Geometric Vascular Remodeling After Balloon Angioplasty and ß-Radiation Therapy : A Three-Dimensional Intravascular Ultrasound Study

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Geometric Vascular Remodeling After Balloon Angioplasty and β-Radiation Therapy

A Three-Dimensional Intravascular Ultrasound Study

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Background—Endovascular radiation appears to inhibit intimal thickening after overstretching balloon injury in animal models. The effect of brachytherapy on vascular remodeling is unknown. The aim of the study was to determine the evolution of coronary vessel dimensions after intracoronary irradiation after successful balloon angioplasty in humans.

Methods and Results—Twenty-one consecutive patients treated with balloon angioplasty and β-radiation according to the Beta Energy Restenosis Trial-1.5 were included in the study. Volumetric assessment of the irradiated segment and both edges was performed after brachytherapy and at 6-month follow-up. Intravascular ultrasound images were acquired by means of ECG-triggered pullback, and 3-D reconstruction was performed by automated edge detection, allowing the calculation of lumen, plaque, and external elastic membrane (EEM) volumes. In the irradiated segments, mean EEM and plaque volumes increased significantly (451±128 to 490.9±159 mm^3 and 201.2±59 to 241.7±74 mm^3; $P=0.01$ and $P=0.001$, respectively), whereas luminal volume remained unchanged (250.8±91 to 249.2±102 mm^3; $P=$NS). The edges demonstrated an increase in mean plaque volume (26.8±12 to 32.6±10 mm^3, $P=0.0001$) and no net change in mean EEM volume (71.4±24 to 70.9±24 mm^3, $P=$NS), resulting in a decrease in mean luminal volume (44.6±16 to 38.3±16 mm^3, $P=0.01$).

Conclusions—A different pattern of remodeling is observed in coronary segments treated with β-radiation after successful balloon angioplasty. In the irradiated segments, the adaptive increase of EEM volume appears to be the major contributor to the luminal volume at follow-up. Conversely, both edges showed an increase in plaque volume without a net change in EEM volume. **(*Circulation*. 1999;100:1182-1188.)**

Key Words: balloon ■ angioplasty ■ ultrasonics ■ remodeling ■ radioisotopes

Restenosis after balloon angioplasty (BA) is the major limitation of the technique, occurring after 30% to 40% of procedures despite excellent acute results.[1] Excessive neointimal proliferation and extracellular matrix synthesis by modified smooth muscle cells in response to injury have been suggested as the main mechanisms of restenosis.[2,3] However, recent studies identified geometric vascular remodeling after BA as a concomitant contributor to the process of restenosis.[4,5]

Endovascular radiation appears to be a novel technique, which, by use of either β- or γ-isotopes, has inhibited intimal thickening after overstretch balloon injury in experimental models.[6–8] The theoretical benefit of radiation in preventing neointimal proliferation resides in its killing effect of more rapidly dividing smooth muscle cells.[9] Two randomized studies demonstrated substantial reductions in restenosis rate after treatment of in-stent restenosis.[10,11] The use of either β- or γ-radiation for treatment of de novo coronary lesions has been successfully tested in humans.[12,13]

The effects of brachytherapy on geometric vascular remodeling of de novo treated lesions are still unknown. By allowing direct measurement of the vessel wall, intravascular ultrasound (IVUS) imaging has been used to study the remodeling process in coronary arteries.[14–16] Recently, 3D IVUS reconstruction systems have been introduced, allowing the quantitative analysis of a particular segment of interest during an automated pullback.[17] Furthermore, to prevent artifacts caused by systolic-diastolic dimension changes of the coronary vessel wall, the pullback of the IVUS catheter can be performed with ECG gating.[18]

The purposes of this article were to (1) quantify the volumes of vessel structures by means of 3D reconstruction of IVUS images of coronary segments successfully treated by BA followed by β-radiation therapy, (2) determine the

