Intracoronary Brachytherapy:

a New Technique to Prevent Restenosis after

Percutaneous Coronary Interventions

Cover illustrations (made by Jurgen Ligthart): The upper left panel shows a coronary angiogram with a centered radiation source in place. The upper central panel illustrates a coronary angiogram with a non-centered radiation source in place. The upper right panel shows a radioactive stent after its implantation. In the central panel a longitudinal reconstruction of an intravascular ultrasound image of a radioactive stent is depicted. The lower panels show the intravascular ultrasound images of three cross-sectional areas within a radioactive stent after its implantation.

Intracoronary Brachytherapy: a New Technique to Prevent Restenosis After Percutaneous Coronary Interventions

Intracoronaire brachytherapie: een nieuwe techniek ter voorkoming van restenose na percutane coronaire interventies.

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A la Pilar i a les meves nenes: la Marta i ...,

als meus pares i sogres,

per la seva paciència i sacrifici durant 2 anys.

Us estimo

CONTENTS

Percutaneous transluminal coronary angioplasty (PTCA) is an accepted treatment for coronary artery disease. However, angiographical restenosis is reported in 40-60% of patients after a successful PTCA.[1,2] Mechanisms involved in the restenosis process are elastic recoil of the artery, local thrombus formation, vascular remodeling with shrinkage of the vessel and an overact healing process with neointimal hyperplasia.[2-5] Neointimal hyperplasia develops by migration and proliferation of smooth muscle cells and myofibroblasts after balloon induced trauma of the arterial wall and by deposition of an extracellular matrix by the smooth muscle cells.[5-8] The introduction of the stent in the arsenal of the interventional cardiologist has reduced the restenosis rate to 15-20%,[9-10] by preventing elastic recoil and negative remodeling.[11] However, the occurrence of restenosis after stent implantation remains unresolved, especially in small vessels and long lesions, where it may exceed 30% of the cases.[12] It is primary caused by neointimal hyperplasia, which occurs due to trauma of the arterial wall by the stent-struts. The treatment of in-stent restenosis with conventional techniques (balloon angioplasty or debulking) is rather disappointing with restenosis rates of 27-63%, which increases with the number of re-interventions.[13-17]

Since radiotherapy had proven to be effective in treating the exuberant fibroblastic activity of keloid scar formation and other non-malignant processes such as ocular pterygia[18-19] it was assumed that this adjunctive therapy would also inhibit coronary restenosis.

HISTORY

The first experimental study in this field was carried out in 1964 by Friedman et al, by the use of Iridium 192 (^{192}Ir) in the cholesterol-fed rabbit.[20] In 1992, in Frankfurt, Liermann and colleagues performed the first 4 cases of brachytherapy, in patients who had undergone a femoral percutaneous angioplasty[21] A second wave of experimental work was carried out in the United States by Wiedermann and Weinberger in New York,[22] Waksman and Crocker in Atlanta[23] and Mazur and Raizner in Houston.[24] In parallel, Verin and Popowski in Geneva conducted experimental studies with the pure ß-emitter ^{90}Y in carotid and iliac arteries of rabbits.[25] The first clinical experience in coronary arteries in humans was performed by Condado et al using a hand-delivered ^{192}Ir wire into a non-centered, closed end lumen catheter[26] and by Verin et al using a ß-source and a centered device.[27] Both studies demonstrated that the delivery of radiation in the coronary artery is feasible and safe, although the restenosis rate

remained relatively high. The positive results of the first randomized trial aimed to determine the effectiveness of γ-radiation for the treatment of in-stent restenosis[28] encouraged the investigators to design an extraordinary number of studies that will quickly shed light on the utility of brachytherapy for the prevention of restenosis.

BASIC PRINCIPLES

Radioactive disintegration.- Radioactivity is the process in which atomic unstable nuclei, spontaneously change their configuration and energy content to reach a stable state (ground state). This event normally brings a change in the basic element itself, that is known as radioactive disintegration or radioactive decay. This process is usually associated with the emission of particulate or electromagnetic radiation. The particulate radiation is either α- or ß-emission. Alpha particles are heavyweight charged particles, which can travel very short distances within tissues. Beta particles are lightweight high-energy electrons, with either positive or negative charge. A third type of emission originated from the nucleus, known as γ-emission or photon emission, takes the form of electromagnetic radiation. An alternate way for an unstable nucleus to reach ground state is to capture an electron orbiting just outside the nucleus. This process called electron capture, makes the outer shell where electrons are orbiting become unstable. To fill the void of captured electrons, other electrons from nearby orbits jump to the innermost orbit, which also leads to the emission of photons, called X-rays, which take the form of electromagnetic waves. Gamma and X-rays are both high-energy photons, without charge or mass. The only distinction between gamma and X-rays lies in its origin: γ-rays are emitted by the nucleus, whereas the X-rays emanate from electrons jumping to innermost orbits. Most often an unstable nucleus will emit an alpha or beta particle followed by gamma radiation. Only a few radioisotopes, e.g. Phosphorous-32 (a pure beta-emitter), only emit particles, without gamma radiation.[29-31]

The process of radioactive decay is a spontaneous, random event. In a sample with large number of atoms, the decay follows exponential behavior. The radioactivity of a sample is defined as the number of disintegrations per unit time. The units in which radioactivity has been conventionally measured are:

1 becquerel (Bq) = 1 disintegration /second

1 curie (Ci) = $3.7 * 10^{10}$ Bq

1 millicurie (mCi) = $3.7 * 10^{7}$ Bq

As the nuclei of radioactive material disintegrate, the number of nuclei available for decay decreases. The rate of decrease varies among radioisotopes. This value is unique to each isotope. This rate of decay follows the exponential formula:

$$A(t) = A(0)\, e^{-0.693 * t / T1/2} \text{ where,}$$

A(0) is the known activity of the isotope at a certain time we call zero; A(t) is the activity remaining at time t and T1/2 is a constant called half-life. The half-life of an isotope is the time during which its activity reduces to half its original value.[29-31]

Tissue damage induced by radiation and effective dose.- When radiation is absorbed in a tissue, it can either cause direct damage to a critical target by ionization or it can indirect damage a critical target by interacting with other molecules to produce free radicals, which will subsequently damage the critical target. Approximately 80% of the radiation damage is caused by these free radicals. The most critical target that could be damaged by radiation is DNA. The consequence of this chromosomal damage, specifically the formation of exchange-type aberrations, is that the cell lose its ability to proliferate, which will ultimately lead to its death.[32] This mode of cell death leads to a dose-response relationship where the fraction of cell surviving (S) is a linear-quadratic function of the dose (D):

$$S = e^{-\alpha * D - \beta * D2} \text{ where,}$$

α and ß are constants that are characteristic of a given cell type. At low doses, the linear component dominates, but at higher doses (such as the single doses that are proposed for intravascular radiation) the term that is quadratic start to dominate. Theoretically, a single acute dose of 12 to 20 Gy, would result in a depopulation of smooth muscle cells about 10^{-3} to 10^{-6}, that is, only in about 1 cell in 1000 to 1 million would survive. These survivors cells would need to double between 12 to 20 times to produce sufficient progeny to block the artery. Considering that smooth muscle cells are not malignant and therefore do not have the capacity for indefinite proliferation, it may be that a dose of this magnitude could result in a permanent inhibition of restenosis.[22,32,33]

Target tissue.- Experimental models have suggested that myofibroblasts in the adventitia proliferate after angioplasty and may migrate into the intima where they appear as smooth muscle actin-containing cells.[34,35] The effect of radiation on myofibroblasts proliferation in the adventitia as well as on the vessel remodeling have been recently reported.[36] Endovascular radiation after balloon overstretch injury of porcine coronary arteries significantly reduced the number of proliferating cells in the adventitia and medial wall compared to controls at a dose of 14 or 28 Gy prescribed at 2 mm into the vessel wall. The higher 28 Gy dose resulted in a much

greater inhibition of cell proliferation in the adventitia compared to 14 Gy.[36] In the same study, it was observed a sigificant reduction in the extent of adventitial α-actin staining in the irradiated vessels as compared to controls, suggesting an inhibition of adventitial fibrosis by the radiation treatment, leading to a significant increase in the vessel perimeter (inhibition of constrictive vascular remodeling).[36] These findings support the concept that the adventitia is the target tissue of the intracoronary radiotherapy.

Radiation Therapy Systems

Radiation therapy can be delivered to the coronary arteries by external radiation or by brachytherapy methods either by catheter-based systems or by radioactive stents. Catheter-based systems can use both ß- or γ-emitters, which can deliver the prescribed dose in either high or low-dose rate, manually or automatically. Radioactive stents utilize mainly pure ß-emitters in a very low-dose rate. The dosimetry requirements for intraluminal treatment via the temporary insertion of radioactive sources can be summarized as follows[37]:

1) single fraction acute dose of 10 to 30 Gy to a length of 2 to 4 cm of arterial wall, approximately 2- to 5 mm inner diameter, 0.5- to 3 mm wall thickness.
2) high dose volume confined to the region of angioplasty, with minimum dose to normal vessels and myocardium.
3) dose rates greater than 2 Gy/min (to keep treatment times <15 minutes) thus reducing complications (i.e. thrombosis, ischemia).
4) the radioactive source must have dimensions, stiffness and flexibility compatible for use with angioplasty catheters.
5) source diameter must be less than 0.5 mm, yet stiff enough to be pushed through greater than 100 cm of artery, and flexible enough to negotiate multiple bends in the coronary tree. Source integrity is of great importance, as dislodgement into a coronary artery could be fatal.

The isotopes currently used for intraluminal brachytherapy are depicted in the table:

Isotope	Emission	Maximum Energy (MeV)	Average Energy (MeV)	Half-life
192 Ir	gamma-	0.6	0.37	74 days
32 P	beta-	1.7	0.60	14 days
90 Sr	beta-	0.5	0.20	28 years
90 Y	beta-	2.3	0.90	64 hours
188 Re	beta-	2.2	0.79	17 hours
188 W	beta-	0.5	0.17	60 days

This thesis is aimed to determine the potential of intracoronary brachytherapy as a new technique to prevent restenosis after percutaneous interventions. To that purpose, it has been divided in 5 parts. In **part I** the structural and functional changes that radiation therapy induces in coronary tissue are described. In **part II** dosimetry considerations of this treatment modality are discussed. In **part III**, new methodological concepts derived from the effect of this therapy are defined. In **part IV**, the potential complications secondary to the use of this technique are described. And, finally, in **part V**, the results of clinical trials carried out in our Institution and in the rest of Europe are reported. Specifically, we can summarize the aims of this thesis as follows:

1) To define the morphological changes of vessel structures after intracoronary radiation therapy by means of either catheter-based systems or radioactive stent following percutaneous coronary interventions. This is addressed in chapters 1,2 and 3.
2) To determine the long-term coronary vasomotion of the segment which has been irradiated by means of a catheter-based system. This is addressed in chapter 4.
3) To establish the minimal effective radiation dose to be delivered to the adventitia. This is addressed in chapter 5.
4) To define the dosimetric implications between centering and not centering the radiation source into the vessel lumen. This is addressed in chapters 5 and 6.
5) To determine the intravascular ultrasound predictors of plaque volume at 6-month follow-up. This is addressed in chapter 5.
6) To define a new methodology to study the clinical and angiographic implications of this new technique. This is adressed in chapters 7 and 8.
7) To determine the potential limitations of this technique. This is addressed in chapters 9,10 and 11.
8) Finally, to report on the clinical trials which has been carried out in our Institution and in the rest of Europe by the use of intracoronary radiation therapy. This is addressed in chapters 12, 13 and 14.

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Part I

Mechanism of Action of Intracoronary Radiation Therapy

Chapter 1

Geometric vascular remodeling after balloon angioplasty and beta radiation therapy: a three-dimensional intravascular ultrasound study.

(Circulation 1999;100:1182-1188)

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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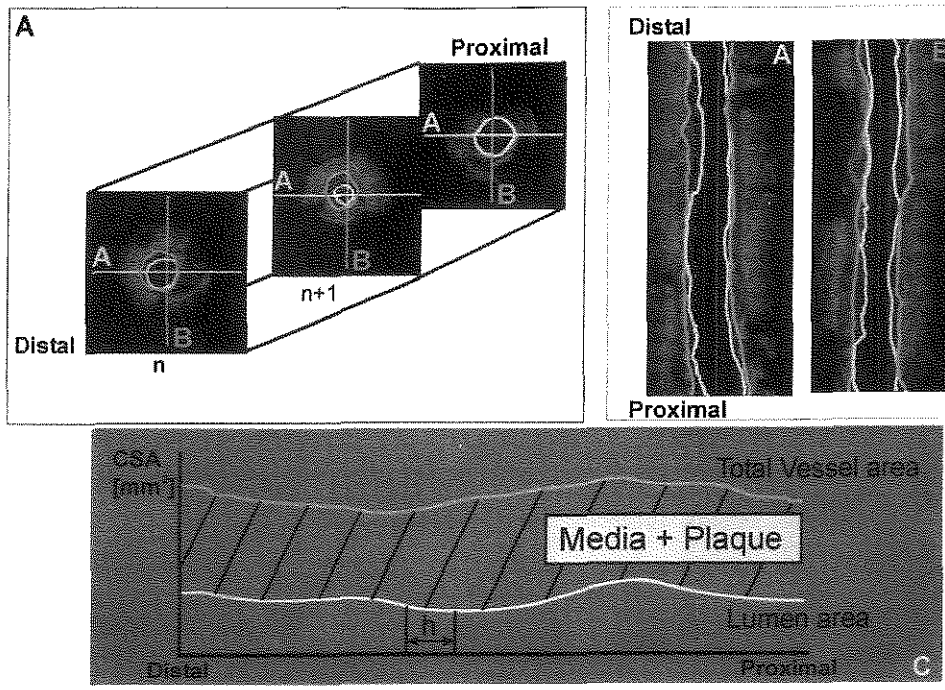

Figure 1. Overview of the applied analysis software package.[18,21] A, Schematic presentation of the IVUS catheter pullback. B, Two computed longitudinal perpendicular views. Corresponding cut-planes in A are represented by the letters A and B. C, Outcome of measurements. CSA indicates cross-sectional 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

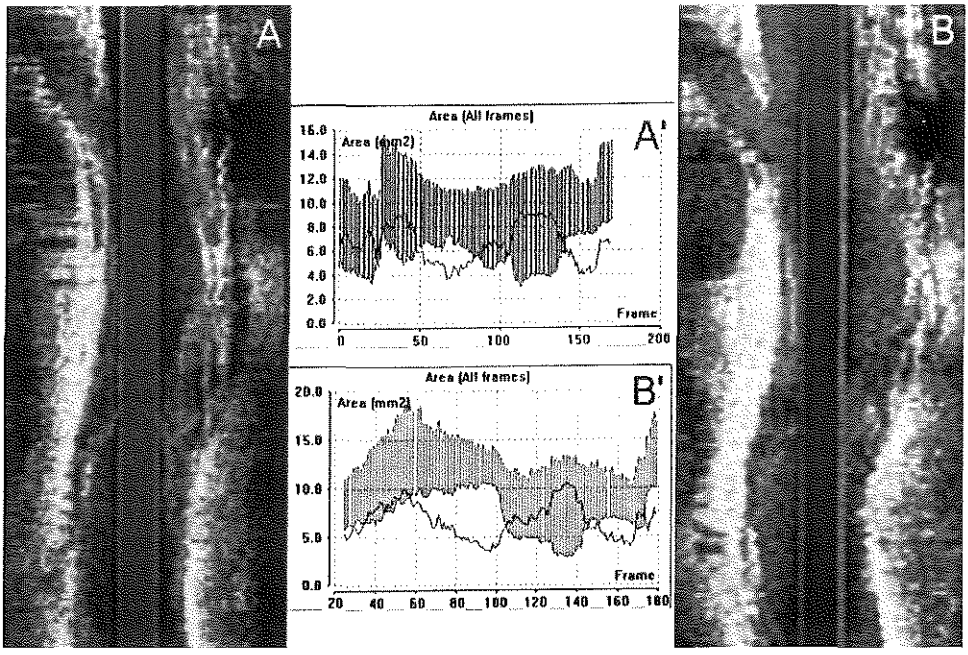

Figure 2. Longitudinal reconstruction of the IVUS cross-sectional images and subsequent volumetric calculations (middle charts) after irradiation (A and A') and at 6-month follow-up (B and B'). Note increase in scale at follow-up chart reflecting increase in total vessel volume.

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: $-0.4\pm1.0\%$, $-0.3\pm1.3\%$, and $-0.2\pm0.9\%$, 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).

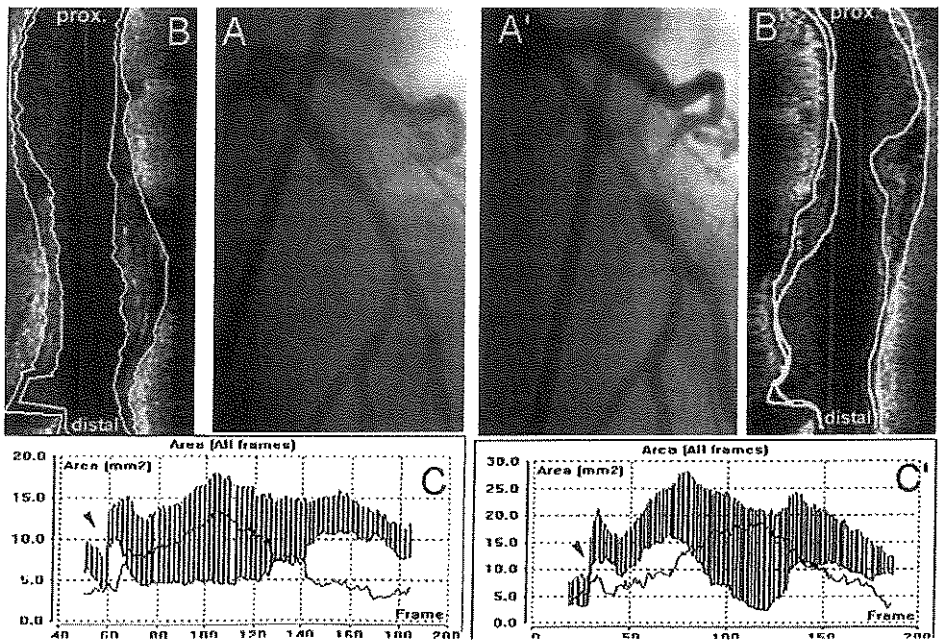

Figure 3. Angiography and 3D reconstruction of an irradiated segment (A, B, and C) that demonstrated restenosis and aneurysmatic formation at 6-month follow-up (A', B', and C'). Contour tracing has been manually corrected for distal side branch (black arrowheads in bottom charts). prox. indicates proximal.

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

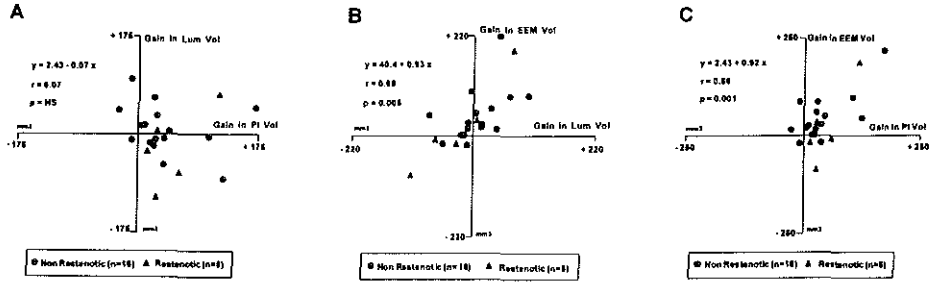

Figure 4. Linear regression analysis between changes in plaque and luminal volumes (A), EEM and luminal volumes (B), and EEM and plaque volumes (C). EEM Vol indicates EEM volume; Pl Vol, plaque volume; and Lum vol, luminal volume.

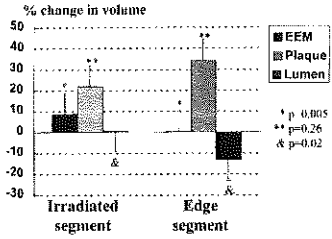

Figure 5. Comparison between patterns of remodeling in irradiated area and at edges.

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±30 mm^3). In 8 of them, the increase in EEM volume (+85.7±75 mm^3) overcame the increase in plaque volume (+53.2±59 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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Chapter 2

The effect of P^{32} beta-radiotherapy on both vessel remodeling and neointimal hyperplasia after coronary balloon angioplasty and stenting. A three-dimensional intravascular investigation.

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The Effect of P^{32} Beta-Radiotherapy on Both Vessel Remodeling and Neointimal Hyperplasia after Coronary Balloon Angioplasty and Stenting. A Three-dimensional Intravascular Ultrasound Investigation.

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Abstract

Intracoronary radiation is a promising therapy to decrease restenosis after percutaneous intervention. The aim of this pilot study was to determine the mechanism of intracoronary beta-radiation after balloon angioplasty and stenting in a double-blind placebo-controlled randomized fashion. Twenty-six patients were randomized to either placebo (n = 6) or 3 doses (28, 35 and 42 Gy) of beta-radiation (n = 20) using the Guidant brachytherapy system (27-mm long P^{32}source wire). Of these, 21 patients underwent post-procedure and 6-month follow-up three-dimensional IVUS assessment. Volumetric quantification was performed by means of a semi-automated contour detection system after an ECG-gated motorized pullback IVUS imaging and three-dimensional reconstruction. We compared the volumetric changes (Δ) of total vessel volume (TVV), plaque volume (PV) and lumen volume (PV) after 6 months between placebo (dummy wire) and irradiated patients. In addition the volume of neointimal hyperplasia was quantified within the stented segments. There was an opposite behavior of TVV and LV change between placebo ($\Delta TVV = -24$ mm^3 and $\Delta LV = -42$ mm^3) and irradiated ($\Delta TVV = +18$ mm^3 and $\Delta LV = +5$ mm^3) patients. The mean neointimal formation within the stented segment in the irradiated patients (n = 7) was 1.9 mm^3 (1.5%). Our results suggest that beta-radiation affects vessel remodeling after percutaneous intervention and inhibit neointimal formation in stented patients.

Key words – Brachytherapy, remodeling, neointimal hyperplasia

Introduction

Restenosis after percutaneous intervention has been reduced with the advent of coronary stents (1, 2). However, further reduction in the incidence of restenosis appears to be difficult using conventional approaches.

The introduction of intravascular ultrasound (IVUS) in the clinical practice has refined our knowledge about the mechanism of restenosis. Thus, the restenotic process can be divided in two components: vessel remodeling and neointimal formation. The former predominates after balloon angioplasty (BA) whereas the latter is the main cause of in-stent restenosis. (3, 4)

Intracoronary radiation is a promising therapy to decrease restenosis after percutaneous intervention. Stimulated by animal studies showing inhibition of neointimal formation by radiation (5-7), two randomized trials have shown the reduction of restenosis by treating restenotic lesions with gamma radiation.(8,9)

Furthermore, a non-randomized study has shown the safety and feasibility of beta radiation, with a satisfactory (15%) rate of restenosis in de novo lesion treated with balloon angioplasty (10). Recent IVUS investigations have shown that beta radiation after BA may affect vessel wall remodeling (11-13). Experimental studies have corroborated these findings. (14,16)

Thus, the relative contribution of radiation on vessel remodeling and neointimal formation remains to be elucidated. The aim of this pilot study was: 1) to assess the effects of beta-radiotherapy on coronary segments successfully treated by BA or stenting, 2) to compare the behavior of irradiated and non-irradiated (sham) coronary segments 6-month after treatment by means of a volumetric three-dimensional (3-D) IVUS assessment.

Methods:

Patient selection

In this double-blind feasibility and safety study, 26 patients (pts) were randomized to either sham (placebo) or 3 different doses of beta-radiation (28, 35 or 42 Gy, as calculated at 0.5 mm into the vessel wall). The Medical Ethic Committee of University Hospital Dijkzigt has approved the use of intracoronary radiation. All patients gave written informed consent.

Radiotherapy system

The Guidant Brachytherapy System used in this study includes a 0.018-inch nitinol wire with 27-mm of P^{32} source at its tips. The use of a centering spiral balloon (27 mm long) allows the administration of prescribed dose homogeneously in the vessel wall as well as distal vessel perfusion during balloon inflation at a maximum inflation pressure of 4 atmospheres. Automated source delivery unit controls dose delivery and source withdrawal, providing "hands-off" radiation delivery (17). The duration of the treatment and dose necessary to reach 0.5 mm into the vessel wall are calculated using the mean reference vessel diameter by IVUS immediately prior to radiation delivery.

IVUS Analysis System

The segment subject to 3-D reconstruction was examined with a mechanical IVUS system (ClearView, CVIS, Boston Scientific Corporation, Maple Grove, MN) with a sheath-based IVUS catheter incorporating a 30 MHz single-element transducer rotating at 1800-rpm (Ultracross, CVIS). An ECG-gated image acquisition and digitization was performed by a workstation designed for the 3-D reconstruction of IVUS images (EchoScan, Tomtec, Munich, Germany) (18). IVUS images were acquired coinciding with the peak of the R wave, which eliminates the artifacts caused by the movement of the heart during the cardiac cycle. Then, the IVUS transducer was withdrawn every 0.2 mm to acquire the next image coincident to the R-wave. (18)

A Microsoft Windows™-based contour detection program, developed at the Thoraxcenter, was used for the 3-D volumetric quantification.(19) The feasibility and intra- and inter-observer variability of this system have been validated in clinical protocols.(20,21). Briefly, this program constructed longitudinal sections from the data set and identified the contours corresponding to the lumen and media and stent boundaries. Careful checking and editing of the contours of the planar images were performed by two independent experts who were blinded to the treatment assignments.

Volumetric data were calculated by the formula: $V = \sum_{i=1}^{n} A_i * H$, where V = volume, A = area of EEM, lumen, stent or plaque in a given cross-sectional ultrasound image, H = thickness of the coronary artery slice, that was reported by this digitized cross-sectional IVUS image, and n = the number of digitized cross-sectional images encompassing the volume to be measured. (19)

The methodology to define the treated segment has been previously described (13). Angiogram was performed after positioning the radioactive source in the centering balloon and the relationship between anatomical landmarks and the two radiopaque markers of the radiation source were noted after contrast injection (figure 1). Typically, the aorto-ostial junction and the side-branches were used as landmarks. The anatomical landmark closest to either of the source markers was used as a reference point. During the subsequent IVUS imaging pullback, this reference point was recognized and used for selecting the area of interest: 27 mm for the irradiated segment analysis. In addition, in a separate analysis we selected only the segment covered by stents within the irradiated area. This was facilitated by the high echogenic characteristics of the stent struts. At follow-up, correct matching of the region of interest was performed by comparing the longitudinal reconstruction to that post-procedure (figure 2).

Procedure

All patients received aspirin (250 mg/day) and heparin IV (10.000 IU) before the procedure and stented patients also received ticlopidine (250mg/day). Heparin was given to maintain the activated clotting time >300 sec. BA and stenting were performed according to standard clinical practice. In the stented patients, high-pressure post-balloon inflation was performed guided by IVUS. The diameter of the centering balloon was chosen based on IVUS mean reference vessel size (average of the mean distal and proximal reference

diameters). This measurement was performed after optimization the results of balloon angioplasty or stenting. Thus, the centering balloon was placed in the target segment and inflated to 4 atmospheres. After testing the perfusion of the distal coronary segment and checking the correct placement of the centering balloon by contrast injection (figure 1), the radioactive or "dummy" source wire (27 mm) was placed in the centering balloon by means of the automatic delivering system. Afterwards, repeat angiography and IVUS pullback were carried out. A continuous motorized pullback at a speed of 0.5 mm/sec was first carried out, followed by an ECG-gated pullback at a stepwise of 0.2 mm/step. Intracoronary nitrates were administered immediately prior to each of the IVUS pullbacks. At 6-month follow-up, further IVUS analysis of the treated area was performed.

Quantitative 3-D IVUS Analysis

The following volumetric measurements were obtained: total vessel (External Elastic Membrane - EEM) and lumen. Plaque volume was automatically calculated by subtracting lumen volume from the total vessel volume.

In stented patients, after selecting only the segment covered by stent, we also calculated neointimal hyperplasia, which was calculated by subtracting lumen volume from stent volume. In-vivo measurement of neointimal formation after stenting has been previously validated (22). Plaque volume outside the stent was also calculated by subtracting stent volume from total vessel volume within the stented segments. The assessment of EEM in stented patients has been reported (23). Although, in this previous report the delineation of EEM was not possible in some patients due to the stent shadowing, in our study the delineation of EEM boundary was possible in all stented patients. When the EEM boundary was not visible in a single cross-sectional view, the computer interpolated it from the contours of the immediately previous and following cross-sections. In addition, the use of three-dimensional reconstruction with multiple longitudinal views facilitates the visualization of vessel structures outside the stent. In all cases, the stented segment was covered by the radiation or dummy source wire.

In order to assess the volumetric changes of the vessel structures after 6 months, the delta value for each measurement was calculated (delta (Δ) = follow-up – post-procedure).

Statistical analysis

Quantitative data are presented as mean ± standard deviation. The comparisons between the volumetric data of placebo versus irradiated patients and stent versus BA patients (in the irradiated group) were performed using an unpaired Student's t-test. A value of $p<0.05$ was considered statistically significant.

Results

All patients have completed 6-month clinical follow-up. Of these, 5 patients (1 placebo) did not undergo IVUS at 6 months: 2 irradiated patients presented sub-acute thrombosis, one presented late (3 months after the procedure) thrombotic occlusion and another irradiated patient had a severe restenotic lesion demonstrated by angiography. The lesion was located in an area not covered by radiation, proximal to the irradiated site where a balloon was inflated to treat a proximal dissection. Thus, only a manual IVUS

pullback was performed in this patient prior to reintervention. The non-irradiated patient was asymptomatic with a negative stress test at the time of follow-up but refused angiographic restudy.

Thus, the results of this study consisted of a cohort of 21 patients with successful post-procedure and 6-month three-dimensional IVUS assessment. Sixteen patients were actually treated with radioactive source, while 5 patients received placebo treatment. In the radiation group, 6 pts received 28 Gy, 5 pts 35Gy and 5 pts 42 Gy. Additional stent was implanted after BA in 7 pts (44%) in the irradiated group and 3 pts (60%) in the placebo group (p = NS). All patients were discharged on day 2 after the procedure without complication. The medication at discharge consisted of: aspirin (250mg/day) and ticlopidine (250 mg/day, only for stented patients). The dwell time for delivering the prescribed radiation dose ranged from 1.5 to 8 minutes. There was no complication related to the radiation treatment protocol. Clinical and demographic characteristics were similar between placebo and irradiated patients (table 1). Post-procedure and follow-up IVUS measurements are summarized in table 2. At 6-month follow-up, we observed a smaller minimal lumen area (MLA) and greater percentage of plaque area in the placebo group compared to irradiated group.

