J Cardiol 2007 Jun; 49(6): 313–321

Impact of Highly Asymmetric Stent Expansion After Sirolimus-Eluting Stent Implantation on Twelve-Month Clinical Outcomes

Masatsugu NAKANO, MD
Kenji WAGATSUMA, MD
Atsushi IGA, MD
Hideo NII, MD
Hideo AMANO, MD
Mikihito TODA, MD
Junichi YAMAZAKI, MD, FJCC*

Abstract

Objectives. This study investigated the impact of highly asymmetric stent expansion after sirolimus-eluting stent (SES) implantation on clinical outcomes from post procedure to 12 months later.

Methods. Subjects were 118 patients with 171 lesions who underwent SES implantation for angina pectoris and were studied by intravascular ultrasound (IVUS) following the procedure. The stent symmetry index (minimal stent diameter/maximal stent diameter) at the minimal stent area was calculated by IVUS analysis. The patients were divided into two groups for comparative study: those with stent symmetry index ≥ 0.7 were classified into the optimal (O) group (93 patients; 145 lesions, mean age 66 ± 12 years) and those with stent symmetry index < 0.7 were the sub-optimal (S) group (25 patients; 26 lesions, mean age 67 ± 10 years).

Results. Angiographic follow up after 8 months showed no differences in target lesion revascularization (TLR) (O group: 3.1% vs S group: 3.8%, $p = 0.833$). Multivariate analysis identified the post minimal stent diameter as the independent predictor of TLR ($p = 0.038$). The stent symmetry index < 0.7 was not a predictor of TLR ($p = 0.887$). Clinical outcomes after 12 months showed both groups had 0% stent thrombosis and there were no differences in deaths (O group: 2.1% vs S group: 4.0%, $p = 0.602$).

Conclusions. Highly asymmetric stent expansion after SES implantation may not have a negative impact on clinical outcomes at 12 months.

J Cardiol 2007 Jun; 49(6): 313–321

Key Words
■ **Coronary artery disease** ■ **Stent** ■ **Intravascular ultrasound** ■ **Prognosis**

INTRODUCTION

Some randomized trials such as the SIRIUS trial have indicated that the sirolimus-eluting stent (SES) reduces the rate of in-stent restenosis (ISR) and target lesion revascularization (TLR) compared to the bare metal stent (BMS). However, TLR still occurs after SES implantation at a rate of 4–5%.[1–3] Previous studies have shown that highly asymmetric stent expansion after BMS implantation with a symmetry index < 0.7 is generally associated with stent underexpansion and that such sub-

東邦大学医療センター大森病院循環器センター 心血管インターベンション室，*内科：〒143–8541 東京都大田区大森西6–11–1
Division of Interventional Cardiology, *Department of Internal Medicine, Cardiovascular Center, Toho University Omori Medical Center, Tokyo
Address for correspondence: NAKANO M, MD, Division of Interventional Cardiology, Cardiovascular Center, Toho University Omori Medical Center, Omori-nishi 6–11–1, Ota-ku, Tokyo 143–8541; E-mail: toho 9686@lily.ocn.ne.jp
Manuscript received December 28, 2006; revised January 25 and March 12, 2007; accepted March 19, 2007

optimal stent expansion is a risk factor for increased incidence of stent thrombosis and ISR.[4–7] In addition, an *in vitro* study has reported that optimization of drug distribution for stent-based delivery requires symmetric expansion of the stent with homogeneous distribution of the struts, suggesting the importance of achieving symmetric expansion after stent implantation for drug eluting stents as well.[8] However, much is still unknown about the impact of highly asymmetric SES expansion on clinical outcomes.

The present study investigated the impact of highly asymmetric stent expansion after SES implantation on clinical outcomes from post procedure to 12 months later.

SUBJECTS AND METHODS

Subjects

A total of 162 consecutive patients with 298 lesions underwent SES implantation for angina pectoris at our institution from April 2004 to October 2005. This study included 118 patients with 171 lesions who underwent intravascular ultrasound (IVUS) following percutaneous coronary intervention (PCI). The subjects were classified into two groups: those with stent symmetry index ≥ 0.7 at the minimal stent area (MSA) site from IVUS observations formed the optimal or O group (93 patients, 145 lesions) and those with stent symmetry index < 0.7[4] formed the sub-optimal or S group (25 patients, 26 lesions). A retrospective study compared the 12-month clinical outcomes.

One hundred twenty-seven lesions that were not studied by IVUS after the procedure were excluded for the following reasons: target lesion with no coronary dissection in coronary angiography(CAG) following SES implantation in PCI for a type A lesion;[9] side branches of true bifurcated lesions in which stent implantation was conducted for both main vessel and side branches; angiographical slow flow/no-reflow[10] after stent implantation; and the IVUS catheter was unable to cross over the lesion site.