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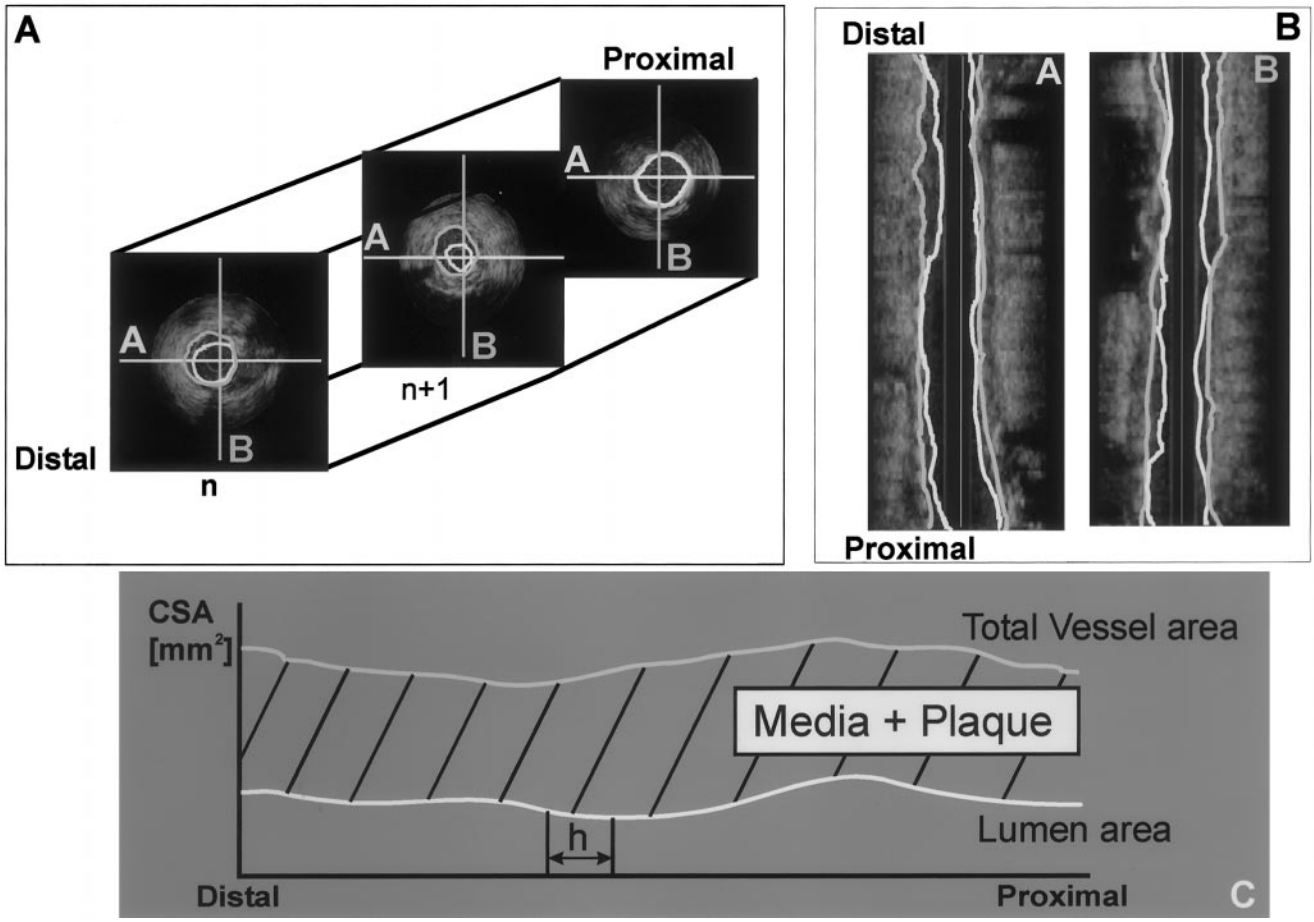

Figure 1. Overview of the applied analysis software package.[18,21] A, Schematic presentation of the IVUS catheter pullback. B, Two computed longitudinal perpendicular views. Corresponding cut-planes in A are represented by the letters A and B. C, Outcome of measurements. CSA indicates cross-sectional area; h, distance between 2 consecutive catheter positions (0.2 mm). Gray boundary lines represent total vessel contours; white lines, luminal contours.

evolution of these vessel parameters to define the pattern of vascular remodeling after coronary irradiation, and (3) evaluate the potential effect of brachytherapy on the remodeling at both edges of the irradiated area.

Methods

Patient Selection

Patients eligible for the study were those treated successfully with BA followed by intracoronary irradiation according to the Beta Energy Restenosis Trial (BERT)-1.5. The purpose of this trial was to evaluate the safety and efficacy of low-dose irradiation after BA with or without stent implantation in patients with single de novo lesions of native coronary arteries. The isotope selected was the pure β-emitting strontium 90, and patients were randomly assigned to receive doses of 12, 14, or 16 Gray. The inclusion and exclusion criteria of this trial have been previously reported.[13] The delivery of the radiation was performed by the use of the Beta-Cath System (Novoste Corp).[19] The radiation source train of this system consists of a series of 12 independent cylindrical seeds that contain the radioisotope sources and is bordered by 2 gold radio-opaque markers separated by 30 mm.[19]

