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Intimal Proliferation After Stenting Reflected by Increased Stent-to-Vessel Cross-Sectional Area Ratio: Serial Intravascular Ultrasound Study

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Abstract

Minimizing the extent of neointimal proliferation helps to maintain the maximal vessel lumen after the treatment of stenosis. The present study examined factors influencing the predisposition to neointimal proliferation, which is a consequence of Palmaz-Schatz stenting.

Serial intravascular ultrasound examinations of 32 lesions (4 lesions/patient) were performed after stenting and at 6 months follow-up in 8 non-restenotic patients. Vessel, lumen and stent cross-sectional areas (CSA) were measured. Stent-to-vessel CSA ratio at stenting, changes of lumen CSA, vessel CSA and intima CSA (neointimal proliferation) were calculated. Six months after stenting, lumen CSA was reduced corresponding to an increase of intima without change of vessel CSA (without remodeling). Greater stent-to-vessel CSA at stenting was associated with higher neointimal proliferation at follow-up. The proliferative response was the same at all stent edges. Stent CSA was reduced as stent dilation was increased. The stent CSA became smaller but stent shrinkage did not account for late lumen loss.

Late lumen loss in stents is the result of neointimal proliferation in cases without restenosis, and a larger stent-to-vessel CSA ratio reflects increased neointimal proliferation, as shown at 6-month follow-up.

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Key Words

■ **Angioplasty** ■ **Stent** ■ **Intravascular ultrasound (cross-sectional area)**

INTRODUCTION

Prevention of restenosis or, in the absence of restenosis, minimizing the loss of lumen diameter over time following alleviation of stenosis is a major goal in the treatment of coronary artery disease. Restenosis after stenting occurs less often than after conventional balloon angioplasty because the initial gain after stenting is much greater than after balloon angioplasty and therefore the restoration after stenting is less[1–5]. However, pathological findings after implantation of a stent in swine coronary arteries show that intimal hyperplasia follows smooth muscle cell proliferation covering stent struts and leads to a subsequent loss in lumen diameter. Intimal hyperplasia consists of not only an increase in cell number but also an increase in matrix production, such as collagen, without an

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increase in cell number[6-9]. Although intimal hyperplasia is a consequence of stenting[10,11], minimizing the extent of this growth will help to maintain the optimal vessel lumen. Unfortunately, the ideal ratio of stent size to vessel size for optimal dilation with minimal compensatory intimal hyperplasia remains unknown because intimal hyperplasia after stenting is a complex and unclear process. However, several possible mechanisms have been studied: endothelial denudation, medial smooth muscle cell injury, inflammatory reactions to the stainless stent wires, and exertion of radial pressure (a stretch effect)[12-18]. Vessel stretch stress was reported to increase the synthesis of collagen without an increase in cell number. Therefore, the stretching of the vessel by stent struts themselves may accelerate the intimal hyperplasia after stenting. Alternatively, over-dilation of the vessel by the stent may cause a severe smooth muscle cell injury resulting in severe intimal hyperplasia.

At the time of the present study, the Palmaz-Schatz stent was the only stent available for use in Japan for the treatment of coronary artery stenosis. Originally, this stent consisted of 2 segments of slotted tubes joined by an articulation. However, accumulated clinical experience and angiographic studies suggested that when in-stent restenosis occurred after stenting, it frequently appeared at the articulation site of the stent[19].

The present study tested the hypothesis that a higher ratio of stent-to-vessel cross-sectional area (CSA) after stenting results in more intimal hyperplasia in the human coronary artery, determined whether there really are differences between stent edges with respect to intimal proliferation responses, and determined by extrapolation the ideal ratio of stent to vessel size that minimizes compensatory hyperplasia.

METHODS

Study patients

Palmaz-Schatz stents were placed in coronary arteries in 8 consecutive patients. Intravascular ultrasound (IVUS) imaging was performed immediately afterward and repeated 6 months after stenting. All patients showed objective evidence of myocardial ischemia by either treadmill exercise testing or thallium myocardial scintigraphy. Patients of advanced age ($\geq$ 70 years old) or with acute myocardial infarction, unstable angina, congestive heart failure and restenosis lesions were excluded from the study, as were those with contraindications to aggressive anticoagulant therapy. The investigational protocol was approved by the Institutional Review Board and all patients gave informed consent.

Selected abbreviations and acronyms

CSA = cross-sectional area
IVUS = intravascular ultrasound

Stents were placed in vessels with a reference diameter of over 3.0 mm and diameter stenosis of over 75% by visual inspection. Six stents were placed in the left coronary artery and 3 in the right coronary artery (in one case, 2 partially overlapping tandem stents were placed in the right coronary artery; all other cases received only a single stent).

