

Impact of Pre-interventional Arterial Remodeling on Subsequent Vessel Behavior After Balloon Angioplasty: A Serial Intravascular Ultrasound Study

Hiroiyuki Okura, MD, Motoya Hayase, MD, Shinichi Shimodozono, MD, Heidi N. Bonneau, RN, MS, Paul G. Yock, MD, Peter J. Fitzgerald, MD, PhD

Stanford, California

OBJECTIVES	The purpose of this study was to assess the impact of pre-intervention arterial remodeling on subsequent vessel behavior following balloon angioplasty.
BACKGROUND	Positive arterial remodeling before intervention has been shown to have a negative impact on the clinical outcome after nonstented coronary interventional procedures. However, the mechanism of interventions in coronary vessel geometry over time is less well characterized.
METHODS	Serial (pre-, post- and follow-up) intravascular ultrasound analysis was performed in 46 native coronary lesions. Positive remodeling (PR) was defined as vessel area (VA) at the target lesion greater than that of average reference segments. Intermediate or negative remodeling (IR/NR) was defined as VA at the target lesion less than or equal to that of average reference segment. Remodeling index was defined as VA at the target lesion site divided by that of average references.
RESULTS	Pre-interventional PR and IR/NR were present in 21 (46%) and 25 (54%) of 46 patients, respectively. At follow-up, the change in plaque area was similar between the two groups (1.3 ± 2.1 vs. 1.2 ± 2.1 mm ² , $p = 0.840$). Lesions with PR showed a significantly smaller change in VA than those with IR/NR (-0.2 ± 2.5 vs. 1.4 ± 2.3 mm ² , $p = 0.03$). As a result, late lumen loss was significantly larger in lesions whose pre-intervention configuration exhibited PR (-1.5 ± 1.8 vs. 0.2 ± 1.6 mm ² , $p = 0.002$).
CONCLUSIONS	Lesions with PR appear to have less capacity to compensate for further plaque growth after balloon angioplasty and thus show a proportional increase in late lumen loss. This may in part explain the less favorable clinical outcomes of positively remodeled lesions. (J Am Coll Cardiol 2001;38:2001-5) © 2001 by the American College of Cardiology

Coronary stenting has been widely used as an alternative strategy to balloon angioplasty in today's cardiac catheterization laboratory (1). Metallic stents, through mechanical scaffolding of the vessel, prevent acute and chronic recoil, which is recognized as a major determinant of the restenotic process after balloon angioplasty alone (2,3). Results of randomized stent trials have demonstrated decreased restenosis rate as well as target vessel revascularization rate for both de novo (4,5) and restenotic lesions (6). In addition, improved efficacy of balloon angioplasty has also been observed in balloon treatment arms of recent randomized trials, probably resulting from a more aggressive balloon strategy "comforted" by the stent as a backup procedure (7,8). Several reports support the concept of "provisional stenting" as an approach aimed at achieving similar restenosis rates, target vessel revascularization rates and possibly lower cost compared to the primary stenting strategy (9,10). Thus, objective assessments of pre-interventional lesions may lead to sufficient triage of lesions achieving similar

short- and long-term results as stenting with an "up-front" cost saving.

Recent reports suggest that patterns of pre-intervention arterial remodeling may be tightly associated with both clinical presentation and long-term clinical outcome after nonstent interventions (11-15) as well as stenting (16). However, the exact relationship between the magnitude and degree of pre-intervention arterial remodeling and long-term geometrical coronary vessel behavior after balloon angioplasty is unknown.

Accordingly, we studied the impact of pre-intervention arterial remodeling on subsequent coronary vessel changes over time after balloon angioplasty by serial intravascular ultrasound (IVUS) studies.

METHODS

Patient and lesion criteria. Lesion inclusion criteria included single de novo native coronary artery disease treated by conventional balloon angioplasty alone with complete serial (pre-, post- and six-month follow-up) IVUS imagings using an automated pullback system. Reasons for exclusion were ostial lesions, extensive target lesion calcifications, and presence of stents at the target segments. Written informed consent was obtained from all study participants. A total of

From the Center for Research in Cardiovascular Interventions, Stanford University Medical Center, Stanford, California. Dr. Okura was supported by a grant from the Uehara Memorial Foundation, Tokyo, Japan, and by the Foreign Cardiovascular Fellow Education Fund from Stanford University, Stanford, California.