IVUS Image Acquisition Analysis System

The segment subject to 3D reconstruction was examined with a mechanical IVUS system (ClearView, CVIS, Boston Scientific Corp) with a sheath-based IVUS catheter incorporating a 30-MHz single-element transducer rotating at 1800 rpm (Ultracross, CVIS). The transducer is placed inside a 2.9F, 15-cm-long sonolucent distal sheath that alternatively houses the guide wire (during the catheter introduction) or the transducer (during imaging). The IVUS transducer was withdrawn through the stationary imaging sheath by an ECG-triggered pullback device with a stepping motor developed at the Thoraxcenter, Rotterdam.[20] The ECG-gated image acquisition and digitization was performed by a workstation designed for the 3D reconstruction of echocardiographic images[20] (EchoScan, Tomtec). This workstation received input from the IVUS machine (video) and the patient (ECG signal) and controlled the motorized transducer pullback device. The steering logic of the workstation considered the heart rate variability and only acquired images from cycles meeting a predetermined range; premature beats were rejected. IVUS images were acquired coinciding with the peak of the R wave. If an R-R interval failed to meet the preset range, the IVUS catheter remained at the same site until a cardiac cycle met the predetermined R-R range. Then, the IVUS transducer was withdrawn 200 μm to acquire the next image.[17,18,20] Given the slice thickness of 200 μm and the length subject to the analysis of 40 mm (distance between the 2 gold markers of the radiation source and 5 mm both edges), 200 cross-sectional images per segment were digitized and analyzed. A Microsoft Windows-based contour detection program developed at the Thoraxcenter was used for the 3D analysis.[21] This program constructs 2 longitudinal sections from the data set and identifies the contours corresponding to the lumen-intima and media-adventitia boundaries (Figure 1). Corrections could be performed interactively by "forcing" the contour through visually identified points, and then the entire data set was updated.[21] Careful checking and editing of the contours of the 200 planar images was performed with an average of

