Published by Elsevier Inc.

ISSN 0735-1097/03/$30.00
doi:10.1016/j.jacc.2003.05.009

Arterial Remodeling Patterns Before Intervention Predict Diffuse In-Stent Restenosis

An Intravascular Ultrasound Study

Makoto Sahara, MD, Hajime Kirigaya, MD, Yuji Oikawa, MD, Junji Yajima, MD, Ken Ogasawara, MD, Hiroshi Satoh, MD, Kazuyuki Nagashima, MD, Hitoshi Hara, MD, Yusuke Nakatsu, MD, Tadanori Aizawa, MD

Tokyo, Japan

OBJECTIVES The aim of this retrospective study was to determine the predictors of diffuse in-stent restenosis (ISR) among the lesions causing the first ISR by intravascular ultrasound (IVUS) studies.

BACKGROUND Although some predictors of diffuse ISR have been reported, parameters on IVUS relating to diffuse ISR are not well characterized.

METHODS We classified 52 ISR lesions that had undergone successful stent implantation and led to restenosis into two types—focal and diffuse ISR—using quantitative coronary angiography. Restenosis was defined as ≥50% diameter stenosis, and diffuse ISR as lesion length ≥10 mm at follow-up. The remodeling index (RI) was defined as the vessel area at the target lesion divided by that of averaged reference segments.

RESULTS There were no significant differences in patient, angiographic, and procedural characteristics between the focal (n = 25) and diffuse (n = 27) ISR groups. Baseline RI was significantly greater in the diffuse ISR group (1.03 ± 0.18 vs. 0.88 ± 0.24, p = 0.0159). Negative remodeling, defined as RI <0.9, was detected in 60% of the focal ISR group and in only 26% of the diffuse ISR group. By logistic regression analysis, baseline RI was the only independent predictor of diffuse ISR (p = 0.0341). Moreover, volumetric analyses revealed that lesions developing into diffuse ISR had less capacity to compensate for further plaque growth.

CONCLUSIONS Among the first ISR lesions, baseline positive remodeling was the most powerful predictor of diffuse ISR. Measuring pre-interventional arterial remodeling patterns by IVUS may be helpful to stratify lesions at higher risk. (J Am Coll Cardiol 2003;42:1731–8) © 2003 by the American College of Cardiology Foundation

Although stents reduce the incidence of restenosis after percutaneous coronary intervention (PCI) (1,2), in-stent restenosis (ISR) still remains an unsolved problem. Angiographic patterns of ISR are closely associated with prognosis after repeated PCI. Compared with focal ISR (lesion <10 mm in length) in which repeated balloon angioplasty is usually successful, diffuse ISR (lesion ≥10 mm in length) is known to have a higher recurrent restenosis rate after treatment with balloon angioplasty (3–6), as well as a higher rate of target lesion revascularization after repeated PCI, including balloon angioplasty, rotational atherectomy, excimer laser coronary angioplasty, and stenting (7). Although predictors of ISR have been reported frequently (8–10), predictors of diffuse ISR have been reported less often. Recently, the clinical, angiographic, and procedural predictive factors of diffuse ISR among ISR lesions have been reported (11,12), whereas parameters on intravascular ultrasound (IVUS) relating to diffuse ISR have not well been characterized. In this retrospective study, we aimed to determine the predictors of diffuse ISR among lesions developing into ISR first by analyses of serial (pre-stent, post-stent, and follow-up) IVUS studies. Moreover, subsequent vessel behavior after stenting in these ISR lesions was evaluated by volumetric analyses of serial IVUS studies.

From the Department of Internal Medicine, the Cardiovascular Institute Hospital, Tokyo, Japan.

Manuscript received March 19, 2003; revised manuscript received May 15, 2003, accepted May 20, 2003.

METHODS

Patient population. From January 1, 1998, through December 31, 2000, a total of 408 native coronary lesions in 305 consecutive patients were treated with stenting alone and without debulking at the Cardiovascular Institute Hospital in Tokyo. The patients were excluded if they had not undergone follow-up angiography. There remained 341 lesions in 258 patients (85% [258/305]), of which 77 lesions led to angiographic restenosis in less than one year (restenosis rate 22.6%). The 77 ISR lesions were excluded when: 1) the stent diameter was <3.0 mm (n = 7); 2) stent implantation was performed without IVUS or with incomplete IVUS guidance (n = 13; including 7 cases with baseline chronic total occlusion); and 3) IVUS imaging precluded accurate assessment because of intimal severe calcification at the target lesion site or other technical reasons (n = 5). Finally, a total of 52 ISR lesions (68% [52/77]) in 48 patients who had undergone successful stenting alone with complete IVUS guidance was included for analysis in this retrospective study. In these 52 ISR lesions, recurrent ISR lesions were not included, although 14 lesions (27% [14/52]) developing into restenosis after plain old balloon angioplasty were included.

JACC Vol. 42, No. 10, 2003
November 19, 2003:1731–8

Abbreviations and Acronyms

ISR = in-stent restenosis
IVUS = intravascular ultrasound
LV = lumen volume
PCI = percutaneous coronary intervention
PV = plaque volume
QCA = quantitative coronary angiography
RI = remodeling index
SV = stent volume
VA = vessel area
VV = vessel volume

The kinds of stents used included tubular slotted stents (Palmaz-Schatz [n = 10], Multi-Link [n = 14], NIR [n = 4], AVE GFX [n = 2], Terumo [n = 2], and BeStent [n = 8]) and coil stents (Wiktor [n = 7], Gianturco-Roubin 2 [n = 3], and S670 [n = 2]). There were 43 men and 5 women, and their mean age was 65.5 ± 8.1 years. These patients underwent follow-up coronary angiography in three to nine months (mean 4.9 ± 1.7 months). Patient characteristics, including risk factors for coronary artery disease, were obtained from clinical records at the time of stenting. Diabetes mellitus (only if treated medically), hypertension (only if treated medically), and hyperlipidemia (only if treated medically or if serum total cholesterol was ≥240 mg/dl) were all examined.

