Long-Term Coronary Endothelial Function After Zotarolimus-Eluting Stent Implantation

A 9 Month Comparison Between Zotarolimus-Eluting and Sirolimus-Eluting Stents

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SUMMARY

Implantation of a paclitaxel- or sirolimus-eluting stent (SES) may be associated with endothelial dysfunction. In the present study, we compared coronary endothelial function after zotarolimus-eluting stent (ZES) implantation to that after SES implantation.

Patients who had one stent implantation for a single lesion in the left anterior descending artery were enrolled. After 6 to 9 months, coronary endothelial function was assessed in patients who showed no angiographic restenosis. Endothelium-dependent vasomotion was determined after intracoronary infusion of acetylcholine. Also, endothelium-independent vasomotion was assessed after nitrate infusion. A total of 23 patients (11 in the ZES group, 12 in the SES group) were included. In distal and far distal segments, the SES group showed significant vasoconstriction by acetylcholine. However, no significant vasomotion was observed in the ZES group (SES versus ZES: -36.1% versus -3.3% for distal; $P = 0.003$, -34.7% versus -3.4% for far distal; $P = 0.003$). Endothelium-independent vasodilatation by nitrates was preserved in all subjects.

SES implantation may induce significant impairment of the endothelium-dependent vasomotor function in the distal portion of the treated vessel, while ZES implantation may not. Our results suggest that the change in coronary endothelial function after stent implantation could be different according to the type of DES. (Int Heart J 2008; 49: 639-652)

Key words: Endothelium, Drug-eluting stent (DES), Zotarolimus-eluting stent (ZES), Vasoconstriction, Acetylcholine

DRUG-ELUTING stent (DES) implantation has become the treatment of choice for patients who undergo percutaneous coronary intervention (PCI) because of its excellent clinical efficacy.¹⁻⁴⁾ However, despite the valuable long-term effects for

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Received for publication July 11, 2008.

Revised and accepted August 4, 2008.

preventing angiographic restenosis as well as improving the clinical outcomes, many recent studies have reported that DES implantation could induce long-term coronary endothelial dysfunction.⁵⁻⁸⁾ Furthermore, concerns have been recently raised that the endothelial dysfunction after DES implantation could play an important role as the most powerful predictor of stent thrombosis, which is a life-threatening complication.^{9,10)} Therefore, determining the changes in coronary endothelial function after DES implantation has emerged as a major concern for the long-term prognosis of patients who undergo PCI.^{7,8)}

The implantation of a first-generation DES, such as the sirolimus-eluting stent (SES) and the paclitaxel-eluting stent (PES), was shown to be associated with coronary endothelial dysfunction in several previous studies.⁵⁻⁸⁾ However, the details of long-term endothelial function after implantation of the second-generation DES, the zotarolimus-eluting stent (ZES), still remains largely unknown.¹¹⁾ Interestingly, in recent animal and human studies, the ZES demonstrated vascular responses that were different from the SES or PES. Treatment with the ZES was associated with increased neointimal hyperplasia and greater endothelialization than that noted with SES or PES implantation.¹¹⁻¹⁴⁾

Thus, we hypothesized that the change in long-term coronary endothelial function after ZES implantation may also be different from that after SES implantation. The present study was designed to compare long-term coronary endothelial function after PCI between the ZES and the SES.

METHODS

Study population: From December 2006 to September 2007, patients who had one stent implanted for treating single significant *de novo* stenosis in the left anterior descending artery (LAD) were evaluated for enrollment into this study. Out of these, 30 patients were included in the study and then classified into two groups according to the type of stent implanted, which was decided upon by clinicians before percutaneous coronary intervention (PCI): a sirolimus-eluting stent (SES) or a zotarolimus-eluting stent (ZES). There were 15 patients in the SES group and 15 in the ZES group. We performed follow-up coronary angiography 6 to 9 months after the initial PCI and assessed coronary endothelial function only in the patients who showed no angiographic in-stent restenosis and no recurrent typical chest pain during the follow-up period.