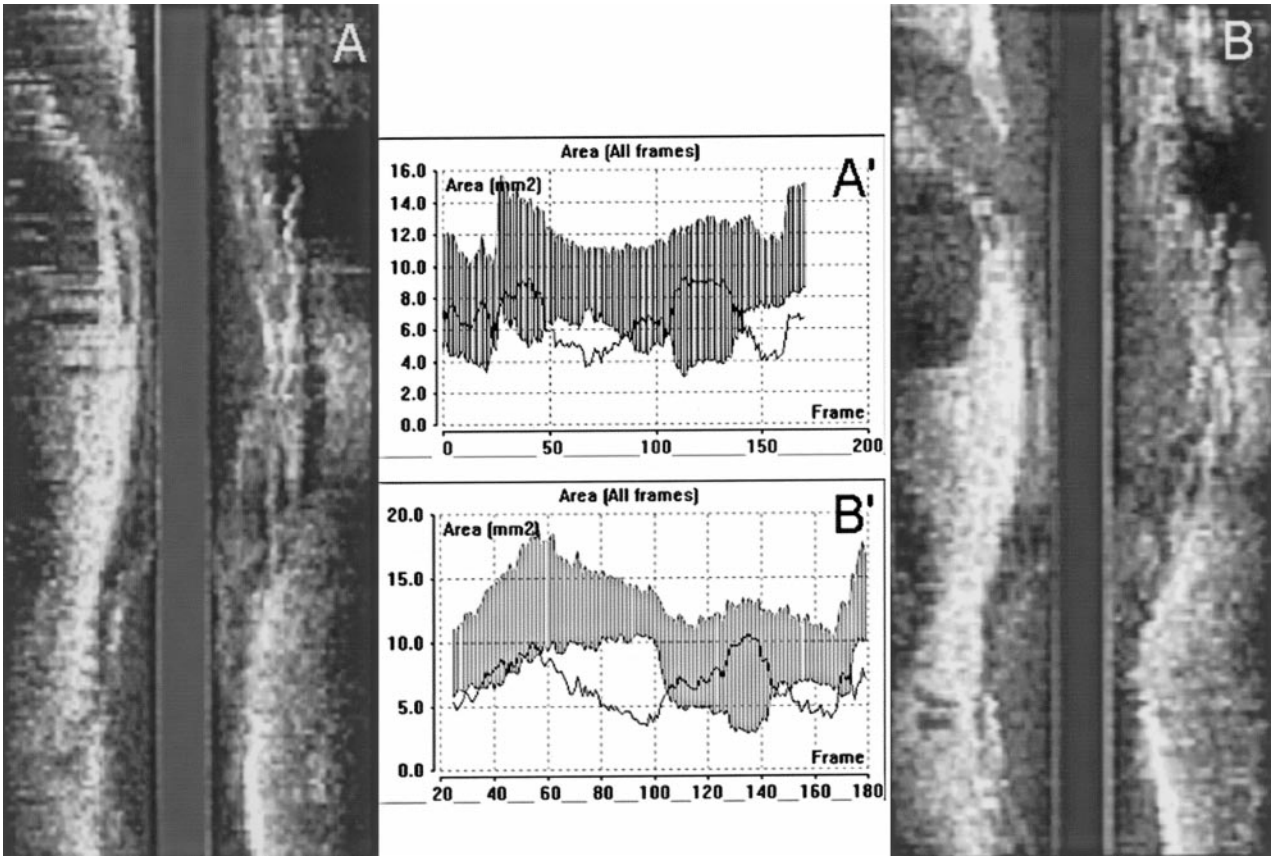

Figure 2. Longitudinal reconstruction of the IVUS cross-sectional images and subsequent volumetric calculations (middle charts) after irradiation (A and A′) and at 6-month follow-up (B and B′). Note increase in scale at follow-up chart reflecting increase in total vessel volume.

60 minutes for complete evaluation. The area encompassed by the lumen-intima and media-adventitia boundaries defined the luminal and the external elastic membrane (EEM) volumes, respectively. The difference between EEM and luminal volumes defined the plaque volume. Volumetric data were calculated by the formula

$$V = \sum_{i=1}^{n} A_i \cdot H$$

where V is volume, A is area of EEM or lumen or plaque in a given cross-sectional ultrasound image, H is thickness of the coronary artery slice reported by this digitized cross-sectional IVUS image, and n is the number of digitized cross-sectional images encompassing the volume to be measured.[21] The feasibility and intraobserver and interobserver variabilities of this system have been previously reported.[17,22] The 3D analysis was performed by 1 investigator. Intraobserver variability was assessed by analyzing a series of 15 IVUS volumetric studies at least 3 months apart. Differences in EEM, plaque, and lumen volumes were as follows: $-0.4 \pm 1.0\%$, $-0.3 \pm 1.3\%$, and $-0.2 \pm 0.9\%$, and the intraclass correlation coefficients were $r=0.97$, $r=0.97$, and $r=0.98$, respectively.

To define the treated segment, a few steps were followed. First, an angiogram was performed after positioning the delivery catheter and the relation between anatomic landmarks and the 2 gold markers were noted. Typically, the aorto-ostial junction and the side branches were used as landmarks. The anatomic landmark closest to either of the gold markers was used as a reference point. During the IVUS analysis, this reference point was identified during a contrast injection with the IVUS imaging element at the same position as the gold marker of the source. At the same time, during the contrast injection, the image from the IVUS imaging element was recorded and the reference point identified. During the subsequent pullback, this reference point was recognized and used for selecting the area subject to the analysis: 30 mm for the irradiated segment analysis and 5 mm at both edges for the "edge effect" evaluation. In cases in which there were no angiographic landmarks bordering either of the 2 gold markers of the delivery catheter, the minimal luminal diameter identified during the IVUS pullback was used as the reference point. Then, the irradiated segment was defined by selecting slices encompassed within 15 mm proximal and 15 mm distal to the minimal luminal diameter. This approach was necessary only in 2 cases. At follow-up, correct matching of the region of interest was performed by comparing the longitudinal reconstruction with that after treatment (Figure 2).

Procedure

The medical ethics committee of our institution approved the study, and all patients signed a written informed consent form. The patients received aspirin (250 mg) and heparin (10 000 IU IV) before the procedure. If the duration of the entire interventional procedure exceeded 1 hour, additional heparin was given to maintain the activated clotting time >300 seconds. In BERT-1.5, BA was performed according to standard clinical practice. After successful angioplasty, intracoronary β-radiation was performed as previously described,[13] and afterward, repeat angiography and IVUS pullback were carried out. On average, IVUS pullback was performed at 12 ± 2 minutes (9 to 15 minutes) after BA. A continuous motorized pullback at a speed of 0.5 mm/s was first carried out, followed by an ECG-gated pullback at a step size of 0.2 mm/step. Intracoronary nitrates were administered immediately before each of the IVUS pullbacks. A final angiogram after the IVUS study concluded the procedure. At 6-month follow-up, further IVUS analysis of the treated area was performed.

