Small Stent Size and Intimal Hyperplasia Contribute to Restenosis: A Volumetric Intravascular Ultrasound Analysis

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Objectives. The purpose of this study was to use volumetric intravascular ultrasound analysis of Palmaz-Schatz stents to assess the in-stent restenotic process.

Background. By reducing lesion elastic recoil and chronic arterial remodeling, stents improve the long-term results of coronary angioplasty. However, stents are prone to the development of neointimal hyperplasia. Angiographic studies of stent restenosis have suggested that these hyperplastic responses are the cause of in-stent restenosis; however, it is difficult to visualize the radiolucent Palmaz-Schatz stent by angiography. Intravascular ultrasound provides detailed cross-sectional imaging of the coronary arteries, especially the intense metallic reflection of endovascular stents.

Methods. Forty-four patients with 60 Palmaz-Schatz stents underwent intravascular ultrasound imaging at follow-up ([mean ± SD] 8.8 ± 7.2 months after implantation). Thirty-four stents were placed in saphenous vein grafts and 26 in native coronary arteries; 30 were placed in restenotic lesions. Intravascular ultrasound with automatic transducer pullback at 0.5 mm/s allowed measurement of stent, lumen and intimal hyperplasia cross-sectional areas at 1-mm axial increments within the stents. Using Simpson's rule, stent, lumen and intimal hyperplasia volumes were calculated. Patterns of in-stent restenosis were then identified.

Results. Restenotic stents had smaller stent volumes (120 ± 41 vs. 147 ± 43 mm³, p = 0.016) and lumen volumes (62 ± 28 vs. 118 ± 42 mm³, p < 0.0001) but larger intimal hyperplasia volumes (58 ± 36 vs. 29 ± 18 mm³, p < 0.001) than nonrestenotic stents. A focal restenosis pattern was more common (20 [77%] of 26) than a diffuse restenosis pattern (6 [23%] of 26). Stents with focal restenosis and stents with diffuse restenosis had equally small stent volumes (120 ± 44 vs. 120 ± 31 mm³, respectively, p = NS); however, stents with diffuse restenosis had larger intimal hyperplasia volumes (84 ± 30 vs. 50 ± 34 mm³, p < 0.05). Focal restenosis was most commonly located at the central articulation (45%); the location of focal restenosis was related to the focal accumulation of neointimal tissue.

Conclusions. Stent volume and magnitude and distribution of intimal hyperplasia are important in the development of in-stent restenosis. Stent volume was smaller and intimal hyperplasia volume greater in restenotic stents. Stent restenosis is more commonly focal in nature and located at the central articulation.

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Stents were developed to improve the short- and long-term results of coronary angioplasty, and studies have shown reduced restenosis rates with Palmaz-Schatz tubular slotted stents compared with balloon angioplasty. These reduced restenosis rates are believed to be the result of both a reduction in the lesion elastic recoil and an inhibition of late arterial remodeling responses.

However, stented vessels are prone to the development of neointimal hyperplasia, which may also lead to restenosis. In fact, some animal models have shown that stent placement actually increases smooth muscle cell proliferation. Because in-stent restenosis continues to be an important clinical problem, a better understanding of the mechanisms involved may prove useful in developing more effective stent deployment and management strategies.

Although selective coronary angiography has been the reference standard for guiding revascularization, it has inherent limitations: errors caused by viewing a three-dimensional, tortuous vascular structure in only two dimensions; the inability to quantify the disease processes with negative contrast imaging; and difficulty in consistently visualizing the relatively radiolucent stainless-steel Palmaz-Schatz prosthesis. Alternatively, intravascular ultrasound allows detailed, cross-sectional imaging of the coronary arteries. The normal coronary arterial wall, the major components of the atherosclerotic plaque, the intense metallic reflection of endovascular stents and the

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quantitative changes in vessel and lumen dimensions can be studied in vivo in a manner otherwise not possible. Recently, volumetric intravascular ultrasound analysis has been applied to the assessment of the mechanisms and results of transcatheter therapies (1). The purpose of the present study was to use volumetric intravascular ultrasound analysis of Palmaz-Schatz stents to assess the in-stent restenotic process (2–4).