The exclusion criteria were acute myocardial infarction within 48 hours after the onset of chest pain, clinical or angiographic coronary vasospasm, and observation of a fresh thrombus on the initial angiography. The patients who demonstrated in-stent restenosis on the follow-up angiography or recurrent chest pain during the follow-up period were also excluded. Further, patients who

showed progression of nontarget lesions or development of *de novo* lesions on the follow-up angiography were excluded. The other exclusion criteria included a LAD diameter < 2.7 mm or > 4.0 mm, lesions treated with a balloon that were < 10 mm in length or > 40 mm in length, the presence of severe left ventricular (LV) systolic dysfunction, and the presence of an unhealed dissection that was identified by intravascular ultrasound (IVUS) performed at the end of the study.

We obtained study approval from the Institutional Review Board (IRB) of the Catholic University of Korea and all subjects provided written informed consent.

Study design and treatments: After making the decision concerning the type of stent to be used, the initial PCI was performed according to standard guidelines. The 15 SES group patients received the Cypher stent (Cordis Corp, Miami Lakes, FL, USA) while the 15 ZES group patients received the Endeavor stent (Medtronic Vascular, Santa Rosa, CA). The optimal medical treatment for all subjects was strongly recommended before and after the initial PCI. All patients were given oral aspirin daily (100 mg), thienopyridine (clopidogrel 75 mg or ticlopidine 500 mg) and other antiplatelet agents if clinically indicated. The patients also received oral beta-blockers, angiotensin receptor blockers, lipid-lowering therapy, and vasodilators, unless contraindicated during the follow-up period.

Follow-up coronary angiography was performed 6 to 9 months after the initial PCI using the standard Judkin's method after injecting 3,000 units of heparin. A 7 French (Fr) Judkins-Left (JL) catheter was used in all subjects to evaluate the left coronary artery. Drugs with potential effects on vasomotor responses were discontinued at least 72 hours prior to the follow-up angiography.

Coronary endothelial function was assessed immediately after the follow-up angiography only in the patients who met the inclusion criteria. Endothelial function was evaluated by determining endothelium-dependent and independent vasomotor responses to an intracoronary infusion of acetylcholine or nitrates. Baseline quantitative coronary angiography (QCA) was performed at 5 different points of measurement in the LAD. The maximal change in LAD diameter after infusion of acetylcholine or nitrates was estimated by QCA at the same points that were measured in the LAD. Finally, the percent change in LAD diameter at each of these 5 points was analyzed and the differences between the SES and ZES groups evaluated.

Assessment of coronary endothelial function: At baseline, an intracoronary infusion of 0.9% normal saline (5 mL for 1 minute) was administered and then baseline angiography was performed. To assess the endothelium-dependent vasomotor response, we administered an intracoronary infusion of acetylcholine (14 μ g/minute for 2 minutes), which yielded an estimated intracoronary concentra-

tion of 10^{-6} mol/L. A temporary two Fr microcatheter (Terumo, Tokyo) was positioned 2 cm proximal to the proximal edge of the stent for selective intracoronary infusion of acetylcholine. The microcatheter was subsequently withdrawn just after the termination of the acetylcholine infusion and the coronary angiography was repeated every 30 seconds for 3 minutes. A temporary pacemaker was inserted through the femoral vein if clinically indicated.

Subsequently, in order to assess the endothelium-independent vasomotor response, 2 mg of nitrates was infused via an intracoronary bolus in all the subjects.

Quantitative coronary angiography: The maximal vasomotor response to acetylcholine or nitrates was determined by QCA using the CAAS II system (Pie Medical Imaging, Maastricht, The Netherlands). An independent reviewer, who was blinded to the type of stent and patient baseline information, performed the QCA right after the baseline angiography and after the infusion of acetylcholine or nitrates. The percent change in LAD diameter was calculated at 5 different points using the baseline QCA as a reference. The 5 different points used for measurement consisted of the proximal and distal segments, the near proximal and far distal segments, and the stented segments. The proximal and distal segments were defined as those areas 5 to 10 mm proximal and distal to the stent edge; the definitions of the near proximal and far distal segments were those at 10 to 20 mm proximal and distal to the stent edge, respectively. Finally, the stented segment was defined as the mid-point of the total stent length. The QCA was performed at the most vasoactive points in each of the 5 segments.

