was a relatively small number of patients and selection bias may have occurred because only patients with IVUS follow-up were studied. The present study hypothesized that stent area and its geometry did not change during the follow-up period because previous studies have shown that stent area does not change during the first 6 months after stent implantation.^{1,19,24–26} Rd and Df were calculated using the stent area, so it is possible to speculate that Rd and Df would not change during this period. In addition, Rd was compared between the time of stent implantation and the follow-up period in 24 stent cross-sections from 4 patients in a pilot study, which revealed no significant changes in Rd during the 6 months following implantation.

In this study, the data were obtained only from patients with Multilink or GFX stents, but it is possible that different results in terms of the impact of stent geometry on INH would be obtained if the patients with a Multilink stent and those with a GFX stent were examined separately, or if other types of stent were evaluated. Therefore, further examinations are needed to clarify the stent-specific data.

Because plaques with severe calcification were excluded, our findings can not be extrapolated to these cases. Another limitation is that the patients who had significant restenosis or who needed reintervention, were excluded because IVUS is not possible in such cases. IVUS miniaturization would allow more detailed research.

Conclusions and Clinical Implications

In-stent neointimal proliferation is more likely to occur in stented coronary arteries with a more oval than rounded cross-section, and particularly within the more curved portion of the oval. Post-deployment cross-sectional stent geometry could prove to be an important determinant of INH. However, further examination of a larger number of patients in a multicenter trial is necessary to determine whether circular stents reduce the risk of in-stent restenosis.

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