TABLE 1. Baseline Characteristics. (n=21)

Male sex, n (%)	16 (76%)
Mean age, y	56±9
Coronary risk factors, n (%)	
Smoking	14 (67%)
Hypercholesterolemia	11 (52%)
Family history	11 (52%)
Hypertension	10 (48%)
Diabetes	4 (19%)
Treated vessel, n (%)	
Left anterior descending	11 (52%)
Left circumflex	6 (29%)
Right coronary artery	4 (19%)
Prescribed dose, n (%)	
16 Gy	9 (43%)
14 Gy	4 (19%)
12 Gy	8 (38%)

Statistical Analysis

Quantitative data are presented as mean±SD. Volumetric data derived from the 3D reconstruction of the IVUS imaging were compared immediately after treatment and at follow-up by use of the 2-tailed, paired Student's *t* test. Linear regression analysis was performed to assess the relation between the change in EEM, lumen, and plaque dimensions. A value of $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

Thirty-one patients were included in BERT-1.5 at our institution. Eight patients who received stent implantation for important recoil or dissection after BA were excluded from the volumetric assessment. At follow-up, the 3D IVUS analysis was not performed in 2 patients: 1 patient refused and the other returned prematurely with unstable angina pectoris secondary to severe restenosis, and only a manual IVUS pullback preintervention was possible. Therefore, 21 patients with volumetric IVUS analysis after treatment and at follow-up formed the study population. The baseline characteristics of the patients are presented in Table 1.

Clinical and Angiographic Follow-Up

At follow-up, 14 (66%) patients remained asymptomatic. Six patients had stable angina pectoris: Canadian Cardiovascular Society class 1 (n=1), class 2 (n=1), and class 3 (n=4). One patient was admitted prematurely because of unstable angina pectoris. The follow-up angiography demonstrated restenosis (>50% diameter stenosis on quantitative coronary angiography) in 5 (24%) patients. One restenotic patient demonstrated aneurysmatic formation within the irradiated area (Figure 3). The prescribed dose in restenotic patients was 12 Gray (n=1), 14 Gray (n=1), and 16 Gray (n=3).