Intravascular ultrasound (IVUS) was performed to detect an unhealed dissection or any significant atherosclerosis ($> 30\%$ reduction of the vessel area) at the 5 points of measurement in all patients at the end of the study, and any patients identified with these findings were excluded.

Definitions: A stenosis with a 50% reduction of a coronary vessel diameter, as estimated by QCA or visual inspection, was defined as a significant angiographic stenosis. We defined severe LV systolic dysfunction as less than a 40% LV ejection fraction according to the echocardiography that was routinely performed in all patients before the initial angioplasty. Coronary endothelial dysfunction was defined by abnormal vasoconstriction of more than 20% in the vessel diameter, as compared with the baseline after the intracoronary infusion of acetylcholine at any of the points of measurement.¹⁵⁾ The proximal and near proximal segments were defined as the proximal portion of the treated vessel, and the distal and far distal segments were defined as the distal portion of the treated vessel.

Statistical analysis: Statistical analysis was performed using the SPSS statistical program (version 15.0, Chicago, IL, USA). Continuous variables are presented as the mean $\pm$ SD, and categorical variables are presented as a number (*n*) or a per-

centage (%). Comparisons between the two groups were performed with the Student's *t*-test and the chi-square test. *P*-values (*P*) less than 0.05 were considered statistically significant.

RESULTS

Out of the 30 patients, 23 patients were enrolled for assessment of their coronary endothelial function. There were no patients who showed in-stent restenosis on the follow-up angiography in either group. One patient in each group demonstrated significant progression of lesions in the nontarget vessel on follow-up angiography and 3 patients (1 in the SES group and 2 in the ZES group) refused follow-up angiography. One patient in the ZES group had regular treatments at another hospital during the follow-up period. In addition, one patient in the SES group died due to a noncardiac cause during the follow-up period. Therefore, in the end the SES and ZES groups consisted of 12 (12/15, 80.0%) and 11 patients (11/15, 73.3%), respectively. IVUS revealed no significant atherosclero-

Table I. Baseline Characteristics of the Patients

	SES (<i>n</i> = 12)	ZES (<i>n</i> = 11)	<i>P</i>
Follow-up period (days)	242.4 ± 43.6	257.5 ± 35.7	0.95
Age (years)	60.8 ± 5.1	62.4 ± 5.2	0.99
Male	6 (50.0%)	8 (72.7%)	0.23
ACS	5 (41.7%)	5 (45.5%)	0.86
Risk Factors for CAD			
Hypertension	8 (66.7%)	10 (90.9%)	0.17
Diabetes	6 (50.0%)	5 (45.5%)	0.83
Smoking	7 (58.3%)	6 (54.5%)	0.86
Family history	5 (41.7%)	6 (54.5%)	0.55
Initial LDL-chol (mg/dL)	122.9 ± 23.1	173.6 ± 12.9	0.03
CRP (mg/L)	0.8 ± 0.6	1.4 ± 1.1	0.08
Post-PCI medications (%)			
Aspirin	12 (100%)	11 (100%)	1.00
Clopidogrel	11 (91.7%)	9 (81.8%)	0.49
Ticlopidine	2 (16.7%)	2 (18.2%)	0.93
Cilostazol	6 (50.0%)	5 (45.5%)	0.83
Beta-blocker	9 (75.0%)	10 (90.9%)	0.33
CCB	3 (25.0%)	1 (9.1%)	0.33
ARB or ACEI	11 (91.7%)	9 (81.8%)	0.49
Lipid-lowering	12 (100%)	11 (100%)	1.00
Others	8 (66.7%)	5 (45.5%)	0.32

SES indicates sirolimus-eluting stent; ZES, zotarolimus-eluting stent; ACS, acute coronary syndrome; CAD, coronary artery disease; LDL-chol, low-density lipoprotein cholesterol; CRP, C-reactive protein; PCI, percutaneous coronary intervention; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; and ACEI, angiotensin-converting enzyme inhibitor. The data are presented as *n* (%) or the mean ± SD.

sis or unhealed dissection at the points of measurement in the LADs of these 23 patients.