Procedure and antiplatelet therapy

All subjects underwent SES implantation after pre-dilation. Determination of stent size and length was left to the discretion of the operator, and dilation was, in principle, performed under maximum inflation pressure of 16 atm or more. Antiplatelet therapy was oral dosage of aspirin 81 or 100 mg/day and ticlopidine 200 mg/day from at least 1 week prior to the procedure, and these agents were continued after the procedure for the lifetime of the patient.

Angiographic analysis

CCIP310 (Catex Co. Ltd.) was used to conduct quantitative coronary angiography (QCA) for calculation of lesion site, reference diameter, minimal lumen diameter (MLD), and percentage diameter stenosis (%DS). Follow-up CAG was performed at a mean of 7.9 ± 1.8 months after the procedure, with binary restenosis within the lesion defined as %DS $\geq 50\%$ including the 5 mm vessel segments proximal and distal to the stented segment. Late loss was calculated by subtracting the follow-up MLD from the post MLD.[2]

Analysis of IVUS images

IVUS studies used a Avanar catheter (Volcano Co. Ltd.) with the lesion observed at 0.5 mm/sec using the auto pull back system. IVUS images were recorded on s-VHS video tape, captured on Netra IVUS (ScImage Co. Ltd.) and analyzed off-line.[11,12] Using Netra IVUS Dual Roy automatic analysis, the minimal lumen or stent diameter, maximal lumen or stent diameter, external elastic membrane cross-sectional area (EEM-CSA), lumen-CSA, plaque-CSA (EEM-CSA minus lumen-CSA) were measured at the MSA site as well as the proximal and distal reference segments.[13] The stent symmetry index at the MSA site was calculated by dividing the minimal stent diameter by the maximal stent diameter (**Fig. 1**).[4] Stent expansion ratio was calculated by dividing the MSA by the average reference lumen CSA.[4] Lesion calcification was diagnosed when IVUS revealed echoes brighter than that of the reference adventitia along with acoustic shadowing in the back.[14]

Other parameters related to IVUS finding

The incidence of calcified lesions behind the stent strut at the MSA site was obtained because stent asymmetrical expansion is caused by calcification in the target lesion.[15] In addition, the mean stent expansion ratio of lesions with stent thrombosis after SES implantation is 0.65,[16] so the incidence in lesions with stent expansion ratio < 0.65 was also obtained.

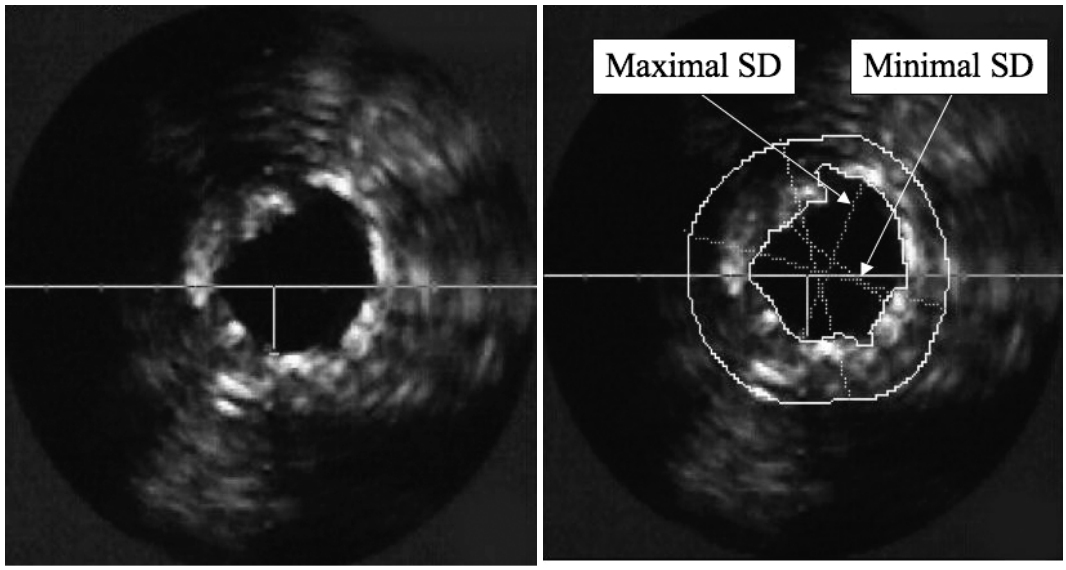

Fig. 1 Calculation of stent symmetry index
Results from NETRA IVUS Dual Roy automatic analysis.
Minimal SD = 2.1 mm, Maximal SD = 3.1 mm, symmetry index = 0.68.
IVUS = intravascular ultrasound; SD = stent diameter.