Angiography and analysis. Initial and follow-up angiograms were obtained in the same angiographic projections. Two independent observers who were blinded to the results of IVUS analysis performed quantitative coronary angiography (QCA) analysis using computerized software (Cardiovascular Measurement System, CMS, MEDIS, Leiden, The Netherlands) with a contrast-filled catheter tip of a known diameter as a scaling device. The reference diameter, minimal lumen diameter, and diameter stenosis at end diastole before intervention, after final balloon expansion of the stent, and at follow-up were calculated on the computer with the use of the view that showed the most severe luminal narrowing. The mean reference artery diameter (or reference diameter) was interpolated from the proximal and distal reference segments. Lesion length was measured from "shoulder to shoulder." Short-term gain, late loss, loss index, and net gain were calculated (13). Angiographic restenosis was defined as ≥50% diameter stenosis at follow-up angiography. Diffuse ISR was defined as a follow-up lesion length ≥10 mm and focal ISR as <10 mm.

Intravascular ultrasound imaging. A commercially available system (Cardiovascular Imaging Systems/Boston Scientific, Natick, Massachusetts) was used for the IVUS studies. 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 or 3.2F monorail imaging catheter. The IVUS studies were also performed before intervention, after final balloon expansion of the stent, and at follow-up, although the follow-up IVUS data could be acquired in only 31 (60%) of the 52 included lesions. Intracoronary isosorbide dinitrate (5 mg) was injected before image acquisition. After the IVUS catheter was advanced at least 10 mm distal to the lesion, a motorized auto pullback was performed at 0.5 mm/s to the aorto-ostial junction. All IVUS images were recorded on half-inch s-VHS videotape for off-line analysis.

IVUS analysis. Two experienced observers performed all IVUS analyses. Quantitative analyses of IVUS images in the end-diastolic phase were performed off-line using commercially available planimetry software (CARDIO 500, Kontron, Munich, Germany). Measured parameters consisted of cross-sectional vessel area (VA), stent area (SA), and lumen area (LA), which were manually traced. The VA was defined as the area within the medial/adventitial border. Plaque area (PA) was calculated as VA − LA, and percent PA was calculated as: (PA/VA) × 100 (%). Two-dimensional analyses were performed at the tightest cross section within the stent and at the sites of proximal and distal reference segments, which were defined as the location in the native vessel with the least amount of disease within 5 mm from stent margins and before the emergence of any major side branches. When the plaque encompassed the IVUS catheter, the LA was assumed to be equal to the size of the catheter. The ratio of change (delta) of each area from post-stenting to follow-up was defined as: (area at follow-up − area at post-stenting)/area at post-stenting × 100 (%). At follow-up IVUS studies, the neointimal area within the stent was calculated as SA − LA.

The remodeling index (RI) before intervention was calculated as the VA at the target lesion site divided by the averaged VA of reference segments. Patterns of arterial remodeling were classified into three categories: 1) positive remodeling was defined as RI >1.1; 2) intermediate remodeling as RI 0.9 to 1.1; and 3) negative remodeling as RI <0.9 (Fig. 1). Moreover, three-dimensional analysis was performed by means of Simpson's method. Vessel volume (VV), stent volume (SV), and lumen volume (LV) were computed for the entire stented segment. Plaque volume (PV) was calculated as VV − LV, and percent PV was also calculated as: PV/VV × 100 (%). The neointimal volume (NV) within the stent was calculated as SV − LV. The NV and PV indexes were calculated as NV and PV divided by stent length, respectively. The ratio of change (delta) of each volume from post-stenting to follow-up was also defined as: (volume at follow-up − volume at post-stenting)/volume at post-stenting × 100 (%).

Statistical analysis. Quantitative data are presented as the mean ± SD, and categorical data as frequencies (percentage). Continuous variables were compared using the unpaired *t* test. Binary variables were compared by means of the Fisher exact test, and the variables comprising more than two categorical factors were compared by means of the chi-square test. To identify the predictors of diffuse ISR, multivariate logistic models were used. Univariate variables