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Abbreviations and Acronyms

DS	= diameter stenosis
IR/NR	= intermediate or negative remodeling
IVUS	= intravascular ultrasound
LA	= lumen area
PA	= plaque area
PR	= positive remodeling
VA	= vessel area

61 native de novo lesions treated with conventional balloon angioplasty alone with serial (pre-, post- and six-month follow-up) IVUS imaging were selected from the Stanford Core Laboratory database. Eleven participants were excluded because baseline IVUS image was inadequate for quantitative analysis due to severe calcification or poor image quality. Three participants were excluded because of ostial location, and one was excluded because distal reference segment was not imaged. Finally, a total of 46 lesions in 46 patients were used in this study. There were 37 men and 9 women, with a mean age of 65 ± 10 years.

The IVUS imaging protocol. A commercially available system (CVIS/Boston Scientific, San Jose, California) was used for IVUS examination. The system consisted of a single-element 30-MHz transducer mounted on the tip of a flexible shaft and rotating at 1,800 rpm within a 2.9F rapid exchange/common distal lumen imaging sheath, or within a 3.2F short monorail imaging sheath. Before imaging, time-gain compensation, overall gain, contrast and reject levels were adjusted to predefined settings to maintain uniform ultrasound image quality (dynamic range). Intracoronary nitroglycerin (200 μ g) or isosorbide dinitrate (2 mg) was given before angiography and repeated immediately before IVUS catheter insertion. The IVUS imaging was performed after the achievement of angiographic success, and images were recorded on half-inch (1.27 cm), high-resolution Super-VHS videotape for off-line quantitative analysis. Motorized pullback of the transducer through a stationary imaging sheath was performed at a speed of 0.5 mm/s. After pre-intervention IVUS imaging, balloon angioplasty was performed under standard protocol, which includes single or multiple balloon inflation using commercially available "conventional" balloon with currently possible inflation pressure (usually higher than previous protocol). Stenting was allowed if the results were suboptimal or flow-limiting dissections were present. Balloon size was selected by each operator based on the visual assessment of the cine angiography and/or IVUS imaging. The end point was determined by each operator's discretion, and no specific IVUS criteria were used. The IVUS imaging was repeated after final interventional procedure and at six-month follow-up.

Analysis by IVUS. All ultrasound images were reviewed and evaluated for both qualitative and quantitative parameters by a core laboratory at the Center for Research in Cardiovascular Interventions, Stanford University Medical Center. The images were digitized to perform morphomet-

ric analysis with commercially available planimetry software (TapeMeasure, Indec Systems, Mountain View, California). Morphometric parameters consisted of vessel and lumen cross-sectional areas. Vessel area (VA) was defined as the area within the media/adventitial border (that is, including lumen, plaque and media).

Plaque area (PA) was calculated as VA minus lumen area (LA). Plaque burden (or percent PA) was calculated as $PA/VA \times 100$. Cross-sectional ultrasound measurements were performed at the lesion site, which is the image slice with the smallest LA prior to interventions; if there were several image slices with an equally small lumen, the image slice with the largest VA and PA was analyzed (2). Cross-sectional ultrasound images in both proximal and distal most-normal-looking reference segments within 10 mm but before any major side branch were also measured as reported previously (2). The same cross-sectional IVUS image was analyzed before intervention, after intervention and at six-month follow-up. Identical cross-sectional slices were carefully selected using intravascular (calcium deposit, side branches) and peri-vascular IVUS landmarks (veins, pericardium) and a constant (0.5 mm/s) pullback speed (2).

Positive remodeling (PR) was defined as VA at the target lesion greater than that of average reference segments. Intermediate or negative remodeling (IR/NR) was defined as VA at the target lesion less than or equal to that of average reference segment. Remodeling index was defined as VA at the target lesion site divided by that of average references.

Changes in VA, PA, and LA before and after angioplasty as well as during six-month follow-up were compared.

Statistical analysis. Quantitative data were presented as a mean value \pm SD, and qualitative data were presented as frequencies. Continuous variables were compared using unpaired *t* tests. Binary variables were examined by use of the Fisher exact test and the chi square test.

To compare the serial change of IVUS measurements, a repeated measures analysis of variance (ANOVA) was used. Statistical significance was a value of $p \leq 0.05$. All statistical analyses were performed with the Statview version 4.5 (SAS Institute).

RESULTS

Pre-intervention lesion characteristics. Pre-intervention PR was present in 21 (46%) lesions and IR/NR in 25 (54%) of 46 lesions. Clinical characteristics in each group are shown in Table 1. There were no significant differences in clinical characteristics between the two groups.

Procedure characteristics. Lesion and procedure characteristics are shown in Table 2. There was no difference in balloon sizes and maximal balloon inflation pressures between the two groups. Balloon-to-artery ratio showed a trend toward higher in the PR group ($p = 0.07$), although it did not reach statistical significance.