Stent deployment

The Palmaz-Schatz stent, balloon and the integrated 5F sheath assembly used were prepackaged as a single unit (Stent Delivery System, Johnson & Johnson Interventional System, USA) with an inflated balloon diameter of 3.0, 3.5, or 4.0 mm. Before stenting, the lesion was pre-dilated by a conventional angioplasty balloon with an inflated balloon diameter of 2.5 or 3.0 mm. After stenting, the diameter of the stent could be enlarged to an appropriate size by a conventional semi-compliant short balloon (balloon length, 9.0 mm) with high pressure (16-18 atm). After the angiographic result was considered acceptable, IVUS was performed. All subsequent treatment decisions were based on the IVUS results in conjunction with angiographic assessment. Further balloon dilation was performed to achieve an acceptable IVUS result. The IVUS criteria for optimal stent expansion were: Qualitative evaluation of the stent as expanded fully and covering the full extent of the lesion to minimize potential impairment to flow; quantitative evaluation of stenting as the achievement of an in-stent CSA at the tightest measurement point that was 70% of the distal reference lumen CSA.

All patients were pretreated with aspirin (100 mg, once daily), isosorbide dinitrate (20 mg, twice daily), ticlopidine (100 mg, twice daily), and long-acting diltiazem (100 mg, once daily). Infusion of dextran (100 ml/hr) was begun 2 hours before the procedure and continued until the total dose was

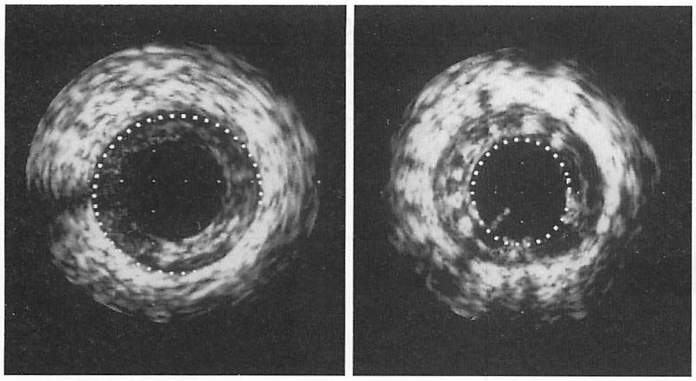

Fig. 1 IVUS images of a proximal left coronary lesion treated with a single Palmaz-Schatz stent
IVUS cross-sectional images illustrate the measurement of the vessel (*left*) and the lumen (*right*) CSA. The intimal CSA was obtained by subtracting the lumen CSA at the stent edge (dotted circle, *right*) from the adjacent reference vessel CSA (dotted circle, *left*).

500 m*l*. All patients received antibiotic prophylaxis before and the day after the procedure. The initial intravenous heparin bolus dose (1×10^4U) was given after placement of the arterial sheath, and additional heparin (3×10^3U every 30 min) was administered to maintain an activated clotting time of over 250 sec. In all patients, oral anticoagulant therapy was started the next day using warfarin, titrated to a thrombotest of 15–25%, and continued for 6 months after stent placement.

Follow-up

All patients were contacted by the investigators every month in the outpatient department of our hospital. All patients underwent angiographic follow-up and IVUS examination at 6 months after stenting.

Angiographic analysis

All cineangiograms were analyzed using a computer-assisted cardiovascular angiography analysis system (Cardio-500, Kontron, USA) by an investigator without knowledge of patient information. Vessel edges were determined by a computerized algorithm, and luminal diameters were measured with a dye-filled catheter of over 6F in diameter as a reference. The diameters of the normal segments proximal and distal to the treated area were averaged to determine the reference diameter. The minimal lumen diameter, reference diameter, and percentage of stenosis were all calculated from projections of the same view at the most severe stenosis. On follow-up angiograms, in-stent stenosis was calculated from the minimal lumen diameter within the stent compared with the reference diameter. Restenosis was defined as a stenosis of $\geq 50\%$ within or immediately adjacent to the stent.

Ultrasound measurements

IVUS imaging was performed immediately and 6 months after stenting using a 3.5F monorail catheter system with a 30 MHz ultrasound transducer (Sonicath, Boston Scientific, USA) and ultrasound system (Sonos M2400A, Hewlett-Packard, USA). The imaging catheter was positioned under fluoroscopic guidance distal to the stent, and images were recorded continuously as the catheter was withdrawn manually through the stent segment to a point proximal to the stent. After the stent was interrogated with a single pullback, the catheter was repositioned to obtain the image of the stent edges and reference segments adjacent to the stent edges and articulation segment. The imaging catheter was moved slowly and carefully. All images were recorded on 0.5 inch Super-VHS videotape.

After the ultrasound examination was completed, the videotape was reviewed and the stent edges, reference segments adjacent to the stent edges and articulation segment were identified. The image was digitized and analyzed using Cardio-500 to perform the quantitative analysis (**Fig. 1**). The lumen-intima border was traced and the area within this border was measured by planimeter as the lumen CSA at the proximal stent edge (Edge 1), at the edge of the proximal half stent facing the articulation (Edge 2), at the edge of the distal half stent facing the articulation (Edge 3), and at the distal stent edge (Edge 4) (**Fig. 2**). The vessel border was defined as the outer boundary of the echo-lucent media and the area within the vessel border was measured as the vessel CSA at the proximal reference vessel just adjacent to Edge 1, at the central articulation, and at the distal reference vessel just adjacent to Edge 4. The area within the stent strut was measured as the stent CSA at 4 stent edges.