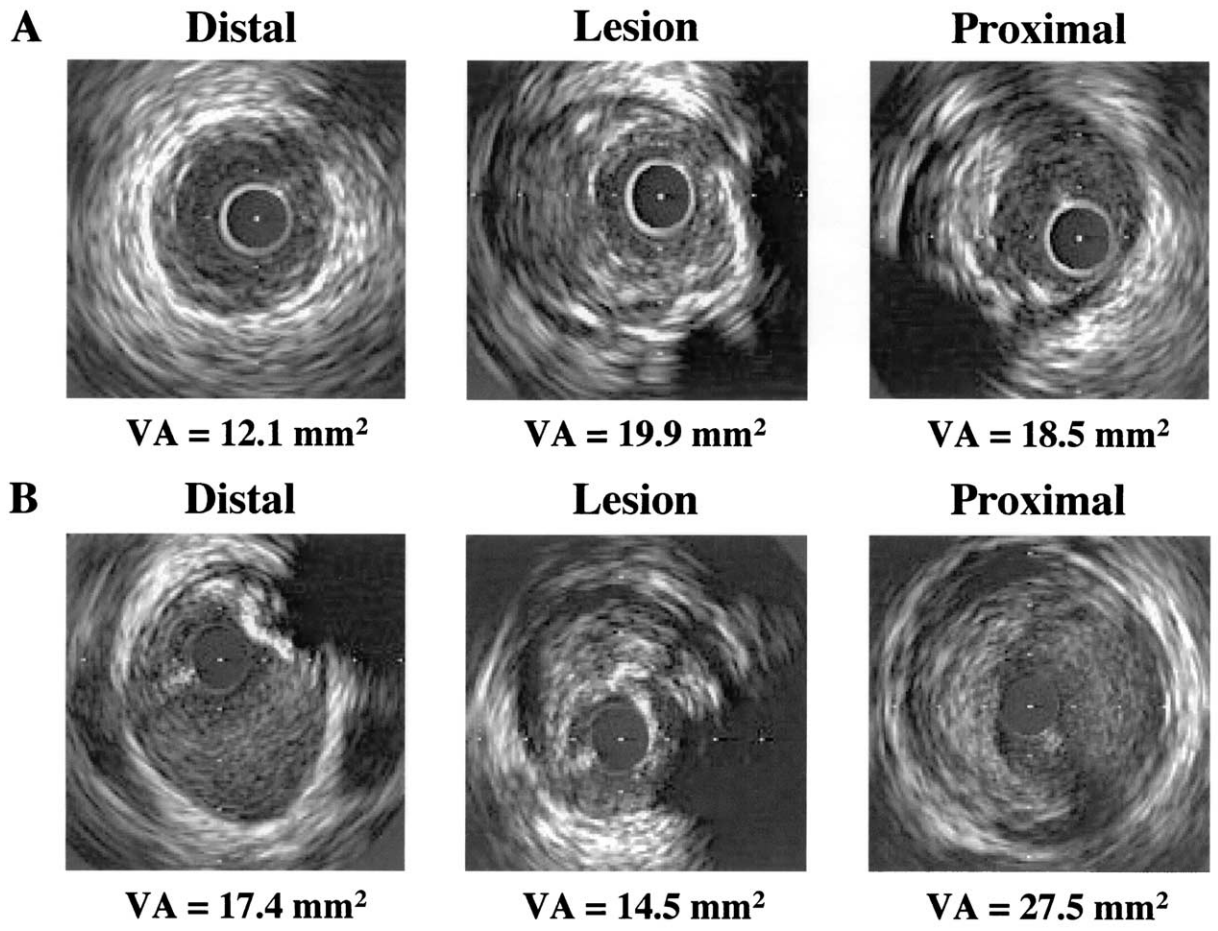

Figure 1. Arterial remodeling patterns. The remodeling index (RI) before intervention was calculated as vessel area (VA) at the target lesion site divided by the averaged VA of reference segments. Patterns of remodeling were classified into three categories: 1) positive remodeling was defined as RI >1.1; 2) intermediate remodeling as RI 0.9 to 1.1; and 3) negative remodeling as RI <0.9. **(A)** Positive remodeling (RI = 1.30). **(B)** Negative remodeling (RI = 0.65).

with $p < 0.20$ were entered into the multivariate logistic models. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed with StatView version 5.0 (SAS Institute, Cary, North Carolina).

RESULTS

Patient, lesion, and procedural characteristics. Focal ISR was present in 25 (48%) of 52 lesions analyzed in this study, whereas diffuse ISR was present in 27 lesions (52%). As shown in Table 1, no significant differences were seen in clinical and lesion characteristics between the focal and diffuse ISR groups. In Table 1, the variables such as "target vessel" and "American College of Cardiology/American Heart Association classification" were compared by the chi-square test, and other categorical variables were compared by the Fisher exact test. For the procedural characteristics, there were trends toward a smaller stent to lesion length ratio (1.3 ± 0.9 vs. 1.7 ± 0.9, $p = 0.11$) and a smaller balloon to artery ratio (1.2 ± 0.2 vs. 1.4 ± 0.3, $p = 0.11$) in the diffuse ISR group, which were not statistically significant. The kinds of stents used were similar between the two groups.

Angiographic results. Angiographic results are shown in Table 2. Both baseline and post-procedural results were similar between the two groups, except for a trend toward a longer lesion length in the diffuse ISR group than in the focal ISR group (17.1 ± 8.6 m vs. 13.2 ± 8.4 mm, $p = 0.10$). At follow-up, the diffuse ISR group had not only a longer lesion length (16.3 ± 4.9 m vs. 8.5 ± 1.4 mm, $p < 0.0001$), but also a smaller minimal lumen diameter (1.0 ± 0.6 mm vs. 1.2 ± 0.3 mm, $p = 0.07$) and a larger diameter stenosis (67.6 ± 15.7% vs. 57.8 ± 6.5%, $p = 0.01$). Consequently, the loss index in the diffuse ISR group was larger than that in the focal ISR group (1.07 ± 0.43 vs. 0.87 ± 0.25, $p = 0.04$). Intra- and inter-observer variabilities on QCA were 0.10 and 0.12 mm ($r = 0.973$ and 0.956) for minimal lumen diameter, respectively; 3.38% and 5.01% ($r = 0.968$ and 0.951) for percent diameter stenosis, respectively; and 0.78 and 0.99 mm ($r = 0.966$ and 0.949) for lesion length, respectively.