Volumetric Changes (Δ) After 6 Months – Placebo *versus* Irradiated

As illustrated in figure 3, the volumetric change of the total vessel volume (ΔTVV) occurred in an opposite direction between irradiated and placebo patients. While the irradiated patients demonstrated a positive ΔTVV (increase of the TVV at follow-up), placebo patients demonstrated a negative ΔTVV (decrease of the TVV at follow-up). Equally, an opposite behavior was observed regarding the volumetric changes of the lumen volume (ΔLV). The placebo group demonstrated a negative ΔLV, whereas irradiated patients showed a positive ΔLV (p = 0.01). However, plaque volume (ΔPV) increased in both groups in a similar degree (positive ΔPV). There was no relationship between prescribed doses and volumetric changes.

Irradiated Patients – Stent *versus* BA

In the analysis of the entire (27 mm) irradiated segment, stented patients (n=7) demonstrated similar volumetric changes after 6 months compared to BA patients (n=9) as illustrated in figure 4. It is of interest to note that, in the stented patients, PV consists of the total amount of plaque outside and inside the stent. In addition, this analysis quantified the entire irradiated segment including segments covered and uncovered by stents.

Analysis of the Stented Segment (Irradiated Patients)

In this analysis, only the segments covered by stent were selected for volumetric quantification. The average stent length (segment analyzed) was 18.1 ± 6.36 mm. Post-balloon dilation was performed in all cases at a mean pressure of 14.6 ± 3.2 atmospheres. At follow-up, we observed a neointimal hyperplasia volume of 1.89 ± 2.99 mm^3 with a mean percentage neointimal formation of 1.47 ± 2.49 %. The TVV within the stented segment demonstrated a non-significant increase after 6 months (post-procedure TVV of 260 ± 68 mm^3 versus 272.2 ± 97 mm^3 at follow-up, p = NS). The plaque volume outside the stent also demonstrated a non-significant change at follow-up (post-procedure PV

of 131 ± 32 mm^3 versus 141 ± 63 mm^3 at follow-up, p = NS). Stent volume remained unchanged (no recoil) after 6 months (129.5 ± 39 mm^3 post-procedure versus 131 ± 39 mm^3 at follow-up, p = NS).

Discussion

This pilot investigation demonstrates that beta-radiation affects vessel remodeling after percutaneous intervention. In addition, neointimal formation within the stented segment was almost absent in our irradiated population. However, the small size of our stented population should be taking into account before drawing any definitive conclusion.

Considering that vessel shrinkage accounts for about 50-70% of the mechanism of restenosis after conventional BA (3) and radiation has been shown to reduce the restenosis rate in the setting of BA (10), the conclusion that radiation affects vessel remodeling seems logical. Clinical (13) and experimental data (14-16) have already suggested the influence of radiation on vessel remodeling.

IVUS analysis of patients enrolled in the BERT trial has also suggested that radiation may prevent vessel shrinkage after BA (11,12). The use of single cross-section planar IVUS images limited the study of Meerkin et al to assess the influence of radiation on vessel remodeling. The 4 coronary aneurysms reported by Condado et al exemplified the extreme expression of this phenomenon in a series of patients receiving high doses of gamma radiation. (24)

In accordance to the findings of the present study, a recent clinical investigation from our group using the same methodology has demonstrated that beta-radiation using a 90Sr/Y-source influence vessel wall remodeling after BA. (13) In 21 patients analyzed, there was a significant increase of the total vessel volume after 6 months in patients enrolled in the BERT 1.5 trial.(13) However, the exclusion of stented patients in this previous study did not allow further insights into the mechanism of radiation on the inhibition of neointimal proliferation.

The opposite pattern of change in total vessel volume between the irradiated population (positive ΔTVV) and placebo (negative ΔTVV) observed in our study may confirm the influence of radiation on vessel wall remodeling. In addition, the combination of a smaller total vessel volume and bigger plaque volume at follow-up accounted for the reduction of lumen observed only in the placebo group. Similar patterns of structural vessel changes have been previously reported after conventional percutaneous intervention in non-irradiated coronary segments. (3)

On the other hand, gamma radiation has been shown to decrease the incidence of restenosis in stented patients treated for in-stent restenosis (8,9). Once again, another logical conclusion may rise in favor of radiation inhibiting neointimal formation. Clinical and experimental reports have emphasized the effect of gamma radiation on inhibiting neointimal formation (5-9). In our stented population, the amount of neointimal formation was only1.89-mm^3, which suggests that beta-radiation also inhibits neointimal formation after conventional stenting.

The assessment of plaque growth outside the stent is a novelty in the setting of brachytherapy. A previous IVUS study (25), has demonstrated the progression of plaque mass within and surrounding conventional

stents. However a recent report investigating 15 non-irradiated stented coronary segments did not demonstrate plaque growth outside the stent. (23) In our study, the plaque volume outside the stent and TVV showed a non-significant increase of 10- and 12-mm^3 after 6 months, respectively. Further IVUS studies should investigate the influence of radiation on neointimal formation, plaque growth (outside the stent) as well as vessel remodeling in stented patients.

This pilot study contributes to a better understanding of the complex interaction between radiation and vascular structures. By comparing, for the first time, three-dimensional IVUS parameters of beta-irradiated and non-irradiated coronary segments our study demonstrates that radiation affects vessel remodeling after percutaneous intervention. In addition, this seminal study suggests that beta-radiation may also inhibit neointimal formation after stenting. It is nevertheless of interest to note that to date only few reports using serial IVUS investigation after either beta-radiation in the setting of BA or gamma radiation in the setting of stenting are available. Thus, the confirmation of these findings by a large population study with volumetric IVUS assessment is required.

Limitations

The size of the population is the major limitation of this pilot study, which has insufficient statistic power to demonstrate some differences. However, this is a pioneering investigation using 3-D IVUS to assess the effects of beta-radiation after either BA or stenting. In addition, this is the first study to compare irradiated versus non-irradiated coronary segments by means of a volumetric assessment in a randomized fashion. The similarity between our findings and those previously reported on either irradiated (13) or non-irradiated coronary segment (3) may endorse our conclusions.

The difficulty to assess patients with severe restenotic lesions is a limitation of the methodology used in this study. Thus, the assessment of the mechanism involved in an "aggressive" vessel wall reaction after intervention, as observed in one patient of this study, cannot be performed.

Although the prescribed dose was not related to any vessel structural change after 6-month the actual dose received by the target segments was not calculated in this study, limiting any dosimetric consideration.

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Table 1. Baseline and demographic characteristics

Variable	Irradiated (n = 16)	Placebo (n = 5)	p value
Age, years	59.2 ± 9.6	56 ± 10.9	NS
Gender, male	11 (79%)	4 (80%)	NS
Diabetes	0	0	NS
Smoking	6 (38%)	2 (40%)	NS
Hypercholesterolemia	9 (56%)	3 (60%)	NS
Hypertension	5 (31%)	0	NS
Family History of CAD	6 (38%)	2 (40%)	NS
Previous MI	7 (44%)	3 (60%)	NS
Angina Status, CCS 3/4	12 (75%)	5 (100%)	NS
Treatment site at LAD	7 (34%)	3(60%)	NS
Restenotic lesion	4 (25%)	1 (20%)	NS

CAD means coronary artery disease, MI means myocardial infarction, CCS means Canadian Class Society, LAD means left anterior descending coronary artery.

Table 2. Post-procedure and follow-up 3-D IVUS measurements.

	TVV, mm^3		PV, mm^3		LV, mm^3		MLA, mm^2		Plaque burden at MLA, %	
	Post	FU	Post	FU	Post	FU	Post	FU	Post	FU
Irradiated (n = 16)	385± 110	403± 133	198± 63	214± 74	185± 60	190± 63	4.8± 2	4.7± 1	63± 9	64± 9
Placebo (n = 5)	415± 101	391± 98	210± 58	228± 69	205± 62	163± 44	4.7± 1	3.3± 1	60± 16	76± 14
P value	NS	NS	NS	NS	NS	NS	NS	0.046	NS	0.042

TVV indicates total vessel volume; PV indicates plaque volume, LV indicates luminal volume; MLA indicates minimal luminal diameter; post indicates post-procedure; FU indicates follow-up.

Figure 1 – A - Pre-procedure angiogram of the left anterior descending artery (LAD)
B - Angiogram to verify the correct position of the spiral centering balloon and source wire. Distal perfusion is also confirmed as well as the anatomical landmarks for 3-D IVUS reconstruction of the irradiated segment.
C - Post-procedure angiogram of the LAD demonstrates good angiographic result.
D – Six-month follow-up angiography without restenosis.

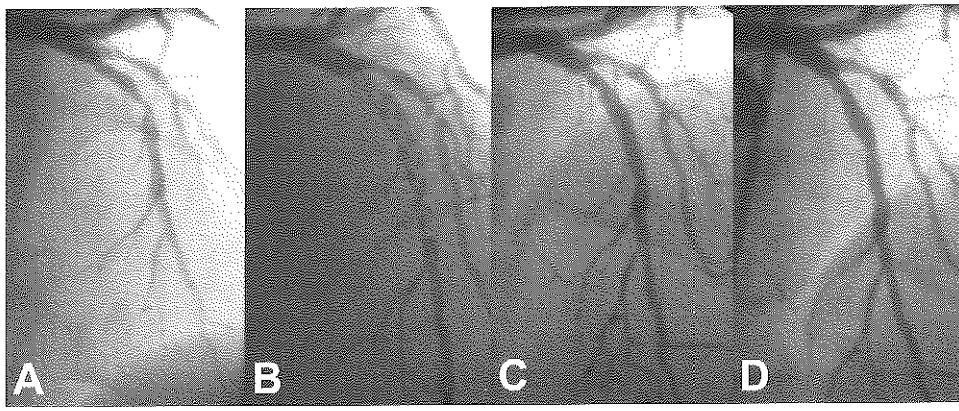


Figure 2 – A –Post-procedure 3D-IVUS imaging and volumetric quantification. Left panel – one planar cross-section view is displayed and the lumen (inner line) and EEM (outer line) area are delineated. Right panel – In the top, one longitudinal view is displayed with the anatomical landmark (side branch – arrowhead) used to determine the segment for volumetric quantification. Lumen and EEM boundaries are delineated in the segment of interest. In the bottom, a graphic displays the consecutive areas of the entire set of planar images – used for volumetric quantification. The values of the plaque area are shown as a gray field between two lines (vessel and lumen areas). The absolute value of the plaque area can be derived from this field, but is also displayed as single black line.
B –3D-IVUS imaging and volumetric quantification at follow-up. The correct match is determined on longitudinal and planar views using the anatomical landmark (arrowhead). Lumen and vessel boundaries are delineated in both planar and longitudinal views. The graphic of the vessel, lumen and plaque areas is also displayed.

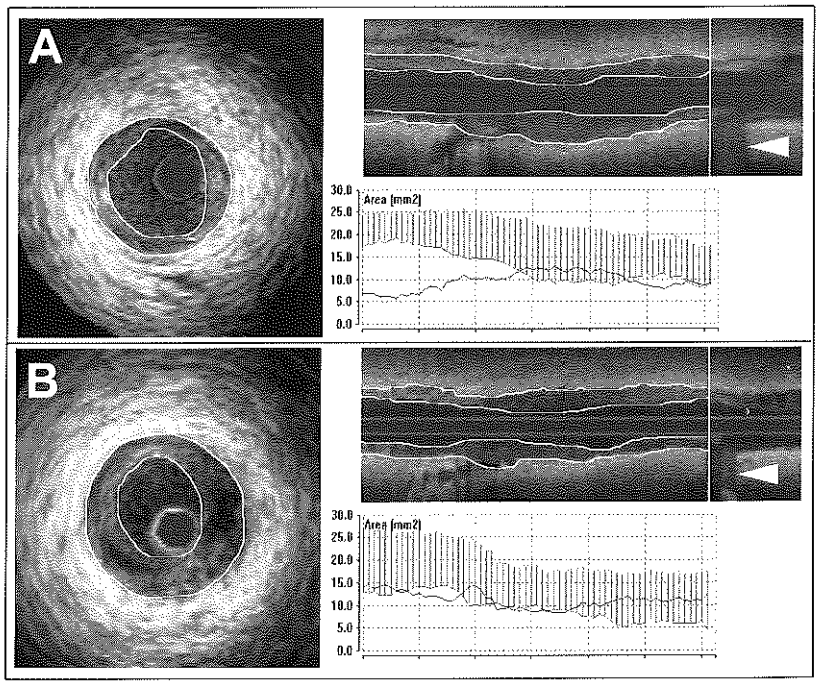


Figure 3 - 3D-IVUS analysis of stented coronary segments. Longitudinal (post-procedure [A] and follow-up [B]) and planar (A' and B') views are displayed. Lumen and stent (white lines), and vessel boundaries (black line) are delineated in the planar image and in one of the longitudinal views. At follow-up (B, B') we can observe the delineation of neointimal hyperplasia between the lumen and stent boundaries (white lines). The visualization of the EEM boundary behind the stent and neointimal hyperplasia are illustrated in the longitudinal views without contours as well as the anatomical landmark (side branch with a spot of calcium in the ostium) used for correct match between post-procedure and follow-up analyses.

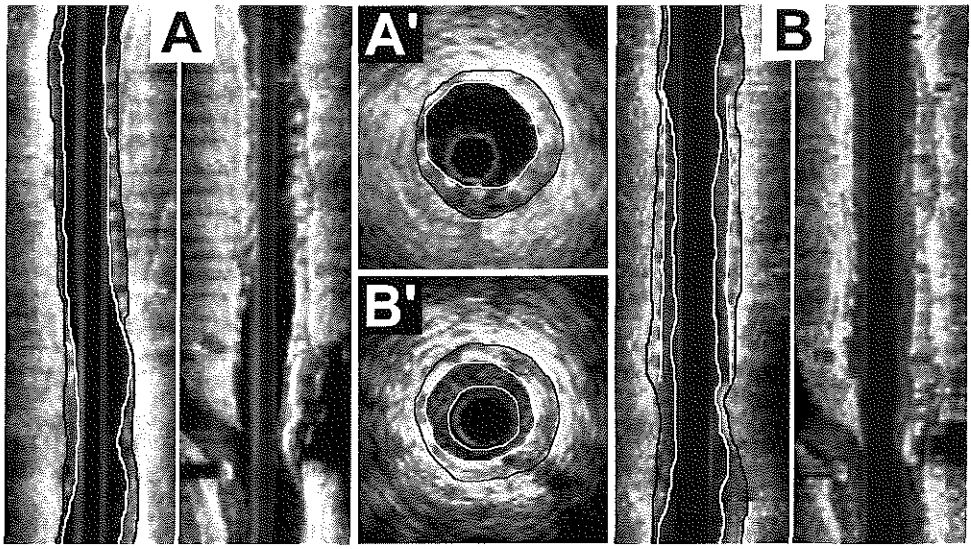


Figure – 4 Volumetric Changes (Δ) of the total vessel (TVV), plaque (PV) and lumen (LV) in the target (27-mm long) coronary segments after 6 months. Comparison between irradiated and placebo patients.

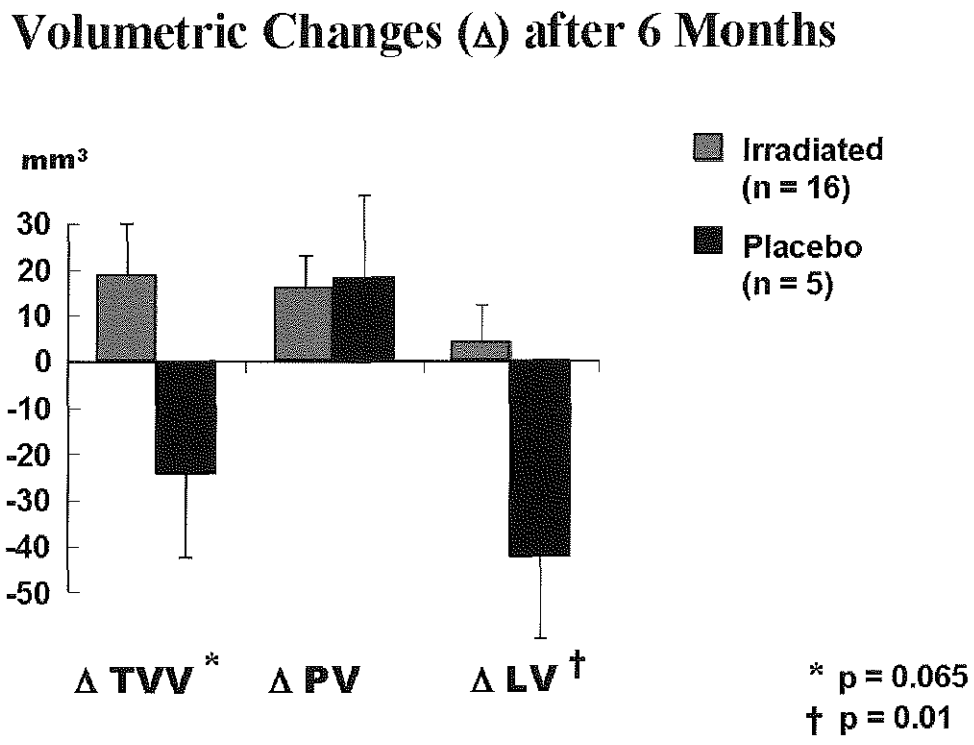
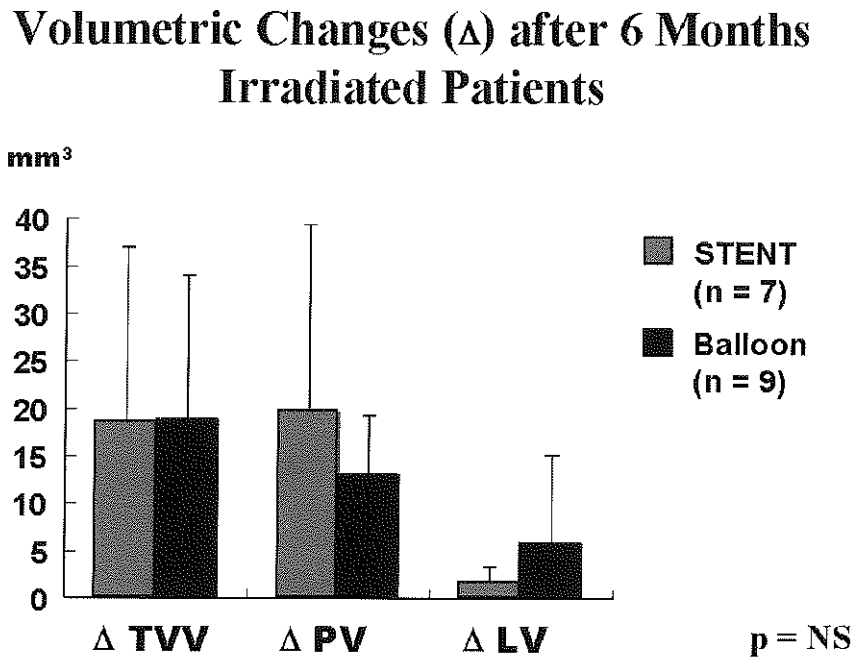


Figure – 5 Volumetric Changes (Δ) of TVV, PV and LV within the irradiated coronary segment (27-mm long) after 6 months. Comparison between balloon angioplasty and stent patients.



Chapter 3

Positive geometric vascular remodeling is seen after catheter-based radiation followed by conventional stent implantation, but not after radioactive stent implantation.

(Circulation (in press))

Positive Geometric Vascular Remodeling is seen after Catheter – Based Radiation Followed By Conventional Stent Implantation, But Not After Radioactive Stent Implantation

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Abstract

Background. Recent reports have shown that intracoronary radiation affects not only neointimal formation but also vascular remodeling. Given the different way in which radioactive stents and catheter – based techniques deliver radiation one may expect different mechanisms of remodeling after each technique.

Methods and Results. We analyzed remodeling in 18 patients after conventional stent implantation (C), 16 patients after low activity (LA) radioactive stent implantation, 16 patients after higher activity radioactive stent implantation (HA) and finally 16 patients who underwent catheter – based radiation followed by conventional stent implantation (CBS). Intravascular ultrasound with 3 – dimensional reconstruction was used post stent implantation and at 6 – month follow – up to assess remodeling at the stent edges and within the margins of the stent. Baseline, vessel and procedural characteristics were similar between groups. In – stent neointimal hyperplasia was inhibited by HA (+9.0mm^3) and by CBS (+6.9mm^3 (compared with LA (+21.2mm^3) and C (+20.8mm^3), $p<0.05$. No difference in plaque or total vessel volumes was seen behind the stent in the C , LA or HA groups. However a significant increase in plaque (+15%) and TVV (+7%) was seen in the CBS group ($p<0.05$). At the stent edges, no edge restenosis was witnessed in the C, LA or CBS groups. Edge restenosis was seen after HA implantation and appeared to be due mainly to an increase in plaque and to a lesser degree to negative remodeling.

Conclusions. Distinct differences in the patterns of remodeling exist between conventional, radioactive and catheter – based radiotherapy with stenting. Users of radiation need to be alerted to the deleterious remodeling seen at the stent edges after higher – dose radioactive stent implantation and behind the stent after catheter – based radiation and stenting.

In our enthusiasm to control vessel recoil and remodeling after balloon angioplasty (BA), stent implantation has become increasingly popular. With conventional stenting we have eliminated recoil and remodeling as components of the restenotic process. However this has been at the cost of exacerbating neo intimal proliferation secondary to chronic vessel wall irritation, leading to in - stent restenosis[1,2]. Intracoronary radiation has been developed in an attempt to decrease restenosis after BA and stent implantation. Two parallel technologies, one employing radioactive stents[3-7], the other catheter – based radiation[8-10], have been the subject of both animal and human studies. Given the different dose rates and total doses delivered by each method, intuitively one may expect different patterns of remodeling subsequent to each approach.

Whereas the effect of catheter-based radiation after BA on vascular remodeling has been described [11], the response of the arterial wall to catheter-based radiation and subsequent stent implantation is not described. Preliminary studies have reported the effect at the stent edge after radioactive stent implantation[4]. These reports do not encompass the response behind the stent in the arterial wall however.

The aim of this study was to describe the response of the coronary artery to radiation and stenting, by looking at the stent and its edges after radioactive stent implantation and also after catheter – based radiation with stent implantation.

Methods

Patient Selection

We analyzed geometric vascular remodeling in 4 groups of patients:

1. those who had undergone implantation of ^{32}P – emitting radioactive stents at activity levels of 0.75-1.5μCi (Isostent™ Inc., San Carlos, CA, USA)
2. those who had undergone implantation of ^{32}P radioactive stents at activity levels of 6.0-12μCi (Isostent™ Inc., San Carlos, CA, USA)
3. those who had undergone conventional stent implantation after suboptimal BA (clinically significant dissection or residual stenosis > 30%) and catheter – based radiation.
4. those who had undergone conventional stent implantation after suboptimal BA.

Stents analyzed were from patients with single native vessel coronary artery disease, normal left ventricular function and objective evidence of ischemia. All groups were matched for patient baseline characteristics, vessel size, lesion and stent length (mean stent length 15mm)

Stents placed in the ostial position or adjacent to major side – branches, such that the stent edges were unable to be analyzed, were excluded from analysis. Only patients who had completed 6 – month angiographic and IVUS follow – up were included.

Implantation technique

The same group of cardiologists, using a similar technique implanted all stents.

Predilation of the lesion was performed, followed by stent implantation using either a pre - mounted stent or the Johnson & Johnson Intervention Systems delivery system (Johnson & Johnson Interventional Systems Co, Warren NJ, USA). Higher – pressure balloon inflation to ensure good strut apposition to the vessel wall then occurred. At this time we used a shorter balloon to ensure that the edges of the balloon did not extend beyond the limits of the stent. Intravascular ultrasound was used to ensure optimal stent deployment.

Medication

Patients received 250 mg aspirin and 10000 international units heparin at the initiation of the procedure and the activated clotting time was maintained at > 300 seconds. All patients received aspirin 80mg daily indefinitely and ticlopidine 250 mg BID for 2 weeks (C) or 4 – 12 weeks (LA, HA and CBS), after stent implantation.

Radioactive stents

The BX™ stent (Isostent™ Inc., San Carlos, CA, USA) was the only radioactive stent implanted in this trial. It was 15mm in length and available in diameters of 3.0 & 3.5 mm. The BX™ stent was made radioactive by Phosphorus-32 (^{32}P). The initial activity of the stents was measured and thereafter it was calculated at what date the activity had decreased to 0.75-1.5 μCi or 6-12 μCi, suitable for implantation. The dose delivered over 100 days at 1 mm from the stent surface was calculated for each implanted stent.

Catheter – based radiation delivery system

The Beta-Cath System (Novoste Corp., Norcross, GA) was used to deliver localized β-radiation ($^{90}Sr/^{90}Y$) to 2mm depth from the center of the source at the site of coronary intervention. The device consisted of 3 components: (1) the transfer device which stores the radiation source train and allows the positioning of these sources within the catheter; (2) the delivery catheter, which is a 5 French (F) multilumen over-the-wire non-centered catheter which uses saline solution to send and return the radiation source train; and (3), the radiation source train consisting of a series of twelve independent cylindrical seeds which contain the radioisotope ^{90}Sr sources and is boundaried by 2 gold radiopaque markers separated by 30 mm. Other device and procedural details have been previously published by this group.[11]

Definitions

Stent Edges: Stent Edges were defined as those volumes axially 5mm proximal and distal to the final stent strut. An edge restenosis was defined as an angiographic restenosis >50% at 6-month follow – up located at either stent edge. An edge - effect was defined as any stent - edge renarrowing.

Patients with balloon – injured edges which failed to receive radiation in the catheter – based radiation group were excluded. In other words no stents implanted in areas of geographical miss were included in this study.

IVUS image acquisition analysis

After the final balloon inflation and administration of intracoronary nitrates, ECG – gated IVUS pullback was performed. This was repeated at 6 month follow-up.

The segment subject to 3-D reconstruction was examined with a mechanical IVUS system (ClearView, CardioVascular Imaging System, CVIS, Sunnyvale, CA) with a sheath-based IVUS catheter incorporating a 30 MHz single-element transducer rotating at 1800 rpm. The IVUS transducer was withdrawn through the stationary imaging sheath by an ECG-triggered pullback device with a stepping motor.[12] IVUS images were aquired coinciding with the peak of the R wave, which eliminates the artefacts caused by the movement of the heart during the cardiac cycle. After each image acquisition the transducer was withdrawn 0.2mm to aquire the next image coincident with the R – wave. The ECG-gated image acquisition and digitation was performed by a workstation designed for the 3-D reconstruction of echocardiographic images [12] (EchoScan, Tomtec, Munich, Germany) A Microsoft Windows™-based contour detection program, developed at the Thoraxcenter, Rotterdam was used for the automated 3-D analysis of up to 200 IVUS images.[13] This program constructs two longitudinal sections and identifies the contours corresponding to the lumen-intima and media-adventitia boundaries using a minimum-cost based software algorithm. The feasibility, reproducibility and the inter- and intraobserver variability of this system have been previously validated in clinical protocols[11].

Quantitative IVUS analysis

At the stent edges the area encompassed by the lumen-intima and media-adventitia boundaries defined the luminal and the total vessel volumes, respectively. The difference between luminal and

total vessel volumes defined the plaque volume. Within the boundaries of the stent total vessel volume (TVV), stent volume, neointimal hyperplasia (NIH = stent volume – lumen volume) plaque behind the stent (PBS = TVV – stent volume) and lumen volumes were obtained. NIH presented is a measured value at follow – up and not derived from subtraction of the post and follow – up measures.

The assessment of TVV or EEM in stented patients has previously been reported[14]. Although, in this previous report the delineation of TVV/EEM was not possible in some patients due to stent shadowing, in our study the delineation of EEM boundary was possible in all stented patients. When the TVV/EEM boundary was not visible in a single cross – sectional view, the computer extrapolated it from the contours of the immediately previous and following cross – sections. In addition the use of 3 – dimensional reconstruction with multiple longitudinal views facilitates the visualisation of vessel structures outside the stent.

Statistical analysis

Quantitative data are presented as mean ± standard deviation. Volumetric data derived from the 3-D reconstruction of the IVUS imaging were compared immediately after treatment and at follow-up using the two-tailed paired Student's t-test. Comparison between groups was performed using one – way analysis of variance (ANOVA) and the Tukey – Kramer multiple comparisons test. A value of $p<0.05$ was considered statistically significant. The Medical Ethical Committee of the University Hospital Rotterdam approved the study and all patients signed a written informed consent before the procedure.

Results

Baseline Characteristics

Eighteen patients were enrolled in the conventional group (C), 16 patients in both the 0.75-1.5μCi (LA) and 6.0-12μCi (HA) radioactive stent groups and finally 17 in the group employing catheter – based radiation plus a stent (CBS). In the conventional group 10 Multilink and 8 NIR stents were implanted. Baseline characteristics are similar between all groups and are described in Table I. Lesion and procedural characteristics are described in Table 2. No statistically significant differences were seen between groups in the parameters described in Table 2. A comparison of volumetric data is presented in Tables 3 and 4.

In stent inhibition of NIH

Intra - stent NIH was decreased after radioactive stent implantation and catheter – based radiation plus stent implantation (C = 20.8mm^3, LA = 18.0mm^3, HA = 8.9mm^3, CBS = 6.9mm^3, $p<0.05$). Lower activity radioactive stents had an effect similar to that of conventional stents.

Behind stent

Conventional stents and both low and higher activity radioactive stents demonstrated an absence of remodeling behind the stent, with no significant changes in TVV or plaque volumes. This is in contrast to the catheter – based / stent group which demonstrated a significant increase in plaque (+15%) and an increase in TVV (+7%), (Table 3, $p < 0.05$).

No chronic recoil of the stent was seen in any group.

Stent edge

At the stent edges remodeling is similar after both conventional and low – activity radioactive stent implantation. In these groups there is evidence of a decrease in TVV, (C= 7%, LD = 8%) with little change in plaque as a cause of late lumen loss. At higher activity levels of radioactive stent the presence of both stent edge - effect and stent edge restenosis becomes apparent. In the ^{32}P group a target segment restenosis (angiographically > 50%) was observed in 7 patients at the stent edges. This was more common at the proximal edge (6/7).

If only edge restenosis is considered, then the major mechanism of restenosis appears to be due to an increase in plaque at the stent edge. In non - restenotic patients the edge effect appears due to a decrease in TVV and an increase in plaque (Figure 3)

After catheter – based radiation / stenting the edge effect is largely due to an increase in plaque, with no negative remodeling seen (CBS Vs LA, HA, C, $p< 0.05$). No patients with edge restenosis after catheter – based radiation was seen in our series of patients.