Statistical analysis

Statistical analysis was performed with StatView 5.0 (SAS Institute Co. Ltd.). Data are presented as frequencies or mean ± SD. Continuous variables were compared by the unpaired students *t*-test, and categorical variables were compared by the χ^2 test.[13] To identify factors related to TLR after SES implantation, logistic regression analysis was used. The variables of univariate logistic regression analysis were determined by referring to the predictors for TLR indicated in previous reports.[17,18] Values of $p < 0.05$ were considered statistically significant. Univariate variables with $p < 0.5$ and the stent symmetry index < 0.7 were entered into the multivariate model to find independent predictors of TLR.[19]

RESULTS

Patient characteristics

No differences existed between the two groups in age, sex, coronary risk factors, ejection fraction, and ratio of subjects discontinuing ticlopidine within 3 months following the procedure, but compared to the O group, the S group had a significantly higher rate of multivessel disease (O group: 72.0% vs S group: 100%, $p = 0.003$; **Table 1**).

Table 1 Patient characteristics

	O group (n=93)	S group (n=25)	p value
Age (yr)	66±12	67±10	0.703
Male	82 (88.1)	24 (96.0)	0.250
Coronary risk factors			
Diabetes mellitus	47 (50.5)	12 (48.0)	0.821
Hypertension	54 (58.1)	17 (68.0)	0.368
Hyperlipidemia	40 (43.0)	8 (32.0)	0.319
Current smoking	46 (49.4)	13 (52.0)	0.822
Ticlopidine off	9 (9.7)	2 (8.0)	0.597
Multivessel disease	67 (72.0)	25 (100)	0.003
Ejection fraction (%)	61±12	60±12	0.712

Continuous values are mean±SD. ( ): %.
O = optimal; S = sub-optimal; Ticlopidine off = patients discontinuing ticlopidine within 3 months after the procedure.

Angiographical and procedural characteristics

There was no difference in target lesions of the two groups, but there were significantly more Type B2 or C lesions in the S group compared to the O group (O group: 69.0% vs S group: 92.3%, $p = 0.014$). Regarding lesion morphology, there were significantly more calcified lesions in the S group compared to the O group (11.7% vs 30.7%, $p =$

Table 2 Angiographic and procedural characteristics

	O group ($n=145$)	S group ($n=26$)	p value
Target vessel			
Left main coronary artery	3(2.1)	0	0.459
Left anterior descending artery	80(55.2)	14(53.8)	0.900
Right coronary artery	36(24.8)	7(27.0)	0.661
Left circumflex artery	26(17.9)	5(19.2)	0.236
ACC/AHA classification			
Type B2 / C	100(69.0)	24(92.3)	0.014
Lesion morphology			
Chronic total occlusion	16(11.0)	3(11.5)	0.940
Calcification	17(11.7)	8(30.7)	0.011
Diffuse	67(46.2)	18(69.2)	0.031
QCA analysis			
Reference diameter (mm)	3.0±0.4	3.1±0.5	0.100
Pre minimal lumen diameter (mm)	0.83±0.43	0.77±0.32	0.411
Post minimal lumen diameter (mm)	2.99±0.49	2.74±0.24	<0.001
Pre% diameter stenosis (%)	74.3±11.2	73.6±10.3	0.767
Post% diameter stenosis (%)	3.2±14.5	5.5±16.1	0.465
Strategy of stenting			
Stent size (mm)	3.0±0.3	3.0±0.4	0.119
Stent length (mm)	26.1±10.8	29.4±17.2	0.352
Maximal inflation pressure (atm)	17.9±2.1	17.4±2.7	0.287
Stent connecting	35(24.1)	10(38.4)	0.260
Post dilation	58(40.0)	12(46.1)	0.557
Use of rotational atherectomy	6(4.1)	1(3.8)	0.945

Continuous values are mean±SD. ( ) : %.
ACC/AHA=American College of Cardiology/American Heart Association; QCA=quantitative coronary angiography; Stent connecting=cases of stent implantation by adjoining two or more stents. Other abbreviations as in Table 1.

0.011) and diffuse lesions (46.2% vs 69.2%, $p=0.031$). Post MLD from QCA analysis was significantly lower in the S group compared to the O group (2.99 ± 0.49 vs 2.74 ± 0.24 mm, $p<0.001$). There was no significant difference between the two groups in strategy of stenting (**Table 2**).