Table 1. Clinical Characteristics of Each Group

	PR (n = 21)	IR/NR (n = 25)	p Value
Age (yrs)	64 ± 10	65 ± 10	0.63
Male gender (%)	81	80	0.94
Prior MI (%)	18	32	0.16
Prior CABG (%)	29	40	0.42
Hypertension (%)	67	44	0.12
Diabetes mellitus (%)	29	28	0.97
Hyperlipidemia (%)	33	48	0.31
History of smoking (%)	33	52	0.20

CABG = coronary artery bypass graft; IR/NR = intermediate/negative remodeling; MI = myocardial infarction; PR = positive remodeling.

The IVUS Results

Comparison between pre- and postangioplasty. Serial IVUS analysis was performed in 46 lesions from 46 patients (Table 3). Baseline morphologic parameters were similar between the two groups. At baseline, VA, PA and plaque burden were significantly larger in the PR group than in the IR/NR group. After balloon angioplasty, VA increased in the IR/NR group but not in the PR group. The PA decreased and LA increased significantly in both groups. Relative contributions of vessel expansion to overall acute lumen gain in the PR and IR/NR groups were 23% and 57%, respectively. The change in VA (pre vs. post in Table 3) was significantly smaller in the PR group than in the IR/NR group (0.9 ± 1.6 vs. 2.0 ± 1.4 mm², $p = 0.01$) (Fig. 1). In the PR group, the change in PA (pre vs. post) was significantly larger than in the IR/NR group (-3.1 ± 1.9 vs. 1.5 ± 1.7 mm², $p = 0.004$). Acute lumen gain was similar between the two groups (PR: 3.9 ± 1.7 vs. IR/NR: 3.5 ± 1.6 mm², $p = 0.319$).

Comparison between postangioplasty and at six months' follow-up. The LA at six-month (6M) follow-up in the PR group was significantly smaller than in the IR/NR group ($p = 0.03$) (Table 3). The PR group showed a smaller change in VA (post vs. 6M in Table 3) than the IR/NR group (PR: -0.2 ± 2.5 vs. IR/NR: 1.4 ± 2.3 mm², $p =$

Table 2. Lesion and Procedural Characteristics

	PR (n = 21)	IR/NR (n = 25)	p Value
Target vessel (%)			0.22
LAD	52	28	
LCX	10	20	
RCA	38	52	
AHA/ACC type (%)			0.34
A	10	8	
B1	33	52	
B2	52	28	
C	5	12	
Balloon size (mm)	3.4 ± 0.3	3.4 ± 0.4	0.74
Balloon-to-artery ratio	1.2 ± 0.3	1.1 ± 0.2	0.07
Inflation pressure (atm)	10.8 ± 3.4	10.8 ± 3.2	0.95

Plus-minus values are mean ± SD.

AHA/ACC = American Heart Association/American College of Cardiology; IR/NR = intermediate/negative remodeling; LAD = left anterior descending coronary artery; LCX = left circumflex artery; PR = positive remodeling; RCA = right coronary artery.

Table 3. Morphologic and Morphometric IVUS parameters

	PR (n = 21)	IR/NR (n = 25)	p Value
Reference			
Vessel area (proximal)	14.7 ± 3.9	15.7 ± 5.0	0.48
Vessel area (distal)	12.9 ± 3.5	13.4 ± 5.2	0.71
Lesion			
Vessel area (pre) (mm ²)	15.1 ± 3.7	12.4 ± 4.0	0.02
(post) (mm ²)	16.0 ± 3.8	14.4 ± 4.0*	0.17
(6M) (mm ²)	15.8 ± 4.7	15.7 ± 4.7	0.98
Plaque area (pre) (mm ²)	13.3 ± 3.7	10.3 ± 3.8	<0.01
(post) (mm ²)	10.2 ± 3.2*	8.8 ± 3.3*	0.15
(6M) (mm ²)	11.3 ± 5.0‡	10.2 ± 3.1‡	0.72
Lumen area (pre) (mm ²)	1.9 ± 0.5	2.1 ± 0.8	0.20
(post) (mm ²)	5.8 ± 1.1*	5.6 ± 1.6*	0.70
(6M) (mm ²)	4.3 ± 2.1†	5.8 ± 2.5	0.03
Plaque burden (%)	87.0 ± 4.6	82.0 ± 6.3	<0.01
Remodeling index	1.1 ± 0.1	0.9 ± 0.1	—
Eccentricity ratio	0.35 ± 0.22	0.32 ± 0.24	0.65
Plaque type			
Fibrofatty, n (%)	9 (43)	13 (52)	0.58
Fibrous, n (%)	6 (29)	4 (16)	
Calcium, n (%)	6 (29)	8 (32)	

* $p < 0.01$ vs. pre-intervention. † $p < 0.01$ vs. post-intervention. ‡ $p < 0.05$ vs. post-intervention. § $p < 0.05$ vs. post-intervention.