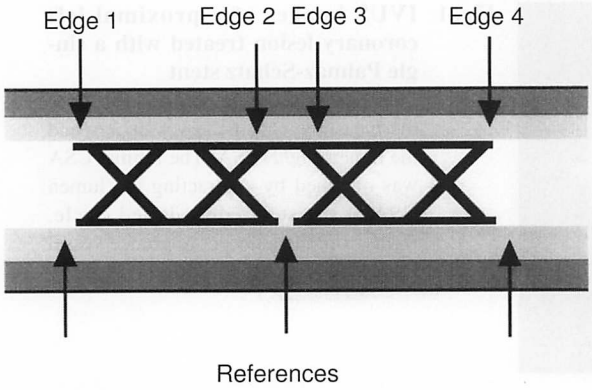

Fig. 2 Illustration of a lesion treated with a Palmaz-Schatz stent
Arrows represent the 7 measured sites.

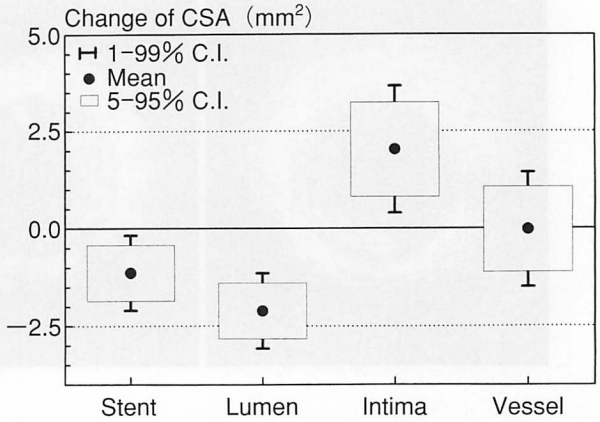

Fig. 3 Changes in stent, lumen, intimal and vessel CSA 6 months after stenting
C.I. = confidence interval.

Stent-to-vessel CSA ratio, intimal CSA, normalized intimal CSA for vessel CSA, neointimal proliferation and normalized neointimal proliferation for vessel CSA were defined and calculated according to the following formulas: stent-to-vessel CSA ratio for Edges 1 or 4 = stent CSA at the proximal or distal stent edge/proximal or distal reference vessel CSA just adjacent to the stent edge; stent-to-vessel CSA ratio for Edges 2 or 3 = stent CSA at the edge of the proximal or distal half stent facing the articulation/vessel CSA at the central articulation; intimal CSA = difference between the lumen CSA at the stent edge and the corresponding reference vessel CSA; normalized intimal CSA = intimal CSA/corresponding reference vessel CSA; neointimal proliferation = difference between intimal CSA just after stenting and intimal CSA 6 months after stenting at the equivalent segment of the stent edge; normalized neointimal proliferation = difference between normalized intimal CSA just after stenting and normalized intimal CSA 6 months after stenting at the equivalent segment of the stent edge.

Reproducibility study

Intraobserver variability of the measurements of IVUS imaging was calculated on 12 segments of coronary artery at random at a 10 day interval. Interobserver variability of the measurements of IVUS imaging was calculated on 12 segments of coronary artery at random at the same time. Two independent observers measured the vessel, lumen and stent CSAs of these segments. These data were analyzed and the correlation coefficient, the mean difference between 2 observations and the range of the differences were derived.

Statistical analysis

All data are presented as mean ± SD. Data derived from angiographic examination before, just after stenting and at follow-up were first analyzed by one-way ANOVA and subsequently by a two-tailed unpaired *t*-test. Data derived from ultrasound examinations just after stenting and at follow-up were analyzed by a two-tailed paired *t*-test with a Bonferoni adjustment. Simple linear regression analysis and an analysis of covariance were performed to determine the correlations between continuous data. Significant differences were considered as $p < 0.05$.

RESULTS

At baseline morphology, all lesions were eccentric and discrete except one tubular lesion. No lesion calcium was detected by fluoroscopy. All lesions were dilated easily by balloon angioplasty. All stents were placed covering the full extent of lesion with both struts of the Palmaz-Schatz stent. Therefore, both stent edges were at lesion-free segments, and the articulation was at the lesion. After stenting, all stents were deployed without stent edge injury. Lesion calcium (arc > 90°) and protrusion of plaque were also not detected by IVUS.