Post procedure IVUS analysis

Minimal stent diameter (O group: 2.51 ± 0.45 vs S group: 2.06 ± 0.31 mm, $p<0.001$) and lumen CSA (6.6 ± 2.0 vs 5.7 ± 1.6 mm, $p=0.031$) at the MSA site was significantly smaller in the S group compared to the O group. The S group also had a significantly lower stent expansion ratio (0.91 ± 0.22 vs 0.76 ± 0.27, $p=0.002$) and a significantly higher incidence of stent expansion ratio <0.65 (8.2% vs 30.1%, $p=0.001$). The incidence of calcified lesions behind the stent strut was significantly higher in the S group than the O group (42.1% vs 100%, $p<0.001$; **Table 3**).

Eight-month angiographic results

Follow-up CAG was performed in 131 lesions (90.3%) of the O group and 26 lesions (100%) of the S group. Follow-up MLD from QCA analysis was significantly lower in the S group compared to the O group (O group: 2.89 ± 0.63 vs S group: 2.57 ± 0.67 mm, $p=0.020$). No significant difference existed between the two groups in rate of TLR (3.1% vs 3.8%, $p=0.833$), and late loss (0.10 ± 0.51 vs 0.17 ± 0.49, $p=0.514$; **Table 4**).

Table 3 Post procedure intravascular ultrasound findings

	O group ($n=145$)	S group ($n=26$)	p value
Reference proximal site			
EEM CSA (mm^2)	19.7±5.5	1.5±5.7	0.128
Lumen CSA (mm^2)	8.3±2.7	9.7±3.9	0.089
Plaque CSA (mm^2)	11.3±4.1	11.9±2.8	0.358
Minimal stent area site			
Minimal stent diameter (mm)	2.51±0.45	2.06±0.31	<0.001
Maximal stent diameter (mm)	3.08±0.50	3.12±0.53	0.710
EEM CSA (mm^2)	17.9±5.1	16.9±3.6	0.231
Lumen CSA (mm^2)	6.6±2.0	5.7±1.6	0.031
Plaque CSA (mm^2)	11.3±4.0	11.2±2.8	0.877
Reference distal site			
EEM CSA (mm^2)	14.4±5.4	13.9±5.8	0.668
Lumen CSA (mm^2)	6.8±2.9	6.7±2.6	0.870
Plaque CSA (mm^2)	7.6±3.7	7.2±4.2	0.620
Stent symmetry index	0.81±0.05	0.63±0.04	<0.001
Stent expansion ratio	0.91±0.22	0.76±0.27	0.002
Stent expansion ratio< 0.65	12 (8.2)	8 (30.1)	0.001
Calcification behind struts at MSA site	61 (42.1)	26 (100)	<0.001

Continuous values are mean±SD. ( ) : %.
EEM=external elastic membrane; CSA=cross-sectional area; MSA=minimal stent area. Other abbreviations as in Table 1.

Table 4 Eight-month angiographic results

	O group	S group	p value
Number of follow-up lesions	131	26	
Binary restenosis	5 (3.8)	1 (3.8)	0.994
Target lesion revascularization	4 (3.1)	1 (3.8)	0.833
QCA analysis			
Minimal lumen diameter (mm)	2.89±0.63	2.57±0.67	0.020
Late loss (mm)	0.10±0.51	0.17±0.49	0.514

Continuous values are mean±SD. ( ) : %.
Abbreviations as in Tables 1, 2.

Table 5 Univariate logistic regression analysis for prediction of target lesion revascularization

	Odds ratio	95% CI	p value
Male	0.69	0.77 − 6.20	0.740
Diabetes mellitus	8.33	0.95 − 51.4	0.087
Multivessel disease	1.61	0.18 − 8.87	0.672
Stent length	1.04	0.94 − 1.06	0.664
Reference diameter	0.27	0.04 − 1.93	0.490
Post minimal stent diameter	0.09	0.01 − 0.82	0.031
Minimal stent area	0.61	0.33 − 1.13	0.119
Symmetry index< 0.7	1.41	0.15 − 13.1	0.763
Stent expansion< 0.65	1.64	0.15 − 13.2	0.666

CI=confidence interval.

Multivariate logistic regression analysis for prediction of TLR showed post minimal stent diameter as measured by IVUS was an independent predictor for TLR ($p=0.038$). Symmetry index < 0.7 was not a predictor for TLR ($p=0.887$; **Tables 5, 6**).

Twelve-month clinical outcomes

Clinical follow-up at 12 months after SES implantation was possible for all subjects. The incidence of stent thrombosis and cardiac death during the observation period was 0% for both groups. Two patients (2.1%) in the O group died of lung fibrosis and lung cancer. One patient (4.0%) died of cerebral infarction in the S group. There was no difference between the two groups in the incidence of non-cardiac death (**Table 7**).