Table 1. Patient, Lesion, and Procedural Characteristics

	Focal ISR Group (n = 25)	Diffuse ISR Group (n = 27)	p Value
Age (yrs)	65 ± 9	66 ± 7	0.6739
Gender (M/F)	21/4	25/2	0.4109
BMI (kg/m^2)	23.9 ± 2.3	24.3 ± 2.6	0.5878
Diabetes mellitus	7 (28%)	7 (26%)	> 0.9999
Hypertension	17 (68%)	16 (59%)	0.5737
Hyperlipidemia	11 (44%)	10 (37%)	0.7780
Smoking	19 (76%)	23 (85%)	0.4922
Previous MI	10 (40%)	10 (37%)	> 0.9999
ACS	4 (16%)	6 (22%)	0.7289
Restenotic lesion	6 (24%)	8 (30%)	0.7587
Multivessel disease	14 (56%)	14 (52%)	0.8691
Target vessel			0.6949
LAD	15 (60%)	19 (70%)	
LCX	3 (12%)	3 (11%)	
RCA	7 (28%)	5 (19%)	
ACC/AHA classification			0.6559
B1	5 (20%)	3 (11%)	
B2	14 (56%)	16 (59%)	
C	6 (24%)	8 (30%)	
Ostial location	2 (8%)	2 (7%)	> 0.9999
Bifurcation lesion	3 (12%)	3 (11%)	> 0.9999
Fluoroscopic calcium	11 (44%)	17 (63%)	0.2655
Number of stents (1/2)	22/3	20/7	0.2957
Type of stent (coil/tube)	5/20	7/20	0.7460
Stent diameter (mm)	3.3 ± 0.4	3.4 ± 0.4	0.5275
Stent length (mm)	18.1 ± 6.9	18.3 ± 5.5	0.8838
Stent/lesion length ratio	1.7 ± 0.9	1.3 ± 0.9	0.1104
Final balloon size (mm)	3.6 ± 0.6	3.5 ± 0.4	0.5149
Balloon/artery ratio	1.4 ± 0.3	1.2 ± 0.2	0.1089
Maximum pressure (atm)	13.6 ± 3.2	14.3 ± 3.4	0.4066

Data are presented as the mean value ± SD or number (%) of patients.
ACC/AHA = American College of Cardiology/American Heart Association; ACS = acute coronary syndrome; BMI = body mass index; ISR = in-stent restenosis; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery.

IVUS results. Two-dimensional quantitative IVUS results are shown in Table 3. The baseline minimal lumen area, vessel and plaque area at the site of the minimal lumen area, averaged reference lumen and vessel area, and minimal stent area after stenting were all similar between the two groups. However, baseline RI in the diffuse ISR group was significantly larger than that in the focal ISR group (1.03 ± 0.18 vs. 0.88 ± 0.24, p = 0.02) (Fig. 2). In addition, negative remodeling (RI <0.9) was seen in 60% of the focal ISR group and, in contrast, in only 26% of the diffuse ISR group (p < 0.05 by the chi-square test) (Fig. 2).

Three-dimensional quantitative IVUS results are shown in Table 4. Both the baseline and post-procedural volumes of each component of the lesion were all similar between the two groups. Among the 52 ISR lesions, follow-up IVUS studies could be evaluated in 31 lesions comprising 16 focal ISR and 15 diffuse ISR lesions. At follow-up, extra-stent PV (calculated as VV − SV), PV, and the deltas of their parameters were not significantly different between the two groups. The NV index in the diffuse ISR group was significantly larger than that in the focal ISR group (4.0 ± 1.5 mm^3/mm vs. 3.0 ± 1.1 mm^3/mm, p < 0.05). Conversely, delta-VV and delta-SV in the diffuse ISR group were significantly smaller than those in the focal ISR group (delta-VV: −0.5 ± 12.2% vs. 5.7 ± 9.9%, p = 0.09; delta-SV: 2.6 ± 12.3% vs. 14.0 ± 15.0%, p = 0.03). Consequently, percent PV in the diffuse ISR group was significantly larger than that in the focal ISR group (76.8 ± 7.2% vs. 67.3 ± 5.9%, p < 0.01). Furthermore, among the 31 ISR lesions that had follow-up IVUS studies, the baseline RI had a significant negative correlation with delta-SV (r = −0.377, p = 0.04) and mildly with delta-VV

Table 2. Results of Quantitative Coronary Angiography

	Focal ISR Group (n = 25)	Diffuse ISR Group (n = 27)	p Value
Before intervention			
Minimal lumen diameter (mm)	0.9 ± 0.3	1.0 ± 0.5	0.8745
Diameter stenosis (%)	64.5 ± 12.0	66.9 ± 14.5	0.5141
Reference diameter (mm)	2.8 ± 0.6	2.9 ± 0.6	0.2970
Lesion length (mm)	13.2 ± 8.4	17.1 ± 8.6	0.1042
After intervention			
Minimal lumen diameter (mm)	2.8 ± 0.5	2.8 ± 0.7	0.8225
Diameter stenosis (%)	8.9 ± 12.8	11.2 ± 14.7	0.5434
Short-term gain	1.8 ± 0.5	1.9 ± 0.6	0.8998
Follow-up			
Minimal lumen diameter (mm)	1.2 ± 0.3	1.0 ± 0.6	0.0739
Diameter stenosis (%)	57.8 ± 6.5	67.6 ± 15.7	0.0057
Reference diameter (mm)	2.8 ± 0.6	2.8 ± 0.7	0.9222
Lesion length (mm)	8.5 ± 1.4	16.3 ± 4.9	<0.0001
Late loss (mm)	1.6 ± 0.6	1.9 ± 0.7	0.1640
Net gain (mm)	0.2 ± 0.5	0 ± 0.7	0.1384
Loss index	0.87 ± 0.25	1.07 ± 0.43	0.0438

Data are presented as the mean value ± SD.
ISR = in-stent restenosis.