Methods

Patients. The study included 44 patients (38 men, 6 women; mean [±SD] age 51 ± 11 years, range 46 to 83). All 44 patients had follow-up coronary angiography and intravascular ultrasound imaging at the Washington Hospital Center a mean of 8.8 ± 7.2 months after stent placement. These patients represent a consecutive series of stents studied at follow-up before April 1994 and met the following criteria: native coronary (not biliary) stents, adequate images performed using motorized catheter pullback and imaging before a subsequent intervention. Stent location was a saphenous vein graft for 34 stents and a native coronary artery in 26. Six stents were placed in the aorto-ostial location. Thirty stents were placed in restenotic lesions. Fourteen stents were 3.0 mm; 25 were 3.5 mm; and 21 were 4.0 mm.

Angiographic analysis. Quantitative coronary angiography was performed by an independent angiographic core laboratory using an automated edge detection system (ImageComm, Santa Clara, CA). Minimal lumen diameter and reference lumen diameter were recorded in two orthogonal projections. Values from the “worst” view were used to calculate the lesion diameter stenosis at the stent site.

Intravascular ultrasound procedure. Follow-up intravascular ultrasound studies of Palmaz-Schatz tubular slotted stents were performed before any subsequent procedure (e.g., balloon angioplasty of in-stent restenosis). To perform volumetric analysis of in-stent restenosis, only imaging systems incorporating motorized transducer pullback (typically at 0.5 mm/s) through a stationary imaging sheath were used for this study. Motorized transducer pullback through a stationary imaging sheath allows the transducer to move at the same speed as the proximal end of the catheter. The first system (Cardiovascular Imaging Systems/InterTherapy) incorporated a single-element 25-MHz transducer coupled to an angled mirror mounted on the tip of a flexible shaft and rotated at 1,800 rpm within a 3.9F (1.3 mm) short monorail polyethylene imaging sheath to form planar cross-sectional images in real time. The second system (Cardiovascular Imaging Systems Inc) incorporated a 30-MHz beveled transducer rotated at 1,800 rpm within a 3.2F (1.07 mm) imaging sheath. All studies were recorded only during transducer pullback onto high quality S-VHS tape for off-line analysis.

Intravascular ultrasound measurements. Validation of measurements of arterial, lumen and plaque cross-sectional areas and volumes has been reported previously (1). In brief, on playback of the recorded studies, a frame was selected every 2 s of videotape (given a pullback speed of 0.5 mm/s, each 2 s of video playback corresponds to 1 mm of axial lesion length). Thus, 15 image slices were identified within each stent (the Palmaz-Schatz stent measures 15 mm in length); these image slices were numbered 1 (distal margin) through 15 (proximal margin). Using computerized planimetry, the stent and lumen cross-sectional areas of each image slice were traced manually, and the cross-sectional area of intimal hyperplasia present within the stent on each image slice was calculated as stent cross-sectional area minus lumen cross-sectional area. Stent and lumen volumes (in mm$^3$) were calculated using Simpson’s rule, and the intimal hyperplasia volume (also in mm$^3$) was calculated as stent volume minus lumen volume. In addition, the minimal stent cross-sectional area and minimal lumen cross-sectional area within the stent were identified.

Each stent was then compared with the reference lumen cross-sectional area, which was the average of the proximal and distal reference lumen cross-sectional areas. The reference lumen cross-sectional areas were the lumen areas at the most visually normal anatomic cross sections within 10 mm proximal and distal to the stent but before any major side branches. If a stent was ostial in location, then only the distal reference lumen was measured. The stent and lumen cross-sectional measurements at each image slice (as well as at the minimal lumen cross-sectional area within the stent) were used to calculate the following:

$$\text{Area stenosis} = \frac{\text{Reference lumen cross-sectional area} - \text{Lesion lumen cross-sectional area} \times 100}{\text{Reference lumen cross-sectional area}}$$

$$\text{Relative stent expansion} = \frac{\text{Stent cross-sectional area} \times 100}{\text{Reference lumen cross-sectional area}}$$

Definitions of restenosis. Stents were considered restenotic if the intravascular ultrasound area stenosis (minimal lumen cross-sectional area vs. reference lumen cross-sectional area) was ≥75% or if the quantitative angiographic diameter stenosis was ≥50%. The length of the stent with an ultrasound area stenosis ≥75% was then tabulated and used to identify two patterns of in-stent restenosis: 1) diffuse = restenotic stent with an ultrasound area stenosis ≥75% involving >50% of the length of the stent; focal = restenotic stent with an ultrasound area stenosis ≥75% involving <50% of the length of the stent. The focal pattern was further divided into 1) a marginal pattern of restenosis (maximal area stenosis within 2 mm of the distal or proximal stent margins as long as the stent margin was also involved); 2) a central articulation pattern of restenosis (maximal area stenosis within 2 mm of the central articulation as long as the central articulation was also involved); and 3) body restenosis (maximal area stenosis was >2 mm away from the margins and central articulation of the stent and no involvement of the margins or central articulation).