Table 6 Multivariate logistic regression analysis for prediction of target lesion revascularization

	Odds ratio	95% CI	*p* value
Post minimal stent diameter	0.05	0.003 − 0.85	0.038
Diabetes mellitus	7.45	0.79 − 71.0	0.077
Minimal stent area	0.93	0.45 − 1.92	0.845
Symmetry index＜0.7	1.27	0.11 − 14.1	0.887
Reference diameter	0.84	0.07 − 10.8	0.893

Abbreviation as in Table 5.

Table 7 Twelve-month clinical outcomes

	O group	S group	*p* value
Number of follow-up patients	93	25	
Stent thrombosis	0	0	
Acute myocardial infarction	0	0	
Cardiac death	0	0	
Non-cardiac death	2(2.1%)	1(4.0%)	0.602

Abbreviations as in Table 1.

DISCUSSION

Relationship between highly asymmetric stent expansion and stent restenosis

Compared to BMS, SES considerably reduces neointimal hyperplasia after stent implantation.[1, 20] ISR is still evident, however, with a greater focal pattern of restenosis compared to BMS.[21] Several studies have reported that stent fracture or nonuniform strut distribution may be associated with a decrease in local drug delivery and that this may affect the incidence of in-stent restenosis after SES implantation.[19, 22] An *in vitro* study similarly reported that local drug underdosing occurred at sites of nonuniform circumferential stent strut distribution.[8] Such outcomes suggest that remarkable asymmetrical SES expansion would trigger an increase of local neointimal hyperplasia by drug underdosing and may cause stent restenosis.

A study on the association between longitudinal and tomographic asymmetric stent expansion after SES implantation and neointimal hyperplasia reported that asymmetric stent expansion did not seem to affect suppression of neointimal hyperplasia.[23] However, the minimum symmetry index in this study was 0.73, and the asymmetry group was defined as having symmetry index＜ 0.86. This was higher than the symmetry index indicated in the previous studies as a risk factor for ISR or SAT.[4−6] In contrast, our study was conducted on lesions with a higher degree of local asymmetric stent expansion. However, we did not find any significant differences in late loss or binary restenosis rate. Moreover, nonuniform strut distribution correlates with more neointimal hyperplasia after SES implantation, but the mean stent symmetry index of the restenosis group(mean symmetry index = 0.88) was higher than the mean stent symmetry index of our O group(mean symmetry index = 0.81), which revealed no significant difference in comparisons with that of their no-restenosis group.[19] This result suggests that asymmetric stent distortion may not necessarily be associated with nonuniform strut distribution.

Several reasons why asymmetric SES implantation may not promote stent restenosis can be surmised: sufficient drug concentration to suppress neointimal hyperplasia although variation in local drug concentration occurs through distortion of the stent within the coronary artery blood flow; no occurrence of local drug underdosing unless distortion of the stent struts is greater than asymmetrical distortion or unless stent fracture results; and a large volume of neointimal hyperplasia is induced following completion of sirolimus release after 3 months post procedure due to an oversensitive inflammatory reaction originating from the presence of metal struts and polymer, which is unrelated to stent asymmetry.[19,23,24]

Low values in post minimal stent diameter and post minimal lumen-CSA are, as for BMS, predictors of ISR or TLR after SES implantation as revealed by QCA or IVUS analysis.[25−27] In addition, as full lesion coverage strategy is recommended for SES implantation,[2,3] the total length of the stent has increased. As a result, long stent length is an ISR or TLR predictor specific to SES.[18,25] A study of 670 native coronary artery lesions treated with SES showed that the IVUS cut-offs that best predicted angiographic restenosis after SES implantation were minimal lumen-CSA = 5.5 mm^2 and stent length = 40 mm. In subjects satisfying the criteria of lumen-CSA ＞ 5.5 mm^2 and a stent length ＜ 40 mm, the restenosis rate was extremely low at 0.4%.[27] In the present study, post minimal stent diameter was identified as a TLR predictor, but although the mean post minimal stent diameter was significantly smaller in the S group compared to the O group, no difference appeared in the TLR rate

between the two groups. The reasons may involve a mean stent length of 40 mm or less and a mean minimal lumen-CSA of 5.5 mm^2 or more in the S group. From these results, we speculate that TLR could be avoided even in cases of highly asymmetrical SES expansion if a minimal lumen-CSA is achieved after the procedure and if the total length of the stent is not excessive.