Reproducibility

For the measurement of lumen CSA, the correlation coefficient between 2 observations by the same observer was 0.99; mean [±SD] difference =

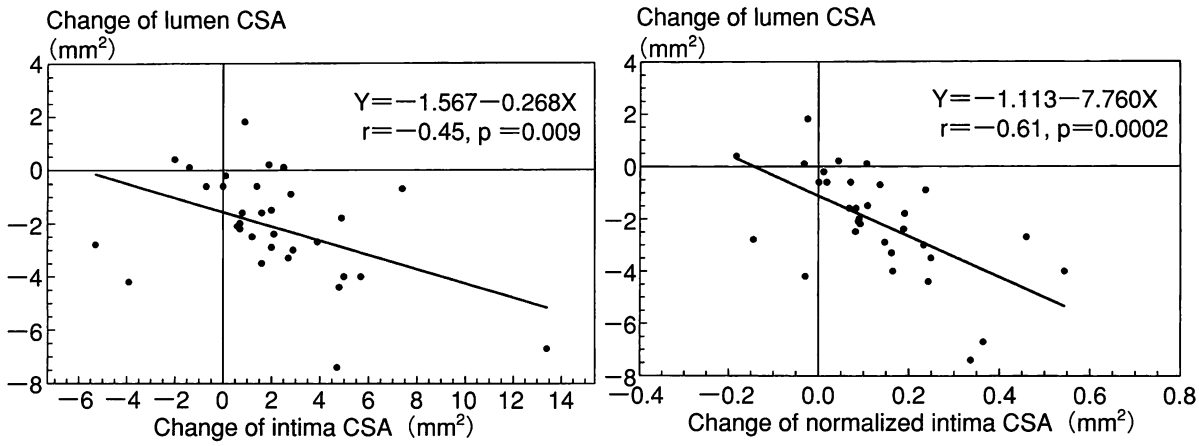

Fig. 4 Loss of lumen CSA correlated with neointimal proliferation (*left*) and normalized neointimal proliferation (*right*)

0.14±0.31 mm. There was no relation between the difference and the mean. Between 2 observers, the correlation coefficient was 0.99; mean [±SD] difference = 0.20±0.20 mm. There was no relation between the difference and the mean.

For the measurement of vessel CSA, the correlation coefficient between 2 observations by the same observer was 0.99; mean [±SD] difference = 0.05±0.3 mm. There was no relation between the difference and the mean. Between 2 observers, the correlation coefficient was 0.99; mean [±SD] difference = 0.22±0.50 mm. There was no relation between the difference and the mean.

For the measurement of the stent CSA, the correlation coefficient between 2 observations by the same observer was 0.99 ; mean [± SD] difference = −0.08±0.20 mm. There was no relation between the difference and the mean. Between 2 observers, the correlation coefficient was 0.99; mean [±SD] difference = −0.13±0.26 mm. There was no relation between the difference and the mean.

Quantitative angiographic results

The minimum lumen diameter increased from 1.07±0.45 mm before stenting to 3.67±0.77 just after stenting, and at follow-up the minimum lumen diameter decreased to 2.39 ± 0.62 mm ($p < 0.0001$; ANOVA). The percentage diameter stenosis decreased from 67 ± 10% before stenting to −8± 10% just after stenting, and increased to 23±18% at follow-up ($p < 0.0001$, ANOVA). There was no angiographic restenosis in any of the 8 cases.

Intravascular ultrasound studies

Lumen loss

Lumen CSA was reduced from 9.8±3.5 to 7.7± 2.7 mm² (mean reduction 2.1 mm², $p < 0.0001$) 6 months after stenting. Stent CSA was reduced from 13.1±4.9 to 11.9±4.6 mm² (mean reduction 1.1 mm², $p < 0.003$) 6 months after stenting, but vessel CSA did not change (16.7±5.3 to 16.7± 5.6 mm²). Intimal thickness was increased from 6.9 ± 3.1 to 9.0 ± 4.0 mm² (mean increase 2.0 mm², $p < 0.0018$) 6 months after stenting (**Fig. 3**). Therefore, neointimal formation but not stent shrinkage accounts for the late loss of lumen CSA. There were single linear correlations between the loss of lumen CSA and neointimal proliferation (**Fig. 4−*left***) and normalized neointimal proliferation (**Fig. 4−*right***).

Neointimal proliferation

The values of stent-to-vessel CSA ratio at 4 stent sites were different in each case (**Fig. 5**). There were no significant differences in vessel CSA, lumen CSA, intima CSA and stent CSA at the 4 stent edges (**Table 1**). Linear regressions of all normalized neointimal proliferations and stent-to-vessel CSA ratio, lumen CSA, stent CSA and vessel CSA at stenting are shown in **Fig. 6−A−D**, respectively. Normalized neointimal proliferation was linearly related to stent-to-vessel CSA ratio at stenting ($r = 0.720$, $p < 0.001$), but not to lumen, vessel and stent CSA at stenting. Neointimal proliferation was also linearly related to stent-to-vessel CSA ratio at stenting ($r = 0.523$, $p < 0.002$; **Fig. 6−E**).

