Comparison of the Effect of Preinterventional Arterial Remodeling on Intimal Hyperplasia after Implantation of a Sirolimus- or Paclitaxel-Eluting Stent

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Key Words

Arterial remodeling • Remodeling index •
Drug-eluting stent • Intimal hyperplasia

Abstract

Background: We compared the effect of arterial remodeling on intimal hyperplasia (IH) after the implantation of a sirolimus-eluting stent (SES) and a paclitaxel-eluting stent (PES).

Methods: The study population consisted of patients with positive or intermediate remodeling and negative remodeling. **Results:** Sixty-nine patients had positive or intermediate remodeling and 107 patients had negative remodeling. At follow-up, late loss was significantly larger (0.58 ± 0.65 vs. 0.38 ± 0.55 mm; $p = 0.026$) in the patients with positive or intermediate remodeling. The IH volume (22.6 ± 26.2 vs. 12.4 ± 17.4 mm³; $p = 0.002$) and the percent IH (12.9 ± 14.8 vs. $7.0 \pm 9.6\%$; $p = 0.002$) were significantly higher in the patients with positive or intermediate remodeling. Compared to negative remodeling, the IH volume was higher in the PES patients with positive or intermediate remodeling, but this difference was not noted in the SES patients. Multiple-regression analysis revealed that arterial remodeling was a significant independent variable for predicting IH volume in

the PES patients ($p = 0.018$). A positive correlation was found between the remodeling index and the IH volume in the PES patients ($r = 0.234$, $p = 0.028$), but not in the SES patients. **Conclusions:** This prospective observational intravascular ultrasound study showed that drug-eluting stents may have a different effect on reducing IH accumulation in lesions with preinterventional positive remodeling characteristics which may be related to the different properties of the drug and delivery platform.

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Introduction

Drug-eluting stents (DESs) with antiproliferative and antimigratory properties appear to be clinically efficacious in inhibiting restenosis via an inhibitory effect on smooth muscle cells. However, different drug mechanisms and delivery platforms may translate into different clinical efficacies. Although previous intravascular ultrasound (IVUS) studies have shown that positive preinterventional arterial remodeling is associated with increased intimal hyperplasia (IH), a higher restenosis and/or target lesion revascularization rate, and a worse clinical out-

come, these relationships need clarification in the DES era [1–6]. We investigated and compared the effect of pre-interventional arterial remodeling (positive or intermediate remodeling and negative remodeling) on IH after the implantation of two different DESs: the sirolimus-eluting stent (SES, Cypher; Cordis, Miami, Fla., USA) and the paclitaxel-eluting stent (PES, Taxus; Boston Scientific, Natick, Mass., USA).

Methods

Study Design and Patient Population

This study was a multicenter, prospective observational study. Three hundred and one consecutive patients were screened from May 2005 through June 2007. The patients underwent percutaneous coronary interventions with a DES at a de novo stenosis of a native coronary artery in a reference vessel between 2.5 and 3.5 mm in diameter that could be covered by a single stent (defined as a decrease of $\geq 70\%$ in the luminal diameter in a major epicardial coronary artery). After an IVUS, the lesions were excluded when (1) intimal calcification at the target lesion was so severe that it precluded accurate quantification of the IVUS imaging, (2) an IVUS study of the target lesion and reference segments could not be performed before the subsequent intervention, (3) there were major side branches between the proximal and distal reference segments, or (4) a distinct dissection was made at the stent edge after stenting. Finally, 176 patients were enrolled into this study. The primary outcomes were the IH volume and percent IH (IH volume/lumen volume, %IH) at follow-up. The study was approved by our Institutional Review Board and all patients gave their written informed consent.