Relationship between highly asymmetric stent expansion and stent thrombosis

Many studies have widely recognized that stent asymmetrical expansion occurs due to calcification in the target lesion,[15, 28, 29] and calcification behind the stent strut at MSA was observed in all cases in the S group. What is more, calcification in the target lesion not only causes stent asymmetrical expansion, but also reduces luminal gain after stent implantation and causes stent underexpansion.[23] The current study also showed the stent expansion ratio of the S group to be significantly lower than that of the O group. Stent underexpansion after SES implantation is a risk factor for stent thrombosis after the procedure and the mean stent expansion ratio in cases of stent thrombosis was 0.65.[16] In the current study, there were a total of 20 lesions with stent expansion ratio < 0.65, but the incidence of stent thrombosis in 12 months after the procedure was 0%. However, a high volume study reported that the incidence of stent thrombosis after SES implantation occurring within 12 months after the procedure was 1% or less,[30, 31] so the incidence of stent thrombosis was not high. Therefore, it is likely that we did not unexpectedly encounter stent thrombosis in patients with stent underexpansion due to the small number of subjects in the present study. Moreover, stent underexpansion, residual stenosis, edge dissection, low MSA values and other indicated predictors of sub-acute stent thrombosis (SAT) within 30 days after BMS implantation were confirmed by IVUS to be present in many of the patients who had SAT after the SES procedure.[32–34] Therefore, it is believed that there are no large differences in risk factors for SAT between SES and BMS.

In contrast, a few reports suggested that there was no specific IVUS findings in cases with late angiographic stent thrombosis (LAST) occurring in the period after 30 days.[33–35] Furthermore, the causes of LAST may consist of delayed coronary artery healing and other clinical and procedural risk factors,[36, 37] suggesting that LAST events may occur even after optimal stent implantation. As many studies indicate that the termination of anti-platelet therapy is a risk factor for LAST,[30,35,38] anti-platelet therapy should be continued for as long as possible regardless of whether stent implantation was optimal or sub-optimal and to conduct long-term, close observation of progress.

Study limitations

The current investigation was conducted only on patients undergoing IVUS study after the procedure. Also, IVUS findings were not observed in the chronic period. The number of cases studied was small in this single-center non-randomized retrospective study.

CONCLUSIONS

Highly asymmetric stent expansion after sirolimus-eluting stent implantation may not have a negative impact on 12-month clinical outcomes.

要　約

シロリムス溶出性ステント植え込み術後の高度非対称性ステント拡張が12ヵ月予後に与える影響

中野　雅嗣　　我妻　賢司　　伊賀　淳　　新居　秀郎

天野　英夫　　戸田　幹人　　山崎　純一

目　的: 本研究ではシロリムス溶出性ステント植え込み術後の高度非対称性ステント拡張が術後12ヵ月の予後に与える影響を検討した．

方　法: シロリムス溶出性ステント植え込み術後，血管内エコー法を施行しえた狭心症118例，171病変を対象とした．血管内エコー法解析から術後最小ステント面積部位におけるステント対称指数（最小ステント長/最大ステント長）を算出し，対象をステント対称指数≧0.7の至適（O）群（93

例；145病変，平均年齢66±12歳）とステント対称指数＜0.7の非至適（S）群（25例；26病変，平均年齢67±10歳）の2群に分け，臨床成績を比較検討した．

結　果：8ヵ月後の冠動脈造影の結果，再血行再建術の比率（O群3.1% vs S群3.8%, $p=0.833$）に差はなかった．多変量解析の結果，術後最小ステント径が再血行再建術の独立した予測因子であった（$p=0.038$）．ステント対称指数＜0.7は予測因子とならなかった（$p=0.887$）．12ヵ月後の予後においてステント内血栓症発生率は両群とも0%であり，死亡率（O群2.1% vs S群4.0%，$p=0.602$）に差はなかった．