Table 3. Two-Dimensional Quantitative Intravascular Ultrasound Results

	Focal ISR Group (n = 25)	Diffuse ISR Group (n = 27)	p Value
Before intervention			
VA (mm^2)	13.0 ± 3.8	14.5 ± 5.3	0.2481
LA (=MLA) (mm^2)	1.9 ± 0.9	1.9 ± 1.0	0.8705
PA (mm^2)	11.1 ± 3.6	12.6 ± 4.8	0.2248
Percent PA	85.0 ± 6.8	86.7 ± 5.5	0.3630
Reference VA (mm^2)	15.2 ± 4.4	14.3 ± 4.8	0.4497
Reference LA (mm^2)	7.6 ± 3.0	7.2 ± 2.8	0.6505
Remodeling index	0.88 ± 0.24	1.03 ± 0.18	0.0159
Remodeling pattern (NR/IR/PR)	15/6/4	7/12/8	0.0456
After intervention			
Minimal stent area (mm^2)	6.1 ± 1.9	6.3 ± 2.1	0.6353
Maximal residual PA (mm^2)	9.0 ± 2.9	8.7 ± 2.8	0.7493
Follow-up (focal: n = 16; diffuse: n = 15)			
VA (mm^2)	16.7 ± 4.5	16.8 ± 4.0	0.9458
Delta-VA (%)	11.1 ± 18.4	5.7 ± 14.4	0.3753
LA (=MLA) (mm^2)	2.3 ± 1.1	2.2 ± 1.3	0.8775
Delta-LA (%)	−29.1 ± 26.2	−33.7 ± 44.3	0.7251
Stent area (mm^2)	7.5 ± 2.1	7.5 ± 2.2	0.9908
Neointimal area (mm^2)	5.3 ± 1.8	5.3 ± 2.1	0.9352
PA (mm^2)	14.4 ± 4.0	14.6 ± 3.7	0.9031
Delta-PA (%)	43.3 ± 49.3	43.1 ± 36.7	0.9896
Percent PA	86.3 ± 5.3	86.8 ± 7.1	0.8329

Data are presented as the mean value ± SD.

Delta = ratio of change; IR = intermediate remodeling; ISR = in-stent restenosis; LA = lumen area; MLA = minimal lumen area; NR = negative remodeling; PA = plaque area; PR = positive remodeling; VA = vessel area.

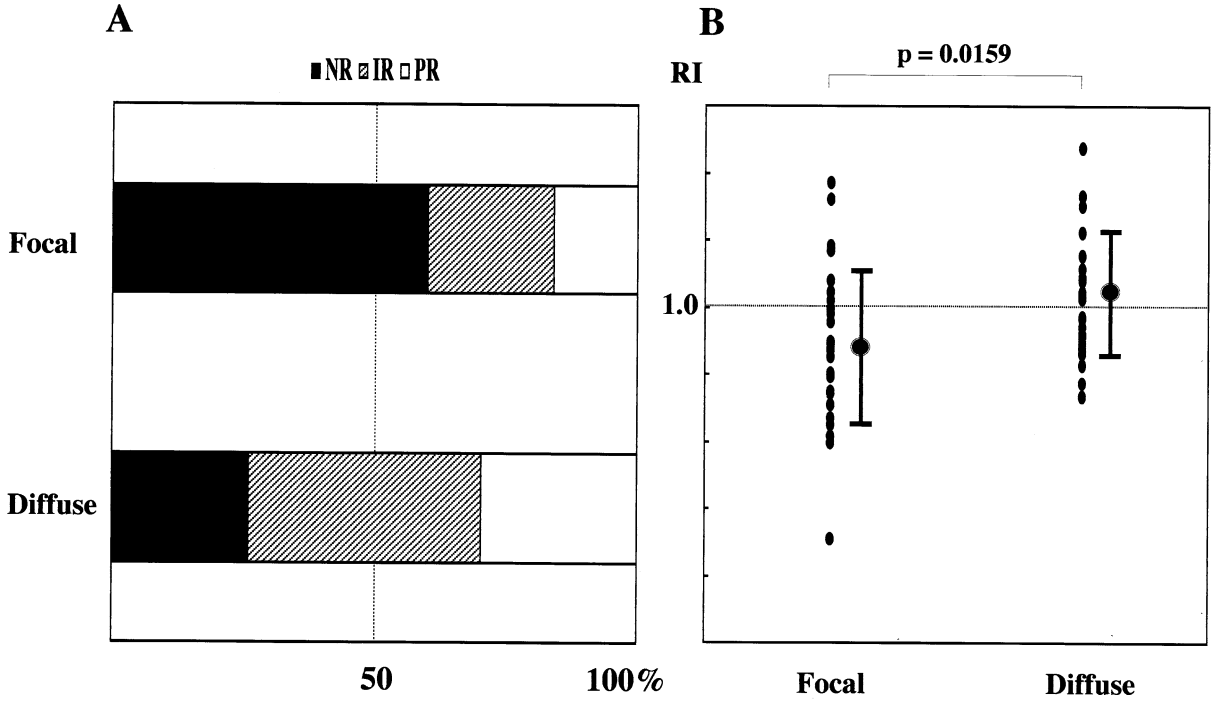

Figure 2. (A) Negative remodeling (remodeling index [RI] <0.9) was seen in 60% of the focal in-stent restenosis (ISR) lesions and, in contrast, in only 26% of the diffuse ISR lesions. Conversely, positive remodeling (RI >1.1) was seen in only 16% of the focal ISR lesions and in 30% of the diffuse ISR lesions (p = 0.0456 by the chi-square test). **(B)** The baseline RI in the diffuse ISR group was significantly larger than that in the focal ISR group (1.03 ± 0.18 vs. 0.88 ± 0.24, p = 0.0159). IR = intermediate remodeling; NR = negative remodeling; PR = positive remodeling.