The relationship between normalized neointimal

Table 1 Changes in IVUS findings at poststenting and 6-month follow-up

		Edge 1	Edge 2	Edge 3	Edge 4	*p* value*
Post stenting	Vessel CSA	16.26±5.16	17.71±5.86		15.14±4.72	NS
	Lumen CSA	9.30±3.17	9.88±3.61	9.80±3.67	10.16±3.97	NS
	Intima CSA	6.95±2.53	7.84±3.35	7.91±3.32	4.98±2.90	NS
	Stent CSA	12.56±4.45	13.23±5.58	13.30±5.47	13.16±4.83	NS
	Stent/vessel CSA	0.78±0.12	0.77±0.16	0.77±0.17	0.88±0.22	NS
Follow-up	Vessel CSA	17.06±5.57	17.28±6.36		15.09±4.56	NS
	Lumen CSA	7.91±2.55	7.39±2.26	7.99±3.45	7.60±2.86	NS
	Intima CSA	9.15±3.99	9.90±5.00	9.30±4.62	7.45±2.08	NS
	Stent CSA	12.34±4.69	11.35±3.67	12.01±5.44	12.00±5.15	NS
Change	Vessel CSA	0.80±1.85	−0.43±4.10		−0.05±1.45	NS
	Lumen CSA	−1.65±2.15	−2.43±2.21	−1.81±1.30	−2.56±2.40	NS
	Intima CSA	2.20±2.24	2.06±5.10	1.39±3.90	2.48±1.80	NS
	Stent CSA	−0.23±0.19	−1.88±2.73	−1.29±0.25	−1.16±0.43	NS

*Determined by ANOVA.

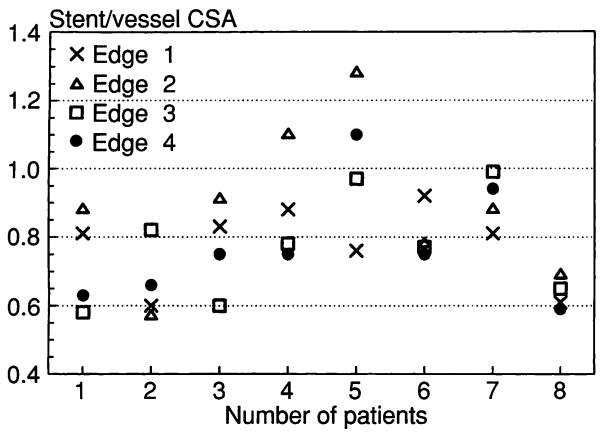

Fig. 5 Plot of stent to vessel CSA ratio in each case

proliferation and stent-to-vessel CSA ratio was analyzed separately at the proximal and distal stent edges (Edges 1+4) and at stent edges facing the articulation (Edges 2+3). The response of neointimal proliferation to stent-to-vessel CSA ratio at the proximal and distal stent edge sites was equal to that at the edges facing the articulation site (**Fig. 7**).

From the linear regression analysis of normalized neointimal proliferation and stent-to-vessel CSA, minimal neointimal proliferation was extrapolated to occur at a stent-to-vessel CSA ratio of 0.7 (intercept at 0 of normalized neointimal proliferation in **Figs. 6−A, 7**).

Stent shrinkage

Overall stent CSA was reduced from 13.1±4.9 to 11.9±4.6 mm^2 ($p = 0.003$) 6 months after stenting. The stent CSA was reduced at follow-up, but the stent shrinkage was not a function of neointimal proliferation.

DISCUSSION

The present study tested the hypothesis that higher vessel stretch by stenting accelerates increased intimal hyperplasia in human coronary arteries after stenting, and found that a higher stent-to-vessel CSA ratio at stenting resulted in more neointimal proliferation at follow-up 6 months after stenting. Thus, the hypothesis is supported.

Serial quantitative coronary angiography is used to assess the progression and regression of coronary artery disease after drug interventions[20]. However, coronary angiography is insensitive to identify atheroma and cannot characterize vessel components[21,22]. Intracoronary ultrasound can reveal an atherosclerotic lesion not detected angiographically, and can measure the components of the arterial wall offering the potential for precise quantitative assessment of disease progression on serial examination[23]. Investigators have used a number of techniques to improve the reproducibility of imaging at the same site twice at intervals of several months to over a year. These include picture recordings of both fluoroscopic and ultrasound images on the same videotape, drawings and photos of the initial angiogram indicating the location of the radiopaque catheter tip for each imaging site, and noting the