結　論：シロリムス放出性ステント植え込み術後の高度非対称性ステント拡張は12ヵ月予後に負の影響を与えない．

J Cardiol 2007 Jun; 49(6): 313−321

References

1) Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE; SIRIUS Investigators: Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003; **349**: 1315−1323
2) Schofer J, Schlüer M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt PG; E-SIRIUS Investigators: Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: Double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003; **362**: 1093−1099
3) Schampaert E, Cohen EA, Schlüer M, Reeves F, Traboulsi M, Title LM, Kuntz RE, Popma JJ; C-SIRIUS Investigators: The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol 2004; **43**: 1110−1115
4) von Birgelen C, Gil R, Ruygrok P, Prati F, Di Mario C, van der Giessen WJ, de Feyter PJ, Serruys PW: Optimized expansion of the Wallstent compared with the Palmaz-Schatz stent: On-line observations with two- and three-dimensional intracoronary ultrasound after angiographic guidance. Am Heart J 1996; **131**: 1067−1075
5) Kuntz RE, Safian RD, Carrozza JP, Fishman, RF, Mansour M, Baim DS: The importance of acute luminal diameter in determining restenosis after coronary atherectomy or stenting. Circulation 1992; **86**: 1827−1835
6) Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, Gaglione A, Goldberg SL, Tobis JM: Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995; **91**: 1676−1688
7) Moussa I, Oi Mario C, Reimers B, Akiyama T, Tobis J, Colombo A: Subacute stent thrombosis in the era of intravascular ultrasound-guided coronary stenting without anticoagulation: Frequency, predictors and clinical outcome. J Am Coll Cardiol 1997; **29**: 6−12
8) Hwang CW, Wu D, Edelman ER: Physiological transport forces govern drug distribution for stent-based delivery. Circulation 2001; **104**: 600−605
9) Ryan TJ, King SB Ⅲ, Bauman WB, Mccallister BD, Kennedy JW, Smith SC Jr, Kereiakes DJ, Ullyot DJ: Guidelines for percutaneous transluminal coronary angioplasty : A report of the American College Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 1993; **22**: 2033−2054
10) Rezkalla SH, Kloner RA: No-reflow phenomenon. Circulation 2002; **105**: 656−662
11) Yamazaki T, Taniguchi I, Kurusu T, Shimazu Y, Hashizume Y, Takikawa K, Kuwata M, Onodera T, Yoshikawa M, Mochizuki S: Effect of amlodipine on vascular responses after coronary stenting compared with an angiotensin-converting enzyme inhibitor. Circ J 2004; **68**: 328−333
12) Kume T, Akasaka T, Kawamoto T, Watanabe N, Toyota E, Neishi Y, Sukmawan R, Sadahira Y, Yoshida K: Assessment of coronary intima-media thickness by optical coherence tomography: Comparison with intravascular ultrasound. Circ J 2005; **69**: 903−907
13) Sato H, Iida H, Tanaka A, Tanaka H, Shimodouzono S, Uchida E, Kawarabayashi T, Yoshikawa J: The decrease of plaque volume during percutaneous coronary intervention has a negative impact on coronary flow in acute myocardial infarction: A major role of percutaneous coronary intervention-induced embolization. J Am Coll Cardiol 2004; **44**: 300−304
14) Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Chuang YC, Ditrano CJ, Leon MB: Patterns of calcification in coroary artery disease: A statistical analysis of intravasucular ultrasound and coroary angiography in 1155 leasions. Circulation 1995; **91**: 1959−1965
15) Albrecht D, Kaspers S, Fussl R, Hopp HW, Sechtem U: Coronary plaque morphology affects stent deployment: Assesment by intracoronary ultrasound.Cathet Cardiovasc Diagn 1996; **38**: 229−235
16) Fujii K, Carlier SG , Mintz GS, Yang Y, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB: Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: An intravascular ultrasound study. J Am Coll Cardiol 2005; **45**: 995−998
17) Suzuki S, Kamihata H, Hata T, Hayashi F, Miura A, Yoshinaga, M, Karakawa M, Kitaura Y: Success rate of

