Regional Remodeling as the Cause of Late Stent Malapposition

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Background—Late stent malapposition (LSM) is only detected if intravascular ultrasound (IVUS) is performed at implantation and follow-up. We used a novel “regional” IVUS analysis to assess the mechanism of LSM.

Methods and Results—Corresponding image slices on postimplantation and follow-up IVUS studies of 11 malapposed stents were identified and electronically rotated until they were aligned. The geometric center of the stent was identified, and the angle of late malapposition measured. Radii were drawn from this center through the transition points between complete apposition and LSM. These two circumferences were divided into equal arcs, and radii were drawn to the external elastic membrane (EEM). Measurements included EEM radius and circumference, plaque and media (P&M = EEM minus stent radius) thickness and area, and stent-intima separation. Mean baseline EEM radius and P&M thickness were similar in apposed and malapposed circumferences. At follow-up, mean EEM radius increase within the malapposed circumference (0.57 ± 0.34 mm) was larger than within the apposed circumference (0.16 ± 0.18 mm; P = 0.0004). ΔEEM for each malapposed radius was greater than for each apposed radius (P < 0.05 for all comparisons). Stent-intima separation correlated with EEM radius increase within the malapposed circumference (r = 0.83, P = 0.0013). At follow-up, the mean P&M thickness decreased in the malapposed circumference (−0.31 ± 0.22 mm; P < 0.0001). However, the decrease in P&M thickness in the malapposed circumference occurred because the same P&M area was distributed over a larger circumference (4.1 ± 1.6 mm to 5.4 ± 3.0 mm; P = 0.05), the result of positive remodeling.

Conclusion—The main cause of LSM is a regional increase in EEM (regional positive remodeling). (Circulation. 2003; 107:2660-2663.)

Key Words: stents ▪ drugs ▪ restenosis ▪ imaging

Late stent malapposition (LSM) has been reported after brachytherapy, drug-eluting stents, and de novo bare-metal stent implantation.1–4 Postulated mechanisms include (1) malapposition not recognized at implantation and only detected at follow-up, (2) decrease in plaque, (3) chronic stent recoil, and (4) increase in arterial dimensions. However, LSM is typically focal. Therefore, analysis of total arterial and plaque dimensions may not be the ideal approach to understanding this focal process. Analysis of total external elastic membrane (EEM) and plaque cross-sectional area or volume may obscure regional changes in remodeling or plaque mass. We hypothesized that analysis of localized changes in EEM dimensions would identify remodeling behind the arc of late malapposition as the primary cause of LSM.

Methods

Patient Selection
From the Washington Hospital Center intravascular ultrasound (IVUS) database, 11 stents (11 patients) with LSM were identified. All patients underwent de novo tubular-slotted stent placement (two were drug-eluting stents) into a native coronary (without adjunct brachytherapy) not in the setting of an acute myocardial infarction. LSM was defined as separation of ≥1 stent strut from the intima, not overlapping a side-branch, with evidence of blood flow behind the strut, where postimplantation IVUS revealed no evidence of blood speckling behind any strut.

IVUS Imaging and Analysis
IVUS imaging was performed after intracoronary administration of 0.1 to 0.2 mg nitroglycerin using motorized transducer pullback and a commercially available scanner (SCIMED). The imaging catheter was advanced 10 mm distal to the stent, and the transducer was withdrawn at 0.5 mm/s back to the guiding catheter. All studies were recorded on 0.5-inch high-resolution s-VHS videotape for subsequent analysis.

Quantitative IVUS analysis was performed using computerized planimetry (Tape Measure, Indec Systems). The follow-up study was reviewed first to select the image slice with the largest LSM area. Then, the postintervention study was reviewed to identify the corresponding image slice; this was facilitated by motorized transducer pullback because the distance from the stent edge could be measured in both studies. Finally, postintervention and follow-up image slices were rotated electronically so that patterns of stent struts and perivessel landmarks were aligned.5,6

The LSM image slice was analyzed first. (1) The geometric stent center was identified, and the angle of LSM measured with an electronic protractor. (2) Radii were drawn from this center through the two transition points between circumferences of complete apposition and LSM. (3) These two circumferences were divided into equal arcs, and 8 additional radii were drawn to the EEM, three

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through the apposed arc and five through the malapposed arc (Figure 1). (4) Radial distances were measured from the stent center to the stent, intima, and EEM. (5) Plaque and media (P&M) thickness was calculated as EEM minus stent radius. (6) Separation of LSM was calculated as intimal minus stent radius. (7) The P&M areas and EEM circumferences in apposed and malapposed segments were measured. These same measurements were performed on postimplantation images.

Statistics
Statistical analysis was performed using StatView 5.0 (SAS Institute). Quantitative data are presented as mean±1SD and compared using paired Student’s t test, correlation coefficient, and analysis of variance for repeated measures (with post hoc analysis using Fisher’s protected least significant difference).