IR/NR = intermediate/negative remodeling; IVUS = intravascular ultrasound; PR = positive remodeling.

0.03) (Fig. 2). However, the change in PA (post vs. 6M) was similar between the two groups (PR: 1.3 ± 2.1 vs. IR/NR: 1.2 ± 2.1 mm², $p = 0.840$). As a result, late lumen loss was significantly larger in lesions with PR than with IR/NR (change in LA: -1.5 ± 1.8 vs. 0.2 ± 1.6 mm², $p = 0.002$).

Angiographic restenosis rates (% diameter stenosis [DS] > 50%) at six months were 38% in the PR group and 20% in the IR/NR group ($p = 0.17$), respectively.

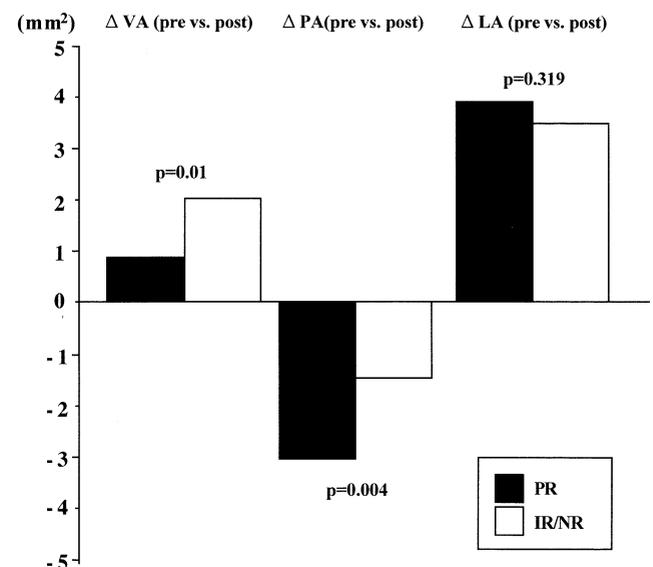


Figure 1. Changes in vessel, plaque and lumen area before and after balloon angioplasty. IR/NR = intermediate or negative remodeling; LA = lumen area; PA = plaque area; PR = positive remodeling; VA = vessel area.

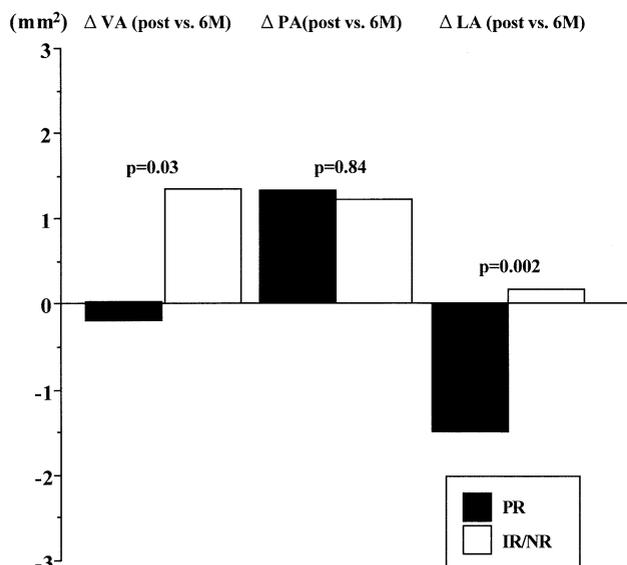


Figure 2. Changes in vessel, plaque and lumen area during six-month follow-up after balloon angioplasty. IR/NR = intermediate or negative-remodeling; LA = lumen area; PA = plaque area; PR = positive remodeling; VA = vessel area.

DISCUSSION

This IVUS time-sequence investigation demonstrates that: 1) mechanisms of acute lumen gain after balloon angioplasty are dependent of baseline patterns of remodeling (i.e., increased plaque reduction and less vessel expansion are observed in lesions with PR), and 2) lesions with PR appear to have less capacity to compensate for further plaque growth after balloon angioplasty and as a result have a proportionally increased amount of late lumen loss.

Previous IVUS studies have shown that positive arterial remodeling or compensatory enlargement of the coronary vessel was observed in up to 54% of lesions in de novo native coronary lesions (17,18), whereas negative or inadequate arterial remodeling was found in 15% of lesions. From a plaque composition standpoint, the exact substance (i.e., fatty, fibrous, or calcium) may have an impact on the time course of arterial remodeling. Mintz et al. (18) reported that IVUS-acquired calcium arc within the target lesion was a predictor of negative remodeling.