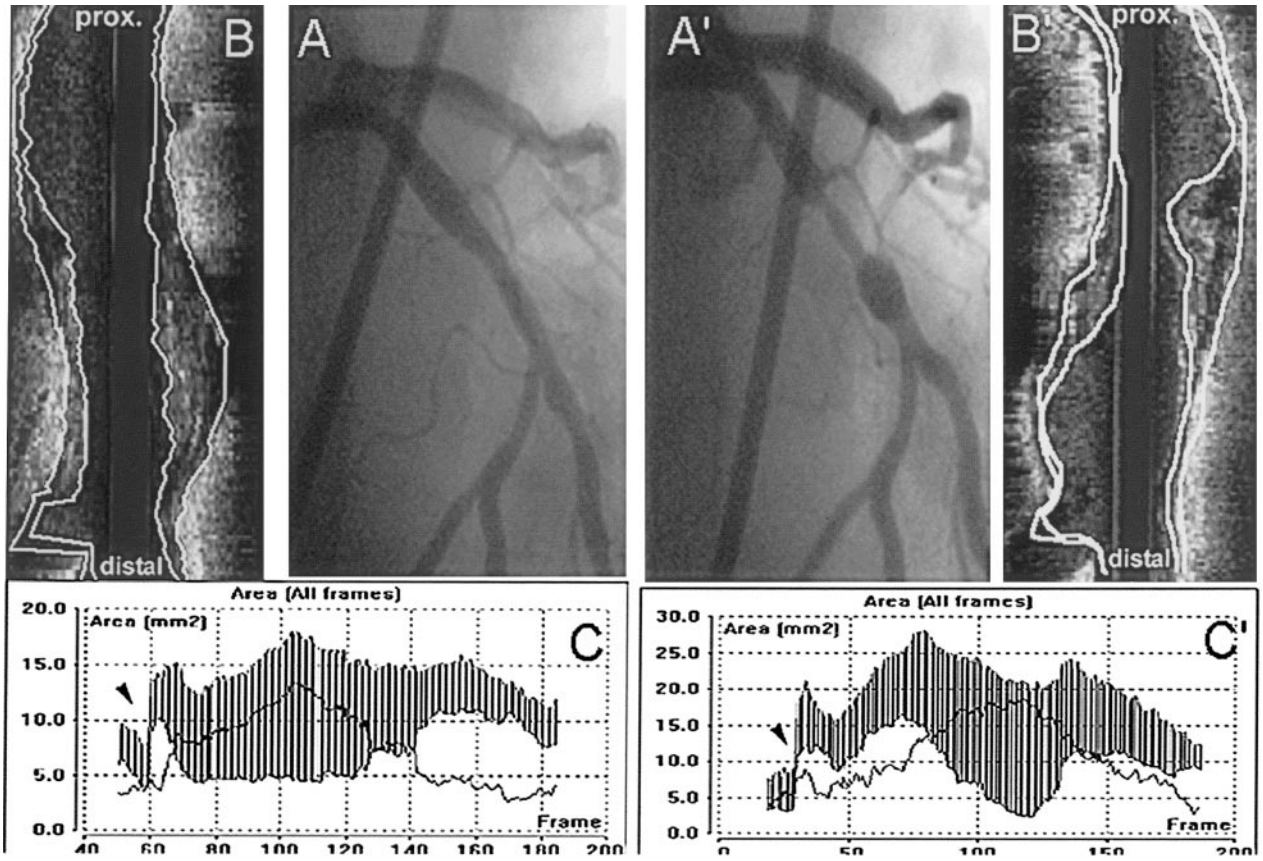

Figure 3. Angiography and 3D reconstruction of an irradiated segment (A, B, and C) that demonstrated restenosis and aneurysmatic formation at 6-month follow-up (A′, B′, and C′). Contour tracing has been manually corrected for distal side branch (black arrowheads in bottom charts). prox. indicates proximal.

TABLE 2. IVUS Volumetric Analysis

Patient	Artery	Dose, Gray	LV Post	LV Follow-Up	ΔLV	EEM Post	EEM Follow-Up	ΔEEM	PV Post	PV Follow-Up	ΔPV
1	LAD	12	143.2	148.4	5.2	321.4	371.9	50.5	178.2	223.5	45.3
2	LAD	14	297.6	289.2	−8.4	605.5	634.8	29.3	307.8	345.5	37.7
3	LCx	16	206.2	222.8	16.6	399.3	426.1	26.8	193.2	203.2	10
4	LAD	12	201.6	186	−15.6	313.1	315.4	2.3	111.5	129.5	18
5	RCA	14	281	213.4	−67.6	493.5	486.1	−7.4	212.5	272.4	59.9
6	RCA	12	228.1	197.9	−30.2	458.7	442.4	−16.3	230.6	244.5	13.9
7	LCx	12	192.1	257	64.9	352.5	439.5	87.0	160.4	182.4	22
8	LAD	16	169.6	176.8	7.2	323.9	359.3	35.4	154.3	182.5	28.2
9	LAD	14	231.2	246.3	15.1	470	489.8	19.8	238.8	243.5	4.7
10	LCx	16	333.2	278.9	−54.3	487.2	470.3	−16.9	154	191.4	37.4
11	LCx	16	392.5	490.9	98.4	718.5	806	87.5	325.9	315.1	−10.8
12	LAD	12	272.6	193	−79.6	452.9	498.2	45.3	180.3	305.2	124.9
13	LCx	12	326.4	321.2	−5.2	578	676	98.0	251.6	354.8	103.2
14	LAD	12	154.8	187.8	33	276.8	337.1	60.3	122	149.3	27.3
15	LAD	16	237.6	216.6	−21	332.1	334.2	2.1	94.5	117.6	23.1
16	LAD	16	341.2	229	−112.2	605.3	520.4	−84.9	264.2	291.4	27.2
17	LCx	16	210.1	278.2	68.1	412.6	600.7	188.1	205.7	322.5	116.8
18	RCA	16	176.6	219.3	42.7	415.1	430.1	15.0	238.5	210.8	−27.7
19	LAD	16	234.2	225	−9.2	446.9	463.2	16.3	212.7	238.3	25.6
20	LAD	14	119	108.5	−10.5	315.7	296.1	−19.6	196.7	187.6	−9.1
21	RCA	12	501.4	548	46.6	694.4	912.2	217.8	193	364	171
Mean		14.1	250.8	249.2	−1.6*	451.1	490.9	39.8†	201.2	241.7	40.5‡
SD		1.8	91.8	102.5	51.5	128.1	159.3	68.7	59.3	74.0	49.4

LAD indicates left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; LV, luminal volume; EEM, external elastic membrane volume; PV, plaque volume; and post, after treatment. All values in mm^3.

*P=NS; †$P<0.01$; ‡$P<0.001$.

