Early Lumen Loss After Treatment of In-Stent Restenosis
An Intravascular Ultrasound Study

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Methods

Background—Mechanisms of recurrence after treatment of in-stent restenosis are unknown.

Methods and Results—We prospectively performed quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) in 37 lesions with Palmaz-Schatz stents enrolled in a study of intracoronary radiation for in-stent restenosis. Primary treatment was at the discretion of the operator: PTCA (n = 8) or ablation + adjunct PTCA (n = 29). Lesions were studied before intervention, immediately after primary intervention, and 42 ± 8 minutes later. QCA measurements included minimal luminal diameter and diameter stenosis. Planar IVUS measurements included arterial, stent, lumen, and in-stent tissue areas. Stent, lumen, and in-stent tissue volumes were calculated by use of Simpson’s rule. Compared with immediately after intervention, the delayed (42 ± 8 minutes) minimal lumen area decreased by 20% (5.8 ± 1.9 to 4.5 ± 1.3 mm², P < 0.0001) and the lumen volume by 12% (58 ± 41 to 52 ± 37 mm³, P = 0.0001). Ten lesions (27%) had a ≥ 20-mm² decrease in minimum lumen area. Lumen loss (1) resulted from increased tissue with the stent, (2) correlated with lesion length and preintervention in-stent tissue, and (3) was not seen angiographically.

Conclusions—There is significant tissue reinsertion shortly after catheter-based treatment of in-stent restenosis. This was greater in longer lesions and those with a larger in-stent tissue burden, was not reflected in the QCA measurements, and may contribute to recurrence. (Circulation. 1998;98:200-203.)

Key Words: restenosis ▪ stents ▪ ultrasonics

Stents have a lower restenosis rate than balloon angioplasty (PTCA). However, in-stent restenosis rates of 20% to 30% persist, in-stent restenosis results from intimal hyperplasia, and treatment remains unsatisfactory. During initial experiences with intracoronary gamma radiation for in-stent restenosis, we observed significant lumen loss between completion of the intervention and the end of the dwell time. The present study used intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) prospectively to assess early lumen loss after transcatheter treatment of in-stent restenosis.

Methods

Patient Population

From February to August 1997, 64 patients were enrolled in a study of intracoronary radiation for in-stent restenosis. In the present study, we analyzed 37 lesions (31 native coronary and 6 vein graft) in 36 patients (age, 62 ± 10 years; 24 men) previously treated with Palmaz-Schatz stents ( Cordis). Reasons for exclusion were restenting of the lesions (n = 13), no delayed (n = 6) or inadequate IVUS (n = 1), stent tissue < 75% of stent cross-sectional area (CSA; n = 2), restenosis localized to stent margin(s) (n = 1), or presence of non-Palmaz-Schatz stents (n = 5). (One patient had 2 lesions; per protocol, only 1 was enrolled in the radiation trial.) There were 65 stents (1.8 per lesion), implanted 9.6 ± 8.3 months previously. Fifteen patients (40%) had prior in-stent restenosis; the last episode was 5.5 ± 3.3 months previously.

Primary treatment strategy was determined by the operator: PTCA (n = 8), excimer laser coronary angioplasty (ELCA; Spectranetics; n = 12) + adjunct PTCA, or rotational atherectomy (RA; SCIMED/Boston Scientific Corp; n = 17) + adjunct PTCA. The largest laser fiber was 1.9 ± 0.2 mm; the largest burr, 2.0 ± 0.1 mm. Primary or adjunct balloon/artery ratio was 1.26 ± 0.21; maximal pressure was 15 ± 3 atm.

After intervention, patients were randomized to catheter-based gamma irradiation or placebo. A 5F closed-end catheter was positioned at the angioplasty site, and a nylon ribbon with active ( 192 Ir) or dummy seeds was introduced. The radiation dose was 15 Gy at 2 mm radially from the source; the dwell time averaged 24 ± 5 minutes. IVUS imaging was then repeated, 42 ± 8 minutes after the postintervention study.

QCA Analysis

By use of an automated edge-detection algorithm (CMS-GFT, Medis) and the outer diameter of contrast-filled catheters for calibration, lesion length ("shoulder to shoulder"), minimal luminal diameter (MLD), reference diameter, and percent diameter stenosis (DS) were measured in the same view before intervention, after intervention, and 42 ± 8 minutes later.

IVUS Image Acquisition and Analysis

All IVUS studies were performed after 200 mg intracoronary nitroglycerin. IVUS was performed before intervention in 27 lesions and after intervention and 42 ± 8 minutes later in all 37 lesions.
Studies were performed with single-element 30-MHz transducers rotating at 1800 rpm and withdrawn automatically at 0.5 mm/s within a 3.2F short monorail imaging catheter (CardioVascular Imaging Systems, Inc). Complete imaging runs were performed from beyond the stent to the aorto-ostial junction. Studies were recorded on 1/2-in high-resolution s-VHS tapes.