Procedure

The percutaneous coronary interventions were performed with 6- or 7-french guiding catheters and conventional techniques. An IVUS study was performed in all patients prior to the intervention. The stent diameter was selected based on the pre-interventional IVUS measurements (with a ratio of the stent balloon diameter to the reference diameter of 1.1:1.0). Stents were selected before angioplasty using a computer-generated random allocation. The stents were initially implanted with a nominal pressure inflation using a stent delivery balloon. An inflation time of 10 s was required. After stenting, angiographic and IVUS assessments were performed to assess the success of the deployment or the need for additional balloon inflation. Before the percutaneous coronary intervention, 200 mg of aspirin was administered orally, followed by oral administration of 100 mg/day. In addition to the aspirin, a 300-mg loading dose of clopidogrel was given and a maintenance dosage of 75 mg/day was recommended for 3–12 months. Antithrombotic regimens, including intravenous heparin and glycoprotein IIb/IIIa inhibitors, were used at the discretion of the treating physicians. Follow-up angiographic and IVUS examinations were performed at 9 months after the index procedure. Clinical follow-up was also performed at 1 and 9 months after the index procedure.

Angiographic Data Analysis

Quantitative coronary angiography was performed using an off-line system (CMS; Medis Medical Imaging Systems, Nuenen, The Netherlands) by a single individual who was blinded to the patient's treatment assignment. The minimal luminal diameter of the treated coronary segments, reference diameter, percent diameter stenosis, and lesion length on the baseline angiogram were determined in the view that demonstrated the lesion to be the most severe and not foreshortened. Angiographic success was defined as a Thrombolysis In Myocardial Infarction (TIMI) flow grade of 3 and a $<20\%$ residual stenosis diameter by visual assessment. Restenosis was defined as a $>50\%$ stenosis diameter determined by quantitative coronary angiography within a previously stented segment.

IVUS Assessment

An IVUS assessment was performed using a commercially available IVUS system (Boston Scientific/Scimed, Natick, Mass., USA). The studies were recorded on an s-VHS tape and an Index system (Echoplague 2; INDEC Systems Inc., Mountain View, Calif., USA) for off-line analysis. A motorized transducer pullback permitted cross-sectional area (CSA) measurements at 0.5 mm axial increments throughout the length of the stent. All IVUS studies were performed after the intracoronary administration of 200 μg of nitroglycerin. The reference segment was the visually most normal cross-section (largest lumen with the least plaque burden) within 10 mm proximal or distal to the lesion. Using the software, the external elastic membrane (EEM) CSA, lumen CSA, minimal stent cross-sectional area, identified as the CSA at the tightest segment within the stent, and stent minimal luminal diameter were determined. The CSA at the proximal and distal reference segments and at the most stenotic lesion as well as the CSA at the proximal and distal stent edges was determined. A volumetric IVUS analysis was also performed. Using computerized planimetry, the postintervention and follow-up vessel, stent, lumen, and IH (stent minus lumen) areas were measured every 1 mm within the stented segment and at both edge segments. The volumes were calculated using Simpson's rule. The remodeling index (RI) was also defined as follows: the target lesion EEM CSA divided by the average of the proximal and distal reference EEM CSAs. The three subgroups were defined as positive remodeling ($\text{RI} \geq 1.05$), intermediate remodeling ($0.95 \leq \text{RI} < 1.05$), or negative remodeling ($\text{RI} < 0.95$) [7].

Statistical Analysis

The values were expressed as means $\pm$ SD. The patient demographics, clinical history, risk factors, and procedure data were summarized using descriptive statistics for continuous variables and frequency tables or proportions for discrete variables. The continuous variables were compared with an analysis of variance. The categorical variables were expressed as frequencies and compared using χ^2 statistics or a Fisher's exact test. A simple regression analysis was used to find the correlation between the baseline RI and IH volume at follow-up. A multivariate logistic regression analysis was undertaken to identify any independent predictors of IH. All statistical analyses were performed with SPSS 13.0 software (SPSS, Inc., Chicago, Ill., USA). $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Of the 176 patients enrolled in this study, 69 patients had positive or intermediate remodeling and 107 had negative remodeling. All the clinical baseline characteristics of the study population are presented in table 1. There was no statistically significant difference in the clinical characteristics except for hypertension, which was more common in the group with negative remodeling.

Angiographic Results

The results of quantitative coronary angiography are summarized in table 2. There was no significant difference in the reference vessel diameter, lesion length, diameter stenosis or minimal lumen diameter at baseline or after the percutaneous coronary intervention between the two groups. At follow-up, the late loss was significantly larger (0.58 ± 0.65 vs. 0.38 ± 0.55 mm; $p = 0.026$) and restenosis rate higher (13.0 vs. 3.7%; $p = 0.036$) in the group with positive or intermediate remodeling than in the group with negative remodeling. All restenoses were observed in the PES patients.