Irradiated Segment IVUS Analysis

Volumetric calculations of the EEM, lumen, and plaque at the site of irradiated coronary segments are presented in Table 2. A significant increase in mean EEM volume was observed at follow-up (451±128 to 490.9±159 mm^3; $P=0.01$) parallel to that in plaque volume (201.2±59 to 241.7±74 mm^3; $P=0.001$). As a result, mean luminal volume remained unchanged (250.8±91 mm^3 after treatment vs 249.2±102 mm^3 at follow-up; P=NS). Patients assigned to receive a dosage of 16 Gray showed no differences in terms of EEM, lumen, and plaque changes as compared with those assigned to receive 12 and 14 Gray. Changes in EEM and plaque volumes showed a significant and positive correlation ($r=0.66$; $P=0.001$). Similarly, changes in luminal volumes correlated significantly with those in EEM volumes ($r=0.69$; $P=0.005$) but not with those in plaque volumes ($r=0.07$, P=NS) (Figure 4). Sixteen (76.2%) patients showed a global increase in EEM volume (+61.3±60 mm^3), whereas 3 (14.3%) patients showed a reduction in plaque volume (−15.7±10 mm^3). Five (23.8%) patients demonstrated angiographic restenosis. In 2 of them, despite the

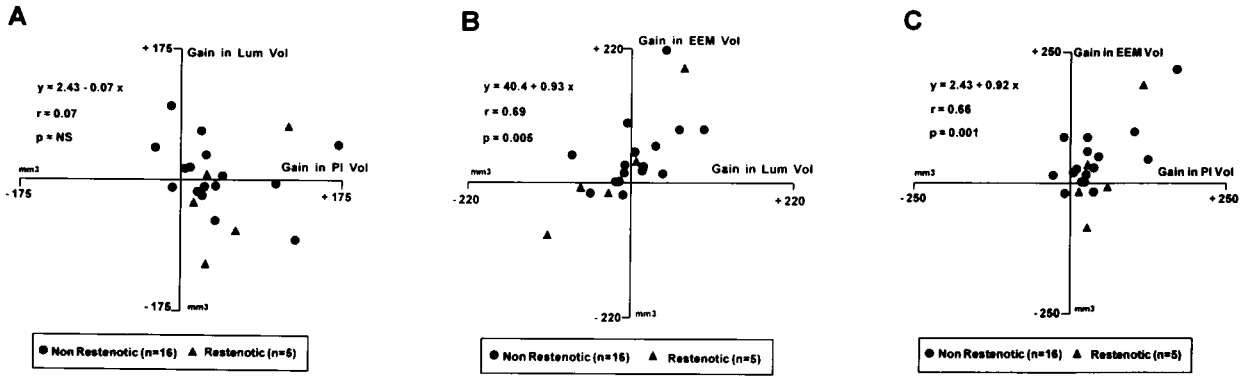

Figure 4. Linear regression analysis between changes in plaque and luminal volumes (A), EEM and luminal volumes (B), and EEM and plaque volumes (C). EEM Vol indicates EEM volume; PI Vol, plaque volume; and Lum vol, luminal volume.

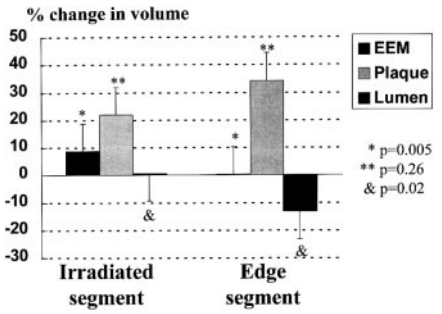

Figure 5. Comparison between patterns of remodeling in irradiated area and at edges.

absolute increase in EEM volume, a focal increase in plaque volume led to restenosis. The remaining 3 patients showed an increase in plaque concomitant to a decrease EEM volume.

Ten (47.6%) patients showed a global increase in luminal volume ($+40.1\pm30$ mm^3). In 8 of them, the increase in EEM volume ($+85.7\pm75$ mm^3) overcame the increase in plaque volume ($+53.2\pm59$ mm^3). In the other 2 patients, enlargement of EEM volume was observed concomitantly to decrease in plaque volume.

"Edge Effect" IVUS Measurements

Significant angiographic reduction in luminal diameter involving the proximal edge of the irradiated area was observed in 1 patient at follow-up. Volumetric calculations demonstrated a significant mean increase in plaque volume (26.8 ± 12 to 32.6 ± 10 mm^3; $P=0.0001$) and no net change in mean EEM volume (71.4 ± 24 to 70.9 ± 24 mm^3; $P=$NS), resulting in a significant decrease of mean luminal volume at follow-up (44.6 ± 16 to 38.3 ± 16 mm^3; $P=0.01$). Changes in luminal volumes correlated significantly with those in EEM and plaque volume ($r=0.87$; $P<0.0001$ and $r=-0.51$; $P=0.03$; respectively). Conversely, changes in plaque did not correlate with those in EEM ($r=-0.03$; $P=$NS). At the edges, percentage of change in EEM and in luminal volume differed significantly from those within the irradiated segment (Figure 5). No differences in volumetric changes were observed regarding the 3 ranges of doses.

