Impact of Preinterventional Arterial Remodeling on Neointimal Hyperplasia After Implantation of (Non–Polymer-Encapsulated) Paclitaxel-Coated Stents

A Serial Volumetric Intravascular Ultrasound Analysis From the ASian Paclitaxel-Eluting Stent Clinical Trial (ASPECT)

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Background—This study used serial volumetric intravascular ultrasound (IVUS) to evaluate the effect of preinterventional arterial remodeling on in-stent intimal hyperplasia (IH) after implantation of non–polymer-encapsulated paclitaxel-coated stents.

Methods and Results—Patients were randomized to placebo or one of two doses of paclitaxel (low dose, 1.28 $\mu g/mm^2$; high dose, 3.10 $\mu g/mm^2$). Complete preinterventional, post–stent implantation, and follow-up IVUS were available in 18 low-dose and 21 high-dose patients. IH volumes were similar in low-dose and high-dose patients: 17.6 ± 15.1 mm^3 in low-dose patients and 13.1 ± 13.3 mm^3 in high-dose patients ($P=0.3$). Therefore, IVUS findings in low- and high-dose patients were combined. Preinterventional remodeling was assessed by comparing lesion site to proximal and distal reference arterial area: positive remodeling (lesion>proximal reference, n=13), intermediate remodeling (distal reference<lesion<proximal reference, n=13), and negative remodeling (lesion<distal reference, n=13). During follow-up, there was a decrease in lumen volume in positive remodeling lesions (from 106 ± 30 to 90 ± 27 mm^3; $P=0.0067$) and in intermediate remodeling lesions (from 97 ± 28 to 76 ± 31 mm^3; $P=0.0004$), but not in negative remodeling lesions (99 ± 27 versus 92 ± 32 mm^3; $P=0.15$). The follow-up IH volume was lower in negative remodeling lesions (5 ± 7 mm^3) compared with positive remodeling (20 ± 14 mm^3; $P=0.0051$) and intermediate remodeling lesions (20 ± 15 mm^3; $P=0.0043$); however, IH volume was virtually identical in positive and intermediate remodeling lesions. Multivariate linear regression analysis determined that remodeling and inflation pressure were independent predictors of IH volume; variables tested in the model included diabetes, acute coronary syndromes, dose, remodeling, and preinterventional plaque burden.

Conclusions—Preinterventional arterial remodeling, especially negative remodeling, influences neointimal hyperplasia suppression after implantation of non–polymer-encapsulated paclitaxel-coated stents. **(*Circulation*. 2003;108:1295-1298.)**

Key Words: stents ■ remodeling ■ ultrasonics ■ hyperplasia ■ paclitaxel

The major limitation of coronary stenting is in-stent restenosis secondary to intimal hyperplasia (IH).[1] Previous studies have shown that preinterventional arterial remodeling—as assessed by intravascular ultrasound (IVUS)—predicts both IH (also as assessed by IVUS) and clinical restenosis.[2,3] Non–polymer-encapsulated paclitaxel-coated stents reduce IH accumulation and angiographic restenosis.[4,5] The aim of the present study was to use serial volumetric IVUS analysis to determine the relationship between IH and preinterventional arterial remodeling after implantation of paclitaxel-coated stents.

Methods

ASPECT (ASian Paclitaxel-Eluting Stent Clinical Trial) was a three-center, triple-blind, randomized, placebo-controlled trial of paclitaxel-coated stents to reduce in-stent restenosis.[4] There was a single-center IVUS substudy of ASPECT (Asan Medical Center).[5] All patients gave their written, informed consent. This study was approved by Asan Medical Center Institutional Review Board.

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TABLE 1. Patient and Lesion Characteristics

	Positive Remodeling	Intermediate Remodeling	Negative Remodeling	*P* ANOVA
No. of patients	13	13	13	...
High dose/low dose, n	9/4	7/6	5/8	0.3
Age, y	62±11	57±11	53±12	0.12
Male gender, n	10	10	12	...
Diabetes, n	1	3	0	0.14
Hypertension, n	5	8	5	0.4
Cholesterol, mg/dL	205±35	186±49	186±26	0.4
Smokers, n	7	6	5	0.7
Acute coronary syndrome, n	7	9	10	0.4
De novo lesion, n	13	13	13	1.0
Inflation pressure, atm	12±3	12±3	12±3	0.8
Angiography				
Lesion length, mm	12±4	11±3	12±2	0.6
Reference vessel size, mm	3.1±0.5	3.1±0.4	3.0±0.4	0.8
Preintervention MLD, mm	0.9±0.4	0.9±0.2	0.9±0.3	1.0
Postintervention MLD, mm	3.4±0.3	3.2±0.4	3.1±0.4	0.3

MLD indicates minimum lumen diameter.