Stent activity and dose prescribed

Mean stent activity at implantation (LA) was 1.1 +/- 0.3 uCi. Mean stent activity at implantation (HA) was 8.6 +/- 1.6 uCi. For CBS mean dose prescribed was 16.7 +/-2.0 Gy.

Discussion

The development of NIH within the stent witnessed at 6 – month follow – up is well appreciated[15], however the changes that occur at the stent edges or indeed behind the stent struts have not been the focus of attention until recently[4]. This paper is the first describing the difference in vascular remodeling seen after radioactive stent implantation and catheter – based

radiation plus stenting, using modern conventional stents as a benchmark. The key findings of this paper are as follows:

a. Similar inhibition of NIH occurs after radioactive stent implantation and catheter – based radiation and stenting.
b. There was no significant remodeling behind the stent is after conventional or radioactive stent implantation; however the combination of catheter – based radiation and stenting leads to both an increase in plaque outside the stent and TVV.
c. At the stent edge three patterns of remodeling are seen at 6 – month follow - up: firstly a shrinkage in TVV and LV after C and LD radioactive stent implantation. These two subgroups were not associated with stent edge restenosis in this series. After HD stent implantation a pattern similar to C and LD is seen in those edges that remain non – restenotic, however in restenotic edges plaque increase is the major contributor to lumen loss ($p<0.05$). In the CBS group a similar lumen loss to the other groups is seen, however this occurs secondary to an increase in plaque ($p<0.05$) and without a loss in TVV, suggesting that some degree of positive remodeling is occurring to accommodate plaque increase.

Neointimal Hyperplasia

In our study neointimal formation was inhibited after higher dose radioactive stent implantation and after catheter - based radiation plus stenting. The former contrasts with the recent study by Carter et al. using ^{32}P stents in the porcine model[16], but is in keeping with earlier studies of Hehrlein[6] using the rabbit model and recent reports by Albiero[4] in which a dose – dependent inhibition of NIH was noted.

Mechanism of remodeling behind the stent

Catheter – based

After conventional and radioactive stent implantation little remodeling is witnessed behind the stent. In stark contrast to this, is the considerable increase in plaque seen after catheter – based radiation and stenting. Part of the key to understanding this process may be aquired from understanding the healing process after BA. Wilcox and co – workers[17] describe the presence of early proliferation of myofibroblasts expressing contractile proteins in the adventitia surrounding the porcine coronary artery after BA. Tracing studies have indicated that the same cells migrate and form part of the neointima. Wilcox hypothesizes that the adventitial myofibroblasts constrict the artery at the angioplasty site much in the same way that

myofibroblasts participate in scar retraction in dermal healing. The source of these myofibroblasts may be distant to the immediate site of injury including pericardial, adipose and intramyocardial layers.

Radiation treatment of porcine coronary arteries after BA up - regulates p21 synthesis in adventitial cells, inhibits the expression of growth factors, reduces proliferation of adventitial myofibroblasts, decreases the production of α - actin by the adventitial myofibroblasts, preventing the formation of the myofibroblast scar around the angioplasty site and inducing positive vascular remodeling. Data from Fareh and co – workers[18] suggest that inhibition of migration but not of cellular proliferation occurs at lower doses of radiation. Therefore cells may remain in situ, unable to migrate but able to grow in the presence of positive vascular remodeling. After one week the effect of the radiation diminishes and cellular proliferation, possibly as a reaction to the presence of the stent, occurs behind the stent in the context of positive vascular remodeling. In our cohort of patients no cases of stent malapposition were seen at follow – up although our group has described this as a risk of ongoing positive vascular remodeling[19,20].

Radioactive stent

The objective of using the radioactive stent is not to neutralise myofibroblasts in the adventitia. Rather it is the prevention of the migration and invasion of myofibroblasts from the adventitia through the stent struts and into the lumen. As is seen in the HA group this is accomplished due to the continuous and low dose rate provided by the radioactive stent. Due to the range of the 'radioactive fence' created, adventitial cells remain intact without upregulation of growth factors and inhibition of contractile proteins. Consequently no remodeling is seen behind the radioactive stent.

Edge Remodeling

Hoffmann[15] has previously described negative remodeling at the stent edge and of the stent/vessel wall after conventional stent implantation. In our study we have been able to precisely describe the decrease in TVV as the dominant contributor to non – restenotic lumen loss at the stent edge and to confirm the absence of recoil and remodeling in modern stents at 6-month follow – up. Recent reports suggest that the edge effect and edge restenosis may be due to an increase in plaque at the edge and to a component of negative remodeling as one moves axially from the stent[4]. However, the edge response after catheter – based radiation and subsequent conventional stent implantation were undefined until the current paper.

Edge restenosis: is this the result of low – dose radiation?

Radioactive stents have a limited radioactive range of effect. Whereas those cells behind the stent struts may be well fenced at the doses discussed, cells proximal and distal to the extremityof the stent, in injured areas treated by the balloon (up to 3mm outside the stent)[21], may not be effectively covered by the range of the stent radiation. The latter phenomenon is a further example of geographical miss[22]. Whether there is a proliferative effect on tissue secondary to low – dose radiation at the edge of the radioactive stent has yet to be proven in clinical trials. Certainly there is evidence from animal work that low dose radiation may induce a proliferative effect on tissue[23]. If the edge restenosis is the result of an aberrant response by non-injured healthy or diseased tissue subjected to radiation, then this may suggest that low-dose radiation has a stimulatory effect on non-injured tissue. This would be the worst possible scenario, as clearly non-injured healthy or diseased tissue will always be irradiated at some stage.

Implication for the future: Dealing with the edge effect

If the edge effect is the result of balloon-induced trauma and low dose radiation then limiting the trauma outside the stent and expanding the irradiated area beyond the injured area should be attempted. For radioactive stents conceivably the most practical approach may be to extend the area of irradiation beyond the injured area using a 'hot-end stent'. This involves literally concentrating the greatest activity of the stent at the stent edges; such stents are already undergoing multicentre trials.

If the edge restenosis were purely the result of negative remodeling induced by low-dose radiation in an injured area, then the lengthening of the stent by a non – radioactive, cold – end would be a logical solution to prevent remodeling at the extremities. If plaque constitutes a large percentage of the healing process manifested by the restenosis then cold-end stent implantation is unlikely to work as neointimal proliferation may occur at the edges of the radiation within the stent (an in-stent candy-wrapper). In the event that excessive vascular remodeling is present after catheter – based radiotherapy, then a self – expanding stent may play a useful role. The appeal here is that via direct stenting the injury caused by balloon pre - dilation will be avoided and the self expanding stent would be permitted to expand, minimizing geographical miss and stent malapposition[19,20].

Limitations This was a retrospective, non – randomised study of individuals who had completed 6 – month follow – up and in whom IVUS examination was possible. Individuals

who had total occlusion or whom IVUS catheter could not be passed under acceptable clinical circumstances were not included. Although no edge restenosis was seen in the CBS group, both the CBS and the HA groups reflected the larger parent populations from which they were selected in all other features. The dosimetry described in this paper relates to prescribed doses only and does not necessarily reflect the dose delivered 2mm from the source in the adventitia. Description of the dosimetry is beyond the scope of this paper, however previous work by the authors suggest that delivered dose, residual plaque burden and tissue composition play a fundamental role on the volumetric outcome at 6-month follow-up after catheter – based ß-radiation therapy and BA[24].

Conclusion

Distinct differences in the patterns of remodeling exist between conventional, radioactive and catheter – based radiotherapy with stenting. Users of radiation need to be alerted to the deleterious remodeling seen at the stent edges after higher – dose radioactive stent implantation and behind the stent after catheter – based radiation and stenting.

Radiation, whether it be catheter or stent – based has forced the interventional community to look closely not only at effective inhibition of intimal proliferation but also the adverse response of the artery to the combination of injury and radiation.

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Table 1. Clinical Characteristics

	Conventional	LA	HA	CBS
Patient No	18	16	15	17
Age (mean)	58 (42-76)	60 (43-74)	59 (42-75)	57 (45-74)
Male (%)	70	66	70	60
Prior MI (%)	40	40	45	40
Unstable angina (%)	60	50	65	55
Smoking (%)	40	55	40	40
Hypercholestrolemia (%)	60	62	65	55
Family history (%)	33	42	30	40
Hypertension (%)	40	42	30	33
Diabetes (%)	5	5	10	6

Table 2 Procedural characteristics

	C	LA	HA	CBS
Vessel				
LAD	10	9	9	9
LCx	4	3	4	4
RCA	4	4	3	4
Lesion length (mm)	9.6±3.3	12.1±3.8	10.1±3.3	11.9±4
Stent length (mm)	14.6±3.8	15.0	15.0	15.2±4.1
Balloon length-post	14.8±3.4	14.4±2.8	14.1±2.6	15.1±3.6
Final balloon size (mm)	3.2±0.4	3.1±0.6	3.4±0.5	3.2±0.5
Max inflation pressure[1]	11.5±2.4	11.6±2.6	10.2±2.8	12.2±2.6
Max inflation pressure[2]	14.6±3.2	15.2±2.4	15.8±1.7	15.4±3.3
Balloon-to-artery ratio	1.04±0.05	1.12±0.06	1.10±0.06	1.12±0.05

Max inflation pressure[1] = balloon at time of stent implantation
Max inflation pressure[2] = balloon inflation within stent

Table 3: Mean volume for the edge proximal and distal to the stent (10mm length)

Edge (mm^3)	LV post	LV F/UP	TVV post	TVV F/UP	Plaque post	Plaque F/UP
C	67.7	58.3*	124.4	116.5*	56.7	58.2
LD	75.2	67.3*	126.6	116.4*	51.4	49.1
HD	74.9	63.0*	126.2	117.6*	51.3	54.6
CBS	72.6	61.1*	133.2	138.9	60.6	77.8*

* = $p < 0.05$ Post Vs Follow-up
No significant difference between groups seen at baseline (post).

Table 4
Mean volumes for the stent (15mm length)

Stent (mm^3)	LV post	LV F/UP	TVV post	TVV F/UP	PBS post	PBS F/UP	NIH
C	113.9	92.8*	256.1	257.3	142.2	143.7	20.8
LA	127.3	105.5*	266.6	264.5	139.3	137.8	21.2
HA	122.4	111.7*	267.8	265.3	145.4	144.6	9.0
CBS	128.6	121.8*	258.9	278.0*	130.3.0	149.3*	6.9

* = $p < 0.05$ Post Vs Follow-up
No significant difference between groups seen at baseline (post).

Figure 1

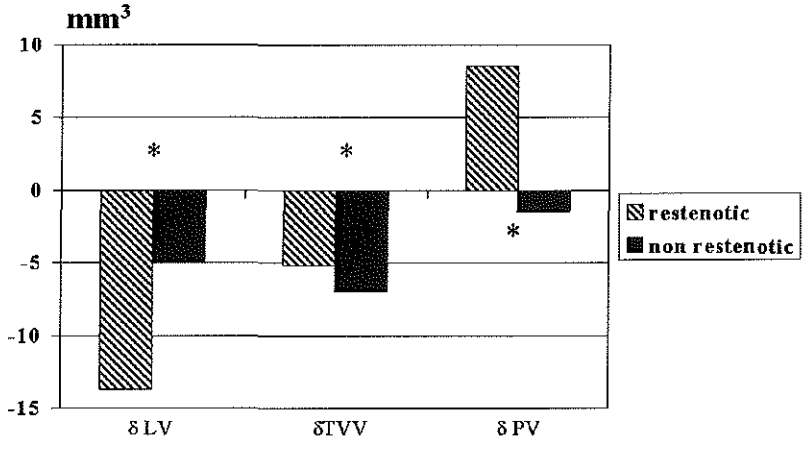

Figure Legend: 6.0-12.0μCi activity level stents. Restenotic edges Vs Non - Restenotic. * = $p < 0.05$. δ LV = change in lumen volume (post - follow-up). δ TVV = change in total vessel volume (post - follow-up). δ PV = change in plaque volume (post - follow-up).

Figure 2

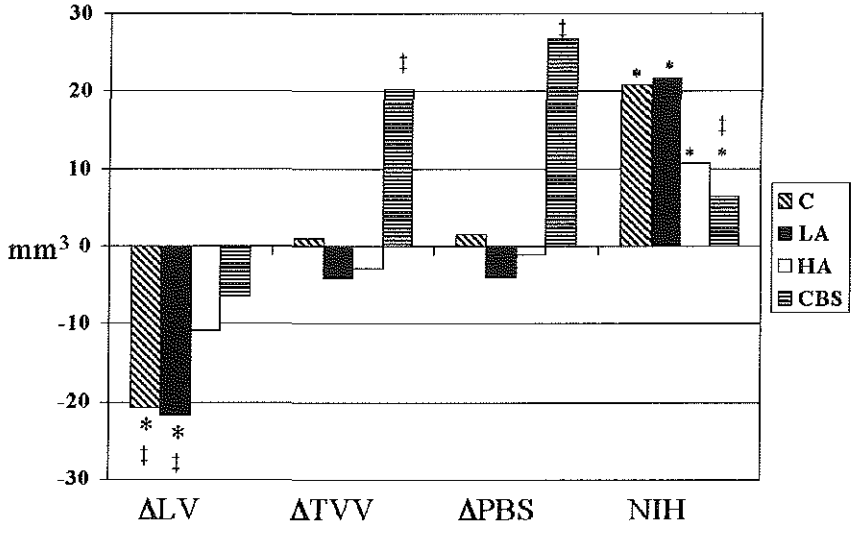

Figure Legend: Remodeling within the stent
* = P < 0.05; baseline Vs follow-up
‡ = p < 0.05; ANOVA

Figure 3

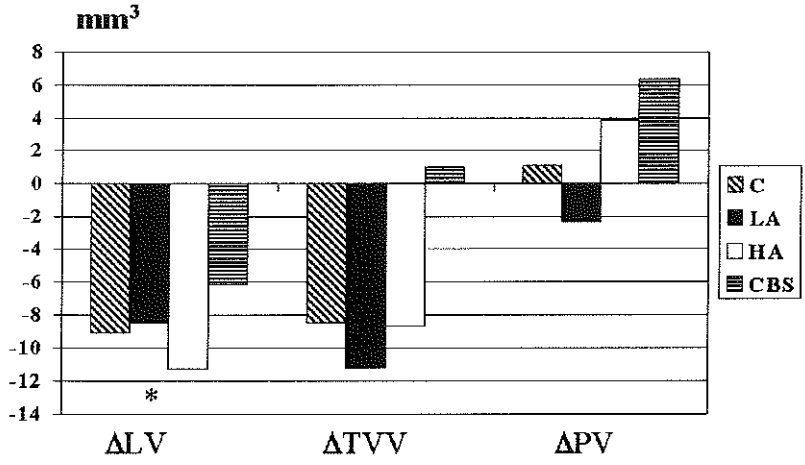

Figure Legend:Stent Edge
Δ LV for all groups: p<0.05, baseline Vs follow-up; between groups:p=NS, ANOVA.
Δ TVV for C, LA, HA,:p<0.05, baseline Vs follow-up;between groups: p<0.05, ANOVA.
Δ PV for LA&C Vs HA(trend only) &CBS; p<0.05, ANOVA

Chapter 4

Preserved endothelium-dependent vasodilation in coronary segments previously treated with balloon angioplasty and intracoronary irradiation.

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Preserved Endothelium-Dependent Vasodilation in Coronary Segments Previously Treated With Balloon Angioplasty and Intracoronary Irradiation

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Background—Abnormal endothelium-dependent coronary vasomotion has been reported after balloon angioplasty (BA), as well as after intracoronary radiation. However, the long-term effect on coronary vasomotion is not known. The aim of this study was to evaluate the long-term vasomotion of coronary segments treated with BA and brachytherapy.

Methods and Results—Patients with single de novo lesions treated either with BA followed by intracoronary β-irradiation (according to the Beta Energy Restenosis Trial-1.5) or with BA alone were eligible. Of these groups, those patients in stable condition who returned for 6-month angiographic follow-up formed the study population (n=19, irradiated group and n=11, control group). Endothelium-dependent coronary vasomotion was assessed by selective infusion of serial doses of acetylcholine (ACh) proximally to the treated area. Mean luminal diameter was calculated by quantitative coronary angiography both in the treated area and in distal segments. Endothelial dysfunction was defined as a vasoconstriction after the maximal dose of ACh (10^{-6} mol/L). Seventeen irradiated segments (89.5%) demonstrated normal endothelial function. In contrast, 10 distal nonirradiated segments (53%) and 5 control segments (45%) demonstrated endothelium-dependent vasoconstriction ($-19\pm17\%$ and $-9.0\pm5\%$, respectively). Mean percentage of change in mean luminal diameter after ACh was significantly higher in irradiated segments ($P=0.01$).

Conclusions—Endothelium-dependent vasomotion of coronary segments treated with BA followed by β-radiation is restored in the majority of stable patients at 6-month follow-up. This functional response appeared to be better than those documented both in the distal segments and in segments treated with BA alone. ***(Circulation.* 1999;100:1623-1629.)**

Key Words: balloon ■ angioplasty ■ radioisotopes ■ endothelium ■ acetylcholine

Abnormal endothelium-dependent coronary vasomotion has been reported both immediately after and up to 6 months after coronary balloon angioplasty (BA).[1–4] The preservation of endothelial function is of the utmost importance to maintain the delicate balance between inhibition and promotion of vascular growth, vasoconstriction, and vasodilation, as well as antithrombotic and hemostatic mechanisms.[5] Intracoronary radiation appears to be a promising new technique to prevent restenosis after BA.[6–8] Experimental studies have demonstrated an impairment of endothelial function in the short term after high-dose intracoronary γ-irradiation, which was restored at follow-up.[9] However, the effect of brachytherapy after balloon-induced injury on vasomotor function in patients remains unknown. The aim of the present study was to assess the long-term effect of intracoronary radiation therapy after successful BA on coronary vasomotion.

Methods

Patient Selection

Two groups of patients were compared: patients with single de novo lesions successfully treated with BA followed by intracoronary β-irradiation (n=23) and patients with single de novo lesions successfully treated only with BA (n=16). Patients receiving radiation were included in the Beta Energy Restenosis Trial (BERT-1.5). Patients in the control group were individuals treated with BA alone and matched for age, sex, and vessel size. Those patients in stable condition who returned for 6-month angiographic follow-up formed the study population (n=19, irradiated group and n=11, control group). BERT-1.5 was a prospective multicenter feasibility study. The isotope selected was pure β-emitting $^{90}Sr/^{90}Y$, and patients were randomized to receive 12, 14, or 16 Gy at 2 mm from the source. The

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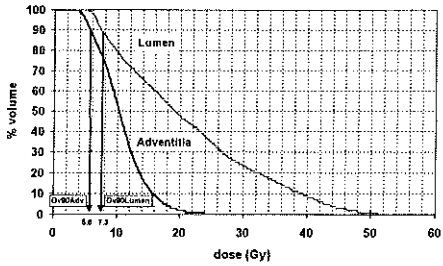

Figure 1. Dose-volume histogram showing cumulative dose received at level of luminal surface and adventitia layer. Minimal dose received by 90% of lumen (D_{v90} Lumen) and adventitia (D_{v90} Adv) was calculated.

inclusion and exclusion criteria of this trial have been reported previously.[19]

Radiation Delivery System

The Beta-Cath System (Novoste Corp) was used to deliver localized β-radiation to a coronary artery at the site of coronary intervention. The device consists of 3 components: (1) the transfer device, which stores the radiation source train and allows the positioning of these sources within the catheter; (2) the delivery catheter, which is a 5F multilumen, over-the-wire, noncentered catheter that uses saline solution to send and return the radiation source train; and (3) the radiation source train, which consists of a series of 12 independent 2.5-mm-long cylindrical seeds that contain the radioisotope $^{90}Sr/^{90}Y$ sources and is bordered by 2 gold radiopaque markers at the distal and proximal parts of the 30-mm source train.[11]

Dose Calculation

The actual dose received by the luminal surface was retrospectively calculated by means of dose-volume histograms.[12] This method is based on quantitative intravascular ultrasound (IVUS) under the assumption that the radiation source is positioned at the same place as the IVUS catheter. The method of selection of the area of interest on IVUS has been reported previously.[13] The IVUS system used was a sheath-based IVUS catheter (ClearView, CVIS, Boston Scientific Corporation) incorporating a 30-MHz single-element transducer rotating at 1800 rpm (Ultracross, CVIS). Image acquisition and digitization were performed by means of an ECG-gated pullback at a step size of 0.2 mm/step.[14,15] Volumetric analysis of the irradiated area was performed by a semiautomatic contour detection program developed at our institution.[16] The feasibility and intraobserver and interobserver variabilities of this system have been reported previously.[17–19] The distance between the center of the catheter and both the lumen-intima and media-adventitia interfaces was calculated in 24 pie slices (15° each) in all cross sections corresponding to the irradiated area (30-mm length of the train source). Considering the prescribed dose and the accurate geometric data obtained from the IVUS, the cumulative curve of the dose-volume histogram for a predefined volume (ie, intima or adventitia) can be obtained (Figure 1). From this curve, for example, the minimal dose received by 90% of either the intimal volume (D_{v90} lumen) or the adventitial volume (D_{v90} Adv) was calculated.

Endothelial Function Study

Long-acting vasoactive drugs were discontinued ≥48 hours before the study. A percutaneous femoral artery approach and 8F guiding catheter were used in all cases. Endothelium-dependent and -independent coronary vasomotion were studied as described previously in detail[20]: after the administration of 10 000 IU of heparin, a 3F infusion catheter (Transit, Cordis) was advanced over a guidewire and placed proximally to the irradiated segment. To avoid wire-induced coronary spasm, the wire was removed. The irradiated segment was identified on the basis of the anatomic landmarks visible on the angiogram performed at the time of the placement of the radiation source. To ensure that the segments were fully bathed by the infusion of acetylcholine chloride (ACh), the tip of the infusion catheter was placed 2 to 3 mm proximal to the proximal border of the irradiated area. To determine the baseline vasomotion, an initial infusion of saline solution for 1 minute through the infusion catheter was performed and a baseline angiogram taken. This was followed by infusion of serial doses of intracoronary ACh, with final estimated intracoronary concentrations of 10^{-8} to 10^{-6} mol/L, to assess endothelium-dependent coronary vasomotion. The duration of each infusion was 2.5 minutes, followed immediately by angiography. All angiograms were taken with identical views and radiographic characteristics. All infusions were delivered at a rate of 2 mL/min by use of a precision pump injector (Mark V, Medrad, Europe BV). The final blood concentrations of ACh were estimated with the assumption that blood flow in the coronary artery was 80 mL/min.[21] Finally, to evaluate endothelium-independent vasomotion, a nitroglycerin (NTG) bolus (2 mg) was administered through the guiding catheter, after which an angiogram identical to those performed previously was done.[20] Throughout each infusion, the heart rate, systemic arterial pressure, and ECG were monitored continuously. Because ACh causes endothelium-dependent vessel relaxation in experimental models and in humans,[22,23] a paradoxical vasoconstriction after the infusion of this substance is an indicator of endothelial dysfunction.[20]

The study was approved by the Medical Ethics Committee of our institution, and written informed consent was obtained from all patients in accordance with the guidelines established by the Committee for the Protection of Human Subjects.

Quantitative Coronary Angiography

Quantitative coronary angiography was performed after the infusion of saline solution, at the end of each ACh infusion, and after NTG bolus. Angiograms were performed in the 2 orthogonal projections that best showed the artery of interest, without overlapping of side branches and with less foreshortening. Offline analysis was performed by means of the CAAS II system (Pie Medical BV). Calibration of the system was based on dimensions of the catheters not filled with contrast medium. The intraobserver and interobserver variabilities of this method of analysis have been reported previously.[24–26] Mean luminal diameter was determined after the infusion of each substance in the irradiated area, in a 15- to 20-mm-long segment distal to the irradiated area and in a contralateral nontreated artery that served as a control. Mean luminal diameter was averaged for the 2 projections, and the percentage of change relative to baseline was noted. All quantitative measurements were performed by the same investigator (M.S.). Intraobserver variability was assessed by reanalysis of the quantitative coronary angiography of a series of 15 studies (150 repeated measures in total) ≥3 months apart. Intraobserver differences (mean±2 SD) in mean luminal diameter were as follows: 0.7±2.7% for baseline values, 0.8±2.9% after maximal dose of ACh, and 0.7±2.6% after NTG. The intraclass correlation coefficient (R^2) for repeated measures was 0.97 for baseline values, 0.96 for maximal-dose ACh values, and 0.98 for NTG values. We considered endothelial dysfunction a vasoconstriction of the segment studied after the maximal dose of ACh beyond the variability of the method of analysis (>3%).

Statistical Analysis

Data are presented as mean±SD or proportions. To compare continuous variables, 2-tailed Student's *t* test, ANOVA for repeated measurements, and linear regression analysis were performed when appropriate. A value of $P<0.05$ was considered statistically significant.

TABLE 1. Baseline Characteristics

	Irradiation Group (n=19)	Control Group (n=11)
Age, y	55±8	58±5
Male sex, n (%)	14 (74)	10 (91)
Treated artery, n (%)		
Left anterior descending	10 (53)	10 (91)
Left circumflex	6 (31)	1 (9)
Right coronary	3 (16)	0 (0)
Coronary risk factors, n (%)		
Systemic hypertension	9 (47)	5 (45)
Diabetes mellitus	2 (10)	1 (9)
Smoking	14 (74)	7 (63)
Hypercholesterolemia	11 (58)	6 (54)
Family history	11 (58)	5 (45)
Minimal luminal diameter, mm	1.7±0.6	1.6±0.3
Diameter stenosis, %	39±17	34±7

Continuous data are presented as mean±SD.

Results

Baseline Characteristics

Baseline characteristics of both irradiated and control patients are presented in Table 1. Angiographic restenosis (diameter stenosis >50%) was observed within the irradiated area in 3 patients (16%). Fourteen patients (74%) remained asymptomatic, whereas 5 (26%) presented with angina pectoris Canadian Cardiovascular Society (CCS) class I (n=1), 2 (n=1), or 3 (n=3). None of the patients in the control group showed angiographic restenosis, and only 2 presented with angina pectoris CCS class 1. No differences were observed between groups regarding age, sex, coronary risk factors, or minimal luminal diameter and diameter stenosis in the diagnostic angiogram performed at the time of the functional study. The left anterior descending coronary artery was assessed more often in the control group.

Coronary Vasomotion Study

No significant changes in mean aortic pressure and heart rate were observed during the ACh infusion in either group. Mean luminal diameters after infusion of each substance in irradiated and distal nonirradiated segments and in the control group are presented in Table 2. Seventeen irradiated segments (89.5%) demonstrated normal endothelium-dependent coronary vasomotion (16 segments with a vasodilatory response [5.0±3% of change in mean luminal diameter after Ach] and 1 with no change in mean luminal diameter [−0.1% of change after Ach infusion]). On the other hand, endothelial dysfunction was demonstrated in 2 irradiated segments (10.5%): 1 with angiographic restenosis and angina pectoris CCS class 3 and the other with angina pectoris CCS class 1 without restenosis (−5.2% and −7.8% of vasoconstriction after maximal dose of ACh, respectively). In contrast, 10 (53%) of the distal nonirradiated segments demonstrated endothelial dysfunction (−19.5±17% of vasoconstriction after maximal dose of ACh). No significant de novo stenosis was observed at

TABLE 2. Coronary Vasomotor Response (Mean Luminal Diameter)

	Irradiated Segment (n=19)	Distal Segment (n=19)	Control Group (n=11)
Baseline	2.46±0.4	2.20±0.4	2.38±0.3
ACh 10^{-8}	2.49±0.4	2.19±0.5	2.35±0.3
ACh 10^{-7}	2.52±0.4	2.13±0.5	2.33±0.5
ACh 10^{-6}	2.55±0.5*	2.07±0.7	2.31±0.3
NTG	2.62±0.4†	2.33±0.6‡	2.58±0.5‡

Data are presented as mean±SD (in mm).
*P=0.03, †P=0.0004, ‡P=0.01 with respect to baseline values.

distal segments. No significant correlation was demonstrated between the degree of stenosis at follow-up and the vasomotor response. Five patients in the control group (45%) showed endothelial dysfunction in the treated area (−9.0±5% of vasoconstriction at ACh 10^{-6} mol/L). Mean percentages of change in mean luminal diameter after infusion of the different substances between the irradiated and control patients and between irradiated and distal nonirradiated segments are presented in Figures 2 and 3. Mean percentage change in diameter after ACh was 3.8±7.1% in the irradiated segments compared with −3.2±7% and −6.6±10% in the control group and in the distal nonirradiated segments, respectively (P=0.01). No significant differences in percentage of change in mean luminal diameter either in irradiated or in distal segments were observed between the 3 coronary vessels after either ACh or NTG. Examples of coronary segments with vasodilation of the irradiated area and vasoconstriction of the distal nonirradiated segment after ACh infusion are depicted in Figures 4 and 5. All of the segments experienced vasodilation after NTG, which is indicative of normal smooth muscle vasomotion (Figures 2 and 3).

Radiation Dose Calculation

Mean prescribed radiation dose was 14±1.9 Gy at 2 mm to the source. However, when dose-volume histograms were applied, the calculated minimal dose received by 90% of the

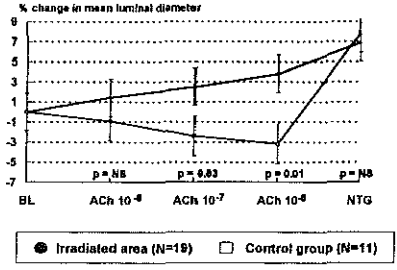

Figure 2. Percentage of change in mean luminal diameter after infusion of each substance in irradiated segments and in control group. Irradiated segments showed, on average, an increase in mean luminal diameter after infusion of ACh, which is indicative of normal endothelial function, whereas control group demonstrated on average vasoconstriction, which is indicative of endothelial dysfunction. Endothelium-independent coronary vasomotion was preserved in both groups. BL indicates baseline.

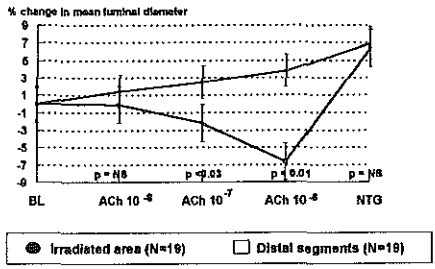

Figure 3. Percentage of change in mean luminal diameter after infusion of each substance in irradiated and in distal nonirradiated segments. Irradiated segments showed, on average, an increase in mean luminal diameter after infusion of ACh, which is indicative of normal endothelial function, whereas distal nonirradiated segments demonstrated, on average, vasoconstriction, which is indicative of endothelial dysfunction. Endothelium-independent coronary vasomotion was preserved in both groups. BL indicates baseline.

luminal surface was 8.2±3.8 Gy, whereas D_{v90} Adv was 5.2±1.9 Gy. Only 6 patients (31.5%) received on average >10 Gy at luminal surface, and only 2 patients (10.5%) received on average >8 Gy at the adventitial layer. No significant correlation was found between endothelium-dependent coronary vasomotion and the calculated D_{v90} lumen ($r=-0.03$; P=NS). Similarly, no significant correlation was observed between the coronary vasomotor response to NTG and D_{v90} Adv ($r=0.03$; P=NS).