IVUS Results

The IVUS results for all patients are shown in table 3. The RI was 1.12 ± 0.16 in the group with positive or intermediate remodeling and 0.75 ± 0.12 in the group with negative remodeling ($p = 0.000$). There was no significant difference between the two groups in the lumen CSA at the minimal lesion site prior to (2.04 ± 1.04 vs. 1.97 ± 0.86 mm²; $p = 0.625$) or after stenting (7.77 ± 2.46 vs. 7.67 ± 2.34 mm²; $p = 0.788$). At 9 months of follow-up although the lumen volume did not differ between the two groups (166.4 ± 67.6 vs. 168.9 ± 60.0 mm³; $p = 0.797$) the IH volume was significantly higher in the group with positive or intermediate remodeling (22.6 ± 26.2 vs. 12.4 ± 17.4 mm³; $p = 0.002$). Further, %IH was also higher in the group with positive or intermediate remodeling than in the group with negative remodeling (12.9 ± 14.8 vs. 7.0 ± 9.6 %; $p = 0.002$). In the analysis of the SES patients, there were no significant differences in the IH volume or %IH at follow-up between the two groups (table 4). Conversely, both the IH volume and %IH were higher in the group with positive or intermediate remodeling than in the group with negative remodeling among the PES patients (table 5). A multiple regression analysis including the pattern of remodeling, hypertension, diabetes, stent diameter and length revealed that the pattern of the arte-

Table 1. Baseline clinical characteristics (all)

	PR/IR (n = 69)	NR (n = 107)	p value
Age, years	62.3 $\pm$ 9.5	61.7 $\pm$ 9.2	0.770
Men	40 (58.0)	62 (27.9)	1.000
Risk factors			
Smoking	18 (26.1)	22 (20.6)	0.518
Diabetes	25 (36.2)	31 (29.0)	0.325
Hypertension	38 (55.1)	77 (72.0)	0.032
Dyslipidemia	14 (20.3)	25 (23.4)	0.710
Prior MI	2 (2.9)	9 (8.4)	0.204
Prior PCI	4 (5.8)	16 (15.0)	0.087
LVEF, %	55.6 $\pm$ 13.4	56.5 $\pm$ 5.2	0.762
Diagnosis			0.008
Stable AP	28 (40.6)	66 (61.7)	
Unstable AP	41 (59.4)	41 (38.3)	

Figures in parentheses are percentages. PR/IR = Positive or intermediate remodeling; NR = negative remodeling; AP = angina pectoris; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2. Quantitative coronary angiographic results (all)

	PR/IR (n = 69)	NR (n = 107)	p value
<i>Before the intervention</i>			
Lesion length, mm	20.8 $\pm$ 6.6	20.4 $\pm$ 6.7	0.689
RVD, mm	3.00 $\pm$ 0.39	3.04 $\pm$ 0.45	0.583
MLD, mm	0.65 $\pm$ 0.48	0.60 $\pm$ 0.49	0.405
DS, %	69.2 $\pm$ 16.8	67.1 $\pm$ 16.0	0.408
<i>After the intervention</i>			
Stent diameter, mm	3.23 $\pm$ 0.30	3.23 $\pm$ 0.29	0.909
Stent length, mm	24.5 $\pm$ 5.4	23.7 $\pm$ 5.5	0.369
Stent pressure, atm	10.5 $\pm$ 2.0	10.8 $\pm$ 2.0	0.345
Post-stent pressure, atm	19.1 $\pm$ 2.4	18.7 $\pm$ 1.7	0.249
MLD, mm	2.92 $\pm$ 0.38	2.98 $\pm$ 0.37	0.342
DS, %	14.0 $\pm$ 10.2	13.6 $\pm$ 9.6	0.875
<i>Follow-up</i>			
MLD, mm	2.34 $\pm$ 0.75	2.60 $\pm$ 0.55	0.010
DS, %	19.2 $\pm$ 22.8	11.2 $\pm$ 16.5	0.008
Late lumen loss, mm	0.58 $\pm$ 0.65	0.38 $\pm$ 0.55	0.026
Restenosis	9/69 (13.0%)	4/107 (3.7%)	0.036

PR/IR = Positive or intermediate remodeling; NR = negative remodeling; RVD = reference vessel diameter; MLD = minimal luminal diameter; DS = diameter stenosis.