Baseline characteristics: The baseline characteristics of the 2 groups are presented in Table I. The mean interval from the initial PCI to the follow-up angiography was similar between both groups: 242.4 ± 43.6 days for the SES group and 257.5 ± 35.7 days for the ZES group ($P = 0.95$). The classical risk factors for cor-

Table II. Angiographic Data (Initial Percutaneous Coronary Intervention)

	SES ($n = 12$)	ZES ($n = 11$)	<i>P</i>
Mean stent length (mm)	24.4 ± 4.9	26.4 ± 3.9	0.97
Nominal stent diameter (mm)	3.15 ± 0.27	3.27 ± 0.26	0.74
Stent deployment pressure (bar)	15.0 ± 2.6	14.8 ± 1.7	0.31

SES indicates sirolimus-eluting stent and ZES, zotarolimus-eluting stent.

The data are presented as the mean $\pm$ SD.

Figure 1. Coronary angiographic findings with typical responses to intracoronary infusion of acetylcholine (Ach) and nitrates 6 to 9 months after SES (sirolimus-eluting stent) or ZES (zotarolimus-eluting stent) implantation.

In the SES group (upper row), significant diffuse vasoconstriction was induced by Ach in the long distal portion of the treated vessel. However, the ZES group (lower row) demonstrated no significant vasoconstriction after Ach infusion. The vasodilatory response by nitrates was preserved in all groups. The distal edge of the implanted stent is indicated by the black arrows.

onary artery disease, except dyslipidemia, were similar in both groups. However, the ZES group patients showed significantly higher levels of low density lipoprotein (LDL)-cholesterol compared to the patients in the SES group ($P = 0.03$). Other characteristics of the 2 groups, such as patient age, gender, and the proportion of patients with acute coronary syndrome were not significantly different. All patients received aspirin and lipid-lowering therapy during the follow-up period. There were no significant differences between the 2 groups with respect to other aspects of the medical therapy (Table I).

The initial angiographic characteristics were very similar for the 2 groups with regard to the nominal diameter and mean length of the stent, and the deployment pressure of the stent (Table II).

Endothelium-dependent vasomotor response: Figure 1 illustrates the coronary angiographic findings of the typical responses to intracoronary infusion of acetylcholine and nitrates 6 to 9 months after SES or ZES implantation. Table III shows the mean luminal diameter after the maximal changes in LAD diameter in response to intracoronary infusion of acetylcholine and nitrates.

The maximal change in LAD diameter from baseline in response to the infu-

Table III. Changes in Luminal Diameter After Intracoronary Infusion of Acetylcholine and Nitrates (Quantitative Coronary Angiography)

	SES (mm)	ZES (mm)	<i>P</i>
Near proximal segment			
Baseline	3.06 ± 0.26	3.22 ± 0.21	0.19
Acetylcholine	3.11 ± 0.26	3.29 ± 0.23	0.35
Nitrates	3.63 ± 0.29*	3.69 ± 0.21*	0.49
Proximal segment			
Baseline	3.03 ± 0.29	3.19 ± 0.23	0.11
Acetylcholine	3.06 ± 0.28	3.21 ± 0.31	0.73
Nitrates	3.55 ± 0.30*	3.63 ± 0.25*	0.41
Stented segment			
Baseline	3.12 ± 0.24	3.09 ± 0.23	0.78
Acetylcholine	3.08 ± 0.22	3.08 ± 0.23	0.70
Nitrates	3.13 ± 0.24	3.12 ± 0.22	0.77
Distal segment			
Baseline	2.83 ± 0.24	2.97 ± 0.20	0.67
Acetylcholine	1.81 ± 0.27*	2.86 ± 0.17	0.04
Nitrates	3.32 ± 0.23*	3.41 ± 0.26*	0.97
Far distal segment			
Baseline	2.68 ± 0.24	2.83 ± 0.15	0.31
Acetylcholine	1.75 ± 0.27*	2.72 ± 0.11	0.04
Nitrates	3.19 ± 0.27*	3.31 ± 0.21*	0.48

SES indicate sirolimus-eluting stent and ZES, zotarolimus-eluting stent.