Discussion

This study demonstrates for the first time that the endothelium-dependent vasomotor function of coronary segments treated with BA followed by β-radiation is restored in the majority of stable patients at 6-month follow-up. This functional response observed in irradiated segments appeared to be better than that documented both in distal nonirradiated segments and in segments treated only with BA.

An impairment of endothelial function has been reported at up to 3 to 6 months after BA.[4] It has been demonstrated that soon after balloon-induced injury, there is a release of von Willebrand factor[27] and endothelin[28] as markers of endothelial injury. Experimental studies have demonstrated that the endothelium regenerates at follow-up. However, the endothelium appeared to still be dysfunctional,[29,30] which may cause the release of endothelium-dependent contracting factors and the alteration of endothelial muscarinic receptors.[31–33]

Endothelial dysfunction in distal nontreated segments is a common finding in atherosclerotic coronary arteries after percutaneous interventions.[3] An alteration of autoregulation due to chronic hypoperfusion may be implicated in the distal abnormal responsiveness to ACh.[2] Furthermore, the presence of coronary risk factors may have a deleterious effect on distal coronary vasomotion.[34,35]

In contrast, most of the irradiated segments exhibited normal endothelium-dependent vasomotion, and all of them presented a normal response to NTG. Wiedermann et al[9] demonstrated restoration of endothelial function after high-dose (20 Gy) γ-radiation in a non–balloon-injured animal

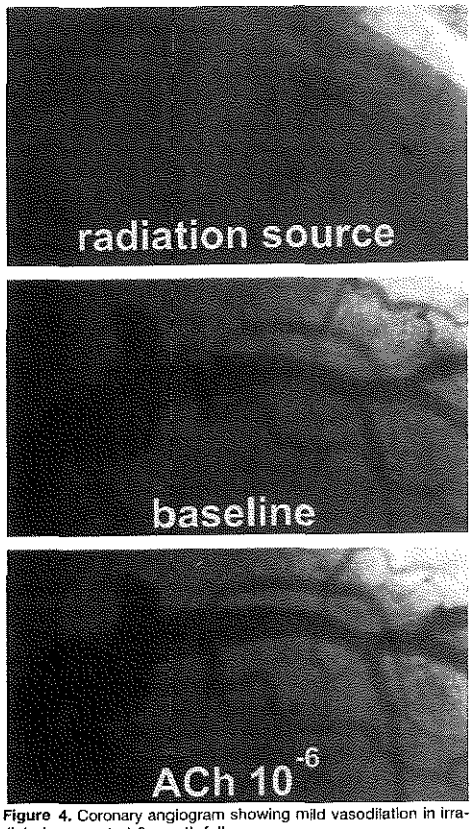

Figure 4. Coronary angiogram showing mild vasodilation in irradiated segment at 6-month follow-up.

model. However, a diffuse fibrosis of the smooth muscle layer, probably responsible for the loss of response to NTG, was detected on histological analysis.[9] Our findings confirmed these experimental observations in terms of endothelium-dependent coronary vasomotion. The lack of paradoxical vasoconstriction may be explained by an alteration of the muscular media, which may demonstrate an impairment in response to endothelium-dependent vasoregulatory signals. However, vasodilation rather than lack of constriction was the vasomotor response demonstrated in all but 1 of the irradiated segments with normal endothelial function. The vasomotor response to NTG remained unaltered and comparable between groups, which suggests an absence of radiation-induced impairment of the medial layer. In an experimental model, endothelial cells as well as vascular smooth muscle cells were inhibited in a dose-dependent manner. However, at a moderate range of β-particle delivery (0.4 to 6 Gy), but not at a high dose (10 Gy), endothelial cells appeared to be more radioresistant than vascular smooth muscle cells.[36] The relatively low dose of radiation received by the treated segments may account for this normal functional behavior. In fact, none

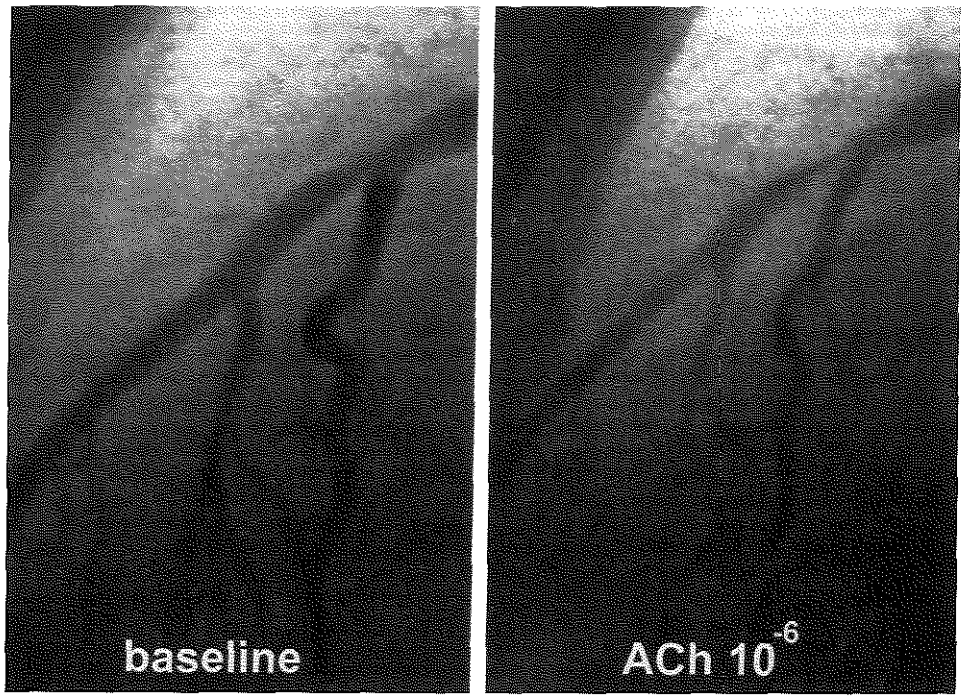

Figure 5. Coronary angiogram showing moderate vasoconstriction of distal nontreated coronary segment after infusion of maximal dose of ACh, which is indicative of endothelial dysfunction.

of the patients actually received on average >10 Gy at the level of the adventitia, as assessed by dose-volume histograms.

On the other hand, an experimental model of porcine coronary arteries subjected to balloon overstretch injury and either placebo or radiation with 18 Gy[37] demonstrated that expression of enzyme-inducible nitric oxide synthase (iNOS), responsible for NO production, was enhanced, whereas expression of the cytokine transforming growth factor-β_1 (TGF-β_1) was suppressed in the irradiated group. iNOS is potentially responsible for inhibition of neointimal hyperplasia and stimulation of reendothelialization, whereas TGF-β_1 would enhance intimal hyperplasia and fibrosis by negatively modulating the expression of iNOS.[37] Moreover, it has been demonstrated in experimental models that radiation causes dose- and time-dependent impairment of endothelium-dependent relaxation[38] and that low-dose radiation would induce an anti-inflammatory reaction through specific dose-dependent modulation of the NO pathway.[39] It remains to be seen whether this chain reaction after radiation would result in a late reduction in the restenosis rate. However, restoration of endothelial function may play an important role in this regard.

Study Limitations

Because the use of ACh in unstable patients is not exempt of risk of coronary occlusion, only stable patients were evaluated.

This study assessed patients receiving β-radiation by means of a noncentering device. The actual dose received by the treated segment was rather low; thus, the effect of a higher dose or of different devices that allow a more homogeneous dose distribution remains to be evaluated.

We assessed the vasomotion of the 3 coronary arteries in the irradiated group, which have a potentially different degree of vasoreactivity to ACh. However, the 3 arteries demonstrated comparable vasomotor responses to ACh and NTG both at the irradiated and the distal segments, which overcomes this potential limitation.

We assumed that coronary vasomotion immediately after treatment is markedly impaired, as demonstrated in experimental models and in humans.[1–4,9] Taking into account the risk of coronary occlusion in such situation, it was considered unethical to determine endothelium-dependent vasomotion immediately after the coronary intervention. Thus, the degree of recovery of coronary vasomotion could not be evaluated.

We also assumed that the IVUS and delivery catheters were lying in the same position in the treated coronary

segment. The size of the IVUS catheter is smaller (2.9F, ≈1 mm) than the brachytherapy device (5F), which is thus to some extent more centered in the lumen. Although the catheters should be on the shortest 3D path in the lumen, coronary arteries have a complex curved geometry in space and can be partially deformed by the catheters. Thus, catheters with different rigidity may occupy different positions. The development of new systems that incorporate the IVUS imaging element on the delivery catheter might resolve this drawback.

During irradiation, the position of the delivery catheter inside the lumen is not fixed and may vary during the cardiac cycle because of ventricular contractions, which may lead to some degree of inhomogeneity not assumed by data derived from the static end-diastolic IVUS images.

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Part II

Dosimetry Considerations

Chapter 5

Residual plaque burden, delivered dose and tissue composition predict the 6-month outcome after balloon angioplasty and ß-radiation therapy.

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RESIDUAL PLAQUE BURDEN, DELIVERED DOSE AND TISSUE COMPOSITION PREDICT THE 6-MONTH OUTCOME AFTER BALLOON ANGIOPLASTY AND ß-RADIATION THERAPY

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ABSTRACT

Background. Inhomogeneity of dose distribution and anatomical aspects of the atherosclerotic plaque may influence the outcome of irradiated lesions after balloon angioplasty (BA). We evaluated the influence of delivered dose and morphological characteristics of coronary stenoses treated with beta-radiation following BA.

Methods and results: Eighteen consecutive patients treated according to the BERT-1.5 Trial were included in the study. The site of angioplasty was irradiated using a ß-emitting $^{90}Sr/^{90}Y$ source. Using the sidebranches as anatomical landmarks, the irradiated area was identified and volumetric assessment was performed by three-dimensional intracoronary ultrasound imaging after treatment and at 6-months. The type of tissue, the presence of dissection and the vessel volumes were assessed every 2mm within the irradiated area. The minimal dose absorbed by 90% of the adventitial volume (D_{v90}Adv) was calculated in each 2mm-segment. Diffuse calcified subsegments and those containing sidebranches were excluded. Two-hundred and six coronary subsegments were studied. Of those, 55 were defined as soft, 129 as hard and 22 as normal/intimal thickening. Plaque volume showed a less increase in hard segments as compared to soft and normal/intimal thickening segments ($p<0.0001$). D_{v90}Adv was associated with plaque volume at follow-up following a polynomial equation with linear and non-linear components ($r=0.71;p=0.0001$). The multivariate regression analysis identified the independent predictors of the plaque volume at follow-up: plaque volume post-treatment, D_{v90}Adv and type of plaque.

Conclusion: Residual plaque burden, delivered dose and tissue composition play a fundamental role on the volumetric outcome at 6-month follow-up after ß-radiation therapy and BA.

KEY WORDS: balloon, angioplasty, radioisotopes, dosimetry, ultrasonics, restenosis.

Endovascular radiation therapy is a promising new technique aimed to prevent restenosis after percutaneous coronary intervention.[1-3] Although its effectiveness has been proven in the treatment of instent restenosis,[4,5] the value of intracoronary irradiation in "de novo" coronary lesions remains to be established. Radiation delivered to the coronary artery by means of catheter-based systems can use both gamma and beta emitters.[6] Long-term results after treatment may be influenced by absolute dose and by the homogeneity in dose distribution. Beta-emitters demonstrate a more rapid dose fall-off than gamma emitters because of the short range of electrons.[7] This feature may lead to a less homogeneous dose distribution when treating coronary segments with variable degree of curvature, tapering, remodeling and plaque extent. The use of dose-volume histograms allows one to evaluate the cumulative dose received by a certain specified tissue volume[8] and has been recently implemented in the field of intracoronary brachytherapy as a tool for dosimetry.[9] Aims of the study were (1) to determine, by the use of dose-volume histograms, the dose distribution of the beta-emitter Strontium 90 / Yttrium 90 ($^{90}Sr/^{90}Y$) along the coronary irradiated segment when delivered by a non-centered device, (2) to establish the dose which could be predictive of efficacy in intracoronary brachytherapy, and, (3) to determine the intravascular ultrasound (IVUS) predictors of the plaque volume at 6-month follow-up, of coronary segments treated with balloon angioplasty (BA) followed by beta-radiation therapy.

METHODS

Patient selection

Eighteen consecutive patients presenting with single "de novo" coronary stenosis, successfully treated with BA followed by intracoronary beta-radiation therapy were included in the study. Patients receiving a stent were excluded from the analysis. Beta-radiation was delivered according to the Beta Energy Restenosis Trial 1.5. The isotope selected was the pure beta-emitting $^{90}Sr/^{90}Y$, and patients were randomized to receive 12,14 or 16 Gray (Gy) at 2mm from the source axis. The inclusion and exclusion criteria of this trial have been previously reported.[10] The delivery of the radiation was performed by the use of the Beta-Cath System™ (Novoste Corp., Norcross, GA).[11] The radiation source train of this system consists of a series of twelve independent 2.5mm-long cylindrical seeds which contain the $^{90}Sr/^{90}Y$ sources and is bordered by 2 gold radiopaque markers at distal and proximal part separated by 30mm.[11]

Intravascular Ultrasound analysis

The treated coronary segment was evaluated by means of three-dimensional IVUS imaging, which allowed volumetric calculations of the irradiated area. The selection of the area of interest has been

reported elsewhere.[12] In brief, a few steps were followed: first, an angiogram was performed after positioning the delivery catheter and the relationship between anatomical landmarks and the two gold markers were documented. The anatomical landmark closest to either of the gold markers was used as a reference point. This angiographic reference point was identified during a contrast injection with the IVUS imaging element at the same position as the gold marker of the source. 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: 30mm for the irradiated segment[12]. The system used for imaging was a mechanical IVUS system (ClearView, CVIS, Boston Scientific Corporation, Maple Grove, MN) with a sheath-based IVUS catheter incorporating a 30MHz single-element transducer rotating at 1800 rpm (Ultracross, CVIS). The transducer is placed inside a 2.9 French 15cm-long sonolucent distal sheath which alternatively houses the guidewire (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 using a stepping motor.[13] The ECG-gated image acquisition and digitization was performed by a workstation designed for the 3-D reconstruction of echocardiographic images[13] (EchoScan, Tomtec, Munich, Germany). Description of this system has been previously reported in detail.[13-15] In brief, the steering logic of the workstation considered the heart rate variability and only acquired images from cycles meeting a predetermined range and coinciding with the peak of the R wave. If an R-R interval failed to meet the pre-set 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 0.2 mm to acquire the next image.[13-15] This system assures the segment to segment independence by avoiding taking images during the axial movement of the IVUS catheter which occurs during the cardiac cycle. Given the slice thickness of 0.2 mm and the length subject to the analysis of 30 mm (distance between the two gold markers of the radiation source), 150 cross-sectional images per segment were digitized and analyzed. A semiautomatic contour detection program, was used for the 3-D analysis.[16] This program constructs two longitudinal sections from the data set and identifies the contours corresponding to the lumen-intima and media-adventitia boundaries. Corrections could be performed interactively by "forcing" the contour through visually identified points, and then the entire data set was updated.[16] Careful checking and editing of the contours of the 150 planar images was performed with an average of 45 minutes for complete evaluation. The area encompassed by the lumen-intima and media-adventitia boundaries defined the luminal and the total vessel volumes, respectively. The difference between total vessel and luminal volumes defined the plaque volume. Because media thickness cannot be measured accurately, we assumed that the plaque volume

included the atherosclerotic plaque and the media.[17] Volumetric data were calculated by the formula: $V = \sum_{i=1}^{n} A_i * H$, where V = volume, A = area of total vessel or lumen or plaque in a given cross-sectional ultrasound image, H = thickness of the coronary artery slice, that is reported by this digitized cross-sectional IVUS image, and n = the number of digitized cross-sectional images encompassing the volume to be measured.[16] At follow-up, meticulous matching of the region of interest was performed by comparing the longitudinal reconstruction to that after treatment as previously described.[12] (figure 1) The feasibility and intra- and inter-observer variability of this system have been previously reported.[12,14,18,19] For the purposes of the study, the computed volume of the irradiated segment was divided in 2 mm-long subsegments. Since the irradiated segment measured 30 mm, 15 subsegments were defined per patient, each of them presenting 10 IVUS cross-sections. (0.2mm/cross-section). All individual cross-sections were studied by 2 investigators, blinded to the dosimetry results. Type of plaque and the presence of dissection were qualitatively assessed. Type of plaque was defined in every cross-section, as intimal thickening, soft, fibrous, mixed and diffuse calcified according to the guidelines previously reported.[20] Intimal thickening was defined when the thickness of the intima-media complex was smaller than 0.3mm.[20] Soft tissue was defined when at least 80% of the cross-sectional area was constituted by material showing less echoreflectivity than the adventitia, with an arc of calcium <10°, fibrous plaque when the echoreflectivity of at least 80% of the material was as bright as or brighter than the adventitia without acoustic shadowing; diffuse calcified plaque when it contained material brighter than the adventitia showing acoustic shadowing in >90°; and mixed, when the plaque did not match the 80% criterion.[20] We categorized the 2-mm-long subsegments as normal/intimal thickening, soft, hard (fibrous and mixed) and diffuse calcified, when at least 80% of the cross-sections within the subsegment were of the same type. In those cross-sections containing up to 90° of calcium arc, the contour of the external elastic membrane was imputed from non-calcified slices. Dissection of the vessel was defined as a tear parallel to the vessel wall.[20] Changes in luminal, plaque and total vessel volume between immediately post-treatment and at follow-up, were also computed per subsegment. Those subsegments in which the origin of sidebranches involved >90° of the circumferential arc in more than 50% of the cross-sections, or were defined as diffuse calcified, were excluded from the analysis.

Dose calculation

The actual dose received by the vessel was retrospectively calculated by means of dose-volume histograms[8] in every 2mm-long subsegment. This method is based on quantitative

IVUS under the assumption that the radiation source is positioned at the same place as the IVUS catheter.[9] The distance between the center of the catheter and media-adventitia interface was calculated in 24 pie-slices (15°) in all cross-sections corresponding to the irradiated area.[9] Considering the prescribed dose and the accurate geometric data obtained from the IVUS, the cumulative curve of the dose-volume histogram for a pre-defined volume (i.e. adventitia as calculated at 0.5mm outside the external elastic membrane) can be obtained (figure 2). From this curve, the minimum dose received by 90% of the adventitia volume (D_{v90}Adv) was calculated. The methodology and feasibility of this dosimetry approach in vascular brachytherapy has been previously reported.[9]

Statistical analysis

Data is presented as mean ± SD or proportions. Differences in quantitative IVUS data between the types of tissue were assessed by means of one-way analysis of Variance (ANOVA). Differences in quantitative IVUS data between subsegments with and without dissection and with and without calcium or were evaluated by the use of unpaired Student's t-test. To determine the relationship between the dose received by the adventitia and the plaque volume at follow-up, linear regression analysis was performed first. Then, non-linear components were added to the equation (x^{-1} and x^{-2} were added to describe the steep increase of plaque volume at low dose). These components were included in the model if they described a the relationship significantly better. Finally, the model was corrected for the plaque volume post-treatment. Multivariable regression analyses were performed to identify independent predictors of plaque volume at follow-up among IVUS-derived (types of tissue, dissection, plaque volume post-treatment) and dosimetric variables (D_{v90}Adv). All tests were two-tailed and a p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Two hundred and seventy subsegments were defined in 18 patients successfully treated with BA followed by intracoronary brachytherapy. Sixty-four subsegments were excluded from the final analysis due to either diffuse calcified plaque which precluded the quantification of the total vessel volume (n=30) or sidebranches which involved >90° of the circumferential arc in more than 50% of the cross-sections (n=34). Therefore, 206 irradiated subsegments were the subject of the study. Fifty-five subsegments (27%) were defined as soft, 129 (62%) as hard and 22 (11%) as normal/intimal thickening. Dissection was observed in 34 subsegments (16.5%).

Volumetric changes and dosimetry

On average, total vessel volume increased at follow-up (32.5±9mm^3 post-treatment to 35.5±11mm^3 at follow-up; p<0.0001), accommodating a parallel increase in plaque volume (15.3±6mm^3 to 18.3±7mm^3; p<0.0001). As a result, mean luminal volume remained unchanged (17.1±7mm^3 to 17.0±7mm^3; p=NS). Subsegments with hard tissue demonstrated a less increase in plaque resulting in an increase in luminal volume as compared to soft and normal/intimal thickening subsegments (figure 3). The behavior of those hard subsegments containing mixed-calcified tissue (up to 90°; n=104) was compared to those containing mixed-non-calcified tissue (n=25). Mean changes in plaque and total vessel volumes were comparable (delta plaque (mm^3): +1.3±4.2 in mixed-calcified versus +1.8±5.2 in mixed non-calcified; p=NS; delta total vessel volume (mm^3): +2.6±6.2 in mixed-calcified versus +4.2±5.8 in mixed non-calcified; p=NS), resulting in a comparable mean increase in luminal volume at follow-up (+1.3±5.2 mm^3 in mixed-calcified versus +1.9±5.7 mm^3 in mixed non-calcified; p=NS). Dissected subsegments demonstrated a trend towards a smaller increase in plaque as compared to non dissected subsegments (+1.2±3 mm^3 vs. +3.3±6 mm^3; p=0.08). Mean of all 3 prescribed doses at 2 mm from the source was 14±1.8 Gy. The calculated D_{v90}Adv was 5.5±2.5 Gy (range: 0.2-12.4). A wide range of dose distribution was observed in the irradiated coronary subsegments (figure 4). The association between D_{v90}Adv with the plaque volume at follow-up is depicted in figure 5. The model appeared to follow a polynomial equation with linear and non-linear components. Non-linear components described the increase in plaque volume at lower dose, whereas the residual plaque volume post-treatment accounted for the linear relationship of the curve. Changes in plaque volume appeared to decrease with dose (figure 6). Four Gy was the minimum effective dose to be delivered to 90% of the adventitia since subsegments receiving at least this dose, demonstrated a significantly smaller increase in plaque volume as compared to those receiving <4Gy (p<0.001). As a result, luminal volume decreased significantly less in those subsegments receiving at least 4 Gy and even increased when the minimal dose to the adventitia was higher than 6 Gy. Multivariable regression analyses identified plaque volume post-treatment as a positive predictor of plaque volume at follow-up, whereas Dv90Adv and type of plaque (hard) were negative predictors (table).

DISCUSSION

This study demonstrates for the first time, the relationship between plaque increase, as assessed by IVUS, and the dose received by the adventitia, as calculated by means of dose-volume histograms. A plot of dose-volume histogram is a standard method used in radiotherapy which condenses the large body of information available from conventional three-dimensional

distribution data into a plot summarizing graphically the radiation distribution throughout the target volume.[8]

The assumption of the adventitia as the target tissue is supported by experimental studies.[21,22] Scott et al, localized the proliferating cells in the adventitia and their migration into the neointima after angioplasty, using bromodeoxyuridine immunohistochemistry.[21] Similarly, Waksman et al, demonstrated a greater cell proliferation in control vessels 3 days after angioplasty in the adventitia at the site of the medial tear as compared to the medial wall in the same region.[22] In this study, the proliferation was significantly reduced in irradiated vessels using either a source of $^{90}Sr/^{90}Y$ or ^{192}Ir which delivered 14 or 28 Gy at 2mm into the artery wall.[22]

The actual dose received by the adventitia appeared to be rather low as compared to the prescribed dose at 2mm from the source. Furthermore, the dose varied considerably between coronary subsegments as demonstrated by the dose distribution depicted in the figure 4. The use of beta-radiation may account in part for this dose inhomogeneity. As compared to gamma radiation, beta-sources have more fall-off because of the short range of electrons.[7] This feature may become crucial when treating vessels with a great degree of vessel tapering or, alternatively, lesions showing positive remodeling where the distance from the source to the surrounding adventitia may be smaller or greater than expected. In this regard, the use of IVUS as a tool for dosimetry in beta-radiation therapy may become mandatory. In contrast, gamma-sources may present with more homogeneous dose distribution. Therefore, in the SCRIPPS trial, a retrospective analysis of dosimetry, demonstrated a mean minimal dose of 7.7±0.7 Gy at the target site and only 10.9% of the targets receiving <7Gy.[23] Dose uniformity may also be influenced by the source centering in the lumen.[24] By the use of dose-volume histograms, Carlier et al, demonstrated in 10 patients treated with balloon angioplasty followed by intracoronary beta-radiation, that the prescribed dose was administered in only 35% of the adventitia. After centering the source in the lumen, up to 60% of the adventitia may have received this dose.[9]

The remnant plaque burden at the site of angioplasty becomes a powerful predictor of the outcome. This is in accordance with other studies which identified, either in non-stented or stented coronary segments, postintervention cross-sectional area as a predictor of restenosis.[25,26] In this regard, the usefulness of a debulking technique prior to radiation therapy should be addressed in further studies.

D_{v90}Adv was also identified as an independent predictor of the plaque volume at follow-up. The relationship between D_{v90}Adv and plaque volume at follow-up appeared to be polynomial with linear and non-linear components. This may model the survival curve of mammalian cells.[27] The minimal effective dose to be delivered to 90% of the adventitia volume appeared to be 4Gy. Further increase in dose resulted in net increase in luminal volume at follow-up. Similarly, in a subgroup analysis of the SCRIPPS trial late loss was significantly lower when the entire circumference of the adventitial border was exposed to at least 8Gy.[28] Radiation doses greater than 20Gy have been suggested to be able to completely eliminate the smooth muscle cell population from the treated area.[29] However, since cells from normal tissue have a limited capacity to proliferate[30], lower doses would probably be sufficient to permanently prevent restenosis.

Finally, subsegments containing hard tissue (fibrotic and calcified material up to 90 degrees of the circumferential arc) demonstrated a trend to be a negative predictor of plaque volume at follow-up. Hard plaque on IVUS, consists of a more mature tissue with low cellularity and high content of extracellular matrix.[31,32] These features may induce either a physical barrier for migration of smooth muscle cells from the surrounding layers or a reduced capacity to proliferate when injured as compared to that of the soft tissue with a high concentration of smooth muscle cells.[31-33] Further, it is hypothesized that tissue composition may potentially exert a different degree of shielding effect on radiation and thus, become less effective. However, the degree of remodeling was similar between the different types of tissue, suggesting that the effects of attenuation of radiation induced by hard material (either containig calcium up to 90° of circumferential arc or mixed non-calcified tissue) may be negligible as compared to that of soft tissue.

Study Limitations

We assumed that the IVUS and the delivery catheters were lying in the same position in the treated coronary segment. The size of the IVUS catheter is smaller (2.9 Fr ~ 1 mm) than the brachytherapy device (5 French), which is thus to some extent more centered in the lumen. Although the catheters should be on the shortest three-dimensional path in the lumen, coronary arteries have a complex curved geometry in space and can be partially deformed by the catheters. Thus, catheters with different rigidity may occupy different positions. The development of new systems incorporating the IVUS imaging element on the delivery catheter might resolve this drawback.

During irradiation, the position of the delivery catheter inside the lumen is not fixed and vary along the cardiac cycle because of ventricular contractions, which may lead to some degree of inhomogeneity not assumed by data derived from the static end-diastolic IVUS images.

The behavior of diffuse calcified plaques after radiotherapy has not been evaluated because the acoustic shadowing would have impeded the reliable analysis of total vessel and plaque volumes.[20] It has not been possible to differentiate those areas which have been traumatized and irradiated from those only irradiated. Thus, no conclusions regarding the effect on radiation in irradiated but non-injured segments can be drawn. Further studies will address this problem by defining meticulously the injured and the irradiated areas either on IVUS or quantitative coronary angiography.

Finally, the dose as presented by the use of dose-volume histograms is not a direct measurement. The theoretical value obtained at the level of the adventitia is derived from the fall-off of the isotope and the geometrical data obtained from the IVUS study. The influence of the attenuation of the radiation due to different tissue characteristics has not been taken into consideration. Future investigations should address the implementation of dosimetry program on-line in order to prescribe the radiation dose in a more refined fashion.

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Table. Parameters associated with plaque volume at follow-up (mm^3).

	Parameter estimate	95% CI	p value
Plaque volume post-treatment (mm^3)	0.6	0.8 / 0.5	0.0001
D_{v90}Adv (Gy)	-4.4	-5.6 / -2.9	0.0001
Type of plaque (hard vs. other)	-1.6	-3.4 / 0.1	0.06

95%CI indicates 95% confidence intervals

Figure 1. Longitudinal reconstruction and volumetric calculations (charts) of irradiated coronary segments post-treatment (A and A') and at 6-month follow-up (B and B').

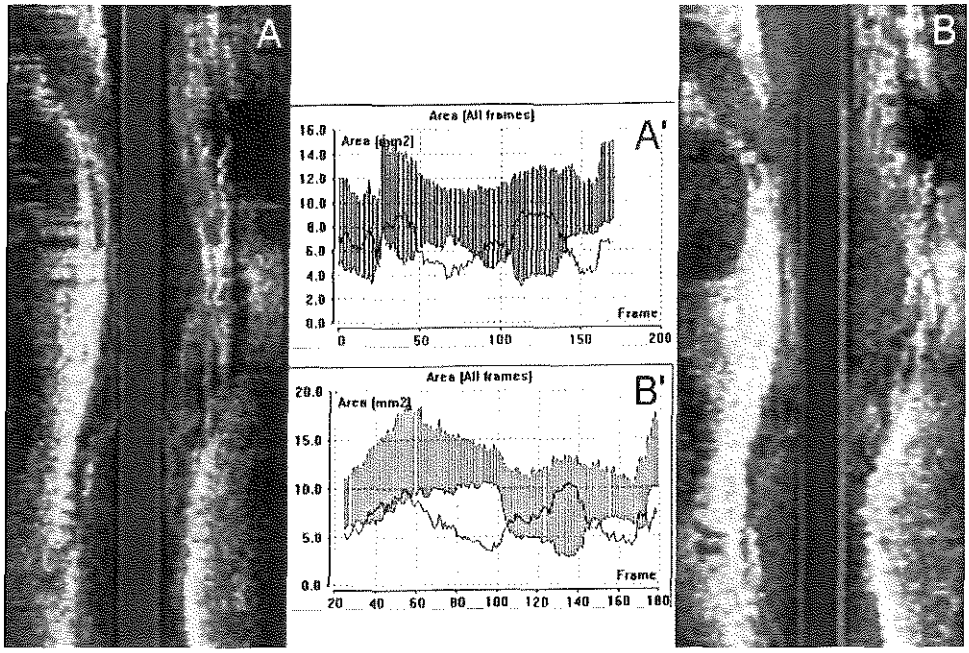


Figure 2. Dose volume histogram showing the cumulative dose received at the level of the adventitia layer. The minimal dose received by 90% of the adventitia volume (D_{v90}Adv) is calculated.