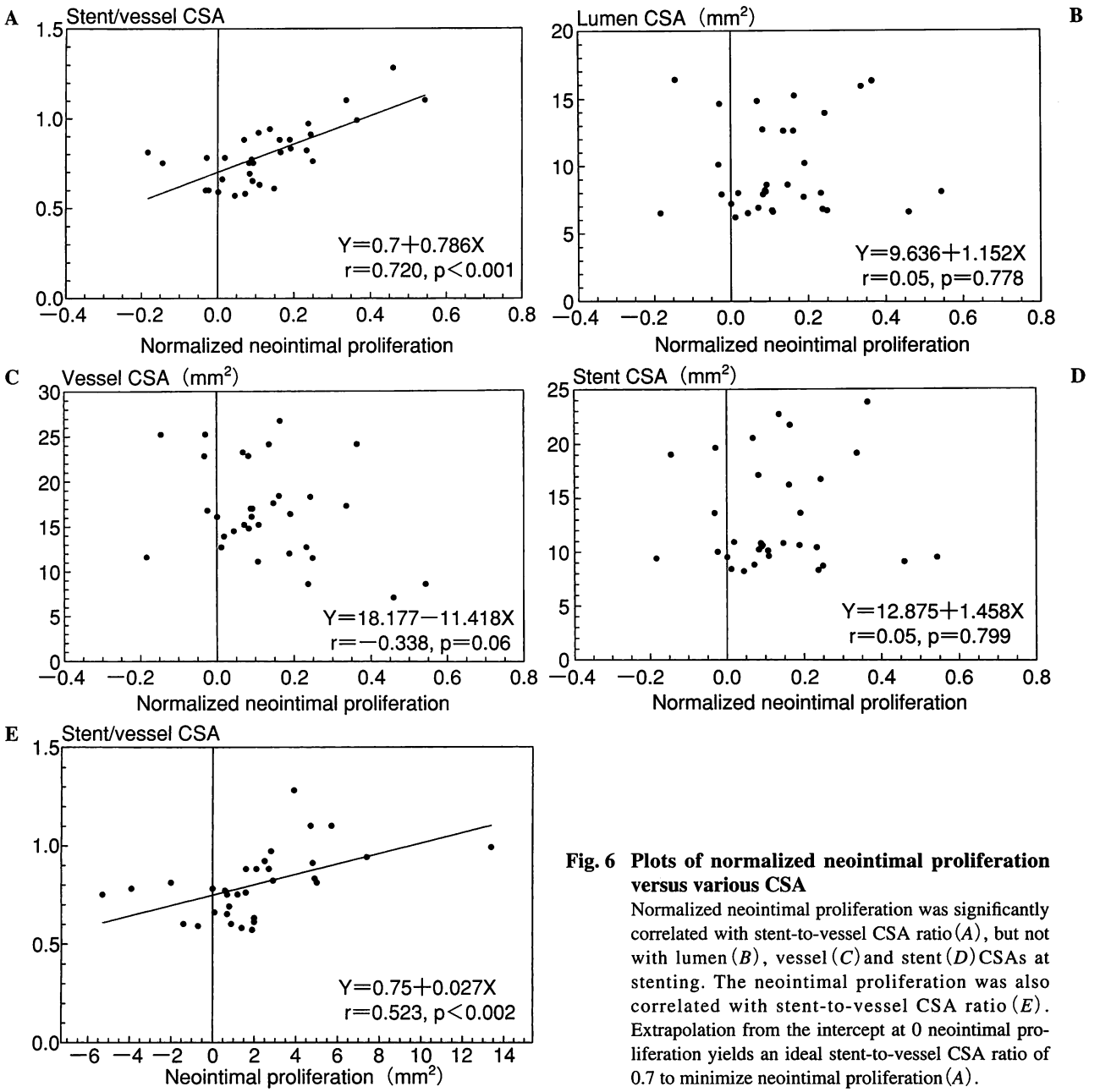

Fig. 6 Plots of normalized neointimal proliferation versus various CSA

Normalized neointimal proliferation was significantly correlated with stent-to-vessel CSA ratio (*A*), but not with lumen (*B*), vessel (*C*) and stent (*D*) CSAs at stenting. The neointimal proliferation was also correlated with stent-to-vessel CSA ratio (*E*). Extrapolation from the intercept at 0 neointimal proliferation yields an ideal stent-to-vessel CSA ratio of 0.7 to minimize neointimal proliferation (*A*).

location of the imaging transducer within a segment defined by side branches established as landmarks. After stenting of a Palmaz-Schatz stent, stent struts are clearly identified by IVUS. Replication of imaging sites is aided by noting the proximal and distal stent edges and those facing the articulation site. Matching of stent edge sites on the second examination is easily achieved by visual inspection and is accurate when the observation site is defined at 4 previous stent edges. Therefore, the reproducibility of imaging the same site twice at an interval of half a year is very high.

Lumen and vessel CSAs are usually measured in IVUS studies of indigenous coronary arteries because the sonolucent zone reported to represent the media is relatively clear and the border between the adventitia and surrounding connective tissue is difficult to differentiate. After stenting, the sonolucent zone usually becomes unclear at the stented site. Therefore, vessel CSA was measured at the reference vessel just adjacent to the stent edge and central articulation site.

