Brief Rapid Communication

Impact of Peri-Stent Remodeling on Restenosis
A Volumetric Intravascular Ultrasound Study

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Background—Vessel remodeling is an important mechanism of late lumen loss after nonstent coronary interventions. However, its impact on in-stent restenosis has not been systematically investigated.

Methods and Results—Serial volumetric intravascular ultrasound analyses (poststent and follow-up) were performed in 55 lesions treated with a balloon-expandable stent (ACS MultiLink) using standard stent deployment techniques. The vessel volume (VV), lumen volume (LV), and volume bordered by the stent (SV) were measured using Simpson’s method. The volume of plaque and neointima outside the stent (peri-stent volume, PSV) and volume of neointima within the stent (intrastent volume) were also measured. The change of each parameter during the follow-up period (follow-up minus poststent) was calculated and then divided by SV to normalize these values (designated as percent change [%Δ]). As expected, %ΔPSV directly correlated with %ΔVV (P<0.0001, r=0.935), with no significant ΔSV. A highly significant inverse correlation was seen between %ΔPSV and the percent change of intrastent volume (P<0.0001, r=0.517). Consequently, %ΔLV significantly correlated with peri-stent remodeling, as measured by %ΔVV (P<0.0001, r=0.602).

Conclusion—Positive remodeling of the vessel exterior to a coronary stent occurs to a variable degree after stent implantation. There is a distinct trade-off between positive remodeling and in-stent hyperplasia: in segments in which the degree of peri-stent remodeling is less, intrastent neointimal proliferation is greater and accompanied by more significant late lumen loss. (Circulation. 2001;103:2130-2132.)

Key Words: coronary disease ▪ plaque ▪ remodeling ▪ stents ▪ restenosis

Negative remodeling has been identified as a major contributor to restenosis after angioplasty or atherectomy.1,2 The placement of a coronary stent effectively prevents negative remodeling, so the primary factor producing late lumen loss is proliferation of neointima within the stent.3,4 The occurrence of positive, peri-stent remodeling has been previously reported5,6; however, the potential link between positive remodeling, intimal proliferation, and late lumen loss has not been clearly defined. The aim of this study was to determine the association between vessel remodeling and the degree of peri-stent versus intrastent neointimal proliferation using volumetric intravascular ultrasound (IVUS) analysis.

Methods

Patient Population
The IVUS database of the Cardiovascular Core Analysis Laboratory at Stanford University was queried to identify patients with coronary artery disease who met the following criteria: (1) high-quality, automated pullback IVUS images with adequate visualization of the media-adventitia border throughout the entire stented segment after implantation and at follow-up; (2) successful treatment with a single MultiLink stent (Guidant Corporation) using standard stent implantation techniques without atheroablation; and (3) angiographically noncurved stented segment. Patients with IVUS images demonstrating severe lesion calcification or severe nonuniform rotational distortion or patients receiving >2 stents per lesion were excluded from this study. A total of 55 patients (50 men and 5 women; mean age, 61±10 years) with 55 lesions met the enrollment criteria. All stents were 15 mm in length with a mean follow-up period of 6.1±0.6 months. Lesion location included the left anterior descending artery (n=41), left circumflex artery (n=4), and right coronary artery (n=10). The protocol was approved by the institutional review board, and written informed consent was obtained from each patient before the IVUS procedure.

IVUS Imaging
All patients were premedicated with aspirin and received heparin (100 U/kg) before the procedures. Both poststent and follow-up ultrasound studies were performed using a commercially available imaging system with either a 3.2 F, 30 MHz or a 2.6 F, 40 MHz mechanical ultrasound catheter (Boston Scientific Corporation). After the intracoronary administration of 200 μg of nitroglycerin, the imaging catheter was advanced distal to the stented segment under fluoroscopic guidance. Using automated pullback (0.5 mm/s), ultra-
sound images were obtained and recorded on 0.5-inch S-VHS videotape for off-line quantitative analysis.

Quantitative IVUS Analysis
All measurements were performed by one individual who was blinded to clinical and angiographic information. Three-dimensional reconstruction of IVUS images was performed using a commercially available quantitative analysis system, which runs on an Intel Pentium-based PC system with Windows NT (echoPlaque, Indec Systems, Inc.). After digitization of IVUS recordings at a frame rate of 15 images per second, longitudinal views of the studied segments were automatically processed by the system. Lumen, stent, and external elastic membrane areas were manually traced at 16 frame intervals (Figure 1), and the interpolated measurements of the remaining frames were automatically generated. Using Simpson’s method, lumen volume (LV), stent volume (SV), and vessel volume inside the external elastic membrane (VV) were calculated, and the following volumetric parameters were defined for analysis: (1) intra-stent neointimal volume (ISV)=SV–LV and (2) peri-stent plaque plus neointimal volume (PSV)=VV–SV. The change of each parameter (Δ) was calculated as follow-up minus poststent measurements. To normalize the data for vessel size, these parameters were divided by the implanted SV in each case (thus correcting for the fact that for the same percentage change in neointima, the absolute volume change of each parameter would be much greater in a large vessel than a small vessel). Both the normalized (designated as percent change [%Δ]) and absolute data are presented.