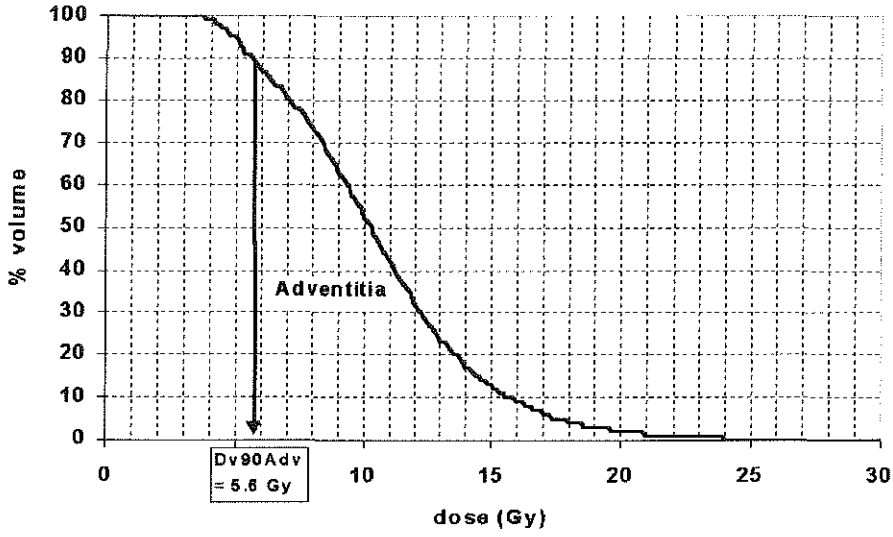


Figure 3. Changes between the post-procedure and 6-month measurements in total vessel, plaque and luminal volumes regarding different types of tissue. TVV= total vessel volume; PV= plaque volume; LV= luminal volume.

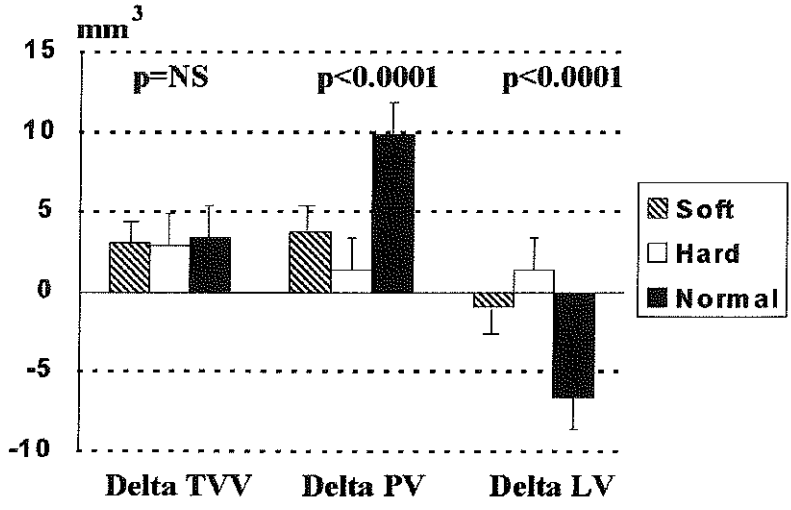


Figure 4. Range of dose distribution in irradiated coronary subsegments as calculated by dose-volume histograms.

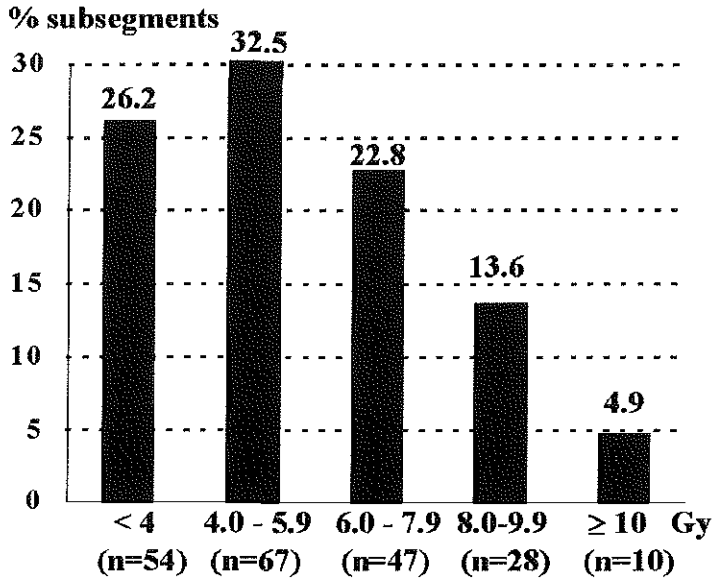


Figure 5. Relationship between plaque volume at follow-up and D_{v90} Adv.

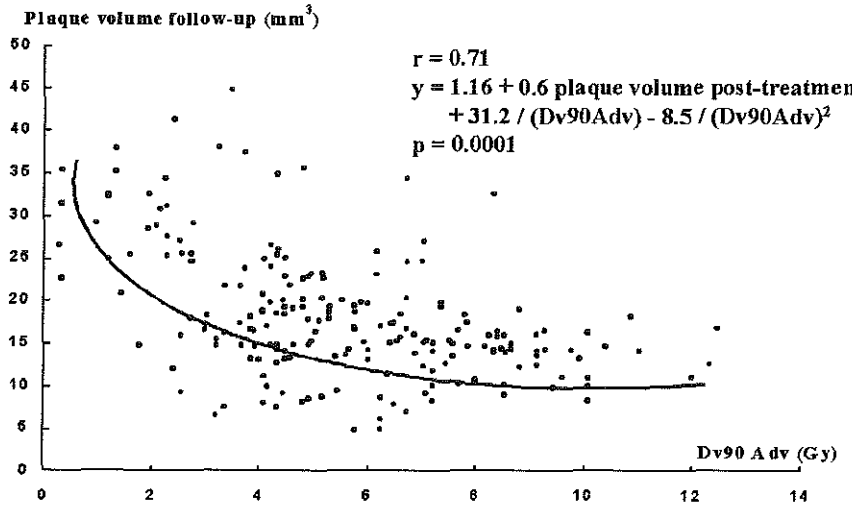
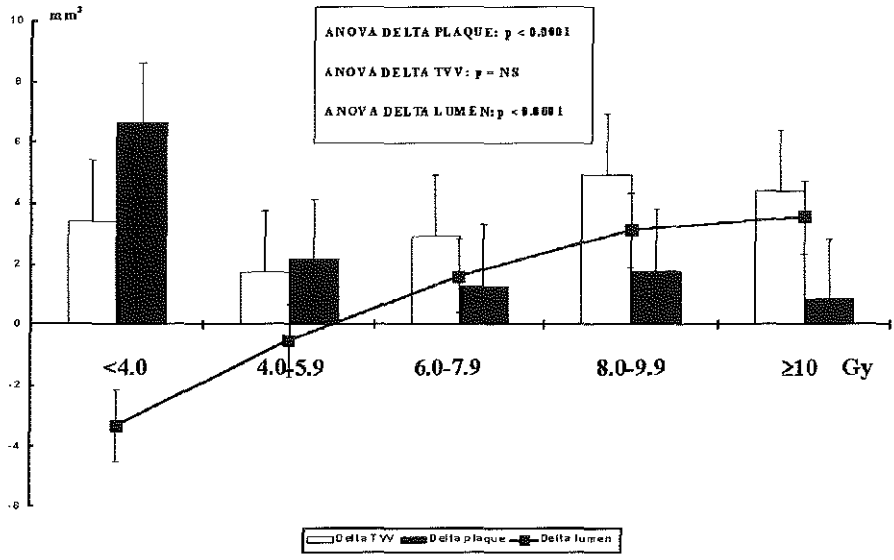


Figure 6. Changes in total vessel, plaque and luminal volumes regarding 5 ranges of doses as calculated by dose-volume



Chapter 6

Comparison of brachytherapy strategies based on dose-volume histograms derived from quantitative intravascular ultrasound.

(Cardiovascular Radiation Medicine 1999;2:115-124)

CLINICAL ORIGINAL ARTICLE

COMPARISON OF BRACHYTHERAPY STRATEGIES BASED ON DOSE-VOLUME HISTOGRAMS DERIVED FROM QUANTITATIVE INTRAVASCULAR ULTRASOUND

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Purpose. We present in this paper the comparison, by simulation, of different treatment strategies based either on β- or γ-sources, both with and without a centering device. Ionizing radiation to prevent restenosis is an emerging modality in interventional cardiology. Numerous clinical studies are presently being performed or planned, but there is variability in dose prescription, and both γ- and β-emitters are used, leading to a wide range of possible dose distributions over the arterial vessel wall. This paper discusses the potential merits of dose-volume histograms (DVH) based on three-dimensional (3-D) reconstruction of electrocardiogram (ECG)-gated intravascular ultrasound (IVUS) to compare brachytherapy treatment strategies.

Materials and Methods. DVH describe the cumulative distribution of dose over three specific volumes: (1) at the level of the luminal surface, a volume was defined with a thickness of 0.1 mm from the automatically detected contour of the highly echogenic blood-vessel interface; (2) at the level of the IVUS echogenic media-adventitia interface (external elastic lamina [EEL]), an adventitial volume was computed considering a 0.5-mm thickness from EEL; and (3) the volume encompassed between the luminal surface and the EEL (plaque + media). The IVUS data used were recorded in 23 of 31 patients during the Beta Energy Restenosis Trial (BERT) conducted in our institution.

Results. On average, the minimal dose in 90% of the adventitial volume was 37 ± 16% of the prescribed dose; the minimal dose in 90% of the plaque + media volume was 58 ± 24% and of the luminal surface volume was 67 ± 31%. The minimal dose in the 10% most exposed luminal surface volume was 296 ± 42%. Simulations of the use of a γ-emitter and/or a radioactive source train centered in the lumen are reported, with a comparison of the homogeneity of the dose distribution.

Conclusions. It is possible to derive DVH from IVUS, to evaluate the dose delivered to different parts of the coronary wall. This process should improve our understanding of the mechanisms of action of brachytherapy. © 1999 Elsevier Science Inc.

Keywords: Brachytherapy; Restenosis; Vascular; Intravascular ultrasound (IVUS); Dosimetry.

Introduction

Coronary artery diseases remain the major cause of death and disabilities in industrialized countries. The

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only revascularization procedure available up to 1977 was bypass surgery. Percutaneous transluminal coronary angioplasty (PTCA) introduced by Andreas Grüntzig [1] profoundly modified our therapeutic arsenal with a minimally invasive alternative. Presently, interventional cardiology consists of several techniques to cut, drill, scrape, burn, and otherwise remove atherosclerotic plaque [2]. With more than one million interventions undertaken per year worldwide, angioplasty is now a cornerstone therapy for coronary artery diseases. However, despite a high acute procedural success rate, the long-term benefit is hindered by the phenomenon of restenosis. Mechanisms involved in the restenosis process are the elastic recoil of the artery, local thrombus formation, vascular remodeling with shrinkage of the vessel, and exuberant healing process with neointimal cellular proliferation and matrix synthesis [3–5]. Stent implantation minimizes elastic recoil and remodeling of vessels, and carefully controlled and randomized clinical trials have demonstrated a significant decrease in the rate of restenosis [6–8]. However, stents increase the proliferative response of tissue to the intervention and, depending on the type of lesions treated, a significant restenosis rate of 15–50% remains the key limitation of transcatheter procedures. Restenosis is the subject of numerous investigations to further improve applicability and cost-effectiveness of angioplasty and to reduce the need of reinterventions. Virtually all attempts to limit restenosis with systemic drugs have failed, with the recent exceptions of abciximab, probucol, and cilostazol [9–11].

Some investigators have considered restenosis as an accentuation of the wound healing process associated with the trauma of angioplasty, and because radiotherapy had proved effective for the treatment of keloid formation and other nonmalignant diseases, radiation therapy for intravascular application was attempted. The therapy was introduced by Friedman *et al.* [12] early in 1964, for the prevention of atherosclerosis, and subsequent animal experiments demonstrated a reduction of intimal hyperplasia following endovascular irradiation. Waksman [13] has recently reviewed these early studies. Three clinical studies have been reported that confirmed a significant reduction in the restenosis rate using additional brachytherapy [14–16].

Currently, the vascular brachytherapy devices available for clinical trials are radioactive stents and catheter-based systems using a radioactive wire advanced with an afterloader, or radioactive seeds delivered with a hydraulic delivery system. Other systems based on radioactive balloons are in development. There is variability in the dose prescription, and both γ- and β-emitters are used. These variations lead to a wide range of dose distributions over the arterial vessel wall requiring a careful interpretation and comparison of the results of the ongoing studies. The typical dose prescription distance in the coronary arteries is in the range of 2 mm from the source axis. Because of the steep dose fall-off, particularly for β-emitters, accurate dosimetry requires precise knowledge of geometry.

In this paper, we describe a dosimetry evaluation tool for coronary brachytherapy based on three-dimensional (3-D) reconstruction of electrocardiogram (ECG)-gated intravascular ultrasound (IVUS) images. IVUS was developed to overcome the limitations of x-ray angiography. Its methodology and clinical applications have been reviewed extensively [17]. IVUS, by its tomographic approach, provides a mean for the evaluation of both lumen and vessel wall morphology. Assuming that the catheter containing the radioactive source is lying in the same position as the IVUS catheter, it is possible to measure the distance from the source to any vascular structure in one cross-sectional image, and to construct isodose plots. IVUS recordings can be performed with a constant speed motorized pull-back device (*e.g.*, 0.5 mm/s), which permits the evaluation of the length of a stenosis. Recently, 3-D image reconstruction and analysis systems have been introduced that can be used for complete quantitative analysis of IVUS images [18–21]. However, image artifacts that result from cyclic changes in coronary dimensions and from the movement of the IVUS catheter in the arterial lumen limit the accuracy of the 3-D boundary detection systems [22]. This problem led to the development of a new approach in our institution. To limit cyclic movement artifacts, we use an ECG-gated image acquisition workstation that controls a dedicated pull-back device. Feasibility, reproducibility, and improvement in the quantitative parameters analyzed have been reported recently [23, 24]. The complete 3-D data set of the coordinates of the automatically detected lumen corresponding to the highly echogenic blood–vessel interface, and of the echogenic media–adventitia interface can be used for dosimetry evaluation.

Dose-volume histograms (DVH) are used everyday in radiotherapy to condense the large body of information of the complete 3-D dose distribution data into a plot graphically summarizing the radiation distribution throughout the target volume and the anatomical structures of interest [25, 26]. We have recently reported preliminary data on the methodology to compute DVH for coronary brachytherapy from 3-D IVUS data [27].

Material and Methods

Study population

We used the IVUS data acquired during the Beta Energy Restenosis Trial conducted in our institu-

tion (BERT 1.5 arm). Thirty-one patients were enrolled. We report the data of the 23 patients who had an ECG-triggered pull-back available before a stent implantation (18 men, 5 women, mean age: 58 ± 9 years). All were in sinus rhythm. The Medical Ethics Committee of our institution approved the study and all patients signed a written informed consent form. Before catheterization, the patients received 250 mg aspirin and 10,000 IU heparine parenterally. If the duration of the intervention exceeded 1 h, the activated clotting time was measured and intravenous heparin was used to maintain an activated clotting time >300 s. The coronary segments examined were the right (n = 7) and left (n = 10) anterior descending coronary arteries, and the left circumflex coronary artery (n = 6).

Interventional procedure and BERT 1.5 trial

The BERT 1.5 trial was the European arm of a feasibility study of coronary radiation therapy with a ^{90}Sr/Y source delivered by a hydraulic system (Beta-Cath™ System, Novoste Corp., Norcross, GA) [16]. All patients had a single *de novo* coronary stenotic lesion >60% with a maximal length of 15 mm and a reference vessel diameter of 2.5–3.5 mm. After successful PTCA, irradiation using a 5 Fr (~1.6 mm) over-the-wire triple-lumen delivery catheter was performed. The catheter has one open lumen and two closed lumens. The open lumen allows for advancement of the device over a 0.014-inch guide wire, and positioning at the site of the PTCA (Fig. 1). One of the closed lumens permits the hydraulic advancement of the radiation source train (12 independent cylindrical sealed ^{90}Sr/Y sources, total length 30 mm) to the lesion site. This advancement is performed manually, with a saline-filled syringe connected to the delivery system. The other closed lumen, in communication with the first one at the tip of the delivery catheter, permits the opposite fluid flow direction at the end of the irradiation time (~3 min) for the retrieval of the sources into the back in the shielded transfer device. A randomized dose of either 12, 14, or 16 Gy was prescribed at a distance of 2 mm from the source axis.

IVUS image acquisition

IVUS was performed prior to the insertion of the radiation delivery catheter. Intracoronary nitrates were administered before the coronary segments were examined. The ClearView™ (CardioVascular Imaging System [CVIS], Sunnyvale, CA) was used with IVUS catheter incorporating a 30-MHz single-element rotating transducer in a 2.9 Fr sheath (~1 mm). The ECG-gated image digitization system (EchoScan, TomTec, Munich, Germany) received the video signal input from the IVUS console, and the ECG signal from the patient. This system steered the ECG-gated stepping pull-back device by increments of 0.2 mm. Images were acquired at end-diastole for heart cycles falling within a predetermined range (0.125 s) around the heart rate of the patient. Premature beats and RR-intervals outside this range were excluded and the IVUS catheter remained at the same site. By experience, we have noticed that with these settings, on average 10–15% of the RR intervals are rejected, and that for a heart rate of 60 beats/min, on average, the pull-back speed is 1 cm/min.

Image analysis system

A contour detection program developed in our laboratory [28] was used for the automated 3-D analysis of the IVUS images corresponding to the irradiated segment. Two longitudinal sections (corresponding to the A and B lines on the IVUS cross-section in Fig. 2) were constructed from the data set. The contours of the lumen–intima (internal contour on Fig. 2, lower left panel) and the media–adventitia (ex-

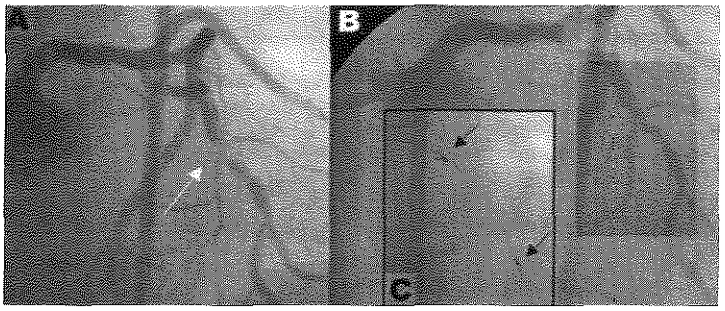

Figure 1. Angiograms of one patient included in the Beta Energy Restenosis Trial (BERT). (A) The initial lesion in the mid-portion of the left anterior descending artery at a bifurcation point with a diagonal and a septal side-branches is indicated by an arrow. (B) The angiogram after successful percutaneous transluminal coronary angioplasty (PTCA). (C) The triple-lumen delivery catheter advanced to the angioplasty site. The sealed radioactive cylinders (total length 30 mm) will be between the two gold markers (small arrows).

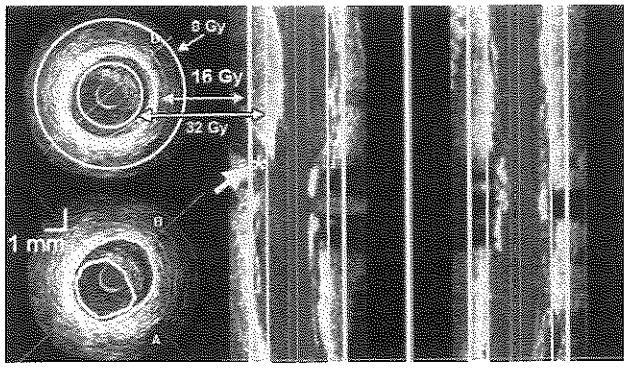

Figure 2. The three-dimensional intravascular ultrasound (IVUS) data set: the bottom left panel demonstrates an IVUS cross-section image, with the catheter in the center, surrounded by blood. The catheter is against the lumen wall at 2 o'clock. The first detected contour that corresponds to the blood–vessel wall interface is highlighted. The second highlighted contour, more externally, corresponds to the media-adventitia interface, which encompasses the residual plaque lying between 11 and 4 o'clock. Lines A and B correspond to the cutting planes of the corresponding longitudinal views on the right panel. The isodoses of 32 and 16 Gy are superimposed on the longitudinal views and on the IVUS cross-section of the upper left panel.

ternal contour on Fig. 2) boundaries were identified using a minimum-cost-based analysis algorithm. These longitudinal contours were used to guide automated contour detection in every planar cross-sectional image. Scrolling through the entire data set is possible in this Windows™-based program, for manual corrections of the contours. From these tracings, the total vessel area (encompassing the media–adventitia border) and the lumen area were determined for each cross-section. The residual plaque burden (%) on each cross-section was calculated as total vessel area minus lumen area divided by the total vessel area.

DVH

Selection of the IVUS segment matching the irradiated site was based on anatomical landmarks lying next to the treated segment (side branches, bifurcations, *etc.*). For example, the diagonal artery seen on the angiogram of Fig. 1 is marked with an arrow on the longitudinal IVUS pull-back of Fig. 2 (right panel). The coordinate of the center of the IVUS catheter was used as a reference, and was considered at the same location as the center of the radiation train. This assumption is probably violated when looking at the differences in size of the IVUS and delivery catheters (2.9 vs 5 Fr), but it has to be kept in mind that the source does not occupy the center of the delivery catheter, and that no easy correction might be applied. The radii of the lumen and the media–adventitia contours were calculated in 24 pie-slices (15°), in all the cross-sections corresponding to the irradiated site (30-mm length of the train source). The number of required slices was a function of their thickness, which was on average 0.2 mm.

DVH describe the cumulative distribution of dose over a specific volume, and summarize the dosimetry that would otherwise have to be interpreted from numerous IVUS cross-sections with superimposed isodoses plotted (Fig. 2, upper left panel). Three volumes have been studied: the first one at the level of the luminal surface is arbitrarily defined with a thickness of 0.1 mm from the automatically detected lumen contour. The second volume, defining the adventitia volume, is computed considering a thickness of 0.5 mm from the second contour detected, corresponding to the echogenic media–adventitia interface. The third volume, corresponding to the plaque and media structures, is encompassed between the two detected contours. The dose distribution over the total vessel wall was calculated with 0.1 mm spatial resolution. The DVH provided a tool for reporting the actual delivered dose in different arterial structures, or to detect excessive radiation at the luminal level. From the complete 3-D IVUS data set, simulations of DVH of alternative brachytherapy strategies such as the use of a γ-emitter or a centered radioactive source were tested. To compute the isodoses and the DVH for the Novoste system, we used the dose distribution and dose rate around the source train as provided by the manufacturer in the user manual. Calibration was performed at the National Institute of Standards Technology, using both an extrapolation chamber and GafChromic Dosimetry media. For the γ-source, data were derived from Amols *et al.* [29].

Results

No complications related to the brachytherapy and IVUS procedures were seen. Figure 1 demonstrates a typical procedure on a lesion situated in the mid-portion of the left anterior descending coronary artery, at the level of the emergence of a septal and a diagonal side branch. These anatomical landmarks observed on the angiograms were used for positioning both the IVUS catheter and the irradiation device at the site of the lesion. The angiogram after PTCA is shown in Fig. 1B. The corresponding ECG-triggered IVUS pull-back performed at that time is illustrated in Fig. 2. The position of the side-branch is clearly seen on the mid-portion of the longitudinal view (* and arrow in right panel of Fig. 2). After withdrawal of the IVUS catheter, the brachytherapy delivery catheter was positioned at the PTCA site, using its two radio-opaque gold markers as landmark (Fig. 1C).

Of the 31 patients included in the BERT 1.5, a total of 7 required stent implantation. In 3 of these patients, the IVUS was performed before stenting. Absence of an ECG-triggered pull-back or technical problems limited the total number of analyzable patients without a stent to 23. Quantitative IVUS data analysis of these 23 patients demonstrated a mean lumen area of 7.7 ± 3.0 mm^2 (~150 cross-sections per patient). The mean vessel area was 14.8 ± 3.9 mm^2 and the residual plaque area was 7.1 ± 1.6 mm^2, corresponding to a residual plaque burden of 49 ± 8%. For each patient, the minimal, mean and maximal distance (~radius *r*) between the center of the IVUS catheter and the lumen or the media–adventitia interface were computed along the complete pull-back. The minimal *r* was 0.51 ± 0.02 mm, the mean *r* was 1.42 ± 0.25 mm, and the maximal *r* was 3.36 ± 0.70 mm. For the vessel (media–adventitia interface) minimal *r* was 0.88 ± 0.17 mm, mean *r* was 2.07 ± 0.25 mm, and maximal *r* was 3.80 ± 0.63 mm. Computer simulation of the placement of the IVUS catheter in the center of the lumen in each cross-section of the pull-back demonstrated a significant increase of minimal *r* ($p < 0.0001$): 0.67 ± 0.17 mm and 1.23 ± 0.25 mm, respectively, for the lumen and the vessel. In parallel, there was a significant decrease of maximal *r* ($p < 0.0001$): 2.46 ± 0.42 mm and 3.41 ± 0.41 mm, respectively, for the lumen and the vessel.

On the longitudinal view (right panel) of the IVUS pull-back in Fig. 2, and on one cross-section (upper left panel), the isodoses corresponding to 8, 16, and 32 Gy are superimposed. The derived DVH for this patient for the luminal surface and adventitial volumes are plotted on Fig. 3. The minimal dose in 90% (DV90*adv*) of the predefined adventitial volume was 47% (this corresponds to the *x*-axis value of the DVH plot with the *y*-axis value = 90%). Among the 23 patients, the average DV90*adv* was 37 ± 16% of the prescribed dose and the minimal dose in 90% (DV90*lum*) of the luminal surface volume was 67 ± 31% of the prescribed dose, and was 58 ± 24% in 90% of the plaque + media volume. The average minimal dose in the upper 10% (DV10*adv*) of the adventitial volume exposed to the highest dose (the *x*-axis value of the *y*-axis value 10%) was 133 ± 19% of the prescribed dose. For the luminal surface volume, DV10*lum* was 296 ± 42%. Figure 3 summarizes these data with a plot of the mean ± SD of DV95, DV90, DV75, DV50, DV25, DV10, and DV05 for the luminal surface and the

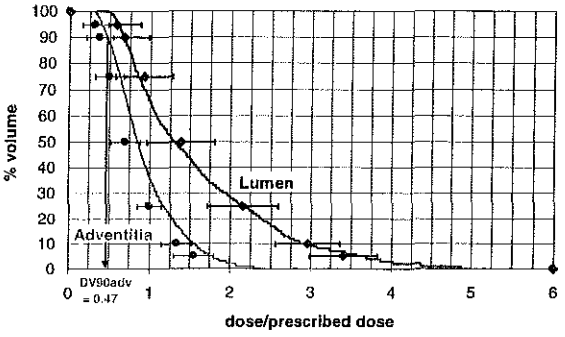

Figure 3. Example of integral dose-volume histograms (DVH) at the level of the luminal surface and adventitial volumes of the patient illustrated in Figures 1 and 2, representing the fraction of volume (*y*-axis, % volume) receiving greater than or equal to a specific relative dose (*x*-axis, dose/dose prescribed). For this patient, the minimal dose in 90% of the adventitial volume (DV90*adv*) was 47% of the prescribed dose. The superimposed plots with the error bars correspond to the average among the 23 investigated patients of the DV95, DV90, DV75, DV50, DV25, DV10, and DV05 of the predefined luminal surface and adventitial volumes.

Table 1. Summary of the computer simulations of the use of a β- or a γ-source (with the same dose prescribed at 2 mm from the center of the catheter) or a centering device

	Noncentered		Centered	
	DV90	DV10	DV90	DV10
β				
Lum.	0.67 ± 0.31*†	2.96 ± 0.42*†	1.06 ± 0.31	2.03 ± 0.49†
P + M.	0.58 ± 0.24*†	2.16 ± 0.32*†	0.73 ± 0.20†	1.66 ± 0.35†
Adv.	0.37 ± 0.16*†	1.33 ± 0.19*†	0.49 ± 0.14†	1.05 ± 0.20
γ				
Lum.	0.79 ± 0.21*	2.34 ± 0.31*	1.05 ± 0.21	1.70 ± 0.32
P + M.	0.72 ± 0.17*	1.78 ± 0.21*	0.83 ± 0.13	1.45 ± 0.23
Adv.	0.58 ± 0.12*	1.24 ± 0.13*	0.67 ± 0.09	1.05 ± 0.13

DV90 = relative minimal dose (dose/dose prescribed) of 90% of the predefined luminal surface (lum. thickness = 0.1 mm), adventitial (adv. thickness = 0.5 mm), and plaque + media (P + M = between luminal and external elastic lamina contours) volumes. Means ± SD for the 23 available electrocardiogram-triggered pull-backs performed during the Beta Energy Restenosis Trial (BERT) 1.5. Means were compared by paired *t*-test.

*$p < 0.0001$, centered vs. noncentered radiation catheter; †$p < 0.0001$, β- vs γ-source.

adventitial volumes. By randomization, the actual doses administered were 12 Gy in 8 patients, 14 Gy in 6 patients, and 16 Gy in 9 patients. Plots of relative dose (dose/dose prescribed) allow the pooling of data from patients who received different randomized doses.

The simulations (assuming that the source was centered in the lumen and/or the use of a γ-source [^{192}Ir]), with the same dose prescribed at 2 mm from the catheter as in the BERT protocol, are summarized in Table 1. A direct comparison of the homogeneity of the absorbed dose or of the high dose absorbed by the upper 10% of the luminal surface and adventitial volumes is possible. Figure 4 illustrates the improvement of the homogeneity of the dose distribution for the case of Figs. 1–3 when simulating a source situated in the center of the lumen. Figure 5 illustrates similar improvement of the homogeneity when considering a γ-source. Optimally, DVH should demonstrate a right step at the dose prescribed (*x*-axis = 1).

Discussion and Conclusion

Restenosis rates of 15–50% after percutaneous angioplasty procedures are the major hindrance to the success of transcatheter therapies. Supported by encouraging results obtained in animal models of coronary restenosis [13], several clinical trials of vascular brachytherapy have been designed, but with different systems and isotopes [30]. The discussion below focuses on the catheter-based device like the one used in this work. Dosimetry for radioactive stents has been described recently by Janicki *et al.* [31].