Finally, to further analyze the focal patterns of in-stent restenosis, the 15 image slices/stent were grouped into five segments: 1) slices 1 to 3 = the distal margin; 2) slices 4 and 5 = the distal body; 3) slices 6 to 10 = the central articulation; 4) slices 11 and 12 = the proximal body; and 5) slices 13 to 15 =
the proximal margin. The stent, lumen and intimal hyperplasia cross-sectional areas at these five segments were then compared.

Statistics. Statistical analysis was performed using StatView 4.02. Continuous data are presented as mean value ± SD and categoric values as frequencies. Comparisons between restenotic and nonrestenotic stents were performed using the student t test. Comparison of stent segments was done using factorial analysis of variance with post hoc analysis using the Fisher protected least significant difference. A p value < 0.05 was considered statistically significant.

Results

Quantitative angiographic results. Table 1 compares the quantitative angiographic and intravascular ultrasound lesion site measurements in nonrestenotic and restenotic stents. Twenty-six stents had in-stent restenosis. Restenotic stents had smaller minimal stent cross-sectional areas (7.3 ± 3.29 vs. 8.97 ± 3.01 mm², p < 0.05) and more intimal hyperplasia (5.49 ± 3.31 vs. 3.06 ± 1.88 mm², p < 0.001). Relative stent expansion was similar in both groups but overall was only 77.7% ± 25.0% of the reference lumen cross-sectional area.

Volumetric intravascular ultrasound results. Table 2 compares the stent, lumen and intimal hyperplasia volumes for restenotic and nonrestenotic stents. Restenotic stents had smaller stent volumes (120 ± 31 vs. 147 ± 43 mm³, p = 0.016), smaller lumen volumes (62 ± 28 vs. 118 ± 42 mm³, p < 0.0001) and larger intimal hyperplastic volumes (58 ± 36 vs. 29 ± 18 mm³, p < 0.001). Intimal hyperplasia volumes did not correlate with duration of stent implantation.

Patterns of restenosis. Focal restenosis was the most common pattern of in-stent restenosis (20 [77%] of 26); diffuse restenosis was seen in only six stents. As shown in Table 3, there was no difference in volume between stents with a diffuse pattern of in-stent restenosis and stents with a focal pattern of in-stent restenosis (120 ± 31 vs. 120 ± 44 mm³, respectively, p = NS). However, in a diffuse pattern of restenosis, the lumen volumes were smaller (36 ± 15 vs. 70 ± 26 mm³, p < 0.005) and the intimal hyperplastic volumes larger (84 ± 30 vs. 50 ± 34 mm³, p < 0.05). Focal restenosis was localized to the central articulation in nine stents (45%), to the stent margins in six stents (30%) and to just the body of the stent in five stents (25%). The duration of implantation of stents with a diffuse pattern of restenosis tended to be shorter than nonrestenotic stents or stents with a focal pattern of in-stent restenosis; however, this difference did not reach statistical significance.

Analysis of the five stent segments (distal margin, distal body, central articulation, proximal body and proximal margin) in all 60 stents is shown in Table 4. There was no significant difference in stent cross-sectional area among these five segments. Mean lumen cross-sectional area was significantly smaller at the central articulation (5.7 ± 3.3 mm²) than at both stent margins, whereas mean lumen cross-sectional area was larger at the proximal margin (7.2 ± 3.5 mm²) than at all other stent segments. The differences in lumen dimensions are

| Table 1. Comparison of Lesion Site Quantitative Coronary Angiographic and Planar Intravascular Ultrasound Analysis in Nonrestenotic Versus Restenotic Stents |
|---------------------------------|---------------------------------|---------------------------------|----------------|
|                                 | No Restenosis (n = 34)          | Restenosis (n = 26)             | p Value       |
|                                 | (mean ± SD)                     | (mean ± SD)                     |               |
| Quantitative angiography        |                                 |                                 |               |
| Reference (mm)                  | 3.38 ± 0.51                     | 3.14 ± 0.43                     | 0.076         |
| Minimal lumen diameter (mm)     | 2.53 ± 0.52                     | 0.90 ± 0.57                     | < 0.0001      |
| Diameter stenosis (%)           | 24.8 ± 11.9                     | 73.0 ± 17.0                     | < 0.0001      |
| Intravascular ultrasound        |                                 |                                 |               |
| Reference lumen CSA (mm²)       | 11.7 ± 4.2                      | 9.74 ± 2.36                     | < 0.05        |
| Minimal lumen CSA (mm²)         | 5.90 ± 2.48                     | 1.79 ± 0.89                     | < 0.0001      |
| Minimal stent CSA (mm²)         | 8.97 ± 3.01                     | 7.30 ± 3.29                     | < 0.05        |
| Intimal hyperplasia CSA (mm²)   | 3.06 ± 1.88                     | 5.49 ± 3.31                     | < 0.001       |
| Area stenosis (%)               | 48.9 ± 16.4                     | 80.8 ± 8.93                     | < 0.0001      |
| Stent expansion (%)             | 79.7 ± 19.8                     | 74.8 ± 31.1                     | 0.572         |