Ninety-eight patients were enrolled in the IVUS substudy. Complete preinterventional, post–stent implantation, and 6-month follow-up IVUS data were available in 18 of 32 low-dose and 21 of 33 high-dose patients, excluding those in whom the proximal reference (n=2) or distal reference (n=4) could not be assessed. Preinterventional IVUS imaging was not specified in the protocol; therefore, this represents a post hoc analysis of patients in whom preinterventional IVUS was performed and complete preinterventional IVUS analysis was possible. Because, in the overall IVUS cohort, follow-up IH volume was similar in low-dose and high-dose patients,[5] all patients treated with paclitaxel-coated stents were combined for the present analysis.

Stents were placed after predilation. Glycoprotein IIb/IIIa inhibitors were not used. Quantitative angiography was performed using the guiding catheter for magnification calibration and an online analysis system (ANCOR V2.0, Siemens).

IVUS Imaging and Analysis

IVUS imaging was performed after intracoronary administration of 0.2 mg nitroglycerin using a motorized transducer pullback system (0.5 mm/s) and commercial scanner (SCIMED) consisting of a 30-MHz transducer within a 3.2F imaging sheath.

Quantitative volumetric IVUS analysis was performed using computerized planimetry (Indec Systems) by an independent core laboratory (Washington Hospital Center, Washington, DC) according to published standards.[6] Preinterventional lesion and proximal and distal reference segment external elastic membrane (EEM), lumen, and plaque and media (P&M=EEM−lumen) cross-sectional areas (CSAs) and plaque burden (P&M/EEM) were measured. The lesion was the site with the smallest lumen CSA; if there were multiple image slices with the same minimum lumen CSA, then the slice with the largest EEM and P&M was measured. The proximal and distal reference segments were the least-diseased image slices (largest lumen with least plaque) proximal and distal to the lesion, but within the same segment and before any major side branch. Preinterventional remodeling was assessed by comparing the lesion site EEM to the proximal and distal reference EEM CSA: positive remodeling (lesion>proximal reference), intermediate remodeling (distal reference<lesion<proximal reference), and negative remodeling (lesion<distal reference).

Postinterventional and follow-up stent, lumen, and IH (stent minus lumen) areas were measured every 1 mm within the stented segment. Volumes were calculated using Simpson's rule.

Statistical Analysis

Statistical analysis was performed with StatView 4.5 (SAS Institute). Data are presented as mean±1SD or frequencies and compared using factorial ANOVA with post hoc comparisons using the Bonferroni correction for student's *t* test or χ^2 statistics.

Results

The numbers of patients treated with high-dose versus low-dose stents were similar in all three groups, and there were no differences in patient, lesion, or procedural variables (Table 1). As in the previous IVUS report from ASPECT, IH volumes were similar in low-dose and high-dose patients: 17.6±15.1 mm^3 in low-dose patients and 13.1±13.3 mm^3 in high-dose patients ($P=0.3$) with %IH (IH volume/stent volume) measuring 13±13 in low-dose and 19±20 in high-dose patients ($P=0.3$).

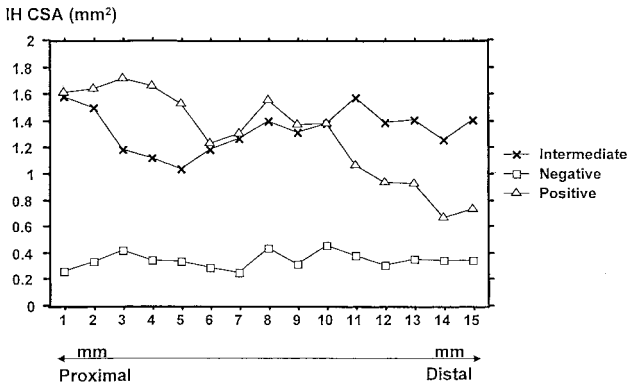
Preinterventional IVUS measurements are shown in Table 2. In keeping with the remodeling classification, lesion segment EEM and P&M CSA were largest in positive remodeling lesions and smallest in negative remodeling lesions. Distal reference EEM measurements were larger in positive remodeling lesions compared with intermediate and negative remodeling lesions ($P=0.0104$ and $P=0.0481$, respectively), but otherwise, reference segment measurements were similar among the three groups.

Postinterventional and follow-up IVUS measurements are shown in Table 2. Baseline stent volumes and minimum stent CSA were similar among the three groups. During the follow-up period, there was a decrease in lumen volume in the positive remodeling lesions (from 106±30 to 90±27 mm^3; $P=0.0067$) and in the intermediate remodeling lesions (from 97±28 to 76±31 mm^3; $P=0.0004$), but not in