implantation and mid-term outcomes of the sirolimus-eluting stent. Circ J 2007; **71**: 15−19
18) Ong AT, van Domburg RT, Aoki J, Sonnenschein K, Lemos PA, Serruys PW: Sirolimus-eluting stents remain superior to bare-metal stents at two years: Medium-term results from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. J Am Coll Cardiol 2006; **47**: 1356−1360
19) Takebayashi H, Mintz GS, Carlier SG, Kobayashi Y, Fujii K, Yasuda T, Costa RA, Moussa I, Dangas GD, Mehran R, Lansky AJ, Kreps E, Collins MB, Colombo A, Stone GW, Leon MB, Moses JW: Nonuniform strut distribution correlates with more neointimal hyperplasia after sirolimus-eluting stent implantation. Circulation 2004; **110**: 3430−3434
20) Sousa JE, Costa MA, Abizaid A, Feres F, Seixas AC, Tanajura LF, Mattos LA, Falotico R, Jaeger J, Popma JJ, Serruys PW, Sousa A: Four-year angiographic and intravascular ultrasound follow-up of patients treated with sirolimus-eluting stents. Circulation 2005; **111**: 2326−2329
21) Popma JJ, Leon MB, Moses JW, Holmes DR Jr, Cox N, Fitzpatrick M, Douglas J, Lambert C, Mooney M, Yakubov S, Kuntz RE; SIRIUS Investigators: Quantitative assessment of angiographic restenosis after sirolimus-eluting stent implantation in native coronary arteries. Circulation 2004; **110**: 3773−3780
22) Sianos G, Hofma S, Ligthart JM, Saia F, Hoye A, Lemos PA, Serruys PW: Stent fracture and restenosis in the drug-eluting stent era. Catheter Cardiovasc Interv 2004; **61**: 111−116
23) Kaneda H, Ako J, Honda Y, Terashima M, Morino Y, Yock PG, Popma JJ, Leon MB, Moses JW, Fitzgerald PJ: Impact of asymmetric stent expansion on neointimal hyperplasia following sirolimus-eluting stent implantation. Am J Cardiol 2005; **96**: 1404−1407
24) van der Gissen WJ, Lincoff AM, Schwartz RS, van Beusekom HM, Serruys PW, Holmes DR Jr, Ellis SG, Topol EJ: Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation 1996; **94**: 1690−1697
25) Holmes DR Jr, Leon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald PJ, Brown C, Fischell T, Wong SC, Midei M, Snead D, Kuntz RE: Analysis of 1-year clinical outcomes in the SIRIUS trial: A randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. Circulation 2004; **109**: 634−640
26) Sonoda S, Morino Y, Ako J, Terashima M, Hassan AH, Bonneau HN, Leon MB, Moses JW, Yock PG, Honda Y, Kuntz RE, Fitzgerald PJ; SIRIUS Investigators: Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: Serial intravascular ultrasound analysis from the SIRIUS trial. J Am Coll Cardiol 2004; **43**: 1959−1963
27) Mitz GS, Weissman NJ: Intravascular ultrasound in the durg-eluting stent era. J Am Coll Cardiol 2006; **48**: 421−429
28) Moussa I, Di Mario C, Moses J, Reimers B, Di Francesco L, Martini G, Tobis J, Colombo A: Coronary stenting after rotational atherectomy in calcified and complex lesions: Angiographic and clinical follow-up results. Circulation 1997; **96**: 128−136
29) Hoffmann R, Mintz GS, Pompa JJ, Satler LF, Kent KM, Pichard AD, Leon MB: Treatment of calcified coronary lesions with Palmaz-Schatz stents: An intravascular ultrasound study. Eur Heart J 1998; **19**: 1224−1231
30) Bavry AA, Kumbhani DJ, Helton TJ, Bhatt DL: Risk of thrombosis with the use of sirolimus-eluting stents for perucutaneous coronary intervention (from registry and clinical trial data). Am J Cardiol 2005; **95**: 1469−1472
31) Urban P, Gershlick AH, Guagliumi G, Guyon P, Lotan C, Schofer J, Seth A, Sousa JE, Wijns W, Berge C, Deme M, Stoll HP; e-Cypher Investigators: Safety of coronary sirolimus-eluting stents in daily clinical practice: One-year follow-up of the e-Cypher registry. Circulation 2006; **113**: 1434−1441
32) Cheneau E, Leborgne L, Mintz GS, Kotani J, Pichard AD, Satler LF, Canos D, Castagna M, Weissman NJ, Waksman R: Predictors of subacute stent thrombosis: Results of a systematic intravascular ultrasound study. Circulation 2003; **108**: 43−47
33) Regar E, Lemos PA, Saia F, Degertekin M, Tanabe K, Lee CH, Arampatzis CA, Hoye A, Sianos G, de Feyter P, van der Giessen WJ, Smits PC, van Domburg RT, Serruys PW: Incidence of thrombotic stent occlusion during the first three months after sirolimus-eluting stent implantation in 500 consecutive patients. Am J Cardiol 2004; **93**: 1271−1275
34) Takebayashi H, Kobayashi Y, Mints GS, Garlier SG, Fujii K, Yasuda T, Moussa I, Mehran R, Dangas GD, Collins MB, Kreps E, Lansky AJ, Stone GW, Leon MB, Moses JW: Intravascular ultrasound assessment of lesions with target vessel failure after sirolimus-eluting stent implantation. Am J Cardiol 2005; **95**: 498−502
35) Ong ATL, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW: Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005; **45**: 2088−2092
36) Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD: Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: Should we be cautious ? Circulation 2004; **109**: 701−705
37) Joner M, Fine AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R: Pathology of drug-eluting stents in humans: Delayed healing and late thrombotic risk. J Am Coll Cardiol 2006; **48**: 193−202
38) Park DW, Park SW, Park KH, Lee BK, Kim YH, Lee CW, Hong MK, Kim JJ, Park SJ: Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. Am J Cardiol 2006; **98**: 352−356