Discussion

Previous studies with γ-radiation for the treatment of in-stent restenosis have demonstrated a reduction in the restenosis rate mainly as the result of a reduction in neointimal formation, as assessed by IVUS.[10,11] Our study provides the mechanistic interpretation of β-radiation on remodeling of de novo lesions treated with BA. On average, adaptive vessel enlargement is the main contributor to luminal volume at follow-up by accommodating the increase in plaque volume.

The importance of geometric remodeling after BA has been studied both in experimental models[5,23,24] and in humans.[14–16] Di Mario et al[15] reported that shrinkage of the vessel accounted for 68% of the late loss after BA. Similar results were obtained by and Mintz et al,[14] who reported 73% of late loss caused by chronic vessel constriction. A serial IVUS study[16] described a biphasic time course of the geometric remodeling after BA. Thus an initial adaptive vessel enlargement was observed up to the first month, followed by a late constriction phase during the next 5 months.

Only 5 (23.8%) patients demonstrated shrinkage of vessel volume 6 months after radiation, whereas the remaining 16 (76.2%) patients showed vessel enlargement. Furthermore, luminal volume appeared to increase in 10 (47.6%) patients. These results are in concordance with those obtained by Condado et al,[12] who reported a negative late loss in 10 (45%) of 22 patients treated with γ-radiation. We demonstrated that the increase in luminal volume was mainly due to vessel enlargement rather than plaque reduction, which was observed only in 2 patients.

The severity and depth of the arterial wall injury caused by the balloon overstretching might induce adventitial inflammation and subsequent fibrosis, which, in turn, might lead to contraction of the vessel.[24,25] The beneficial effect of intravascular radiation on the arterial remodeling after angioplasty may be explained by a reduction of either cell proliferation in the media and adventitia or the expression of α-smooth muscle actin in the adventitia, which is responsible for fibrotic scar formation after BA.[26] A potential concern regarding coronary brachytherapy is the fact that initially favorable adaptive remodeling would lead to late undesired aneurysm formation. The incidence of coronary aneurysm after BA or stent implantation, as defined as a coronary dilatation that exceeded the diameter of normal adjacent segments by 1.5 times,[27] ranges between 3.9% and 5.4% and has not been associated with angiographic restenosis or unfavorable clinical outcome.[28,29] The incidence and prognosis of aneurysm formation after radiation is unknown. In our cohort, 1 patient demonstrated this complication at 6-month follow-up. Condado et al[12] reported 4 (20%) cases of aneurysmatic formation within 2 months after γ-radiation. In 2 of them, a further increase of the size was observed at 6 and 8 months, respectively.[12]

An interesting finding was the concurrent vessel enlargement and focal plaque increase, as observed in 12 patients, resulting in restenosis in 2 of them. Inhomogeneity of dosing caused by the lack of centering might account for this paradox. Therefore the actual dose to the luminal surface and adventitia appeared to be highly variable between patients as calculated by means of dose-volume histograms.[30] A more homogeneous dose distribution might be achieved by use of a centering catheter or a γ-source.[30]

As opposed to the pattern of remodeling within the irradiated area, the edge segments demonstrated a significant decrease in mean luminal volume. A lack of adaptive remodeling concomitantly to an increase in plaque volume accounted for the residual luminal volume at the edges. The edge of the radiation source represents an area receiving low-dose radioactivity. It is hypothesized that a low activity could have a proliferative effect, especially when associated with injury induced by BA.[31]

Study Limitations

This study was not placebo-controlled. Consequently, no conclusion about the effectiveness of β-irradiation in preventing neointimal formation can be extrapolated.

A potential source of error is germane to the presence of the IVUS catheter in the lumen. In relatively small vessels, this can result in vessel stretching, resulting in volumetric

overestimation. Alternatively, the distending pressure on the vessel may be substantially decreased by the presence of the catheter that fills a significant part of the lumen. This limitation could be especially relevant in studies evaluating only 1 cross-section at the narrowest part of the segment. However, in our cohort, none of the segments showing adaptive remodeling demonstrated any area in which the lumen were occluded by the IVUS catheter.

The method of selection of the area of interest is the best available. However, despite the meticulous procedure followed, a small inaccuracy cannot be completely ruled out. Ideally, new systems incorporating the IVUS imaging element on the delivery catheter would resolve this drawback.

The follow-up period of our cohort might be short, considering the fact that vascular irradiation may delay restenosis by 1 to 3 years.[32] Therefore the observed vessel enlargement might represent an early phase of the effect of β-radiation therapy after BA.

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