The data are presented as the mean ± SD.

* $P < 0.05$ versus the baseline.

sion of acetylcholine was determined in order to assess endothelium-dependent vasomotor function. In the near proximal, proximal, and stented segments, no significant vasomotion was seen in either group and there was no difference between the ZES and SES groups. Although slight vasodilatation by acetylcholine was observed in the near proximal and proximal segments, there was no statistically significant change in LAD diameter in either group (versus baseline: $P > 0.05$, Figure 2). More active vasomotion was observed in the distal portion than in the proximal portion. The distal and far distal segments in the SES group demonstrated significant vasoconstriction in response to acetylcholine (versus baseline: $-36.1 \pm 6.5\%$ for the distal; $P = 0.001$ and $-34.7 \pm 7.6\%$ for the far distal; $P = 0.001$). However, no significant vasomotor response to acetylcholine in the distal and far distal segments was observed in the ZES group. Although some ZES group patients exhibited mild vasoconstriction, the change in LAD diameter was not statistically significant compared to the baseline diameter. Thus, the ZES group showed only a slight vasoconstrictive response in the distal and far distal segments (versus baseline: $-3.3 \pm 5.1\%$ for the distal; $P = 0.06$ and $-3.4 \pm 5.2\%$ for the far distal; $P = 0.07$). A comparison of the SES and ZES groups revealed more severe vasoconstriction by acetylcholine in the SES group than in the ZES group (SES versus ZES: $-36.1 \pm 6.5\%$ versus $-3.3 \pm 5.1\%$ for the distal; $P = 0.003$ and $-34.7 \pm 7.6\%$ versus $-3.4 \pm 5.2\%$ for the far distal; $P = 0.003$).

Figure 2. Percent change in mean luminal diameter of the left anterior descending artery (LAD) in response to an intracoronary infusion of acetylcholine.

* $P < 0.05$ versus the baseline diameter.

Figure 3. Percent change in mean luminal diameter of the left anterior descending artery (LAD) in response to an intracoronary bolus of nitrates. *P* < 0.05 versus the baseline diameter.

The degree of vasoconstriction in the SES group was estimated to be more than a 20% reduction of the LAD diameter. However, in the ZES group, the mild degree of vasoconstriction did not match with the definition of endothelial dysfunction. Thus, according to the definition adopted for our study, these results reflect coronary endothelial dysfunction in the distal portion of the treated vessel in only the SES group (Figure 2).

Endothelium-independent vasomotor response: Endothelium-independent vasomotor function was assessed by determining the maximal vasodilatory response after an intracoronary bolus of nitrates. All of the subjects demonstrated significant vasodilatation in response to nitrates at each measurement point, with the exception of the stented segments. In the stented segment, no active vasomotion was observed in either group. There was no significant difference in endothelium-independent vasodilatation between the ZES and SES groups (Figure 3).

DISCUSSION

The present study is the first, to the best of our knowledge, to compare coronary endothelial function between ZES and SES implantation. The most important findings can be summarized as follows: The SES group demonstrated abnormal coronary vasoconstriction by acetylcholine at the long distal portion

(the distal and far distal segments) of the treated vessel, which means there was impairment of endothelium-dependent vasodilatation in those segments. However, endothelium-independent vasodilatation, after the infusion of nitrates, was preserved. In contrast to the SES group, no significant impairment of vasomotor function was observed in the ZES group. These results suggest that long-term coronary endothelial function could be different between ZES and SES implantation. In other words, SES implantation may be associated with significant coronary endothelial dysfunction in the long distal portion of the treated vessel, while the ZES implantation is not.