To assess the reproducibility of IVUS measurements, follow-up images of 10 cases were randomly selected and reanalyzed at least 4 weeks after the initial reading. The intraobserver correlation coefficients for VV and IV were 0.997 and 0.998, and the percent errors were 1.82±1.04% and 2.93±1.73%, respectively.

Statistical Analysis
Statistical analysis was performed using StatView 4.5 (SAS Institute). Quantitative data, presented as mean±SD, were compared using a 2-tailed, paired Student’s t test or linear regression analysis. P<0.05 was considered significant.

Results
Overall, SV did not change between poststent and follow-up, indicating that no recoil or compression occurred during the follow-up period (107.4±24.8 to 107.8±25.7 mm³, P=0.59). LV significantly decreased from 107.4±24.8 mm³ at stent implantation to 71.4±26.0 mm³ at follow-up (P<0.0001); this was accompanied by neointimal proliferation inside the stent (0 to 36.6±18.0 mm³). VV significantly increased from 216.7±44.7 to 229.2±49.6 mm³ (P<0.0001), and PSV increased from 109.3±29.6 to 121.4±31.8 mm³ (P<0.0001).

%ΔLV correlated strongly with %ΔISV by linear regression analysis (P<0.0001, r=0.943), which is consistent with the observation that intrastent neointimal growth was the mechanism of LV reduction, as reported previously. A strong inverse correlation was seen between normalized %ΔPSV and %ΔPSV (P<0.0001, r=0.517; Figure 2). A significant correlation was also noted between absolute ΔISV and ΔPSV (P<0.01, r=0.346). As expected, %ΔVV directly correlated with %ΔPSV (P<0.0001, r=0.935). Accordingly, %ΔLV was inversely correlated with %ΔPSV (P<0.0001, r=0.505) and, therefore, it correlated with %ΔVV (P<0.0001, r=0.602).

Regarding the potential effect of the stent implantation technique, there was only a weak positive correlation between the maximum inflation pressure and peri-stent positive remodeling (P=0.05, r=0.33). No significant correlation was observed between the maximum inflation pressure and neointimal growth inside the stent.

Discussion
The major finding from this study is that peri-stent, positive remodeling occurs to a variable extent and is inversely correlated with the degree of neointimal proliferation. That is,
segments in which there is greater positive remodeling (a larger increase in peri-stent plaque plus neointimal volume) have smaller volumes of neointima within the stent and thus have less late lumen loss.

Coronary artery remodeling is a major factor contributing to restenosis after balloon angioplasty and atherectomy.1,2 The existence of positive, peri-stent arterial remodeling has been suggested in a study of first-generation stents3 and in a trial of stenting plus brachytherapy.4 However, whether or not there is an association between positive peri-stent remodeling and intrastent neointimal proliferation has remained controversial. In their recent study using second-generation stents, Kay et al5 suggested that positive remodeling occurs in radiated segments but not in normally stented segments. The present study, involving a single current-generation stent and complete volumetric IVUS analysis, showed a significant inverse correlation between peri-stent remodeling and intrastent neointimal proliferation in normal (nonirradiated) segments. This observation provides a new perspective on some other important issues in restenosis. The link between remodeling and in-stent restenosis is consistent with the fact that patients with impaired glucose tolerance, who are known to have a blunted adaptive remodeling response, show exaggerated intimal proliferation after stenting.6,7,8 The trade-off between positive remodeling and intimal proliferation could also help explain the beneficial effect of presten debulking on restenosis for some patients. Previous studies have shown that a proportion of atherectomy cases have significant positive remodeling,9 perhaps associated with weakening or excision of external lamina and other support structures in the arterial wall. Finally, as Kay et al5 have suggested, the impact of brachytherapy on intimal proliferation after stenting may also be due in substantial part to the effects of this treatment on positive remodeling.

The results of the current study clearly demonstrate the relationship between neointimal growth and vessel remodeling after conventional stent implantation. An important implication of this study is that the search for treatments of in-stent restenosis should include approaches to facilitate positive remodeling in the stented segment.

Study Limitations
First, this study is based on a relatively small, retrospectively selected patient population in whom a single stent was used, raising the possibility of selection bias. Second, in general, vessel dimensions beyond metallic stents may be obscured by struts and thus may not reflect the true vessel size of the stented segment. In this study, however, we included only the cases treated with a single MultiLink stent, the design of which permits fairly even transmission of the ultrasound beam around the stent struts. Furthermore, we excluded the cases in which complete tracking of the peri-stent vessel boundary was not available throughout the stented segment. These strict criteria for study patients minimized the influence of stent struts on the measurement of peri-stent vessel dimensions. Third, the current study does not address the extent of vessel remodeling beyond the stent edge to the adjacent reference segments. Also, the volumetric analyses used in this study may not represent well localized vessel responses in a specific subsegment. Therefore, further study to focus on these issues is needed. Finally, there are several inherent limitations in 3D analysis techniques, including the effects of movement artifacts and distortion due to curvature of the vessels.10

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References
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