In the ongoing clinical trials, there is variability in the dose prescribed; the target site for the dose prescription, and both γ- and β-emitters are used.

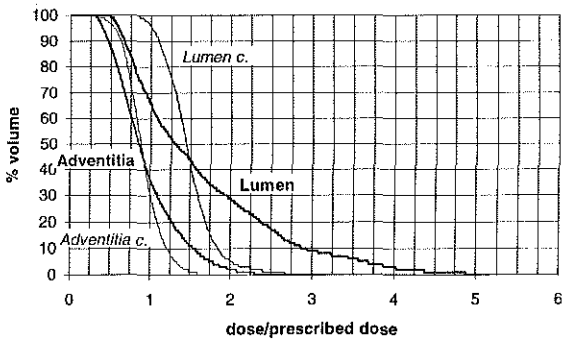

Figure 4. Illustration of the beneficial effect of a centering device on the homogeneity of the dose distribution for the same patient as in Figures 1–3. The dose-volume histograms (DVH) were recalculated simulating the irradiation source (^{90}Sr/Y) lying in the center of the lumen. The DVH curves for the centered position (Lumen c. and Adventitia c.) are steeper, with a DV10 for the lumen decreasing from 2.9 to 1.8.

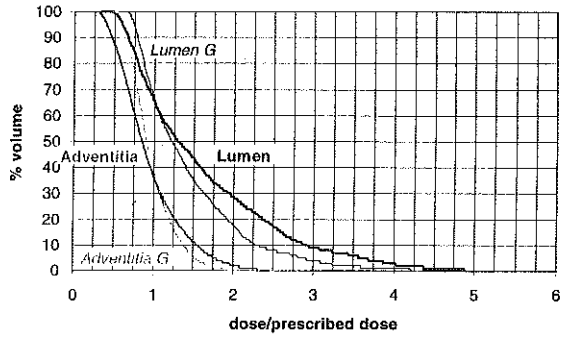

Figure 5. Illustration of the improvement of the dose homogeneity for the same patient as in Figures 1–3, simulating the use of a γ-source for which the same dose would have been prescribed at 2 mm from the center of the catheter (noncentered situation). The DVH curves for the γ-source (Lumen G and Adventitia G) are steeper, with a DV10 for the lumen decreasing from 2.9 to 2.3.

The consequence is a wide range of possible dose distributions over the arterial vessel wall requiring a careful interpretation and comparison of the results of these studies. The typical dose prescription distance in the coronary arteries is in the range of 2 mm. As the dose fall-off at this close vicinity is steep, particularly for β-emitters, accurate dosimetry requires knowledge of the exact geometry, which can be only partly assessed by coronary angiography.

Among the four published clinical brachytherapy studies today, Condado *et al.* [14] used a manual afterloader, noncentered, in 22 lesions, with a ^{192}Ir γ-source. The doses were prescribed at 1.5 mm (single doses of 18 Gy, n = 1; 20 Gy, n = 11; 25 Gy, n = 9) and only angiographic assessment was used. Although reported as positive, an unexplained early reduction of the minimal lumen diameter of 0.45 mm on average after only 24 h might have blurred the real efficacy of the applied radiotherapy in these patients [32] who presented no additional loss in minimal lumen diameter at the 6 months follow-up. However, doses of up to 92.5 Gy could have been delivered to the lumen wall because of the noncentered device. This maximum dose may well be over the vascular tolerance limits [32]. This finding could partly explain the observation that two patients experienced early total vessel occlusion, and four others developed a pseudoaneurysm at 2 years follow-up. In Geneva, Verin *et al.* [33] developed a mean for β-irradiation in human coronary arteries using a radioactive wire (^{90}Y) in a centering balloon device. The dose prescribed was 18 Gy at the surface of the balloon corresponding to the vessel luminal surface. No IVUS was performed. The findings were disappointing, with a restenosis rate of 40% among the 15 patients studied. A retrospective analysis of the dose prescribed in the vessel wall revealed that at a depth of 2 mm, the dose was only ~2.7 Gy, probably below the nominal effective dose against the proliferating cells involved in the post-angioplasty restenosis process [34]. The only placebo-controlled study of coronary brachytherapy published to date demonstrated a substantial reduction of the restenosis rate (17% vs 54%) among 55 patients presenting with in-stent restenosis [15]. A sealed ^{192}Ir γ-source in a noncentered catheter was used. The dosimetry was calculated, based on IVUS measurements, to be in the range of 8–30 Gy. Finally, King *et al.* [16] recently reported a restenosis rate of 15% and a late loss index of 4% for the American arm of the BERT, using the same hydraulic delivery system as the one we used in this study.

IVUS was developed to overcome the limitations of x-ray angiography, which portrays only overlapping shadows of the lumen of the coronary arteries (luminogram) [35]. In the field of vascular radiation therapy it is important to characterize precisely the dose prescribed in the vessel wall. IVUS imaging, by its angiotomographic nature, can be used to evaluate both lumen and vessel wall morphology. The results of our preliminary investigation, using the complete 3-D information available from carefully recorded ECG-triggered IVUS pull-back, demonstrate the potential applications for dosimetry and the possibilities for the evaluation of doses in specific target volumes of the vessel wall. DVH appear to be a valuable tool and summarize, in a graphic form, the large amount of information included in the dose distribution of the complete 3-D IVUS data sets. DVH cannot be used alone because of the lack

of information regarding the spatiality of the dose distribution [25]. For the spatiality, two-dimensional isodose displays, such as in Fig. 2, superimposed on IVUS images will still be required for the guidance of a vascular irradiation plan. In our study, there was no direct guidance of the brachytherapy with IVUS because of the nature of this trial, which was a feasibility study in which the prescribed dose was predetermined. However, the data set constitutes a preliminary database for the assessment of several radiation strategies, as illustrated in Table 1. The homogeneity of the dose distribution might be estimated by the difference between the DV10 and the DV90. Ideally, a DVH should demonstrate a steep curve around the desired prescribed dose. Flattening reflects that some regions are underexposed, whereas others are overexposed. Potential advantages of a centering device for a β-source, as illustrated in Table 1 and Figs. 4 and 5, are that the DV90 increases for the luminal (1.06 ± 0.31 vs 0.67 ± 0.31, $p < 0.0001$ by paired *t*- test), the adventitial (0.49 ± 0.14 vs 0.37 ± 0.16, $p < 0.0001$) and the plaque + media (0.73 ± 0.20 vs 0.58 ± 0.24, $p < 0.0001$) volumes. In parallel, DV10 decreases for the luminal (2.03 ± 0.49 vs 2.96 ± 0.42, $p < 0.0001$), the adventitial (1.05 ± 0.20 vs 1.33 ± 0.19, $p < 0.0001$) and the plaque + media (1.66 ± 0.35 vs 2.16 ± 0.32, $p < 0.0001$) volumes. As a consequence, the homogeneity, which can be expressed as DV10 − DV90, is improved for the lumen (0.97 vs 2.29), the adventitia (0.56 vs 0.96), and the plaque + media (0.93 vs 1.58, respectively, for a centered and a noncentered delivery system). However, only one number, such as DV10 − DV90, cannot summarize a complete DVH curve. The complete shape of the curve, as presented in the figures, is important. Several other parameters have been proposed [36, 37], but no definitive one has emerged as a gold-standard to assess the dose homogeneity. Looking at the slope of the DVH, for example, is a proposed alternative, but the slope will vary with the interval chosen to compute it. The DVH presented in this study are cumulative plots: this integral format shows the fraction of volume receiving greater than or equal to a specific dose. Another format is the differential DVH constructed by dividing the range of dose values into equal intervals and accumulating partial volumes in those bins according to their dose values. Plots of dose–volume distributions have also been proposed [38]. Our definition of the thickness of the luminal and adventitial volumes is arbitrary. The intima is formed only by a superficial layer of endothelial cells and a thin subendothelial layer of connective tissue. Its thickness increases with age and reaches 250 μm at 40 years. Diffuse thickening is common in older patients, even without atherosclerosis. The adventitia is composed of loose collagen and elastic tissue, which merge with the periadventitial tissue. The normal thickness of the adventitia is 300–500 μm [17]. However, we evaluated these DVH for another thickness (0.2 mm) and the results are in close agreement with the data presented in Table 1 (J.P.A. Marijnissen *et al.*, personal communication). The differences found with the simulations of the use of a γ-emitter or a radioactive source train centered in the lumen are also present for the plaque + media volume for which no arbitrary choice has been made.

On average, in the conditions of our study, whereas only 10% of the advential volume were exposed to a minimal dose 1.33 times the prescribed dose, 10% of the luminal surface volume absorbed at least 2.96 times the prescribed dose. For a prescribed dose of 16 Gy, this corresponds to an actual dose of 47.2 Gy, which may well be above the recognized vascular tolerance limit. The simulations in Table 1 demonstrate that the use of a device to maintain the source in the center of the arterial lumen would decrease this overexposure, which has potential deleterious effect such as the development of an aneurysm. With centering, the upper 10% of the luminal surface volume is exposed to a reduced minimal relative dose of 2. Following our results, the best strategy could be the use of a centered γ-source: the minimal relative dose would then be reduced to 1.7 for the upper 10% of the luminal surface volume. No clinical data presently support these potential advantages, and to our knowledge, no trial is planned to address this issue. Nevertheless, γ-sources have other drawbacks, at the radioprotection level, for example, because these more penetrating radiations require stringent shielding precautions [39]. These radiation safety issues may be improved if lower energy gamma sources can be manufactured.

There is an interindividual variability related to the geometry of the lesion and the morphology of different coronary arteries, as demonstrated by the rather large standard deviations in Table 1. The choice of the brachytherapy modality (centering device or not, β- vs γ-) cannot be only guided from DVH, but must integrate all the information available from the angiogram and the 3-D IVUS pullback (such as morphology of the lesion, length, eccentricity of the plaque). Potentially, catheters combining IVUS and asymmetric sources might be helpful in the guidance of a radiation treatment for eccentric lesions. Such a device with a C-shape shielding screen around a radioactive wire has been described recently [40].

Another limitation of our approach is that we reconstructed an artificially straight coronary segment. However, this limitation might be overcome

by image fusion of biplane angiography and IVUS, as developed in our center, to assess the true 3-D geometry of coronary vessels [41]. Presently, we also do not implement different dose fall-off characteristics in function of the type of plaque seen (fibro-fatty, calcified, *etc.*). Although there are probably differences, no data are available.

One major assumption made in this work was to consider that the IVUS and delivery catheters were lying in the same position in the treated coronary segment. It is important to realize first that because the size of the IVUS catheter is smaller (2.9 Fr ~ = 1 mm in diameter) than the brachytherapy device we used (5 Fr ~ = 1.6 mm), it lies in a more eccentric position in the coronary lumen. However, no easy correction can be applied because the channel source in the delivery device is not in the center of the catheter. The real average DV10*lum* in our patients is thus in the range 2.03–2.96 given in Table 1. Moreover, even with the use of radiotherapy and IVUS catheters of the same size, it is not certain that when advanced sequentially in the arterial lumen, they will occupy the same position. Although they should be on the shortest 3-D path in the lumen, coronary arteries have a complex curved geometry in space, and are partially deformed by the catheter lying in their lumen. Thus, catheters with differing rigidity will occupy different positions. Finally, it is important to understand that the position of a catheter inside the arterial lumen is not fixed and varies along the cardiac cycle because of ventricular contractions. These methodological limitations could be partially overcome with existing imaging wires, which could be introduced in the lumen of the irradiation delivery catheter itself. Presently, another limitation we face in our catheterization laboratory is that DVH are not obtained on-line. Further implementations with faster processing of the 3-D IVUS data set for optimal automatic contour detection are under study.

In conclusion, we think that the body of additional information available from IVUS and derived dosimetry parameters such as DVH should improve our understanding of the mechanisms of action of brachytherapy and be helpful for the comparison of trials based on different dosimetry strategies. In our center, we systematically assess the lesions treated by vascular radiation therapy by IVUS.

Acknowledgments

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Part III

Methodology Considerations

Methodological implications of the relocation of the minimal luminal diameter after intracoronary radiation therapy.

(J Am Coll Cardiol (in press))

METHODOLOGICAL AND CLINICAL IMPLICATIONS OF THE RELOCATION OF THE MINIMAL LUMINAL DIAMETER AFTER INTRACORONARY RADIATION THERAPY

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(J Am Coll Cardiol (in press))

ABSTRACT

Objectives: The aims of the study were to determine the incidence of relocation of the minimal luminal diameter (MLD) after ß-radiation therapy following balloon angioplasty (BA) and to describe a new methodological approach to define the effect of brachytherapy on treated coronary arteries.

Background: Luminal diameter of irradiated coronary lesions, may increase over time following dilatation and irradiatation. As a result, the MLD at follow-up may be relocated from its location pre-intervention, which may induce misleading results when a restricted definition of the target segment by quantitative coronary angiography (QCA) is performed.

Methods: Patients treated with BA followed by intracoronary brachytherapy according to the Dose-Finding Study constituted the study population. A historical cohort of patients treated with BA was used as control group. To be included in the analysis, an accurate angiographic documentation of all instrumentations during the procedure was mandatory. In the irradiated patients, 4 regions were defined by QCA: vessel segment (VS), target segment (TS), injured segment (INS) and irradiated segment (IRS).

Results: Sixty-five patients from the Dose-Finding Study and 179 control patients were included. At follow-up, MLD was relocated more often in the radiation group than in the control group (78.5% versus 26.3%; $p<0.0001$). The rate of > 50% diameter stenosis differed between the 4 pre-defined regions: 3.1% in the TS; 7.7% in the INS; 9.2% in the IRS and 13.8% in the VS.

Conclusions: Relocation of the MLD is commonly demonstrated after BA and brachytherapy and it should be taken into account during the analysis and report of the results of radiation clinical trials.

Key words: intracoronary brachytherapy, quantitative coronary angiography, minimal luminal diameter, balloon angioplasty.

During the past 10 years the efficacy of percutaneous interventions in preventing restenosis after percutaneous interventions has been assessed by the use of quantitative coronary angiography (QCA).[1-4] This technique of analysis has become the gold standard for the assessment of coronary angiograms in the context of scientific research due to its superior accuracy and objectivity as compared to visual and hand-held caliper measurements, as well as possessing a better inter- and intraobserver variability.[5,6] Consequently, the percent diameter stenosis has become the usual output of this analysis and the value of 50% has gained widespread acceptance to define the presence of restenosis in the treated coronary segment.[7] Intravascular ultrasound (IVUS) studies demonstrated that restenosis after balloon angioplasty (BA) is mainly due to neointimal hyperplasia and vessel shrinkage at the site of the injury.[8-10]

Pioneers in intracoronary radiation therapy have demonstrated that in a majority of patients the luminal diameter at the site of the treated lesion may increase during the follow-up, rather than decrease.[11] Three-dimensional IVUS analysis has shown that this phenomenon is induced by positive remodeling of the vessel wall at the site of the irradiated segment.[12] As a result, the minimal luminal diameter (MLD) of coronary segments treated with brachytherapy following percutaneous interventions may be relocated at follow-up from its location pre-intervention. A restricted definition of the target segment by QCA could induce misleading results and make any comparison to previous non-radiation studies unfair. This study was aimed to (1) determine the incidence of the relocation of the MLD after ß-radiation therapy following successful BA and, (2) describe a new methodological approach to accurately analyze and report the effect of brachytherapy on the treated coronary artery.

METHODS

Patient selection. Patients eligible for the study were those successfully treated with BA followed by intracoronary radiation according to the Boston Scientific/Schneider Dose-Finding Study.[13] The purpose of this trial was to determine the effect of various doses of ß-irradiation on coronary artery restenosis after BA with or without stent implantation, in patients with single de novo lesions of native coronary arteries. The isotope selected was the pure ß-emitting ^{90}Y and patients were randomized to receive doses of 9,12,15, or 18 Gray (Gy) at 1mm tissue depth. The delivery of radiation was carried out by the use of the Schneider-Sauerwein Intravascular Radiation System.[14] In brief, this system comprises (1) a flexible coil made of titanium-coated pure yttrium affixed at the end of a thrust wire between proximal and distal tungsten markers, (2) a centering catheter which is a segmented balloon consisting of 4 interconnected compartments which allows centering of the source lumen relative to the arterial

lumen, and (3) a computerized afterloader which allows automated advancement and positioning of either the dummy or the active source.[14]

QCA analysis and definitions. QCA analysis was performed off-line by an independent corelab (Cardialysis, Rotterdam, the Netherlands). All angiograms were evaluated after intracoronary administration of nitrates. The analysis was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters unfilled with contrast medium. This method of analysis has been previously validated.[4,15-16] The area of interest was selected after reviewing all cinefilms performed during the index procedure. Any angiographic sequence showing the lesion pre-intervention, positions of angioplasty balloon, and radiation source may be displayed simultaneously on the screen using the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands). The ECG tracing is also displayed in any angiographic sequence. By selecting frames in the same part of the cardiac cycle, we were able to define the location of the radiation source and angioplasty balloon relative to the original lesion. The analyst defined a coronary segment bordered by angiographically visible sidebranches which encompassed the original lesion, angioplasty balloon and radiation source. This segment was defined as the *vessel segment (VS)*. (figure 1) The MLD was determined in the VS pre-intervention by edge detection and was averaged from the two orthogonal projections. Reference diameter was automatically calculated for the VS by the interpolated method.[4] The percent diameter stenosis was calculated from the MLD and the reference diameter.[7] At the time of the procedure, all angioplasty balloons, when deflated, were filmed in place with contrast injection in the same projections as were the VS. After successful BA, intracoronary brachytherapy was performed. Both the location of the centering balloon and the active wire in place were filmed in the same projections as performed previously. The proximal sidebranch within the VS was used as an index anatomical landmark. Distances from this proximal sidebranch to: (1) the inner part of the proximal tungsten marker; (2) the proximal marker of the angioplasty balloon; (3) the proximal margin of the obstruction segment; (4) the distal margin of the obstruction segment; (5) the distal marker of the angioplasty balloon; and, (6) the inner part of the distal tungsten marker were computed by the CAAS software. The *target segment (TS)* was encompassed by the proximal and distal margin of the obstructed segment. The segment encompassed by the most proximal and most distal marker of the angioplasty balloon defined the *injured segment (INS)*. The segment encompassed by the inner part of the 2 tungsten markers defined the *irradiated segment (IRS)*. (figure 1) All regions of interest were superimposed on the pre-,

post-procedural and follow-up angiograms. *Geographical miss* was defined for those cases where the entire length of the injured segment was not fully covered by the IRS.[17]

Using the softwear of the CAAS system the analyst is able to perform a subsegmental analysis within the VS. The segment is automatically divided into subsegments of equidistant length (on average, 5.0±0.3 mm). The subsegment containing the MLD was taken as the index segment and enabled relocation of the MLD to be defined (figure 2). *Relocation pre-post* was defined as those cases where the MLD of the VS post-treatment was located in a different subsegment in the 2 orthogonal projections from that of the index procedure. *Relocation post-fup* was defined as those cases where the MLD of the VS at follow-up was located in a different subsegment in the 2 orthogonal projections from that post-procedure. *Relocation pre-fup* was defined as those cases where the MLD of the VS at follow-up was located in a different segment in the 2 orthogonal projections from that at the index procedure (figure 2).

Additionally, the analyst computed the MLD in every region of interest and calculated the acute gain, late loss and the frequency of > 50% diameter stenosis on a regional basis. Acute gain was defined as MLD post-treatment minus MLD pre-intervention. Late loss was defined as MLD post-treatment minus MLD at follow-up. Restenosis was defined as diameter stenosis >50% at follow-up.

Control Group. A historical cohort of consecutive patients treated with BA from the BENESTENT II trial[18] presenting with matched views and correct angiographic documentation, was used as the control group. VS, TS and relocation of the MLD were defined in this cohort as above described.

Statistical analysis. Data are presented as mean ± standard deviation or proportions. To compare qualitative variables, the Chi-square test was carried out. To compare quantitative variables, the Student's test was performed. All tests were two-tailed and a value of $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics. One hundred and eighty one patients were included in the Dose-Finding study. Of these, 51 patients received a stent. The remaining 130 patients treated with BA alone followed by ß-radiation were eligible for the study. By comparing the technician worksheet with the angiograms recorded, the analyst was able to identify those patients in whom all balloon inflations and source positioning were filmed and all target views were matched. Using this systematical approach, 65 patients who did not accomplish these technical requirements to perform an accurate QCA, were excluded from the study. Thus, the study

population comprised the 65 patients presenting with complete and correct angiographic documentation. All patients, regardless of the dose prescirbed (9,12,15, or 18 Gray (Gy) at 1mm tissue depth), were pooled together.

Of 410 patients enrolled in the balloon arm of the BENESTENT II trial, 179 presenting with all the above mentioned technical requirements constituted the control group. Baseline characteristics of both the study population and control group are described in the table 1. No differences were observed between the 2 groups.

Incidence and location of the relocation of the MLD. Relocation pre-post of the MLD was defined in 36 patients (55.4%) in the Dose-Finding cohort and in 62 pts (34.6%) in the control group (p=0.005); relocation post-fup was defined in 37 patients (56.9%) in the Dose-Finding cohort and in 59 patients (33.0%) in the control group (p=0.001); and, relocation pre-fup in 51 patients (78.5%) in the Dose-Finding cohort and in 47 patients (26.3%) in the control group (p<0.0001). Geographical miss was identified in 2 patients (3%). At follow-up, 45 patients (69.2%) presented with an increase in the value of MLD at TS, whereas 20 patients (30.8%) demonstrated either a decrease (18 patients) or no change (2 patients) in the value of MLD at TS. The location of the MLD in cases of relocation is presented in the table 2. This new MLD was most commonly located within the IRS and INS, followed by those regions within the VS but outside the IRS and the INS. Typically, when the new MLD was located outside the INS and IRS, distal subsegments were most often involved rather than the proximal ones (88% vs. 12%, respectively).

Methodological implications of the relocation of the MLD. QCA data derived from the analysis of the pre-defined regions are presented in the table 3.

DISCUSSION

Incidence and causes of relocation of the MLD. This study demonstrates that the relocation of the MLD is a common phenomenon in coronary segments treated with BA followed by intracoronary beta-radiation therapy. Although relocation of the MLD at follow-up was significantly more frequent in the irradiated group, control patients demonstrated also a notable incidence of relocation. This phenomenon noted after radiation was witnessed in previous studies that showed that the restenosis process affected the entire vessel segment which was dilated and not just the obstructed segment.[19,20] This may explain the mismatch between good angiographic results of previous radiation trials and the poor clinical outcome (i.e., high target vessel revascularization rates) observed in these studies[21].

Further, as changes in the reference diameter may occur during the follow-up period, the use of the percent diameter stenosis measurements is questioned as an accurate estimate of lesion severity.[19,20] In this regard, 2 thirds of our study population demonstrated an increase in the value of the pre-intervention MLD. In the radiation group, increase of vessel dimensions at the site of the index MLD may play an important role in the relocation of the MLD.

Previous three-dimensional intravascular ultrasound observations demonstrated that the vessel wall enlarges after catheter-based radiation therapy either following conventional BA or stent implantation.[12,22] This vessel enlargement was able to accommodate the mean increase in plaque volume, resulting in a net increase in the irradiated luminal volume at follow-up.

In our study, the MLD was mainly relocated within the IRS and the INS and outside the INS and the IRS (typically at distal segments). In such regions, the presence of pre-existing plaques which became angiographically apparent or progressed after the treatment and tapering of the vessel may have accounted for the relocation of the MLD. On top of these causes of relocation, we cannot exclude the influence of the natural atherosclerotic process on this phenomenon in the context of patients with coronary risk factors by inducing development of new coronary lesions in any of the pre-defined regions of interest.

Methodological consequences of relocation. When the analysis was restricted to the TS, this lumen gain at follow-up resulted in a negative mean late loss and a very low restenosis rate (3.1%). The TS represents a region which was injured by the angioplasty balloon and theoretically presented with the peak stress and vessel stretch after BA. Further, this segment was fully covered by the radiation source in all cases. Thus, the results of the analysis of the TS may demonstrate the effect of brachytherapy in optimal conditions. On the other site of the spectrum, when the analysis included the entire VS, both the late loss and the restenosis rate were significantly higher (table 3). This latter analysis was performed in most of the historical trials aimed to determine effectiveness of new therapeutic agents on restenosis process after BA.[23-26] Since the MLD of the entire treated coronary segment is the flow-limiting lesion for the patient, the results of the VS should also be presented in intracoronary radiation trials. Finally, analyses of INS and IRS may be helpful to identify the potential causes of failure after brachytherapy (i.e. geographical miss, not-injury related edge effect).

Limitations. The definition of relocation of the MLD depends decisively on the accurate documentation of all steps followed during the procedure. This was accomplished only in 50% of the cases treated with BA in the Dose Finding Study and in 44% of the historical control group.

The QCA data presented in this study represent only the results of the pooled cohort of patients enrolled in the Dose-Finding study and not the entire population.

Conclusions. Relocation of the MLD is a common phenomenon after successful BA followed by intracoronary beta-radiation. This feature may induce controversial results related to the methodology used in the QCA analysis and should be considered when reporting the results of subsequent radiation studies. The new methodological approach proposed may better determine the efficacy of this technique by defining different regions of interest within the target coronary segment.

Appendix:

The participating centers and investigators of the Dose-Finding Study Group are listed with the number of included patients under parentheses.

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University Hospital, Essen, Germany (26): Baumgart Dietrich, MD, Sauerwein Wolfgang, MD, Erbel Raimund, MD, von Birgelen Clemens, MD, Haude Michael, MD.

University Hospital, Kiel, Germany (22): Lins Markus, MD, Simon Ruediger, MD, Kovacs Gyorgy, MD, Thomas Martin, MD, Herrmann Gunhild, MD, Wilhelm Roland, MD, Kohl Peter, MD.

Kings College Hospital, London, United Kingdom (22): Thomas Martin, MD, Calman Francis, MD, Lewis Niel, PhD.

Data Monitoring: Thaler Thomas, MD (Boston Scientific)

Angiographic Core-Laboratory and Data Analysis:

Teunissen Yvonne, PhD, (Clinical Trial Manager), Spierings Astrid, Van derWiel Connie, Kloek Gitte, MSc, Disco Clemens, PhD

Critical Events Committee: Dekkers Jaap, MD, Serruys Patrick, MD, PhD.

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Table 1. Baseline Characteristics (n=65).

	Dose-Finding Group (n=65)	Control Group (n=179)
Age, years	64±9	62±10
Gender, male	46 (70.7%)	137 (76.5%)
Treated artery:		
Left anterior descending	28 (43.1%)	80 (44.7%)
Left circumflex	7 (10.8%)	22 (12.3%)
Right coronary	30 (46.1%)	77 (43%)
Coronary risk factors:		
Systemic hypertension	35 (53.8%)	89 (49.7%)
Diabetes mellitus	12 (18.5%)	27 (15%)
Smoking	33 (66.1%)	123 (68.7%)
Hypercholesterolemia	38 (58.5%)	98 (54.7%)
Family history	23 (35.4%)	60 (33.5%)
Dose:		
9 Gy	18 (27.7%)	_
12 Gy	11 (16.9%)	_
15 Gy	20 (30.8%)	_
18 Gy	16 (24.6%)	_

All p=NS. Gy indicates Gray.

Table 2. Location of the relocated MLD

	Relocation pre-post (n=36)	Relocation post-fup (n=37)	Relocation pre-fup (n=51)
Within INS – IRS	19 (52.9%)	23 (62.2%)	24 (47%)
Outside INS – IRS	9 (25%)	10 (27%)	18 (35.3%)
Within IRS–outside INS	6 (16.6%)	4 (10.8%)	8 (15.7%)
Within INS–outside IRS (geographical miss)	2 (5.5%)	0 (0%)	1 (2%)

INS indicates injured segment; IRS indicates irradiated segment.

Table 3. QCA data from the 4 pre-defined segments.

	TS	INS	IRS	VS
MLD pre, mm	1.06±0.2	1.06±0.2	1.06±0.2	1.06±0.2
MLD post, mm	2.17±0.5	1.99±0.4	2.00±0.4	1.91±0.4
MLD fup, mm	2.36±0.5	1.97±0.5	1.97±0.5	1.84±0.5
%DS fup	20.3±11	33.2±11	33.4±11	37.9±10
Acute gain, mm	1.12±0.4	0.93 ±0.4	0.94±0.4	0.85±0.4
Late loss, mm	-0.18±0.4	0.01±0.4	0.03±0.4	0.07±0.3
Restenosis rate, n (%)	2 (3.1)	5 (7.7)	6 (9.2)	9 (13.8)
Segment length, mm	5.0±0.3	18.7±4.2	22.9±3.5	36.9±8.4

TS indicates target segment; INS indicates injured segment; IRS indicates irradiated segment; VS indicates vessel segment; MLD indicates minimal luminal diameter; DS indicates diameter stenosis; pre indicates pre-intervention; post indicates post-intervention; fup indicates follow-up.

Figure 1

A. Target segment (TS) is between proximal and distal margin of the target lesion automatically defined by the quantitative coronary angiography system. Vessel segment (VS) is bordered by visible sidebranches, which encompass the target segment (TS), and the position of the angioplasty balloon and radiation source.

A'. Original lesion in the middle part of the right coronary artery before intervention.

B. Injured segment (INS) is defined as the segment encompassed by the most proximal and most distal marker of the angioplasty balloon.

B'. Arrows indicate the markers of the deflated angioplasty balloon filmed in place with a contrast injection.

C. The segment encompassed by the inner part of the 2 tungsten markers of the radiation delivery system defined as the irradiated segments (IRS).

C'. Arrows indicate the inner parts of the radiation source tungsten markers filmed with a contrast injection.

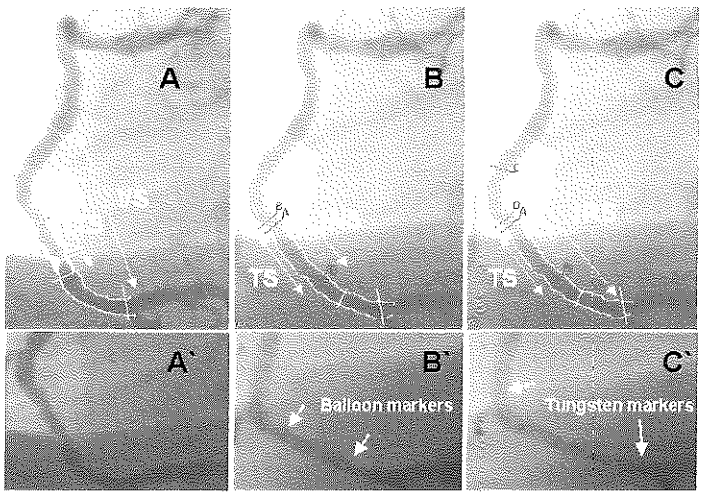


Figure 2

A. Subsegmental analysis before procedure. Vessel segment (VS) was automatically divided into 5-mm subsegments by the CAAS II system. The original lesion is located at segment No.5 pre-procedure as the arrow indicates.