Coronary endothelial function and acetylcholine: Coronary endothelial dysfunction could play a key role as an independent predictive factor for an adverse long-term cardiovascular prognosis.^{16,17)} The “gold standard” for assessing coronary endothelial function is determining the vasomotor responses to intracoronary acetylcholine.¹⁸⁾ In coronary arteries with normal endothelium, acetylcholine induces epicardial and microvascular dilation by promoting the release of endothelial nitric oxide.¹⁹⁾ However, when the endothelial lining is disrupted or dysfunctional, acetylcholine induces a paradoxical response, for example, vasoconstriction.¹⁸⁻²⁰⁾

Vessel diameter decreased, due to acetylcholine, in the distal and far distal segments in both the SES and ZES groups. However, interestingly, the degree of vasoconstriction was remarkably different between the two groups. The SES group showed definite paradoxical vasoconstriction, while the ZES group demonstrated only slight vasoconstriction. As previously stated, the physiologic response to acetylcholine is vasodilatation in the normal coronary artery with intact endothelium.^{19,20)} Thus, it is possible to suggest that the normal physiologic response to acetylcholine was not observed in the ZES group. However, some previous studies have reported that mild vasoconstriction that does not exceed a 20% reduction of the vessel diameter can physiologically occur in response to acetylcholine in normal healthy persons.¹⁵⁾ The ZES group in our study showed only about a 3% diameter reduction and it was not a statistically significant change from the baseline diameter. Although a previous study that used a similar dosage of acetylcholine defined endothelial dysfunction as vasoconstriction of more than a 3% diameter change from baseline,⁵⁾ we defined it more strictly (abnormal vasoconstriction of more than 20% diameter change) taking into consideration the variations in the normal physiologic response to acetylcholine. Based on our definition, the change in LAD diameter in the ZES group could not be regarded as the result of endothelial dysfunction.

Endothelial dysfunction and SES implantation: Sirolimus has direct inhibitory effects on re-endothelialization in the injured arterial wall.^{21,22)} Yet the sirolimus coated on the stent is fully eluted from the strut by 60 days and its direct effect is

sustained only during the early phase after stent implantation.²³⁾ Therefore, endothelial dysfunction 6 to 9 months after SES implantation could not be due to the direct effect of sirolimus.^{5,6,8)} However, it was reported that implanted SES had incomplete coverage above the stent struts long after implantation.^{24,25)} Considering this result, it may be possible that coronary endothelial dysfunction induced by the direct effect of sirolimus in the early phase may be sustained for several months.

Other explanations for endothelial dysfunction could be supported by the results of recent studies that focused on the cellular or molecular responses after SES implantation. Inoue, *et al* have recently showed in the human stent model that the mobilization of CD34-positive stem cells, which potentially differentiate into both endothelial and vascular smooth muscle cells, was strongly suppressed after SES implantation.²⁶⁾ It was previously revealed that regenerated endothelial cells that are differentiated from CD34-positive stem cells may contribute to re-endothelialization.²⁷⁾ Further, Obata, *et al* recently demonstrated that SES implantation adversely affected the endothelial function of infarct-related arteries in patients with myocardial infarction, and this was associated with a reduction in the secretion of myocardial vascular endothelial growth factor (VEGF).²⁸⁾ VEGF is produced and expressed in both the myocardium and the coronary beds, and it plays a role in the process of endothelial repair.^{28,29)} However, further evaluation is still needed to clarify the mechanism of endothelial dysfunction associated with SES implantation.