Patterns of pre-intervention arterial remodeling have been shown to affect the mechanism of lumen gain following balloon angioplasty in both peripheral (19) and coronary arteries (20). Pasterkamp et al. (19) reported that the degree of vessel stretch following balloon angioplasty was significantly larger in femoral artery lesions with arterial shrinkage (or NR) compared to the lesions with PR. In addition, their report demonstrated the lack of correlation between balloon/media-bounded area and elastic recoil in lesions with NR, suggesting that balloon oversizing in the femoral artery may lead to larger immediate gain with minimal elastic recoil. Similarly, Timmis et al. (20) analyzed 47 coronary lesions and showed that vessel stretching is greater and plaque reduction is smaller in negatively remodeled

lesions. Despite the significant difference in acute vessel response to balloon angioplasty between PR and NR, its impact on the chronic restenotic process was not addressed in their series. Results from our present study showing differences in the mechanism of acute lumen gain between each remodeling group seems consistent with these previous reports.

A recent study (15) of lesions treated by nonstent interventions demonstrated that PR was associated with an increased long-term target lesion revascularization rate. The investigators suggest several possibilities to explain this less favorable result in vessels with PR. Our results not only confirm their observation but also help to clarify the geometric impact of arterial remodeling on subsequent vessel behavior by IVUS at six-month follow-up that may explain their clinical findings. Several studies suggest a higher incidence of PR in lesions involved with unstable angina or myocardial infarction, implying that lesions with PR may be more biologically active (11-14,21). However, our study did not demonstrate differences in the amount of neointimal and/or plaque increase after balloon angioplasty between the lesions with PR versus IR/NR. Interestingly, the lack of post-intervention adaptive remodeling to compensate for the neointimal proliferation after balloon injury (2,3) was observed in lesions with PR, which may explain larger late lumen loss, higher restenosis rate, and thus possibly higher target lesion revascularization rates.

Glagov et al. (22) reported in their landmark study that human coronary arteries enlarge in relation to plaque increase until the lesion occupies 40% of the vessel. If so, stenotic lesions with PR may have already increased maximally to their arterial dimensions. Thus, they may not have the capacity to dilate further to accommodate subsequent neointimal plaque increase after interventions. Consequently, in positively remodeled lesions, the major contributor for late lumen loss was plaque increase, as opposed to vessel shrinkage (23). On the other hand, in lesions with NR, further vessel remodeling (either positive or negative) contributed to lumen changes after balloon angioplasty (2,3,24). One possible explanation for these differences is a greater vessel stretching observed in the IR/NR group, which may suggest the presence of the bigger vessel injury. Adventitial injury and subsequent inflammation have been shown to play an important role in the arterial remodeling process after interventions (25). Therefore, a smaller acute vessel expansion in the lesions with PR might have caused a lesser degree of adventitial injury. The IVUS-guided balloon oversizing may be helpful to achieve larger vessel expansion and possibly cause subsequent adaptive arterial remodeling (26).

Study limitations. Several limitations need to be mentioned in the present study. We excluded extremely tight lesions not accommodated by the IVUS catheter prior to the intervention. We also excluded heavily calcified lesions because of the inability of IVUS to delineate and trace vessel

area over time. Both of these exclusions may lead to bias in the conclusion drawn from this cohort of patients.

Although our results suggest that lesions with IR/NR respond well and have favorable long-term results after balloon angioplasty, it does not necessarily mean that primary stenting is indicative for the lesions with PR. The impact of pre-interventional arterial remodeling on in-stent neointimal proliferation after stent implantation may, in fact, lead to accelerated neointimal increase (especially if the PR lesions are more biologically active).

Although our present data suggest the impact of remodeling pattern on subsequent vessel changes, it is difficult to confirm whether either pattern of remodeling or plaque burden itself primarily affected subsequent coronary vessel behavior.

Finally, because this was a retrospective study selected from an IVUS database, a prospective study may be necessary to confirm present results.

Clinical implications. These findings may help in selecting lesions suitable for conventional balloon angioplasty. In addition, the differences in the restenotic process for PR versus IR/NR vessels may have implications for adjunctive anti-restenotic therapy selection.

Reprint requests and correspondence: Dr. Peter J. Fitzgerald, Center for Research in Cardiovascular Interventions, Stanford University Medical Center, 300 Pasteur Drive, H3554, Stanford, California 94305. E-mail: peter_fitzgerald@cvmed.stanford.edu.

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