Table 3. Quantitative intravascular ultrasound results (all)

	PR/IR (n = 69)	NR (n = 107)	p value
<i>Before the intervention</i>			
Proximal reference			
EEM CSA, mm ²	13.39 ± 4.25	14.26 ± 4.34	0.195
Lesion segment			
EEM CSA, mm ²	12.77 ± 4.75	9.39 ± 3.34	0.000
Lumen CSA, mm ²	2.04 ± 1.04	1.97 ± 0.86	0.625
P+M CSA, mm ²	10.63 ± 4.56	7.43 ± 3.18	0.000
RI	1.12 ± 0.16	0.75 ± 0.12	0.000
Distal reference			
EEM CSA, mm ²	10.41 ± 4.10	10.54 ± 3.95	0.841
<i>After the intervention</i>			
Minimal stent CSA, mm ²	7.77 ± 2.46	7.67 ± 2.34	0.788
Symmetry index	1.07 ± 0.56	1.09 ± 0.68	0.256
<i>Follow-up</i>			
Lumen volume, mm ³	166.4 ± 67.6	168.9 ± 60.0	0.797
IH volume, mm ³	22.6 ± 26.2	12.4 ± 17.4	0.002
%IH	12.9 ± 14.8	7.0 ± 9.6	0.002

PR/IR = Positive or intermediate remodeling; NR = negative remodeling; P+M = plaque plus media.

Table 4. Quantitative IVUS results for SES implantations

	PR/IR (n = 27)	NR (n = 53)	p value
<i>Before the intervention</i>			
Proximal reference			
EEM CSA, mm ²	12.92 ± 2.55	14.31 ± 4.57	0.148
Lesion segment			
EEM CSA, mm ²	12.41 ± 3.29	9.36 ± 3.42	0.000
Lumen CSA, mm ²	2.28 ± 1.17	2.08 ± 0.75	0.346
P+M CSA, mm ²	10.14 ± 3.07	7.28 ± 3.27	0.000
RI	1.12 ± 0.14	0.75 ± 0.11	0.000
Distal reference			
EEM CSA, mm ²	9.47 ± 2.59	10.45 ± 4.13	0.261
<i>After the intervention</i>			
Minimal stent CSA, mm ²	7.29 ± 1.60	7.11 ± 1.59	0.645
Symmetry index	1.06 ± 0.63	1.07 ± 0.59	0.483
<i>Follow-up</i>			
Lumen volume, mm ³	175.0 ± 73.3	166.2 ± 53.8	0.797
IH volume, mm ³	5.8 ± 10.4	3.8 ± 6.2	0.287
%IH	3.8 ± 7.1	2.5 ± 4.1	0.272

PR/IR = Positive or intermediate remodeling; NR = negative remodeling; P+M = plaque plus media.

Table 5. Quantitative IVUS for PES implantations

	PR/IR (n = 42)	NR (n = 54)	p value
<i>Before the intervention</i>			
Proximal reference			
EEM CSA, mm ²	13.70 ± 5.06	14.21 ± 4.14	0.589
Lesion segment			
EEM CSA, mm ²	13.00 ± 5.51	9.43 ± 3.29	0.000
Lumen CSA, mm ²	1.88 ± 0.93	1.86 ± 0.95	0.929
P+M CSA, mm ²	10.96 ± 5.32	7.57 ± 3.12	0.000
RI	1.12 ± 0.17	0.76 ± 0.13	0.000
Distal reference			
EEM CSA, mm ²	11.02 ± 4.76	10.62 ± 3.81	0.648
<i>After the intervention</i>			
Minimal stent CSA, mm ²	7.24 ± 1.96	7.21 ± 1.70	0.929
Symmetry index	1.07 ± 0.72	1.08 ± 0.49	0.620
<i>Follow-up</i>			
Lumen volume, mm ³	160.7 ± 63.9	171.5 ± 61.9	0.797
IH volume, mm ³	33.7 ± 27.6	20.9 ± 20.5	0.011
%IH	18.9 ± 15.6	11.5 ± 11.3	0.008

PR/IR = Positive or intermediate remodeling; NR = negative remodeling; P+M = plaque plus media.

rial remodeling was a significant independent variable for predicting the IH volume in the PES patients (p = 0.018).