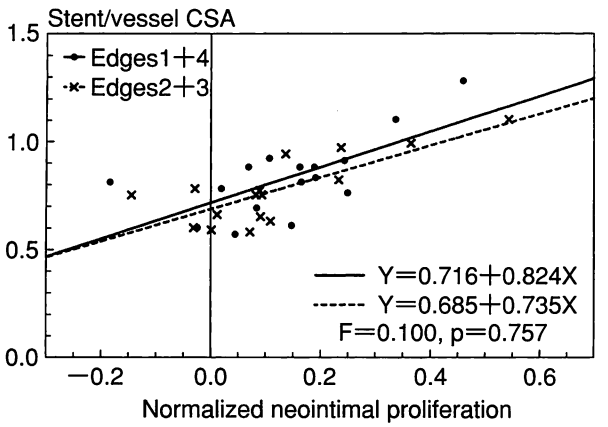

Fig. 7 Plots of normalized neointimal proliferation versus stent-to-vessel CSA ratio for lesions treated with stents at the proximal and distal stent edges (Edges 1 and 4) and the stent edges facing the articulation (Edges 2 and 3)

Extrapolation from the intercept at 0 neointimal proliferation (*x*-axis) yields an ideal stent-to-vessel CSA ratio of 0.7 to minimize neointimal proliferation.

To test intra- and inter-observer variability for the measurement of lumen, vessel and stent CSAs, the difference between 2 measurements were plotted against their means[24]. Ninety-five percent of the differences lay between 2SD and there were no obvious relationships between the differences and the means. Thus, the measurements are considered to be reproducible and reliable.

Lumen loss

After balloon angioplasty or stenting, intimal smooth muscle proliferation followed by an increase of extracellular matrix resulted in intimal hyperplasia[6-9]. Extracellular matrix production was seen without an increase in cell number in restenotic lesions several months after stenting. Clinical and pathological studies showed the lumen loss and in-stent restenoses were the result of neointimal tissue proliferation, not of vessel and stent remodeling[5,6]. In our study, the lumen was reduced by 2.1 mm^2 (mean) and neointimal hyperplasia increased by 2.0 mm^2 (mean). On the other hand, stent CSA decreased by only 1.1 mm^2 and vessel CSA was unchanged. Since anticoagulant therapy was continued for 6 months until the follow-up IVUS study, thrombus did not seem to be a possible cause of lumen loss. Therefore, our results also indicate that the lumen loss after stenting is the result of neointimal hyperplasia, not vessel remodeling.

Stent-to-vessel CSA ratio

Leung *et al.*[17] cultured aortic medial smooth muscle cells on an elastin membrane suspended in culture medium and coupled to an apparatus that was subjected to stretch stimulation. They found that the stretching stimulation accelerated the synthesis of extracellular matrix, such as collagen and mucopolysaccharide. Beatt *et al.*[18] reported clinically that the principal determinants of restenosis were found to be a large improvement in the minimum lumen diameter at balloon angioplasty, and suggested that the degree of mechanical stretch produced by the dilating balloon on the vessel stimulated the restenosis process. At stenting, the stented vessel is usually dilated at a pressure of 12 to 20 atm and is sometimes overstretched. Therefore, vessels exposed for long periods to stretch stimulation by stent develop intimal hyperplasia. Greater stretching of the vessel may lead to more intimal hyperplasia.

In an animal restenosis model using swine, Karas *et al.*[25] reported that the degree of intimal proliferation is more prominent after stenting than after balloon injury. They speculated that prominent intimal proliferation occurred after stenting because stenting induced more uniformly severe vascular injury. Schwartz *et al.*[6] evaluated the extent of vascular injury quantitatively after stenting in a swine coronary artery, and obtained a histopathologic score proportional to injury depth at the stent wire site. They found that the deeper vessel injury at adjacent stent wires resulted in a more prominent neointimal proliferation. IVUS could reveal the stent strut positioning in the view of a cross-sectional coronary artery and the stent-to-vessel CSA ratio could be measured. The more the vessel was dilated by stent struts, the deeper might be the vessel injury. Therefore, the stent-to-vessel CSA ratio derived from IVUS imaging may reflect the degree of vascular injury. However, at present IVUS does not have enough resolution to evaluate vascular injury or injury depth caused by stent struts.

Previous angiographic and IVUS studies suggest an increased proliferative response at the central articulation[19,26]. However, Nakamura *et al.*[27] and Hoffmann *et al.*[5] reported that angiography overestimated lumen diameter at articulation and late lumen diameter loss, as compared to IVUS. The proliferative response was not much greater at the

central articulation than at the edges and bodies of the stent. We found that neointima increased as the stent-to-vessel CSA ratio increased at follow-up, and this proliferative response was the same at all stent edges. We also found that minimal neointimal proliferation after stenting is associated with a stent-to-vessel CSA ratio of 0.7. Thus, the optimal degree of vessel stretch stimulation or vascular injury and good stent apposition that minimizes potential impairment to flow appears to be achieved at a ratio of 0.7.