TABLE 2. IVUS Findings

	Positive Remodeling	Intermediate Remodeling	Negative Remodeling	*P* ANOVA
No. of patients	13	13	13	...
Preintervention				
Proximal reference				
EEM CSA, mm^2	13.3±3.2	11.7±2.5	12.1±3.9	0.4
Lumen CSA, mm^2	6.1±2.2	6.0±1.7	6.8±2.1	0.7
P&M CSA, mm^2	7.2±2.1	5.7±2.1	5.5±3.0	0.16
Lesion segment				
EEM CSA, mm^2	14.7±3.4	10.3±2.6	9.7±4.5	0.0018
Lumen CSA, mm^2	1.7±0.7	1.2±0.3	1.5±1.0	0.16
P&M CSA, mm^2	13.0±2.9	9.1±2.7	8.2±4.1	0.0016
Plaque burden	88±3%	87±6%	83±6%	0.0464
Distal reference				
EEM CSA, mm^2	13.3±3.9	9.3±2.7	10.2±3.9	0.031
Lumen CSA, mm^2	7.5±3.3	5.1±2.0	5.7±2.7	0.053
P&M CSA, mm^2	5.8±1.9	4.2±1.7	4.6±2.3	0.13
Postintervention				
Stent volume, mm^3	106±30	98±28	99±27	0.7
Minimum stent CSA, mm^2	5.7±1.6	5.5±1.9	5.6±1.7	0.9
Follow-up				
Stent volume, mm^3	110±30	96±25	99±26	0.4
IH volume, mm^3	20±14	20±15	5±7	0.0054
%IH	18±13	23±22	6±10	0.0275

the negative remodeling lesions (99±27 versus 92±32 mm^3; $P=0.15$). Overall, IH volumes and %IH were similar in patients with diabetes versus no diabetes and acute coronary syndromes versus stable angina; IH volumes and %IH did not correlate with preinterventional plaque burden or lesion length. The follow-up IH volume was lower in negative remodeling lesions compared with positive remodeling and intermediate remodeling lesions ($P=0.0051$ and $P=0.0043$, respectively). However, IH volumes were virtually identical in positive and intermediate remodeling lesions. The Figure shows the comparison of the distribution of IH over the length of the stent according to the baseline pattern of arterial remodeling. Multivariate linear regression analysis determined that remodeling and inflation pressure were independent predictors of IH volume; variables tested in the model included diabetes, acute coronary syndromes, inflation pressure, dose, remodeling, and preinterventional plaque burden.



Follow-up IH CSA over the length of the paclitaxel-coated stents is shown for lesions with positive, intermediate, and negative preinterventional remodeling.

Discussion

The present IVUS study demonstrated that, as in bare metal stents, IH accumulation after implanting non–polymer-encapsulated paclitaxel-coated stents is related to the baseline remodeling characteristics of the lesion.

Pathological studies have suggested that in the early stage of atherosclerosis, human coronary arteries enlarge (positive remodeling) in parallel with the formation of atherosclerotic plaque and that the lumen area is preserved until progressive plaque accumulation exceeds compensatory mechanisms.[7] IVUS studies have confirmed the presence of positive remodeling, especially in acute coronary syndromes.[8] However, these IVUS studies have also shown that negative remodeling (shrinkage of EEM CSA at the lesion site) is observed in 15% to 34% of stenotic lesions and, along with the plaque accumulation, contributes to luminal narrowing.[9,10] Studies correlating IVUS and clinical findings have suggested that positive remodeling lesions may be more biologically active and negative remodeling lesions more inert.

Nishioka et al[10] first proposed the classification of remodeling used in the present study. Using this classification, Endo et al[2] showed that preinterventional remodeling influenced IH in 113 selected patients treated with a single stent. In this

study, %IH measured 51±19% in positive remodeling, 42±18% in intermediate remodeling, and 35±20% in negative remodeling lesions. Using other definitions of remodeling and different end points, the relationship between preinterventional remodeling and in-stent restenosis was substantiated by other investigators.[3,11,12] The present study suggests that drug-eluting stents may have a greater effect on reducing IH accumulation in lesions with preinterventional negative remodeling characteristics. However, %IH in ASPECT (overall 16%) was greater than in sirolimus-eluting stents in RAVEL (RAndomized study with the sirolimus-eluting Bx VELocity balloon-expandable stent) (overall IH=1%)[13] or SIRIUS (a multicenter randomized double-blind study of the SIRolImUS-coated Bx Velocity stent) (overall IH=3%, unpublished observations, M. Leon, MD, Cardiovascular Research Foundation, New York, NY, September 2002) as well as in polymer-based paclitaxel-eluting stents (overall IH=8%, unpublished observations, A. Colombo, MD, Columbus Hospital, Milan, Italy, September 2002). It is likely that greater suppression of neointimal hyperplasia will blunt the relationship between preinterventional remodeling and subsequent IH accumulation.

Limitations

Complete (pre- and postinterventional and follow-up) IVUS analysis was available in only a subset of patients in ASPECT. The control group of ASPECT with complete IVUS (n=16) was too small for meaningful analysis in the present study. Although there was no difference between IH in the low- versus high-dose patients (which was why the two groups were combined), the small number of patients in each group might have masked any differences between low- and high-dose patients. As noted, the present findings will likely not apply to other, more "powerful," drug-eluting stents. This was a retrospective analysis.

Conclusions

Preinterventional arterial remodeling, especially negative remodeling, influences neointimal hyperplasia suppression after implantation of non–polymer-encapsulated paclitaxel-coated stents.

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