Table 4. Three-Dimensional Quantitative Intravascular Ultrasound Results

	Focal ISR Group (n = 25)	Diffuse ISR Group (n = 27)	p Value
Before intervention			
VV (mm^3)	276.7 ± 172.5	275.5 ± 166.3	0.9786
LV (mm^3)	91.0 ± 60.9	83.0 ± 56.7	0.6271
PV (mm^3)	185.7 ± 120.8	192.4 ± 120.8	0.8422
Percent PV (%)	66.7 ± 9.4	69.6 ± 8.3	0.2409
After intervention			
VV (mm^3)	323.7 ± 199.3	322.7 ± 177.5	0.9846
LV (= SV) (mm^3)	151.5 ± 99.7	146.9 ± 80.2	0.8526
PV (mm^3)	172.1 ± 103.2	175.8 ± 102.9	0.8989
Percent PV (%)	53.7 ± 6.7	54.3 ± 6.5	0.7668
Follow-up (focal, n = 16; diffuse, n = 15)			
VV (mm^3)	344.6 ± 208.4	292.6 ± 92.0	0.3814
Delta-VV (%)	5.7 ± 9.9	−0.5 ± 12.2	0.0928
SV (mm^3)	174.5 ± 114.8	141.3 ± 48.6	0.3081
Delta-SV (%)	14.0 ± 15.0	2.6 ± 12.3	0.0284
LV (mm^3)	116.6 ± 82.4	68.2 ± 38.6	0.0470
Delta-LV (%)	−26.2 ± 13.2	−51.1 ± 15.1	<0.0001
NV (mm^3)	57.9 ± 37.2	73.1 ± 32.2	0.2342
NV index (mm^3/mm)	3.0 ± 1.1	4.0 ± 1.5	0.0362
PPV (mm^3)	170.1 ± 96.6	151.3 ± 52.0	0.5099
Delta-EPV (%)	−0.5 ± 12.8	−2.6 ± 16.9	0.6997
PV (mm^3)	228.0 ± 129.6	224.4 ± 68.1	0.9250
PV index (mm^3/mm)	11.3 ± 2.9	12.2 ± 2.9	0.4076
Delta-PV (%)	35.4 ± 15.9	46.0 ± 28.1	0.2017
Percent PV (%)	67.3 ± 5.9	76.8 ± 7.2	0.0004

Data are presented as the mean value ± SD.
Delta = ratio of change; ISR = in-stent restenosis; LV = lumen volume; NV = neointimal volume; EPV = extra-stent plaque volume; PV = plaque volume; SV = stent volume; VV = vessel volume.

(r = −0.268, p = 0.09), whereas it did not correlate with either delta-LV or delta-PV.

Finally, intra- and inter-observer variabilities on IVUS were 0.28 and 0.46 mm^2 for minimal lumen area (r = 0.977 and 0.969), respectively; 5.71 and 7.72 mm^3 (r = 0.982 and 0.975) for vessel volume, respectively; and 2.68 and 4.93 mm^3 (r = 0.983 and 0.968) for lumen volume, respectively. These results of variabilities on QCA and IVUS are comparable to the previous reports.

Multivariate analysis. In this retrospective study, univariate predictors of diffuse ISR with p value <0.20 were as follows: higher baseline RI (p = 0.02), longer baseline lesion length (p = 0.10), smaller stent to lesion length ratio (p = 0.11), and smaller balloon to artery ratio (p = 0.11). Multivariate logistic regression analysis revealed that the RI was the only independent predictor of diffuse ISR (odds ratio per 0.10 increment of RI: 1.46 [95% confidential interval 1.03 to 2.08], p = 0.0341).

DISCUSSION

This study demonstrated that the presence of the arterial positive remodeling before stenting was associated with a worse clinical outcome, such as diffuse ISR, after IVUS-guided stent implantation. In addition, volumetric IVUS analyses revealed that lesions developing into diffuse ISR had not only more development of neointimal hyperplasia but also less capacity of compensatory enlargement for further plaque growth than did those developing into focal ISR.

Predictors of diffuse ISR. Previous studies have shown that the lesions with diffuse ISR had a high rate of recurrent restenosis, which was a two- to threefold higher rate than that of focal ISR lesions. Therefore, target lesion revascularization for diffuse ISR lesions was much more frequently required (3–7). In addition, thus far, no devices have significantly improved clinical outcomes after the treatment of diffuse ISR, except for intracoronary radiation therapy (14). Moreover, as shown in the previous report (7) and this study, diffuse ISR lesions were not only longer but also tighter than focal ISR lesions, suggesting that diffuse ISR represented biologically more active disease. On this basis, early triage of lesions expected to develop into diffuse ISR before the initial intervention is clinically important.