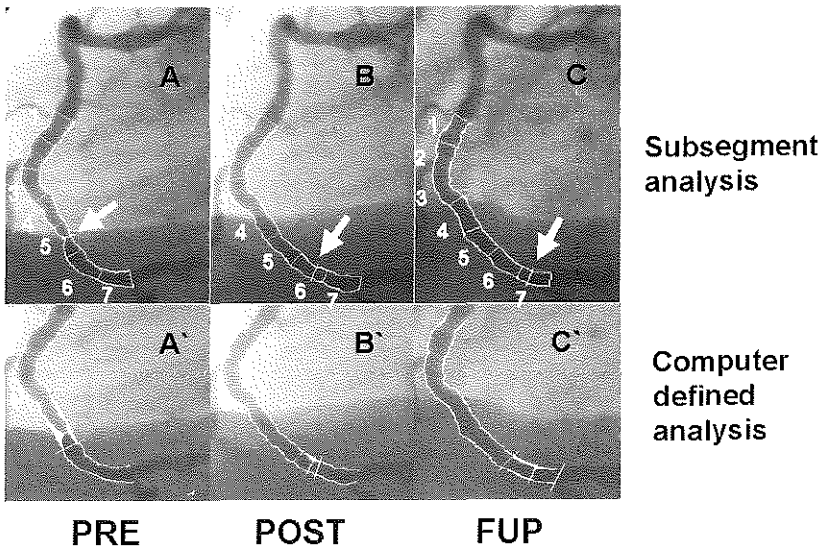
A'. Computer defined analysis pre-procedure.

B. Subsegmental analysis at post-procedure. Minimum lumen diameter is located at segment No.6 (arrow).

B'. Computer defined analysis post-procedure.

C. Subsegmental analysis at follow-up. Minimum lumen diameter is located at segment No.7 (arrow).

C'. Computer defined analysis at follow-up.



Part IV

Complications After Intracoronary Brachytherrapy

Late coronary occlusion after intracoronary brachytherapy.

(Circulation 1999;100:789-792)

Late Coronary Occlusion After Intracoronary Brachytherapy

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Background—Intracoronary brachytherapy appears to be a promising technology to prevent restenosis. Presently, limited data are available regarding the late safety of this therapeutic modality. The aim of the study was to determine the incidence of late (>1 month) thrombosis after PTCA and radiotherapy.

Methods and Results—From April 1997 to March 1999, we successfully treated 108 patients with PTCA followed by intracoronary β-radiation. Ninety-one patients have completed at least 2 months of clinical follow-up. Of these patients, 6.6% (6 patients) presented with sudden thrombotic events confirmed by angiography 2 to 15 months after intervention (2 balloon angioplasty and 4 stent). Some factors (overlapping stents, unhealed dissection) may have triggered the thrombosis process, but the timing of the event is extremely unusual. Therefore, the effect of radiation on delaying the healing process and maintaining a thrombogenic coronary surface is proposed as the most plausible mechanism to explain such late events.

Conclusions—Late and sudden thrombosis after PTCA followed by intracoronary radiotherapy is a new phenomenon in interventional cardiology. (***Circulation.* 1999;100:789-792.**)

Key Words: thrombosis ■ angioplasty ■ radioisotopes

Thrombotic occlusion after PTCA is associated with increased morbidity and mortality rates.[1] Current techniques of stenting followed by antiplatelet therapy have dramatically reduced the incidence of this event to <1.5%.[2,3]

See p 780

Intracoronary radiation is a promising new therapy to prevent restenosis. Recent randomized trials demonstrated a reduction in the restenosis rate and maintenance of benefits up to 2-year follow-up.[4-6] Presently, limited data are available regarding long-term safety after intracoronary brachytherapy.[5,7] Although subacute thrombosis has been reported after radiotherapy,[4,8,9] the incidence of late thrombotic events has not been determined.

The aim of this study was to document the incidence of late (>1 month) thrombotic events after elective PTCA followed by intravascular radiotherapy.

Methods and Results

From April 1997 to March 1999, 108 consecutive patients were successfully treated with catheter-based intracoronary β-radiation at the Thoraxcenter (Rotterdam, The Netherlands). The Medical Ethical Committee approved the use of radiation therapy and informed consent was obtained from every patient. All patients presented with stable angina pectoris and single vessel disease. Brachytherapy was performed using the Beta-Cath system (Novoste Corporation)[10] (n=76 patients, 32 stents and 44 balloon angioplasty [BA]), or the Guidant intravascular brachytherapy system (Guidant Corporation Vascular Intervention)[11] (n=32 patients, 13 Stents and 19 BA). BA and stenting were performed according to standard techniques. Intravascular ultrasound (IVUS) was performed after radiation with a mechanical ultrasound catheter (CVIS, Boston Scientific). Off-line quantitative coronary angiography was performed using CAAS system (Pie Medical Imaging BV). Six-month angiographic and IVUS follow-up was scheduled in all patients.

All patients were discharged without complications. Ninety-one patients completed at least 2-month clinical follow-up. We observed 1 case of subacute thrombosis occurring 15 days after stenting. This patient received an 18-mm long stent (postdilated at 10 atm) with optimal IVUS result. Ticlopidine withdrawal (12 days after stenting) was the plausible explanation of thrombosis in this case.

Six patients (6.6%) presented with sudden late thrombotic coronary occlusion. Two of them were treated with BA and the remaining 4 received an additional stent after radiation. Their clinical characteristics are summarized in

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Clinical and Angiographic Variables

Variables	1	2	3	4	5	6
Age, y	57	58	49	73	52	62
Sex	Male	Female	Male	Female	Female	Female
Pre-procedure						
Target vessel	LCX	RCA	LCX	LAD	RCA	RCA
Type of lesion	B	B	B	A	A	B
RD, mm	2.5	2.8	2.67	2.66	2.84	2.6
MLD, mm	0.9	1.12	0.64	1.09	0.65	0.55
DS, %	66	60	76	60	77	78
Lesion length, mm	13	15	18	11.2	9.6	9.7
Procedure						
Brachytherapy system	Beta-Cath	Guidant	Beta-Cath	Beta-Cath	Beta-Cath	Beta-Cath
Source length, mm	30	27	30	30	30	30
Prescribed dose, Gy	12*	35†	12*	14*	18*	14*
Stent/angioplasty	Stent	Balloon	Balloon	Stent	Stent	Stent
Total stent length, mm	41			25	25	16
Postprocedure						
Dissection/type	No	Yes/B	Yes/B	No	No	No
MLD, mm	2.47	2.07	2.15	2.4	2.34	2.4
DS, %	−1	26	21	9.5	17	7
Clinical success	Yes	Yes	Yes	Yes	Yes	Yes
Follow-up						
Event	VF	Inferior MI	Postlateral MI	Anterior MI	Inferior MI	Inferior MI
Time, mo	2	3	15	10	3	2.5
Antiplatelet medication	Yes	Yes	Yes	No	Yes	Yes
Associated factors	Long stent	Dissection	Dissection at 6-mo	Aspirin withdrawal	No	No

LCX indicates left circumflex artery; RCA, right coronary artery; LAD, left anterior descending artery; RD, reference diameter; MLD, minimal lumen diameter; DS, diameter stenosis; VF, ventricular fibrillation; and MI, myocardial infarction.
*At 2 mm from the source; †at 0.5 mm into the vessel wall.

the Table. No clinical or anatomic characteristic appeared to be related to these events.

In patient 1, overlapping 9- and 32-mm NIR stents (Medinol Ltd) were optimally implanted as assessed by IVUS. Patients 2 and 3 (BA) showed type B dissections without compromising flow postprocedure. Patients 4 and 5 both received a Multilink 25-mm stent (Advanced Cardiovascular Systems/Guidant), and patient 6 received a NIR 16-mm stent with optimal angiographic results. Stent patients were discharged on aspirin (250 mg/d) and ticlopidine (250 mg BID for 15 days in patients 3 and 4, and for 30 days in cases 5 and 6). BA patients received aspirin alone.

Patient 1 was readmitted with ventricular fibrillation 2 months after the procedure, whereas, patients 2, 5, and 6 sustained inferior myocardial infarctions (MI) between 2.5 and 3 months after the treatment. The irradiated segment was occluded at 6-month angiogram in patients 1 and 2 (Figure 1). Thrombotic occlusion was successfully treated by primary angioplasty in patients 5 and 6.

In patient 3, the 6-month IVUS control revealed a persistent (unhealed) submedial dissection (Figure 2) with no signs of restenosis. Nine months later, this patient sustained a posterolateral MI which was treated with thrombolytics. Two weeks after this treatment, an angiogram performed because of recurrent angina showed the occlusion in the irradiated area. Similarly, the 6-month IVUS control of patient 4 showed no neointimal hyperplasia. Four months after control, she had a stroke and aspirin was replaced by acenocoumarol. Ten days later, she sustained an anterior MI. The thrombotic occlusion in the treated site was confirmed by angiography.

Discussion

Progression to total occlusion after BA is a stable process in the general nonirradiated population which occurs in approximately 4% of patients, leading to a MI in <0.5%.[12] In contrast, our study shows a high incidence (6.6%) of thrombotic clinical events 2 to 15 months after PTCA and brachytherapy.

Coronary dissection after BA is associated with abrupt closure; however, type B dissections (NHLBI classification), as observed after BA in our patients, have not been related to thrombotic events.[13] The normal healing process, present after dissections, may be impaired after intracoro-

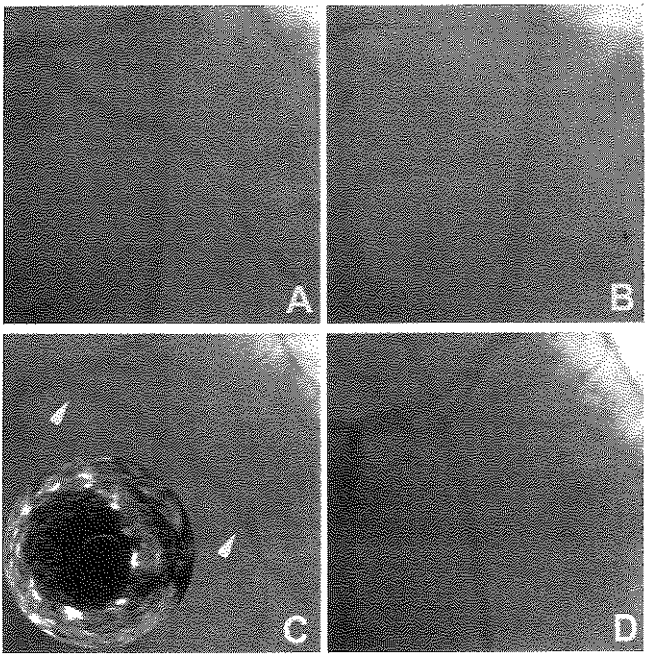

Figure 1. Patient 1. A, Preprocedure angiography shows a significant lesion in the mid-third of left circumflex artery. B, Radioactive source placed in treated site. C, Postprocedure angiography and IVUS images show an optimal result (arrowheads). D, At 2 months, the proximal part of stent appeared occluded.

nary radiation.[14] Whether unhealed dissections, as demonstrated in patient 3, is related to late thrombosis remains to be elucidated in a larger population. Further, the necessity of stenting mild dissections without compromising flow after radiotherapy should be investigated.

The mean time of subacute thrombosis after stenting is approximately 5 to 6 days.[2,3] In a recent study, subacute thrombosis occurred within the first 24 hours in 86% of patients treated with aspirin and ticlodipine for 14 days, with no case of thrombotic events occurring after 15 days.[15] Colombo et al reported only 2 cases (0.6%) of thrombosis occurring 2 to 6 months after stenting.[2] In contrast, in our study, 4 patients receiving a stent (8.8%) experienced thrombosis late after radiation.

Experimentally, reendothelialization after injury takes >4 weeks to be completed.[16] However, the clinical presentation of subacute thrombosis infrequently occurs later than 15 days after stenting,[15] when the reendothelialization process may still be incomplete. Delayed reendothelialization as a trigger mechanism of late stent thrombosis after antineoplastic therapy has been hypothesized previously.[17] Farb et al reported incomplete endothelialization 3 months after placement of β-radioactive stent.[18] Nevertheless, the same group showed no differences regarding endothelial cell growth between radioactive and control stents in another experimental model.[19] Further studies should address the timing of stent reendothelialization after brachytherapy to determine its role on the pathogenesis of late thrombosis.

Although multiple stents have been related to subacute thrombosis,[20] the significance of multiple stent implantation (patient 1) on late thrombotic phenomena has not been demonstrated.

The use of intracoronary β-radiation is a common feature in our patients. However, the judgment of whether radiation is the key factor in the pathogenesis of late thrombosis should await the analysis of ongoing trials. Concomitantly, the benefit of prolonged antiplatelet therapy with the combination of aspirin, clopidogrel, or ticlopidine should be considered.

Limitations

Our patients were included in well-controlled β-radiation studies with similar baseline characteristics and inclusion criteria (lesion length <15 mm, treatment of single vessel). However, 2 different systems to deliver β-radiation were used.

In addition, it is not possible to rule out the natural history of coronary disease as a cause of late thrombosis. However, the incidence of total occlusion in the general nonirradiated population is much lower than that observed in our study. In fact, the incidence of late thrombotic events would be even higher if, in the interest of completeness, we waited for 1-year follow-up in the total patient population.

Finally, whether late thrombosis is a generic complication of intracoronary radiotherapy or is restricted to the use of β-sources cannot be extrapolated from our findings.

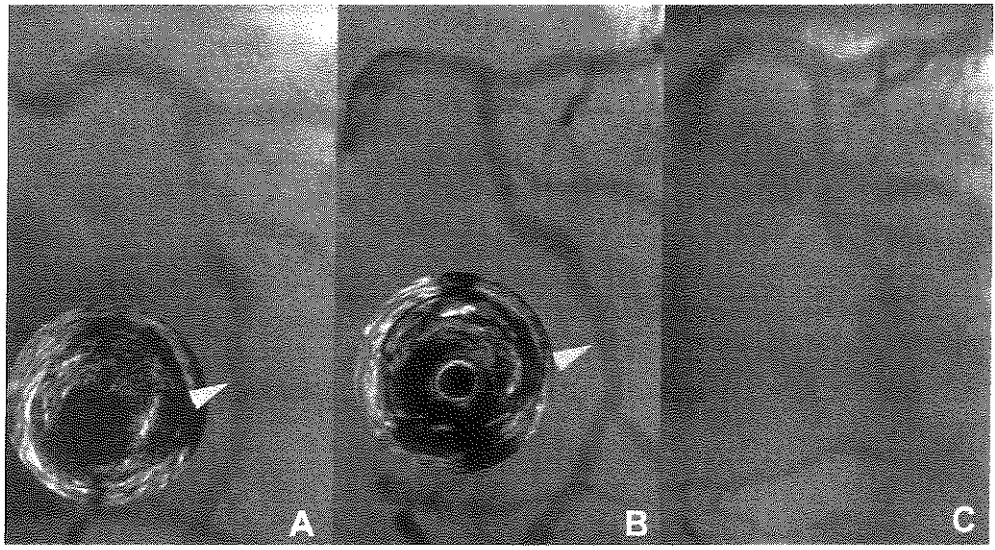

Figure 2. Patient 3. A, Postprocedure coronary dissection, demonstrated both on angiography and IVUS, did not compromise flow in treated area (arrowhead). B, This dissection persisted unhealed at 6-month control (arrowhead). C, At 15 months, irradiated segment appeared occluded.

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The outcome from balloon-induced coronary artery dissection after intracoronary ß-Radiation.

(Heart 2000;83:332-337)

Outcome from balloon induced coronary artery dissection after intracoronary β radiation

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Abstract

Objective—To evaluate the healing of balloon induced coronary artery dissection in individuals who have received β radiation treatment and to propose a new intravascular ultrasound (IVUS) dissection score to facilitate the comparison of dissection through time.

Design—Retrospective study.

Setting—Tertiary referral centre.

Patients—31 patients with stable angina pectoris, enrolled in the beta energy restenosis trial (BERT-1.5), were included. After excluding those who underwent stent implantation, the evaluable population was 22 patients.

Interventions—Balloon angioplasty and intracoronary radiation followed by quantitative coronary angiography (QCA) and IVUS. Repeat QCA and IVUS were performed at six month follow up.

Main outcome measures—QCA and IVUS evidence of healing of dissection. Dissection classification for angiography was by the National Heart Lung Blood Institute scale. IVUS proven dissection was defined as partial or complete. The following IVUS defined characteristics of dissection were described in the affected coronary segments: length, depth, arc circumference, presence of flap, and dissection score. Dissection was defined as healed when all features of dissection had resolved. The calculated dose of radiation received by the dissected area in those with healed versus non-healed dissection was also compared.

Results—Angiography (type A = 5, B = 7, C = 4) and IVUS proven (partial = 12, complete = 4) dissections were seen in 16 patients following intervention. At six month follow up, six and eight unhealed dissections were seen by angiography (A = 2, B = 4) and IVUS (partial = 7, complete = 1), respectively. The mean IVUS dissection score was 5.2 (range 3–8) following the procedure, and 4.6 (range 3–7) at follow up. No correlation was found between the dose prescribed in the treated area and the presence of unhealed dissection. No change in anginal status was seen despite the presence of unhealed dissection.

Conclusion—β radiation appears to alter the normal healing process, resulting in unhealed dissection in certain individuals. In view of the delayed and abnormal healing observed, long term follow up is indicated given the possible late adverse effects of radiation. Although in this cohort no increase in cardiac events following coronary dissections was seen, larger populations are needed to confirm this phenomenon. Stenting of all coronary dissections may be warranted in patients scheduled for brachytherapy after balloon angioplasty.

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Keywords: dissection; intravascular ultrasound; angiography; coronary artery; brachytherapy; angioplasty

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Despite excellent acute results, restenosis at six month follow up after coronary artery balloon angioplasty remains a serious problem.[1] Excessive neointimal formation, extracellular matrix synthesis, and negative vessel remodelling in response to balloon injury have been documented as the main mechanisms of restenosis.[1-7] Intracoronary radiation treatment has recently emerged as a means of preventing and treating restenosis in coronary arteries treated by balloon angioplasty. The theoretical benefit of radiation in preventing neointimal proliferation resides in the destruction of more rapidly dividing smooth muscle cells.[8-14] It may not be surprising that by inhibiting the above deleterious features of healing after balloon angioplasty, intracoronary radiation may also alter normal healing processes.

Coronary artery dissection is common after balloon angioplasty. This is angiographically visible in 20–45% of cases following balloon angioplasty[15] and present in up to 85% of cases when intravascular ultrasound (IVUS) assessment is used.[16] If further angioplasty of the lesion is not undertaken, then it is recognised that nearly all angiographic dissection will heal over a six month time frame.[15 17] Whether intracoronary radiation will prevent the process of natural healing after balloon induced dissection has not been documented thus far in humans. To examine this, we retrospectively analysed coronary artery dissections using angiography and IVUS, at the time of treatment and at six month follow up, in patients treated with intracoronary radiation following balloon angioplasty. We also aimed to compare the prescribed dose received by the treated area in individuals with non-healing dissection with the dose received by those individuals with healed dissection.

Methods

PATIENT SELECTION

Patients eligible for the study were those treated successfully with balloon angioplasty followed by intracoronary irradiation according

Table 1 IVUS dissection score

Arc	Length	Depth	Flap
< 90° = 1	< 5 mm = 1	Partial = 1	Yes = 1
90–180° = 2	5–10 mm = 2	Complete = 2	No = 0
> 180° = 3	> 10mm = 3		

Table 2 Baseline characteristics (n = 22)

Mean (SD) age (years)	55.7 (9.3)
Coronary risk factors	
Smoking (n (%))	15 (68)
Hypercholesterolaemia (n (%))	12 (55)
Family history (n (%))	12 (55)
Hypertension (n (%))	11 (50)
Diabetes (n (%))	6 (26)
Treated vessel	
LAD (n (%))	12 (55)
LCX (n (%))	6 (26)
RCA (n (%))	4 (18)
Prescribed dose	
16 Gy (n (%))	9 (41)
14 Gy (n (%))	5 (23)
12 Gy (n (%))	8 (36)

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

to the beta energy restenosis trial (BERT-1.5). The purpose of this trial was to evaluate the safety and efficacy of low dose β source irradiation following balloon angioplasty with and without stent implantation in patients with single "de novo" lesions of native coronary arteries. The design of this trial was a prospective multicentre non-randomised feasibility study. We used a strontium 90 (^{90}Sr) source with yttrium as a pure β emitter, and patients were randomised to receive 12, 14, or 16 Gray (Gy). The inclusion and exclusion criteria of this trial have been previously reported.[14]

RADIATION DELIVERY SYSTEM

The Beta-Cath system (Novoste Corp, Norcross, Georgia, USA) was used to deliver localised β radiation to a coronary artery at the site of coronary intervention. The device consists of three components: (1) the transfer device which stores the radiation source train and allows the positioning of these sources within the catheter; (2) the delivery catheter, which is a 5 F multilumen over the wire non-centred catheter which uses saline solution to send and return the radiation source train; and (3), the radiation source train consisting of a series of 12 independent cylindrical seeds which contain the radioisotope ^{90}Sr sources and is bordered by two gold radiopaque markers separated by 30 mm.[18]

IVUS IMAGE ACQUISITION ANALYSIS SYSTEM

The segment subject to analysis was examined with a mechanical IVUS system (ClearView, CardioVascular Imaging System (CVIS), Sunnyvale, California, USA) with a sheath based IVUS catheter incorporating a 30 MHz single element transducer rotating at 1800 rpm. The transducer is placed inside a 2.9 F 15 cm long sonolucent distal sheath which alternatively houses the guidewire (during the catheter introduction) or the transducer (during imaging, after the guidewire has been pulled back). To assure the correct identification and analysis of the irradiated segment, certain steps were followed. First, an angiogram was performed after positioning the delivery catheter, and the relation between anatomical landmarks and the two gold markers was noted. Typically, the aorto-ostial junction and the side branches were used as landmarks. The landmark closest to either of the gold markers was used as a guide. During the motorised IVUS pullback, all side branches were counted and the guiding landmark was identified. The correct selection of the marker was confirmed by visualising the position of the IVUS probe during a contrast injection. Once the acquisition was completed, we selected the segment of interest by taking the digitised cross-sectional images proximal or distal to the guiding landmark up to 30 mm, which is the area encompassed by the two gold markers of the radiation source. At follow up, we selected the same region of interest and compared it with that after treatment.

PROCEDURE

The medical ethics committee of the Erasmus Medical Center, Rotterdam approved the study and all patients signed a written informed consent form. In the BERT-1.5 trial balloon angioplasty was performed according to standard clinical practice. Following successful angioplasty, patients were randomised to receive 12, 14, or 16 Gy, as calculated at 2 mm from the centre of the radiation source. The 5 F delivery catheter of the Beta-Cath

Table 3 Angiographic parameters pre- and postintervention and at six month follow up for patients with dissection

		Pre- procedure	Postprocedure				Follow up				
Patient	Dose prescribed	MLD	Dissection grade	RD	DS (%)	MLD	Dissection grade	RD	DS (%)	MLD	LLI
1	12	0.77	C	2.58	40	1.56	–	2.41	32	1.63	−0.09
2	14	1.23	A	2.72	17	2.25	–	2.84	8	2.60	−0.34
3	12	0.78	B	2.44	26	1.80	–	2.77	36	1.77	0.02
4	12	0.78	B	3.17	31	2.18	–	3.11	44	1.75	0.31
5	14	1.21	B	3.21	34	2.12	B	3.32	35	2.15	−0.03
6	16	0.82	A	2.73	30	1.92	A	3.01	52	1.44	0.44
7	16	0.96	B	2.40	23	1.85	B	2.04	23	1.58	0.31
8	16	1.42	C	2.82	25	2.12	–	2.96	51	1.44	0.97
9	16	0.88	C	2.18	29	1.54	–	2.16	49	1.10	0.67
10	16	1.31	C	3.98	38	2.45	A	3.25	54	1.50	0.83
12	12	1.06	A	2.62	3	2.54	–	3.21	75	0.81	1.17
13	12	1.17	A	2.82	29	2.00	–	3.27	65	1.14	1.04
16	16	1.33	B	3.21	22	2.49	B	3.39	31	2.35	0.12
17	14	1.36	B	2.49	25	1.87	–	2.79	13	2.44	−1.14
19	12	0.61	B	2.68	21	2.12	B	2.80	31	1.94	0.12
20	12	1.70	A	4.69	44	2.63	-	3.86	29	2.75	−0.13
Mean	13.9	1.09		2.92	27.31	2.09		2.95	39.25	1.77	0.27

MLD, minimal luminal diameter; RD, reference diameter; DS, diameter stenosis; LLI, late loss index.

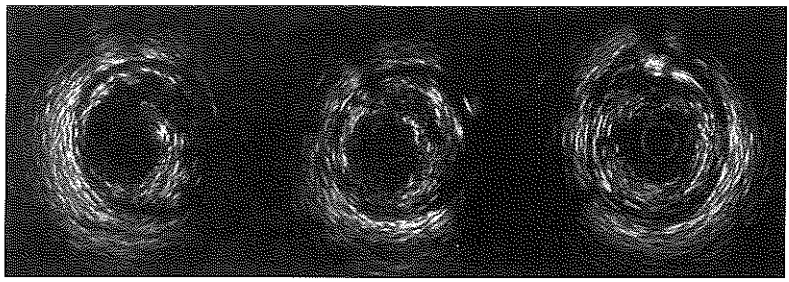

Figure 1 Intravascular ultrasound images (left and centre) showing a double lumen between 12 and 3 o'clock postintervention. The right image shows the same lesion at six month follow up with the unhealed false lumen seen between 11 and 2 o'clock.

system was inserted over the guidewire and advanced such that the two marker bands encompassed the angioplasty site. The guidewire was removed and the radiation source train containing 12 ^{90}Sr seeds was positioned between the gold markers using fluoroscopic visualisation. The seeds remained in place for 2.5–3.5 minutes to deliver the assigned dose of radiation. Following irradiation, repeat angiography and IVUS pullback were performed. Intracoronary nitrates were administered before the treated artery was examined with IVUS. The 2.9 F IVUS catheter (CVIS, Sunnyvale) was advanced distal to the treated site. A continuous motorised pullback at a speed of 0.5 mm/s was carried out, followed by an angiographic control. At six month angiographic follow up, identical quantitative coronary angiography (QCA) and IVUS examination of the treated area was performed.

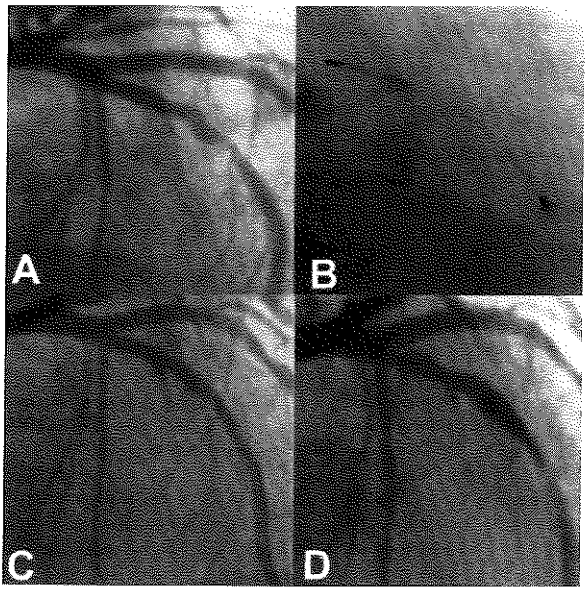

Figure 2 Coronary angiogram showing: (A) lesion pretreatment; (B) radioactive source in situ; (C) postintervention; and (D) the same lesion at six month follow up. Note the presence of an edge effect and absence of angiographic dissection at six month follow up.

DEFINITIONS

Dissection was defined both angiographically and by IVUS. Angiographic dissection was defined using the National Heart Lung and Blood Institute criteria for the classification of dissection.[19] QCA analysis was performed before the intervention, after treatment, and at six month follow up using identical gantry positions. Coronary angiography was performed after intracoronary administration of nitrates. The offline analysis of at least two orthogonal projections was performed by means of the cardiovascular angiography analysis sytem (CAAS II, Pie Medical BV, Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters not filled with contrast medium. This method of analysis has been previously validated.[20–22] The following measurements were obtained in each projection: minimal luminal diameter (MLD), reference diameter, % diameter stenosis, and lesion length. Lesion length was user defined and not done by an algorithm using curvature analysis of the diameter function. The reference diameter was obtained by an interpolated method. Acute gain was defined as MLD measured after treatment minus MLD preintervention. Late loss was defined as MLD after treatment minus MLD at follow up. Late loss index was defined as late loss divided by acute gain. Restenosis was defined as > 50% diameter stenosis at follow up and located within the treated area.

IVUS dissection was defined as a longitudinal tear parallel to the vessel wall.[16] In all patients with IVUS detected dissection, length, arc, and depth were recorded. For inclusion in the study all dissections were located within the area treated by radiation. Axial length was measured in millimetres. Circumferential extension was measured as an arc in degrees. The maximal depth of wall disruption was defined as follows: partial—plaque between tear and adventitia; complete—full thickness tear extending through the plaque to the adventitia.[16]

An IVUS dissection score was created to rank the severity of dissection (table 1). This score facilitates comparison of dissection after the procedure and at follow up. Assuming that a dissection is present, the potential range of the dissection score was 3–9. The dissection was considered to be healed when all features

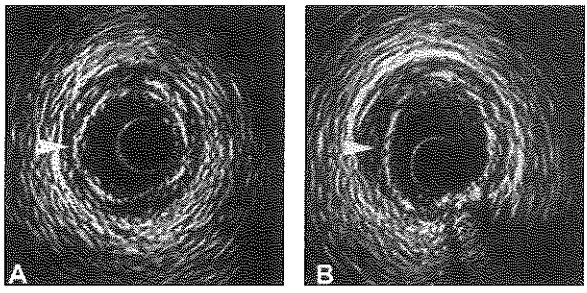

Figure 3 This IVUS image correlates with the angiogram in fig 2. The arrowheads show the presence of an intact lumen (A) and an unhealed flap (B), corresponding to the same area.