CSA = cross-sectional area.

Table 2. Comparison of Lesion Site Volumetric Intravascular Ultrasound Analysis in Nonrestenotic Versus Restenotic Stents

| Table 3. Volumetric Intravascular Ultrasound Analysis of Restenotic Stents According to Patterns of Restenosis |
|---------------------------------|---------------------------------|---------------------------------|----------------|
|                                 | Diffuse (n = 6)                 | Focal (n = 20)                  | p Value       |
|                                 | (mean ± SD)                     | (mean ± SD)                     |               |
| Stent volume (mm³)              | 120 ± 31                        | 120 ± 44                        | 0.999         |
| Lumen volume (mm³)              | 36 ± 15                         | 70 ± 26                         | < 0.005       |
| Intimal hyperplasia volume (mm³)| 84 ± 30                         | 50 ± 34                         | < 0.05        |
Ultrasound-guided high pressure adjunct balloon inflation strategies may further reduce restenosis rates.

During stent implantation procedures have shown that angiography volume was greater in restenotic than nonrestenotic stents; the patterns of in-stent restenosis were related to the axial distribution of neointimal tissue.

Stent volume. Stent volume was smaller in restenotic lesions regardless of the pattern of in-stent restenosis. A small stent volume can be the result of either 1) a long-term and progressive decrease in stent volume due to extrinsic compression (i.e., long-term stent recoil) or 2) a reduced stent volume during initial implantation due to either limited expansion or small intrinsic vessel size. Angiographically, there is minimal acute elastic recoil immediately after Palmaz-Schatz stent implantation and no recoil at 24 h (5,6). Similarly, neither quantitative angiographic nor intravascular ultrasound analysis has shown significant long-term recoil (7–9).

Numerous studies (5,10,11) have shown the importance of achieving a large lumen after catheter-based revascularization. Most of the stents analyzed in the present study had been deployed only with angiographic guidance. Recent reports (12,13) comparing intravascular ultrasound and angiography during stent implantation procedures have shown that angiography often misses early stent underexpansion. Similarly, the average relative stent expansion in the present study was 77%; after ultrasound-guided high pressure adjunct balloon inflation, it is possible to achieve a stent cross-sectional area equal to that of the reference lumen (relative stent expansion of 100%) (12,14). Preliminary studies (14,15) have shown that ultrasound-guided high pressure adjunct balloon inflation strategies may further reduce restenosis rates.

The smaller stent volume in restenotic lesions could also have been related to the fact that these were smaller vessels. Because restenosis has been linked to small vessel size (11,16,17) and because stents may have a greater impact in reducing restenosis in smaller than larger vessels, it may be more important to achieve a larger stent volume and a greater relative stent expansion in smaller vessels.

Intimal hyperplasia. Overall, neointimal hyperplasia volume was greater in restenotic stents than in nonrestenotic stents, and the distribution of neointimal tissue was linked to the pattern of restenosis. Neointimal hyperplasia is a common and nonspecific response to arterial injury. Previous studies (7,18) have shown that intimal hyperplasia covers the entire stent. Similarly, we found some degree of intimal hyperplasia in every stent segment, whether or not the stent was restenotic. However, the degree of intimal hyperplasia was highly variable, from almost none to completely obliterating the lumen.

Neointimal hyperplasia is also one of the main mechanisms of restenosis after angioplasty. Animal studies (19,20) using the pig model have shown that intimal hyperplasia is exaggerated by stent implantation. Similarly, clinical studies (7,11,21,22) with the Palmaz-Schatz, Wallstent and Wiktor stents have pointed to intimal hyperplasia as the cause for in-stent restenosis. Because stents do not recoil, late lumen loss is directly related to the amount of cellular proliferation.