Reproducibility of IVUS in studies of stented lesions has been reported. Reproducibility of IVUS in studies of stented lesions has been reported.\textsuperscript{10} Automatic transducer pullback length measurements have been validated.\textsuperscript{11} External elastic membrane (EEM, visible through the stent in 12 lesions), stent, and lumen CSAs were measured (TapeMeasure, Indec Systems). In-stent tissue CSA was calculated as stent minus lumen CSA, EEM corresponded to the media-adventitia border, a reproducible measure of total arterial CSA. When tissue encompassed the catheter, the lumen was assumed to be 0.9 mm\textsuperscript{2}. The length where in-stent tissue CSA was ≥75% of stent CSA (or was packed around the catheter) defined the in-stent restenotic lesion.

Measurements were made every 1 mm. Stent, lumen, and in-stent tissue volumes were calculated by Simpson’s rule and were measured on the first 20 lesions imaged before intervention.

Planar analysis was performed on all lesions. The delayed IVUS study was analyzed first to identify the smallest lumen CSA. Corresponding image slices were then identified and measured on the preintervention and postintervention studies.

### Statistical Analysis

Statistical analysis was performed with StatView 4.5 (Abacus Concepts) or SAS (SAS Institute). Continuous variables were compared by linear regression analysis, unpaired Student’s \( t \) test, or ANOVA for repeated measures. Post hoc, postintervention, and delayed measurements were compared by paired \( t \) test with the Bonferroni correction for multiple comparisons. A value of \( P<0.05 \) was considered significant except for post hoc comparisons in which \( P<0.017 \) was required (0.05 divided by 3).\textsuperscript{12,13}

### Results

#### QCA Results

Before intervention, lesion length measured 17.0±8.6 mm (range, 5.0 to 33.4 mm), reference diameter 2.82±0.61 mm, MLD 0.70±0.24 mm, and DS 75±9%. Postintervention MLD increased to 2.16±0.56 mm, and DS decreased to 26±15% (both \( P<0.0001 \)). After the delay, there was no significant change in MLD (2.09±0.48 mm, \( P=0.25 \)) or DS (26±17%, \( P=0.79 \)).

#### IVUS Results

The length of in-stent tissue occupying ≥75% stent CSA was 9.8±8.0 mm.

#### Volumetric Analysis

Stent volume increased from 84±63 mm\textsuperscript{3} before intervention to 102±73 mm\textsuperscript{3} after intervention, lumen volume increased from 16±11 to 58±41 mm\textsuperscript{3}, and in-stent tissue volume decreased from 68±52 to 44±33 mm\textsuperscript{3} (all \( P<0.0001 \); Figure 1). After the delay, lumen volume decreased to 52±37 mm\textsuperscript{3}, and in-stent tissue volume increased to 51±38 mm\textsuperscript{3} (both...
Lumen Loss After Treatment of In-Stent Restenosis

By both planar and volumetric IVUS analysis, there was a significant and consistent early lumen loss after “successful” treatment of in-stent restenosis; 27% of lesions had a ≥2.0-mm² decrease in lumen CSA that was not detected angiographically. The mechanism appeared to be tissue reintrusion back into the stent.

The reported recurrence rate after treatment of in-stent restenosis varies but may be greater in diffuse lesions.6,14 The present study found the greatest early lumen loss in lesions with the worst in-stent restenosis (longer lesions, more in-stent tissue).

Previous IVUS studies of in-stent restenosis have indicated that neointimal tissue ablation/extrusion and additional stent expansion are both important mechanisms of lumen recovery.7–9,15 This was confirmed in the present study.

Early lumen loss resulted from tissue reintrusion (decreased EEM and increased in-stent tissue). Despite additional stent expansion during the intervention, there was only a tendency for early stent recoil (decreased stent dimensions).

Early lumen loss correlated with lumen increase and tissue decrease during the intervention, not with additional stent expansion. However, (1) IVUS imaging was not performed after ablation and after adjunct PTCA, (2) ablation using ELCA or RA to treat in-stent restenosis tends to be modest,8,16 and (3) directional coronary atherectomy was not permitted. The present study cannot separate the impact of ablation versus extrusion or determine whether more aggressive tissue removal will limit early lumen loss.

Study Limitations
Only Palmaz-Schatz stents were included; the frequency and magnitude of these findings in other stents are unknown. Only 8 lesions were treated with PTCA alone, and 3 different treatment strategies were used (PTCA, ELCA+PTCA, and RA+PTCA). ELCA and RA device sizes tended to be modest. Not all of the lesions were imaged before intervention. In-stent tissue reintrusion could not be separated from thrombus formation. The EEM was visible through the stent in only 12 lesions. Because this is a randomized, double-
blinded study (not yet unblinded), the impact of radiation versus placebo cannot be determined.

Conclusions
Early tissue reintrusion into the stent after treatment of in-stent restenosis is common and often significant (≥2.0-mm² decrease in lumen CSA in 27%). This was greater in longer lesions and those with a larger in-stent tissue burden, was not reflected in the QCA measurements, and may contribute to recurrence.

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References
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