Different vasomotor responses to acetylcholine between SES and ZES implantation: Although the mechanism for this difference between the ZES and SES has not been made clear, several previous reports have suggested possible clues. The tetrazole-containing macrocyclic immunosuppressant zotarolimus shares structural homology and biological activity with the anti-restenotic agent sirolimus.³⁰⁾ However, many recent trials have shown different angiographic outcomes among patients treated with ZES and SES: the treatment with ZES was associated with increased neointimal hyperplasia, and this resulted in greater late lumen loss than that for the SES.¹²⁻¹⁴⁾ Another report demonstrated that the absence of neointimal growth is associated with a lack of re-endothelialization and delayed arterial healing in patients with an implanted DES.³¹⁾ These findings suggest that a possible benefit of a higher value of late loss in the patients treated with ZES might be that it creates the conditions for complete endothelialization of the stent struts, and this results in early recovery of the injured vessel wall.^{13,31)} In fact, Nakazawa, *et al* recently assessed the endothelialization of SES, PES, and ZES in a rabbit model,¹¹⁾ observing significantly greater endothelialization in the area above the stent strut in the ZES than in the other 2 types of DES.¹¹⁾ Based on these findings, although excessive neointimal growth leads to the need for target lesion revascu-

larization, the coverage of stent struts with a small amount of neointima, as seen in the ZES in many previous reports, may offer a theoretical protective advantage against long-term endothelial dysfunction.¹³⁾ Although we could not determine the difference in the degree of re-endothelialization among the two groups, these previous findings may offer a possible explanation.

Furthermore, the ZES has more rapid elution kinetics than does the SES and PES. Compared with the slower release of sirolimus (95% eluted in approximately 6 weeks), 95% of zotarolimus is eluted in approximately 2 weeks.^{12,30)} The more rapid elution kinetics of the ZES might reduce the local toxicity to the endothelium.¹¹⁾ There are other potential advantages associated with the ZES. The ZES (Endeavor stent) has thin struts (91 μm).⁴⁾ Because the technology of thin struts could lessen the extent of arterial injury, it enabled better re-endothelialization.¹¹⁾ However, healing of the injured vessel and the change in endothelial function after DES implantation are multifactorial processes.^{11,12)} Thus, other factors such as the degree of inflammation, the difference in biological response to either the stent or the polymer itself, and the underlying plaque morphology can contribute to the difference in endothelial function between the ZES and the SES.^{11,32-34)} Further evaluation is needed to clarify the mechanism of this difference according to the type of DES.

Study limitations: The present study has the following limitations. First, only a limited number of patients were included and it was not randomized for the type of implanted stent. Although some of the previous studies that examined coronary endothelial function after DES implantation were also conducted with a limited number of subjects, and our results demonstrated statistically significant differences in the vasomotor response, the results of our study must be confirmed in the future by conducting larger randomized studies.

Second, we did not assess baseline vasomotor function. In addition, vasomotion study was not carried out in a control vessel to exclude the presence of underlying coronary vasospasm that was not related to DES implantation. However, we included only those patients who were without angina during the follow-up period, and the pattern of vasoconstriction in response to acetylcholine in the SES group was similar. Thus, the vasoconstrictive response in the SES group may not be related to any underlying coronary vasospasm, but rather to the SES.

Finally, we could not come up with a clear explanation for the mechanism of the different vasomotor function between the two groups. A different degree of neointimal growth may have contributed to the different vasomotor function. Other factors, such as different elution kinetics and strut thickness, may have contributed as well. However, recent IVUS studies revealed that the amount of neointimal hyperplasia in PES is greater than that in SES and other previous studies that used similar methods to our study reported that endothelial dysfunction

occurs in both SES and PES implantation. Therefore, coverage of stent struts by neointimal hyperplasia could not account for the endothelial dysfunction completely after DES implantation. Further evaluation must be performed to clarify the mechanism of the difference in vasomotor function.

Conclusions: The vasomotor response to acetylcholine that was estimated 6 to 9 months after PCI was significantly different between the SES and ZES groups. SES implantation may induce significant impairment of long-term coronary endothelial function, while ZES implantation may not. The results suggest that coronary endothelial function after coronary intervention may be different depending on the type of DES. If the mechanism of the difference could be elucidated in further studies, it would represent valuable information for clinicians.

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