Goldberg et al. (12) revealed the following characteristics as strongly predictive factors of diffuse ISR among ISR lesions: 1) a longer baseline lesion length; 2) a smaller final minimal lumen diameter after intervention; and 3) the use of coil stents. These were all generally considered as important predictors of usual ISR, too (8–10). In the present study, although there was a trend toward a longer lesion length in the diffuse ISR group, there were no significant differences between the two groups as to the final minimal lumen diameter and minimal stent area after intervention, which was indicated as a powerful predictor of

both ISR and target lesion revascularization after stenting (15,16). The reason for the discrepancy between Goldberg's study (12) and our study is unclear, but it may possibly relate to the difference in the end point in interventional strategies (e.g., aggressive stent implantation techniques using oversized balloons and/or high-pressure inflations) and the number and characteristics of patients studied. Instead, this study demonstrated that the baseline RI on IVUS was the only independent predictor of diffuse ISR, showing that positive remodeled lesions tended to develop into diffuse ISR after stenting among the lesions developing into ISR.

Positive remodeling and clinical presentation. Recent studies have shown that arterial remodeling as the response to plaque growth, which was initially studied by Glagov et al. (17), would play an important role in the complex process of atherosclerosis from compensatory enlargement to plaque disruption. There is evidence that positive remodeling may be initially advantageous in that it prevents luminal stenosis but disadvantageous in that significant expansive remodeling may make the plaque more vulnerable (18,19). Inversely, lesions with negative remodeling may be related to higher grade stenoses (20,21), but may appear more stable. Schoenhagen et al. (18) revealed that larger plaque and vessel areas and positive remodeling were associated with unstable angina pectoris, whereas negative remodeling was more common in patients with stable angina pectoris. In addition, other investigators suggested that in native coronary lesions, pre-interventional arterial remodeling (positive remodeling) was an independent predictor of target lesion revascularization after a nonstent coronary intervention (22) and also after stenting (23). Especially in the latter study, RI was indicated as a more powerful predictor of target lesion revascularization compared with the minimal stent area after intervention, as indicated in the current study.

The mechanism by which coronary lesions showing positive remodeling are associated with a worse clinical outcome after intervention is still uncertain; however, it may be partly related to the properties of lesions showing positive remodeling, which might promote the development of neointimal hyperplasia after stenting (24) and have less capacity of compensatory enlargement for further plaque growth after balloon angioplasty (25), as indicated in the current study. Although the lesions in this study were all the lesions developing into the first ISR, and most of them (81%) were accompanied with stable angina pectoris, the baseline RI was shown as the predictor of diffuse ISR, suggesting that arterial positive remodeling was potentially associated with biologically more active disease, even among this study population.

Volumetric IVUS analyses demonstrated that delta-VV and delta-SV in the diffuse ISR group were significantly smaller than those in the focal ISR group, indicating that lesions developing into diffuse ISR had less capacity to compensate and enlarge for further plaque growth. Furthermore, there was a significant negative correlation between baseline RI and delta-SV, and mildly between baseline RI and delta-VV, supporting the hypothesis that lesions with positive remodeling also had less capacity to compensate for further plaque growth. These results were consistent with the two-dimensional IVUS results after balloon angioplasty in the previous report (25).

Positive remodeling and pathohistologic background. Recent evidence from pathohistologic observations supports the concept that positive remodeling is one of the characteristic features of vulnerable plaques. In autopsy species of human coronary arteries, pathohistologic studies have shown that lesions with positive remodeling, compared with lesions with vessel shrinkage, had a larger lipid core and a higher macrophage count (26,27), which were recognized as histologic markers for plaque vulnerability (28). Moreover, other studies suggested that macrophages promoted expansive arterial remodeling through increased matrix degradation by matrix metalloproteinases, especially 2 and 9 (29,30). These pathohistologic and biochemical investigations currently recognized may, in part, explain the complex process of atherosclerosis and the clinical presentation of coronary lesions with positive remodeling.

Study limitations. This analysis is retrospective and is therefore subject to limitations inherent in this type of clinical investigation. The results of this study should be verified by further prospective investigation. Secondly, because the current study was subject to complete IVUS analyses before and after intervention, lesions with baseline chronic total occlusion, in which the IVUS study before intervention tended to be impossible or incomplete, were excluded from the present study. Therefore, the results of this report could not be applied to lesions with baseline chronic total occlusion, which was shown as having an association with negative remodeling (27). Thirdly, the lesions, which had undergone debulking by directional or rotational atherectomy before stenting, based on each operator's decision, because stenting alone had been considered impossible to acquire the optimal luminal results, were also excluded. This exclusion may also bias the results. Fourthly, the sample size of this study was relatively small. This may partly explain the small discrepancy between the present study and the previous studies about the predictive factors of diffuse ISR. Finally, we did not compare lesions with ISR with lesions without ISR in this study. However, many previous reports revealed that pre-interventional arterial remodeling (positive remodeling) was a powerful predictor of ISR or target lesion revascularization after stenting (23,24), and the ultimate aim of this study was to clarify the differences between focal and diffuse ISR lesions.

Conclusions. This study demonstrated that the baseline RI (positive remodeling) on IVUS was a powerful predictor of diffuse ISR among lesions developing into the first ISR. Measuring arterial remodeling patterns before intervention by IVUS may be helpful to stratify lesions at higher risk of diffuse ISR.

Acknowledgments

We thank all the cardiologists and the catheterization laboratory staff (E. Nouguchi and colleagues) at the Cardiovascular Institute Hospital for their assistance in this study.