Results
Stent-vessel wall malapposition was located almost exclusively at stent edges: 6 proximal edge, 4 distal edge, and 1 within the stent body. The angle of LSM averaged 89±39° (31° to 175°) or 25±11% (9% to 49%) of the stent circumference. The length averaged 3.7±2.8 mm.

Overall, there was a 0.37±0.24-mm increase in EEM radius (2.4±0.3 to 2.8±0.4 mm; P=0.0005), whereas there was no change in P&M thickness (0.8±0.2 to 0.7±0.2 mm; P=0.2). This represented a 15±15 (2% to 33%) increase in EEM radius.

The Table shows index and follow-up IVUS measurements according to the 10 predefined radii. Mean baseline EEM radius and P&M thickness were similar in apposed and malapposed circumferences. At follow-up, there was a consistent increase in EEM of all malapposed radii, but not of all fully apposed radii. The increase in mean EEM radius within the malapposed circumference (0.57±0.34 mm) was larger than within the apposed circumference (0.16±0.18 mm; P=0.0004). This increase averaged 6±8% (0% to 21%) within the apposed circumference versus 24±15% (2% to 56%) within the malapposed circumference. Stent-intima
separation correlated with ΔEEM radius within the malapposed circumference ($r=0.83, P=0.0013$).

At follow-up, mean P&M thickness increased in the apposed circumference (0.18±0.16 mm) and decreased in the malapposed circumference ($−0.31±0.22 \text{ mm}; P<0.0001$). However, there was no actual decrease in plaque mass behind the malapposed part of the stent; P&M area measured 1.9±0.9 mm² at implantation and 2.3±1.4 mm² at follow-up ($P=0.4$). Rather, the same P&M area was distributed over a larger circumference.

Figure 2 shows the distance stent-intima separation (measure of LSM) and changes in EEM radius and P&M thickness for the 10 prespecified radii. ΔEEM radius and ΔP&M thickness were similar for all prespecified radii within the apposed circumference as well as within the malapposed circumference. However, ΔEEM for each malapposed radius was greater than for each apposed radius, and ΔP&M thickness for each malapposed radius was significantly different than for each apposed radius ($P<0.05$ for all comparisons).

**Discussion**

LSM occurs in 4% to 5% of bare-metal stents and in an, as yet, unknown percentage of drug eluting stents. LSM is a focal phenomenon occupying, in the present study, approximately 25% of the stent circumference. In RAVEL, malapposition averaged 154° in sirolimus-eluting stents (43% of the stent circumference) and 131° in placebo stents (36% of the stent circumference). Therefore, LSM is uncommon and focal; mechanistic studies of LSM require assessment of regional remodeling and changes in plaque thickness.

**Mechanisms of Late Malapposition**

In the present analysis, there was no decrease in any of the stent radii eliminating chronic stent recoil as a finding, but allowing the geometric center of the stent to be used as a constant point of reference. In the current analysis, there was an increase in EEM radius (positive remodeling) within the region of LSM, but no change in plaque mass; the separation of the intima from the stent correlated with the increase in EEM radius. Therefore, the main mechanism of LSM is regional positive remodeling occurring in the setting of no increase in plaque mass. These regional changes were not well detected when changes in total EEM radius were assessed. IVUS analysis of LSM, as well as other focal arterial phenomena, requires a methodology appropriate to the problem. It may not be appropriate to assess mechanisms of LSM (a focal phenomenon) by measuring changes in total arterial EEM or plaque CSA or volume—even if these are the “standard” analyses performed in IVUS laboratories. Standard analyses may obscure rather than elucidate the actual mechanism. Similar “regional” methodologies may be useful in understanding remodeling responses to focal, eccentric plaque accumulation in de novo lesion formation.

Using serial IVUS, a number of investigators have reported positive remodeling associated with peri-stent plaque increase after bare-metal stent implantation, presumably reflecting peri-stent intimal hyperplasia. $^7$ The present analysis suggests that EEM increase is not necessarily a response to peri-stent intimal hyperplasia, but can occur independently. Positive remodeling without an increase in intimal hyperplasia has been noted after brachytherapy. $^4,9$ The present analysis suggests that this phenomenon can occur in the absence of brachytherapy.

The decrease in P&M thickness (but not mass) behind the malapposed stent struts was secondary to positive remodeling. Thus, plaque “thinning” may occur in the absence of plaque regression. In the current study P&M thickness decreased by 0.31±0.22 mm, whereas P&M area increased from 1.9±0.9 mm² at implantation to 2.3±1.4 mm² at follow-up.

**Limitations**

The number of patients with late malapposition was small. The current findings only apply to tubular-slotted stents. The present findings do not apply to re-stenting of in-stent restenosis lesions. The range of increase in malapposed arc EEM area was wide and <10% in 2/11 patients. There were only 2 IVUS studies per patient; therefore, the time course of remodeling (early or late) cannot be determined.

**Conclusions**

The main cause of late stent malapposition is a regional increase in EEM (regional positive remodeling) that may not be detected during conventional analyses.

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