We measured the stent-to-vessel CSA ratio at 4 points within the stent, *i.e.*, distal and proximal stent edges and both sides of the stent edges facing the articulation, and the 4 values of this ratio within the same stent were different retrospectively. Even if the stent CSA was uniformly dilated from proximal to distal stent sites after stenting, such variation would occur due to the nature of arterial anatomy (narrowing of a vessel diameter from the proximal to the distal end), and to the remodeling of the vessel diameter at a stenotic lesion. The frequency of restenosis at articulation can be explained by reverse remodeling (shrinkage of vessel diameter at articulation) contributing to a greater stent-to-vessel CSA ratio compared with stent edges and resulting in a prominent proliferative response of neointima.

Stent shrinkage

In contrast to other reports that stent diameter or stent volume did not change at follow-up[5,28], we found (in support of Bonner *et al.*[29]) that stent CSA reduced 6 months after stenting. The degree of stent shrinkage was related to stent CSA just after stenting, not to the extent of neointimal proliferation. The mechanical radial pressure to compress the dilated stent is not equal throughout the dilated diameter of a Palmaz-Schatz stent, from 3.0 to 6.0 mm. Less pressure is required to compress the stent as the dilated stent diameter becomes larger (data provided by Johnson & Johnson Interventional Systems). The radial force to compress a stent with a diameter of 3.0 mm (about 10 psi) is almost twice that required for a 6.0 mm diameter stent (about 5 psi). In our results, the stent was also more reduced as stent dilation increased. The stent diameter calculated from IVUS data varied from 3.2 to 5.4 mm and mean stent CSA was 1.3 times greater than that in other reports. Therefore, the fragility of a stent to radial compression may be related to the shrinkage of stent at follow-up. Although the source of the radial force is unknown, vasoconstriction is a candidate since stent shrinkage itself does not seem to account for the late lumen loss.

Limitation

Patients with restenosis after stenting were not enrolled in this study. The reason for this exclusion is that when in-stent restenosis occurs, the angiographical minimum lumen diameter is around 1.0 mm whereas the diameter of the IVUS catheter is about 1.16 mm (3.5F). Thus, in cases of restenosis after stenting, the IVUS catheter is too close to the vessel lumen to visualize the intimal leading edge by the near field effect. Further, advance of the IVUS catheter to the stenotic lesion pushes the intimal hyperplasia aside so that the lumen CSA is overestimated. For the evaluation of the intimal thickness, it is necessary to visualize clearly the inner leading edge of lumen. In our study, the minimum lumen diameter by IVUS was 1.9 mm, which contributes to achieving a clear inner leading edge.

Hoffmann *et al.*[5] reported that vessel CSA at the stent site was unchanged at follow-up, but reference vessel CSA progressively increased at distances from the edges of the stent. We measured vessel CSA just adjacent to the stent edge as a reference vessel CSA was unchanged at follow-up. Therefore, the vessel CSA just adjacent to the stent edge reflects the vessel CSA at the stent site.

Finally, though the statistical significance is high, the number of patients in the present study is rather small, perhaps too small to firmly conclude that there is a predisposition to neointimal proliferation as the stent-to-vessel CSA ratio increases and that the ideal stent-to-vessel CSA ratio is 0.7. Therefore, we consider the results of the present study to be highly suggestive, and recognize that further work is both needed and warranted.

要　約

ステント血管断面積比が内膜新生に及ぼす影響：血管内エコー法による検討

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血管壁の伸展が内膜新生を促進することが実験的に報告されている．そこで血管壁伸展度をステント血管断面積比で表し，内膜新生に及ぼす影響についてPalmaz-Schatzステント植え込み例で検討した．

Palmaz-Schatzステント植え込み直後と6ヵ月後で血管内エコー法を施行し，かつ再狭窄を認めない狭心症8例を対象とした．測定はステント端部4ヵ所で行い，合計32ヵ所で計測を行った．血管壁伸展度は，ステント端に隣接する対象血管断面積に対するステント端部でのステント断面積との比で表した．ステント端部の血管内腔断面積と同部位の対象血管内腔断面積の差から内膜断面積を求め，内膜断面積を対象血管断面積で除したものを内膜肥厚度とした．ステント植え込み直後と6ヵ月後の内膜断面積および内膜肥厚度の差をそれぞれ新生内膜，新生内膜肥厚度として求めた．血管造影上，ステント植え込み前，直後，6ヵ月後の最小血管径はそれぞれ1.07±0.45，3.67±0.77，2.39±0.62mm，％血管径狭窄度は67±10%，−8±10%，23±18%であった．血管内腔断面積と新生内膜はステント植え込み直後と6ヵ月後でそれぞれ平均2.1 mm^2減少，2.0 mm^2増加し，血管内腔断面積の変化は新生内膜の変化度と負の相関関係があった．新生内膜および新生内膜肥厚度とステント/血管断面積比との関係では，それぞれ$r=0.523$，$p<0.002$；$r=0.720$，$p<0.001$の正相関が得られたが，その関係はステントの部位による差としては認められなかった．

以上から，ステント/血管断面積比が大きいほど内膜新生は促進されることが示唆された．

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