Reprint requests and correspondence: Dr. Makoto Sahara, Cardiovascular Institute Hospital, 7-3-10 Roppongi, Minato-Ku, Tokyo 106-0032, Japan. E-mail: cfo36210@par.odn.ne.jp.

REFERENCES

1. Fischman DL, Leon MB, Baim DS, et al., the Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496–501.
2. Serruys PW, de Jaegere P, Kiemeneij F, et al., the BENESTENT Study Group. A comparison of balloon-expandable-stent implantation with angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489–95.
3. Nakano Y, Nakagawa Y, Yokoi H, et al. Initial and follow-up results of the ACS multi-link stent: a single center experience. Cathet Cardiovasc Diagn 1998;45:368–74.
4. Dauerman HL, Baim DS, Cutlip DE, et al. Mechanical debulking versus balloon angioplasty for the treatment of diffuse in-stent restenosis. Am J Cardiol 1998;82:277–84.
5. Reimers B, Moussa I, Akiyama T, et al. Long-term clinical follow-up after successful repeat percutaneous intervention for stent restenosis. J Am Coll Cardiol 1997;30:186–92.
6. Eltchaninoff H, Koning R, Tron C, Gupta V, Cribier A. Balloon angioplasty for the treatment of coronary in-stent restenosis: immediate results and 6-month angiographic recurrent restenosis rate. J Am Coll Cardiol 1998;32:980–4.
7. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872–8.
8. Kasaoka S, Tobis JM, Akiyama T, et al. Angiographic and intravascular ultrasound predictors of in-stent restenosis. J Am Coll Cardiol 1998;32:1630–5.
9. Kastrati A, Schomig A, Elezi S, et al. Predictive factors of restenosis after coronary stent placement. J Am Coll Cardiol 1997;30:1428–36.
10. Hoffmann R, Mintz GS, Mehran R, et al. Intravascular ultrasound predictors of angiographic restenosis in lesions treated with Palmaz-Schatz stents. J Am Coll Cardiol 1998;31:43–9.
11. Yokoi H, Tamura T, Kimura T, Nosaka H, Nobuyoshi M. Clinical and angiographic predictors of diffuse type in-stent restenosis. J Am Coll Cardiol 1998;31:1060–8.
12. Goldberg SL, Loussararian A, De Gregorio J, Di Mario C, Albiero R, Colombo A. Predictors of diffuse and aggressive intra-stent restenosis. J Am Coll Cardiol 2001;37:1019–25.
13. Kuntz RE, Safian RD, Carrozza JP, Fishman RF, Mansour M, Baim DS. The importance of acute luminal diameter in determining restenosis after coronary atherectomy or stenting. Circulation 1992;86:1827–35.
14. Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. N Engl J Med 1997;336:1697–703.
15. Fitzgerald PJ, Oshima A, Hayase M, et al. Final results of the Can Routine Ultrasound Influence Stent Expansion (CRUISE) study. Circulation 2000;102:523–30.
16. Mintz GS, Popma JJ, Pichard AD, et al. Intravascular ultrasound predictors of restenosis after percutaneous transcatheter coronary revascularization. J Am Coll Cardiol 1996;27:1678–87.
17. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–5.
18. Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. Circulation 2000;101:598–603.
19. Pasterkamp G, Schoneveld AH, van der Wal AC, et al. Relation of arterial geometry to luminal narrowing and histologic markers for plaque vulnerability: the remodeling paradox. J Am Coll Cardiol 1998;32:655–62.
20. Mintz GS, Kent KM, Pichard AD, Satler LF, Popma JJ, Leon MB. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses: an intravascular ultrasound study. Circulation 1997;95:1791–8.
21. Pasterkamp G, Wensing PJ, Hillen B, Post MJ, Mali WP, Borst C. Impact of local atherosclerotic remodeling on the calculation of percent luminal narrowing. Am J Cardiol 1997;79:402–5.
22. Dangas G, Mintz GS, Mehran R, et al. Preintervention arterial remodeling as an independent predictor of target-lesion revascularization after nonstent coronary intervention: an analysis of 777 lesions with intravascular ultrasound imaging. Circulation 1999;99:3149–54.
23. Okura H, Morino Y, Oshima A, et al. Preintervention arterial remodeling affects clinical outcome following stenting: an intravascular ultrasound study. J Am Coll Cardiol 2001;37:1031–5.
24. Endo A, Hirayama H, Yoshida O, et al. Arterial remodeling influences the development of intimal hyperplasia after stent implantation. J Am Coll Cardiol 2001;37:70–5.
25. Okura H, Hayase M, Shimodozono S, Bonneau HN, Yock PG, Fitzgerald PJ. Impact of pre-interventional arterial remodeling on subsequent vessel behavior after balloon angioplasty: a serial intravascular ultrasound study. J Am Coll Cardiol 2001;38:2001–5.
26. Varnava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. Circulation 2002;105:939–43.
27. Burke AP, Kolodgie FD, Farb A, Weber D, Virmani R. Morphological predictors of arterial remodeling in coronary atherosclerosis. Circulation 2002;105:297–303.
28. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes: implications for plaque rupture. Circulation 1994;90:775–8.
29. Ivan E, Khatri JJ, Johnson C, et al. Expansive arterial remodeling is associated with increased neointimal macrophage foam cell content: the murine model of macrophage-rich carotid artery lesions. Circulation 2002;105:2686–91.
30. Pasterkamp G, Schoneveld AH, Hijnen DJ, et al. Atherosclerotic arterial remodeling and the localization of macrophages and matrix metalloproteases 1, 2 and 9 in the human coronary artery. Atherosclerosis 2000;150:245–53.