Patterns of restenosis. We were able to define two main patterns of restenosis: a diffuse pattern and a focal pattern, the latter being more common. In both types, stent volumes were similar and smaller in restenotic than in nonrestenotic stents. Thus, the diffuse restenosis pattern was the result of a larger intimal hyperplasia burden than that with the focal restenosis pattern. This aggressive neointimal growth in the diffuse restenosis pattern has been associated with a higher frequency of recurrent restenosis after angioplasty than that with the focal pattern of restenosis (18).

The location of the focal in-stent restenosis was related to the focal accumulation of neointimal tissue. Although focal restenosis was seen in every stent segment, it was more frequent at the central articulation, which, overall, was the site of the smallest lumen and the largest amount of neointimal tissue. These findings agree with previous angiographic studies that have also pointed to the central articulation as the most frequent site for restenosis in Palmaz-Schatz stents. It has been postulated (23) that the central articulation stimulates smooth muscle cell proliferation, perhaps related to the manner in which the Palmaz-Schatz stent expands. Alternatively, the central articulation may allow tissue intrusion during deployment; the arterial injury at the central articulation may be greater; and the central articulation may allow more long-term intrusion of neointimal hyperplasia. Therefore, if technically possible, it seems prudent to avoid placing the central articulation at the site of tightest stenosis. Furthermore, these data support the development of new stent designs that would eliminate the central articulation as it is currently configured.

Study limitations. The retrospective nature of the present study limited it to patients with angiographic and intravascular...
ultrasound follow-up data. Thus, our patients may not repre-
sent the general population of patients treated with stents,
and there might be an overrepresentation of patients with
restenotic stents. Nevertheless, comparisons between rest-
stenotic and nonrestenotic stents are valid to assess the rest-
enotic process. Additionally, it would have been useful to have
intravascular ultrasound studies before and after stent implan-
tation to analyze and assess stent and reference vessel changes
thoroughly during implantation and follow-up.

References

1. Matar FA, Mintz GS, Farb A, et al. The contribution of tissue removal to
lumen improvement after directional coronary atherectomy. Am J Cardiol

2. Tenaglia AN, Buller CE, Kisslo KB, Stack RS, Davidson CJ. Mechanisms of
balloon angioplasty and directional atherectomy as assessed by intracoronary

sound characterization of the mechanisms of rotational atherectomy and

ultrasound guidance for catheter-based coronary intervention. J Am Coll
Cardiol 1991;17 Suppl B:39B-45B.

5. Kimura T, Nosaka H, Yokoi H, Iwabuchi M, Nobuyoshi M. Serial angiogra-
ic follow-up after Palmaz-Schatz stent implantation: comparison with

after balloon angioplasty and after intracoronary implantation of balloon-

Mechanisms of restenosis and redilation within coronary stents: quantitative

coronary in-stent restenosis: neointimal proliferation or stent compression?
Serial assessment by intravascular ultrasound [abstract]. Circulation 1993;88
Suppl I:1-598.

fail to show evidence of chronic Palmaz-Schatz stent recoil. Am J Cardiol

10. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of
restenosis after conventional balloon angioplasty, stenting, and directional

11. Ellis SG, Savage M, Fischman D, et al. Restenosis after placement of
Palmaz-Schatz stents in native coronary arteries. Initial results of a multi-

Benefit of intracoronary ultrasound in the deployment of Palmaz-Schatz

13. Laskey WK, Brady ST, Kussmaul WG, et al. Intravascular ultrasonic assess-
ment of the results of coronary artery stenting. Am Heart J 1993;125:
1576-83.

observations during stent implantation. Circulation 1994;89:2026-34.


16. Leon MB, Wong SC, Pichard AD. Balloon-expandable stent implantation in
of the Palmaz-Schatz Intracoronary Stent. Armonk (NY): Futura, 1993;111-
21.

17. Sutton JM, Ellis SG, Roubin GS, et al. Major clinical events after coronary
stenting: the multicenter registry of acute and elective Giantarco-Roubin

18. Yokoi H, Kimura T, Nobuyoshi M. Palmaz-Schatz coronary stent restenosis:

19. Schwartz RS, Huber KC, Murphy JG, et al. Restenosis and the proportion-
nal neointimal response to coronary artery injury: results in a porcine model.

20. Karas SP, Gravanis MB, Santoian EC, Robinson KA, Anderberg KA, King
SB. Coronary intimal proliferation after balloon injury and stenting in swine:


resurgence of restenosis after Wiktor stent implantation in native coronary

23. Ikari Y, Yamaguchi T, Tamura T, Sasaki F, Haru K. Site of restenosis in