Correlation between the RI and IH

The correlation between the RI and the IH volume at follow-up in each patient group is shown in figures 1 and 2. Although there was no correlation between the two parameters in the SES patients (r = -0.032, p = 0.775), a positive correlation was noted in the PES patients (r = 0.234, p = 0.023).

Discussion

In the present study population, as in previous studies [3–5, 8, 9], the baseline remodeling characteristics of the lesion appeared to affect the efficacy after PES implantation, but not after SES implantation. The SES was found to suppress IH effectively, irrespective of any arterial remodeling.

Most previous IVUS studies have shown that positive preinterventional arterial remodeling is related to poor long-term outcomes (more frequent restenosis/target le-

Fig. 1. Correlation between the preinterventional RI and volume of IH at follow-up in the patients with PES (a) and SES (b) implantations.

sion revascularization or more IH at follow-up) after bare metal stent implantations [1, 2, 5], whereas some studies have had controversial results [10]. Moreover, positive remodeling lesions had a larger follow-up IH volume after PES implantation [3, 4]. A possible explanation is that positive remodeling lesions are related to unstable patients who have poor clinical outcomes and also that unstable plaques may be biologically more active [7, 11–13]. Histopathologic studies revealed that positive remodeling is associated with the histological characteristics of inflammation including increased macrophage and matrix metalloproteinase expressions which are similar to those unstable and ruptured lesions, suggesting a link between remodeling and inflammation [14–16]. We had reported that an increased inflammatory response, measured by the high-sensitivity C-reactive protein levels, might be associated with an increased IH volume in lesions with positive remodeling after a DES implantation [17]. Mintz et al. [3] reported that preinterventional arterial remodeling, especially negative remodeling, influenced IH suppression after the implantation of non-polymer-encapsulated paclitaxel-coated stents in a small patient population. In their study, the %IH was measured to be $18 \pm 13\%$ for positive remodeling, $23 \pm 22\%$ for intermediate remodeling and $6 \pm 10\%$ for negative remodeling, and the %IH (overall 16%) was greater than that for SESs or polymer-based PESs in other studies [18–20]. They inferred that a greater suppression of IH would blunt the relationship between preinterventional arterial remodeling and subsequent IH accumulation; this assumption is substantiated by the present study. Endo et

al. [1] showed that preinterventional remodeling influenced the IH in 113 selected patients treated with a single bare metal stent. In that study, the %IH was measured to be $51 \pm 19\%$ for positive remodeling, $42 \pm 18\%$ for intermediate remodeling, and $35 \pm 20\%$ for negative remodeling lesions. In the present study, although the overall %IH (2.8%) in the SES patients was similar to previous studies [18, 19], the overall %IH (13.8%) in the PES patients was similar or slightly higher than that in previous studies [21, 22]. On the other hand, Kaneda et al. [8] reported that although the data were analyzed with 2D IVUS, there was no relationship between the arterial remodeling/plaque burden and the IH after SES implantation, a finding compatible with the present study. The present study suggests that DESs may have a different effect on reducing IH accumulation in lesions with preinterventional positive remodeling characteristics, which may be related to the different properties of the drug and delivery platform. Accordingly, further studies are needed to examine whether the lesion characteristics affect IH after implantation of other kinds of DES.

Study Limitations

There are several limitations to be mentioned regarding the present study. First, highly selected lesions were included in this study, raising the possibility of selection bias. Therefore, the findings of this study cannot be applied to all coronary lesions. Second, for the assessment of the vascular remodeling, only a single IVUS image in the culprit lesion was assessed. The lesion may feature various geometric differences along its length, so that the

chosen frame may not be characteristic of certain biological properties of the entire stenosis. Third, 9 months' follow-up duration may not be enough to see subsequent findings or the relationships identified in the present study.

Conclusion

This prospective observational IVUS study showed that DESs may have a different effect on reducing IH accumulation in lesions with preinterventional positive remodeling characteristics, which may be related to the different properties of the drug and delivery platform.

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