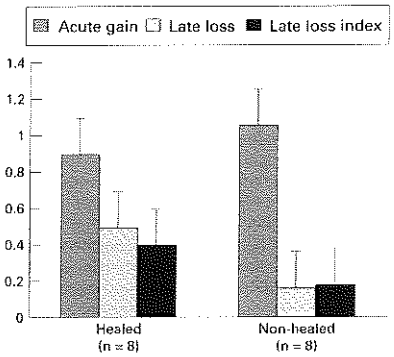

Figure 4 QCA analysis of healed versus non-healed dissection (p = NS).

of dissection had disappeared. Partial healing was considered to have occurred when at least one feature of dissection persisted at follow up. Absence of healing was defined as no change to the dissection on follow up.

The prescribed radiation dose delivered to 2 mm from the source was recorded and compared between individuals with and without healed dissection.

STATISTICAL ANALYSIS

Quantitative data are presented as mean (SD). The non-paired two tailed Student's *t* test was used to compare dose levels and healed/non-healed dissection.

Results

BASELINE CHARACTERISTICS

From April to December 1997, 31 patients were treated at our institution according to the BERT 1.5 trial. Eight patients, who received stent implantation because of important recoil or angiographic and IVUS proven dissection after balloon angioplasty, were excluded from the assessment. One patient refused IVUS at follow up; the same patient had no evidence of dissection following treatment. Therefore the study population was 22 patients. The baseline characteristics of the patients are shown in table 2.

CLINICAL, ANGIOGRAPHIC, AND IVUS FOLLOW UP

At follow up 14 patients (63%) remained asymptomatic. Six patients presented with stable angina pectoris: one with Canadian Cardiovascular Society (CCS) class 1 angina, one with CCS class 2, and four with CCS class 3. The follow up angiography demonstrated restenosis (> 50% diameter stenosis on quantitative coronary angiography) in five patients (24%). These included the four patients with CCS class 3 angina. One restenotic patient showed aneurysmatic formation within the irradiated area. The prescribed dose in restenotic patients was 12 Gy in one patient, 14 Gy in one patient, and 16 Gy in three patients.

Dissection was seen in 16/22 patients (73%) after intervention using both angiographic and IVUS criteria. At six month follow up dissection was seen in six patients on angiography (38%) and eight patients on IVUS (50%) (table 3). Disagreement between IVUS and angiography was caused by the presence of a double lumen in one individual (fig 1) and a flap in another (figs 2 and 3), neither of which was detected by angiography. Angiographic analysis of healed versus non-healed dissection is presented in fig 4. No difference was seen in the reference diameter, % diameter stenosis, and MLD before or after the procedure or at follow up for either the healed or the non-healed dissection groups (table 3). As

Table 4 Postintervention and six month follow up of dissection evaluated by IVUS

	Postintervention					*Follow up*				
Patient	*Arc*	*Length (mm)*	*Depth*	*Flap*	*IVUS score*	*Arc*	*Length (mm)*	*Depth*	*Flap*	*IVUS score*
1	60°	5	P	N	4	60°	5	P	N	4
2	45°	2	P	N	3	–	–	–	–	–
3	90°	5	C	N	6	–	–	–	–	–
4	60°	5	P	N	4	30°	2	P	N	3
5	90°	5	P	N	5	30°	2	P	N	3
6	180°	2	C	Y	7	180°	2	C	Y	7
7	90°	6	P	Y	6	–	–	–	–	–
8	120°	8	P	N	5	–	–	–	–	–
9	180°	3	P	N	5	180°	3	P	N	5
10	270°	25	C	N	8	–	–	–	–	–
12	90°	4	P	N	4	–	–	–	–	–
13	90°	6	P	N	5	–	–	–	–	–
16	90°	7	P	N	5	90°	5	P	N	5
17	120°	6	C	N	6	–	–	–	–	–
19	90°	7	P	N	5	90°	5	P	N	5
20	120°	3	P	Y	5	120°	3	P	Y	5
Mean	112°	6.2	P = 12/16	N = 13/16	5.2	98°	3.4	P = 7/8	N = 6/8	4.6

P, partial; C, complete; N, no; Y, yes

expected late loss and late loss index were greater in the healed dissection group, but the difference was not significant. Eight patients had persisting dissection after IVUS examination—six had no evidence of healing and two had partial healing (table 4). Three of the healed dissections resulted in restenosis. The mean IVUS dissection score was 5.2 (range 3–8) after the procedure and 4.6 (range 3–7) at follow up. IVUS healed dissection received a mean prescribed dose of 14 Gy and non-healed dissection received 13.8 Gy (p value not significant).

Discussion

We describe coronary artery dissection following intracoronary radiation treatment in a group of individuals who had dissection noted angiographically and with IVUS, but who did not undergo stent implantation as the lesion appeared stable under standard clinical conditions. These dissections were not associated with any significant acute or subacute clinical sequelae. What is remarkable is that after six month follow up, six of the angiographic dissections and eight of the IVUS proven dissections persisted. In a similar patient population who had undergone conventional balloon angioplasty (n = 183), 87 patients (47%) suffered a type A–C dissection after coronary angioplasty. Only one dissection persisted at six month follow up coronary angiography (DEBATE 1 subanalysis, unpublished data, 1999).

Why should these dissections fail to heal in a predictable manner as previously described in conventional angioplasty? In an experimental model, a reduction of cell proliferation in the media and adventitia has been observed in the early phase after balloon injury and radiation treatment. Furthermore, the expression of α smooth muscle actin in the adventitia is reduced after radiation treatment, suggesting a positive effect on vascular remodelling.[21] Consequently it appears that radiation treatment is directly implicated in altering the healing process after balloon angioplasty, increasing the potential for positive remodelling,[24] arterial dilatation, and non-healing dissection.

It remains uncertain as to whether the dissections described represent permanent disruptions to the vessel wall or merely a retardation in the healing process. The possible inhibitory healing effect of radiation may diminish with time such that at a critical point there may be a further activation of the restenotic process associated with the healing of the dissection.

In an animal model, Farb and colleagues showed a reduction in neointimal formation in ^{32}P-emitting radioactive stents three months after implantation; endothelialisation was incomplete, however, with only one third of the entire intimal surface showing endothelialisation with poor formation of cell junctions.[25] As a result of incomplete or delayed endothelialisation, late thrombosis may also occur among the described dissections. It therefore would be of considerable interest to repeat IVUS assessment of individuals undergoing intracoronary radiation treatment at a later date (12–18 months postintervention) so as to see if there is evidence of persisting dissection or of wound healing/restenosis, which may present in a delayed fashion.[26]

Although the dissections did not lead to an increase of cardiac events in our population, Preisack and colleagues recently described a higher event rate in patients who suffered coronary dissections after balloon dilatation only.[27] In this study, the dissection type was highly correlated with the probability of a clinical event. Other authors have not found a difference in six month clinical event rate in patients with stable coronary dissections.[28]

We feel that additional stent implantation may be justified in patients with dissections who are about to receive brachytherapy following balloon angioplasty. This approach may be warranted even if the dissection is stable. After stent implantation in these circumstances, we feel that a long term antiplatelet regimen (> 3 months) may prove helpful in the prevention of late thrombotic occlusion, given re-endothelialisation seems to be delayed in this patient cohort.

There have been no reports on γ radiation causing interference with the healing of dissection. Compared with γ radiation a higher dose of β energy is required in the near field to deliver the prescribed dose to 2 mm. This intrinsic feature of β radiation may be causing the deleterious effect witnessed.

The IVUS dissection score was created to obtain a means of ranking and comparing dissection between postprocedural and follow up features. Up to this point, there has been no system that employs the well described features of dissection (arc, length, depth, and presence of flap) to create such a ranking. Clearly, the fate at six month follow up of IVUS proven postprocedural dissection is not well described and we must rely on evidence that is extracted from angiographic follow up data. An IVUS ranking system may be useful to describe the fate at follow up of dissection not only in the context of normal balloon angioplasty, but also after intracoronary radiotherapy.

Using the prescribed dose delivered to the total treated area there was no difference between the dose prescribed and the presence of non-healing dissection. On the one hand this relation may be genuine, on the other it may be argued that this lack of correlation results from the use of the measure of radiation received by the total vessel; this may not reflect the radiation dose received by the specific area of dissection,[29] or the radiation which is potentially transmitted down the disrupted tissue planes of the dissection. It is possible that such tissue planes may permit greater passage of radiation with deleterious consequences such non-healing or aneurysmal change. Equally, it is possible that certain tissue characteristics, such as heavy calcification, may interrupt radiation dosing to the level of the adventitia. Clearly, IVUS provides superior information to angiography in describing tissue characteristics and is likely to be an integral part in the calculation of appropriate radiation dose in the

future,[29] so as to maximise efficacy and minimise the complications of over- and underdosing.

The design of the radioactive source delivery catheter may also be relevant to its efficacy. A non-centred catheter as used in this study may lead to inhomogeneous dosing. Alternative centred devices are available; however, the issue is as yet unresolved and will be the subject of further research.[30]

LIMITATIONS

We describe the phenomenon of non-healing coronary artery dissection after balloon angioplasty in a small group of patients. The outcome of dissection in those with flow limiting dissection has not been defined, as these individuals all had stents implanted. The angiographic dissection control group for this study is historical and there is no good description in the literature on the long term outcome of those with IVUS proven dissection.

CONCLUSION

β Radiation alters the normal healing process, resulting in unhealed dissection in certain individuals. In view of the delayed and abnormal healing witnessed, long term follow up may be prudent. Although no increase in cardiac events at six months following coronary dissection was seen in this cohort, larger populations are needed to confirm this phenomenon. Stenting of all coronary dissections and the use of prolonged courses of antiplatelet agents may be warranted in patients scheduled for brachytherapy following balloon angioplasty.

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Chapter 10

Geographical Miss: a cause of treatment failure in radio-oncology applied to intracoronary ß-radiation.

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GEOGRAPHICAL MISS: A CAUSE OF TREATMENT FAILURE IN RADIO-ONCOLOGY APPLIED TO INTRACORONARY RADIATION THERAPY

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ABSTRACT

Background. A recognized limitation of endovascular ß-radiation therapy is the development of new stenosis at the edges of the irradiated area. The combination of injury and low-dose radiation may be the precursors of this phenomenon. We translated the radio-oncological concept of 'geographical miss' to define those cases in which the radiation source did not fully cover the injured area. Aims of the study were to determine the incidence and causes of geographical miss and evaluate the impact of this inadequate treatment on the outcome of patients treated with intracoronary ß-radiation.

Methods and Results. We analyzed 50 consecutive patients treated with ß-radiation after percutaneous coronary intervention. Prescribed dose ranged between 12 and 20 Gray at 2 mm from the source axis. By means of quantitative coronary angiography, the irradiated segment (IRS) and both edges were studied prior to, after intervention and at 6 month follow-up. Those edges which were injured during the procedure constituted the geographical miss edges. Twenty-two edges were injured during the intervention mainly due to procedural complications which extended the treatment beyond the margins of the IRS. Late loss was significantly higher in geographical miss edges, as compared to IRSs and not-injured edges (0.84±0.6 versus 0.15±0.4 and 0.09±0.4, respectively; $p<0.0001$). Similarly, restenosis rate was significantly higher in those injured edges (10% within IRS, 40.9% in geographical miss edges, and 1.9% in not-injured edges; $p<0.001$).

Conclusion. These data support the hypothesis that the combination of injury and low-dose ß-radiation induce deleterious outcome.

KEY WORDS: geographical miss, radioisotopes, balloon angioplasty, stents, quantitative coronary angiography, restenosis.

Endovascular radiation therapy is a novel technique aimed to prevent restenosis after percutaneous coronary intervention.[1-3] Radiation can be delivered to the coronary artery by means of catheter-based systems or radioactive stents.[4] A potential drawback of this treatment is the development of new stenotic lesions at both edges of the irradiated segment. This so-called "edge effect" has been originally described after high activity (>3 microCi) radioactive stent implantation.[5-6] However, this phenomenon is not exclusive to radioactive stents and may also affect coronary segments treated by means of catheter-based systems.[7] The pathophysiology of the "edge effect" may be the result of vessel wall injury,[8-10] concomitantly to low-dose radiation at the edges of the irradiated area.[11,12] In radio-oncology, the term to define a cause of treatment failure due to low-dose was coined by the Manchester Clinic as 'geographical miss'. In such cases, a small part of the treatment zone has either escaped radiation or been inadequately irradiated because the total volume of the tumor was not appreciated and hence an insufficient margin was taken.[13] This concept is translated in interventional cardiology to define those coronary segments which were injured but received low-dose radiation. Typically, this phenomenon occurs by injuring the edges of the irradiated segment where, by definition, the dose is rather low.

Aims of the study were (1) to determine the incidence and causes of geographical miss in the treatment of patients with intracoronary ß-radiation using a catheter-based system; and (2), to evaluate the impact of this inadequate treatment on the angiographic outcome of these patients.

METHODS

Patient Selection

We retrospectively analyzed 50 consecutive patients treated at our institution with catheter-based ß-radiation by means of the Beta-Cath system™ (Novoste Corp., Norcross, GA). Patients included in the radiation protocol were those with objective signs of ischemia and presence of significant *de novo* lesions (n=39) or recurrent in-stent restenosis (n=11). Detailed description of the radiation system has been reported elsewhere.[14] The radiation source train consists of a series of 12 cylindrical seeds that contain the radioisotope $^{90}Sr/^{90}Y$ sources and is bordered by 2 gold radio-opaque markers separated by 30 mm.[14]

Procedure

The medical ethics committee of our institution approved the investigational use of ß-radiation and all patients signed an informed consent form. Percutaneous intervention was performed according to standard clinical practice. Typically, coronary lesions were treated initially with balloon angioplasty (BA). After successful BA, the target coronary segment was

irradiated. This could be followed by additional stent implantation when clinically indicated. Lesion length measured on average 11.4±4 mm, the mean balloon length was 20.0±3 mm and the number of balloon inflations was 2.9±1.6. Patients received aspirin (250 mg) and heparin (10.000 IU IV) at the initiation of the procedure and an additional dose of heparin was administered to maintain the activated clotting time >300 seconds. After the procedure, aspirin was continued indefinitely. In those patients receiving additional stent implantation ticlopidine was initiated and continued at least for 15 days after the procedure. Radiation dose was prescribed at 2 mm from the source axis. Prescribed dose for the treatment of *de novo* lesions was randomly assigned to 12, 14 or 16 Gray (Gy) for protocol requirements. For the treatment of in-stent restenotic lesions, the prescribed dose was 16 Gy or 20 Gy if the reference diameter, by quantitative coronary angiography (QCA), measured ≤3.25 mm or >3.25 mm, respectively. Mean dwell time to deliver these doses was 143 ± 44 seconds.

Definitions

The irradiated segment (IRS) was defined as the area encompassed by the 2 gold markers of the radiation source train. It was identified on angiography by a contrast injection with the source in place. The edges of the IRS were defined as the 5 mm-long segments proximal and distal from the angiographic location of the gold markers. Those edges which were touched by the angioplasty balloon or received new stent implantation during the procedure were defined as geographical miss edges since represent injured segments receiving low-dose radiation. Not-injured edges were those which were not traumatized during the intervention. To determine whether the edges of the IRS were injured, a few steps were followed: during the procedure every balloon inflation or additional stent implantation were filmed in the same projection as was the radiation source. This approach allowed us the correct matching of the cinefilms in the off-line analysis. Either cineloop showing balloon inflation, stent implantation and the radiation source may be displayed simultaneously on the screen using the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands). ECG tracing is also displayed in either cineloop. By selecting those frames in the same part of the cardiac cycle, we were able to define the location of the radiation source relative to the injured area.

QCA Analysis

The IRS and both edges were analyzed by QCA prior to, after intervention, and at 6-month follow-up. All angiograms were evaluated after intracoronary administration of nitrates. The off-line analysis of two orthogonal projections was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands). Calibration of the system was

based on dimensions of the catheters not filled with contrast medium. This method of analysis has been previously validated.[15-17] The following QCA parameters were computed in the IRS and both edges: minimal luminal diameter (MLD), which was computer defined; reference diameter, which was obtained by an interpolated method;[15-17] and, percentage diameter stenosis. Binary restenosis was defined in every area as diameter stenosis >50% at follow-up. Acute gain was defined as MLD post-treatment minus MLD pre-intervention. Late loss was defined as MLD post-treatment minus MLD at follow-up. Relative late loss was defined as late loss divided by reference diameter.[18]

Statistical Analysis

To compare continuous variables between IRS, geographical miss edges and not-injured edges, one-way analysis of Variance (ANOVA) with post-hoc analysis for multiple comparisons was performed. Unpaired Student's *t* test was performed to compare continuous variables between proximal and distal geographical miss edges and between patients in whom the geographical miss was induced by balloon dilatation or stent implantation. To compare the binary restenosis between groups the Chi-square test was performed. All tests were two-tailed and a p value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Fifty irradiated coronary arteries and 100 edges in 50 patients were eligible for the study. However, 26 edges were finally excluded, due to ostial location of the proximal end of the source in the right coronary artery (n=12) or overlapping of one of the edges with sidebranches (n=14). Thus, finally 74 edge areas and 50 IRS's were studied. Mean age was 55.3±9 and 38 patients (76%) were male. Smoking was the most frequent coronary risk factor involving 33 patients (66%) followed by dyslipidemia in 27 patients (54%) and hypertension in 24 patients (48%). Eight patients (16%) were diabetics. Left anterior descending artery was treated in 21 patients, left circumflex in 10, right coronary artery in 18 and saphenous vein graft in 1. Twelve patients received a stent due to bailout situation.

Incidence and causes of Geographical Miss

Geographical miss was observed in 22 edges (31.9%) induced by balloon dilatation (n=13) or additional stent implantation (n=9). The remaining 51 edges (68.9%) were defined as not-injured edges. Location of the geographical miss was in the proximal edge in 11 patients (50%) and in the distal margin also in 11 patients (50%). The following reasons were responsible for this phenomenon: (1) development of procedural complications which extended the treatment

beyond the margins of the IRS (unexpected geographical miss, n=9); (2) lack of availability of longer radiation source (>30 mm) in the context of patients with diffuse recurrent in-stent restenosis in whom radiation was given on a compassionate use basis (n=8); and (3), the injured segment from prior balloon inflations was not appropriately covered by the source (lack of accurate matching; n=5). An example of a patient with geographical miss induced by a balloon dilatation in the proximal margin is depicted in the figure 1.

QCA Analysis

QCA data is presented in the table. As expected, IRS demonstrated on average a higher acute gain as compared to both injured and not-injured edges. However, geographical miss edges presented, on average, with significantly higher late loss and relative late loss. Restenosis was demonstrated in 5 cases (10%) within the IRS, in 9 cases (40.9%) in the geographical miss edges and in 1 case (1.9%) in the non-injured edges ($p<0.001$). No difference in the pattern of the late loss between the 3 areas were observed in *de novo* lesions as compared to recurrent in-stent restenotic lesions (figure 2). In the geographical miss edges, 4 edge restenosis (44%) were located at the proximal edges, whereas, the other 5 (56%) were located at the distal edges. Mean relative late loss was comparable between those edges with geographical miss located proximally or distally from the IRS (0.31±0.2 versus 0.34±0.2, respectively; p=NS). Those edges in which the geographical miss was due to additional stent implantation presented, on average, higher acute gain than those due to balloon dilatation (0.70±0.4 versus 0.21±0.3, respectively; p=0.005). However, mean late loss and mean relative late loss were comparable between both causes of geographical miss (0.95±0.9 and 0.36±0.3 after stent versus 0.77±0.3 and 0.30±0.1 after balloon dilatation; both p=NS).

DISCUSSION

This study reports on the initial experience of our center with the use of intracoronary ß-radiation. By means of a careful retrospective angiographic analysis of all patients treated with the same radiation system we sought to define the effect of the injury on those areas located at the margins of the source where the delivered dose is potentially rather low. Up to 31.9% of the cases presented with the pre-defined technical error, termed as geographical miss. This concept requires the concurrence of 2 conditions: low-dose radiation and injury. Any other clinical situations which do not include both conditions can not be termed as geographical miss. For instance, (1) the effect of injury on coronary segments not being irradiated (proximal or distal to an irradiated segment but in areas where the calculated dose is almost 0) should fall into the category of normal restenotic process; (2) the effect of low-dose radiation in areas which have

not been injured may be defined as the pure radiation edge effect, since in intracoronary radiation the edges of any irradiated segment will always receive low-dose radiation; (3) finally, the effect of full prescribed dose on segments presenting with or without injury is the situation where the physician may be able to irradiate (with full dose) the entire injured segment and include some not injured margin. A key issue in the definition of geographical miss is to define those segments receiving low-dose. These may vary between systems and sources used. With the BetaCath™ system the longitudinal distance of the 100% isodose is 26mm. Since the ß-emitting $^{90}Sr/^{90}Y$ has an acute fall-off of dose related to the distance, the last 2 mm within the markers of the source should be considered as presenting with lower-than-the-prescribed dose. In fact, the dose received at 1 mm from the 100% isodose is 86% of the prescribed dose, and at 2 mm, 60% of the prescribed dose (inner part of the gold marker). Further, at 3mm the dose is 30% of the prescribed dose, at 4 mm 13% of the prescribed dose and at 5 mm 5% of the prescribed dose. We defined the IRS as the segment encompassed by the 2 gold markers, which included the last 2 mm within the markers with lower-than-the-prescribed dose (up to 60% of the prescribed dose). Using this definition, late loss and restenosis rate were significantly lower that those of the injured edges (analyzed from the inner part of the gold marker). Further, the 5 cases of restenosis within the IRS, were located at the site of the initial MLD. These results may reflect the fact that the dose at these last seeds of the source was high enough to avoid edge effect after being probably injured during the procedure, especially when 20mm-long balloon was used. Thus, the region receiving low-dose may be defined, for this system and source, as the 5mm-long segment located 2 mm further to the 100% isodose boundary, that is beyond the inner part of the gold marker. In this regard, we believe that the injury should be completely restricted to the segment of the 100% isodose curve of the radiation source (26mm), and that the last 2 mm at both extremities of the source and within the gold markers may be considered relatively but probably not completely safe. Finally, any injured segment covered by or beyond the gold marker (up to 5mm) must be considered as of high risk of failure at follow-up.

From the perspective of these findings and future technical developments in the field, the following recommendations are advisable. Filming every single balloon inflation performed during the procedure would allow one to define the injured area. More than ever, tenacious attention to detail when positioning the radiation catheter encompassing the entire injured area must be mandatory. The development of longer sources (>30 mm) would allow one to treat diffuse lesions and completely cover those areas in which an extension of the treatment was

indicated due to procedural complications. Equally, the use of on-line QCA in the decision-making, would avoid appreciation errors due to visual assessment of the target area and subsequent under- or over-estimation of balloon lengths. Finally, the selection of the most suitable fluoroscopic projections (e.g. less fore-shortening, no overlapping) would avoid errors in the quantification of the region of interest.

The fact that the location of most of the restenosis were in geographical miss edges and that late loss in those areas was unexpectedly high, must raise the alarm about the deleterious effect of the combination of injury and low-dose radiation. This hypothesis may be supported by the fact that the late loss observed in those injured edges is higher than that reported in recent clinical trials either after balloon angioplasty or stent implantation[19,20] and than that demonstrated in the not-injured edges. Balloon overstretching injury has been used as an experimental model to study the restenosis process.[8-10] The response of the vessel wall to injury involves both neointimal hyperplasia[8,9] and vessel remodeling.[10,21,22] The stimulatory effect of low-dose radiation after balloon angioplasty on smooth muscle cell proliferation has been previously reported.[11] In the low-dose radiation group of this swine model (10Gy), neointima was composed of smooth muscle cells with a marked increase in inflammatory cells and less medial and intimal fibrosis as compared to higher dose groups (15 and 20 Gy) and control group. It was suggested that at low-dose, inadequate fibrosis was induced to prevent effective smooth muscle cells migration and to act as a diffuse barrier for mediators of chemotaxis, chemokinesis and cellular proliferation.[11] Similarly, after low-activity radioactive stent implantation (1 μCi) in a porcine model, neointima hyperplasia was significantly greater than that after non-radioactive control stents.[12] If ongoing intravascular studies reveal that edge restenosis is mainly due to plaque increase, the former hypopthesis that at low-dose inadequate medial and intimal fibrosis to avoid migration and proliferation predominate, may become a plausible explanation. On the contrary, if negative remodeling is the main contributor to the lumen loss, the excess of inflammatory cells demonstrated at low-dose, may be responsible for subsequent adventitial fibrosis and vessel shrinkage. The development of the so-called "candy wrapper" after radioactive stent implantation[5] may represent the clinical paradigm of the combined deleterious effect of low-dose radiation and injury. The latter is secondary to the angioplasty balloon used for pre-and post-dilatation of the radioactive stent. In this regard, a higher balloon-artery ratio was associated with the presence of this phenomenon.[5]

Future trials must address the benefit of new technical developments in the field (use of square deployment balloons, hot-end, cold-end stents[6], longer sources with smaller radiation

delivery catheters) to minimize the impact of injury at the edges either after radioactive stent or catheter-based systems.

Study Limitations

In this study, only one type of radiation delivery catheter using the ß-source $^{90}Sr/^{90}Y$ has been evaluated. Thus, the effect of either other catheter-based systems using centering balloons and different sources or the γ-radiotherapy on the geographical miss edges cannot be extrapolated from our results. The actual dose at the margins of the radiation source has not been calculated. Low-dose at these edges was assumed by the fact that, the isotope $^{90}Sr/^{90}Y$ demonstrates an acute fall-off related to the distance from the 100% isodose boundary. This angiographic study was aimed to define the concept and the clinical implications of the geographical miss. To define the mechanism of the unexpectedly high late loss and the correlation between radiation dose and plaque extent at the margins of the IRS, intravascular ultrasound studies must be carried out. The location of the segment receiving low-dose may vary between systems and sources. Thus, the confidence margin to be taken may vary accordingly. The position of the source relative to the various balloon inflations was assessed by comparing still frames at the same part of the cardiac cycle from cineangiograms performed in the same projections. However, small inaccuracies in the definition of the IRS and the edges, derived from the axial movement of the radiation source during cardiac cycle cannot be completely ruled out. This study is not placebo-controlled. Thus, the effect of the sham source on the balloon-injured coronary segments have not been determined.

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Table. QCA data.

	IRS (n=50)	Geographical miss edges (n=22)	Not-injured edges (n=52)	p value
MLD pre-intervention, mm	1.20 ± 0.3	2.02 ± 0.6	2.10 ± 0.6	<0.0001
MLD post-intervention, mm	2.02 ± 0.4	2.43 ± 0.5	2.12 ± 0.6	0.01
MLD at follow-up, mm	1.87 ± 0.5	1.59 ± 0.6	2.02 ± 0.5	0.006
Reference diameter, mm	2.69 ± 0.6	2.50 ± 0.6	2.55 ± 0.7	NS
%DS pre-intervention, %	54.9 ± 13	19.8 ± 14	17.9 ± 11	<0.0001
%DS post-intervention, %	28.4 ± 9	19.9 ± 10	20.8 ± 11	0.0003
%DS at follow-up, %	33.3 ± 11	44.3 ± 22	24.3 ± 10	<0.0001
Acute gain, mm	0.81 ± 0.4	0.41 ± 0.4	0.01 ± 0.3	<0.0001
Late loss, mm	0.15 ± 0.4	0.84 ± 0.6	0.09 ± 0.4	<0.0001
Relative late loss	0.06 ± 0.1	0.32 ± 0.2	0.02 ± 0.1	<0.0001

Data is presented as mean ± SD. MLD = minimal luminal diameter; %DS = diameter stenosis

Figure 1. Geographical miss induced by balloon dilatation. A: Lesion located in the proximal segment of the left anterior descending coronary artery; B: One of the balloon dilatations performed during the intervention (black arrowheads indicate the area injured by the balloon); C: Radiation source train in place. The irradiated area is delimited by the gold markers (white arrowheads); D: Final result: proximal traumatized edge presented a residual type B dissection; E: 6-month follow-up: obvious reduction in lumen at the geographical miss edge.

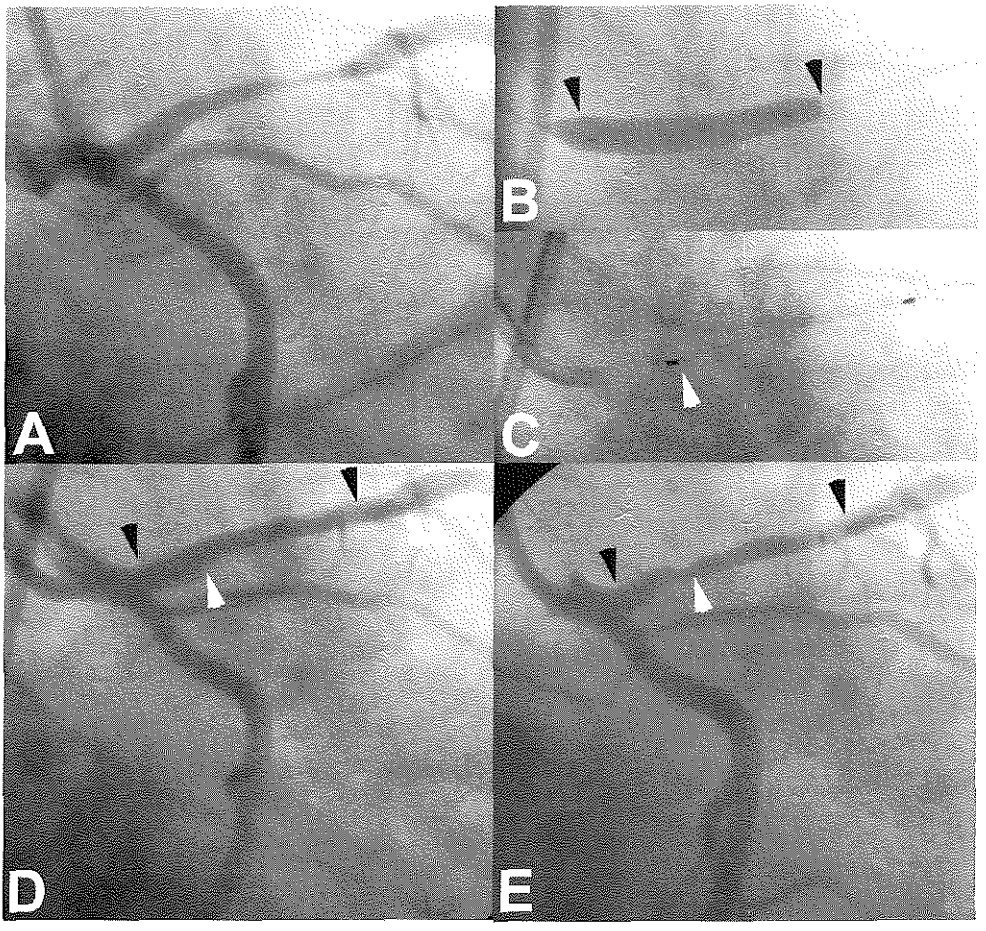
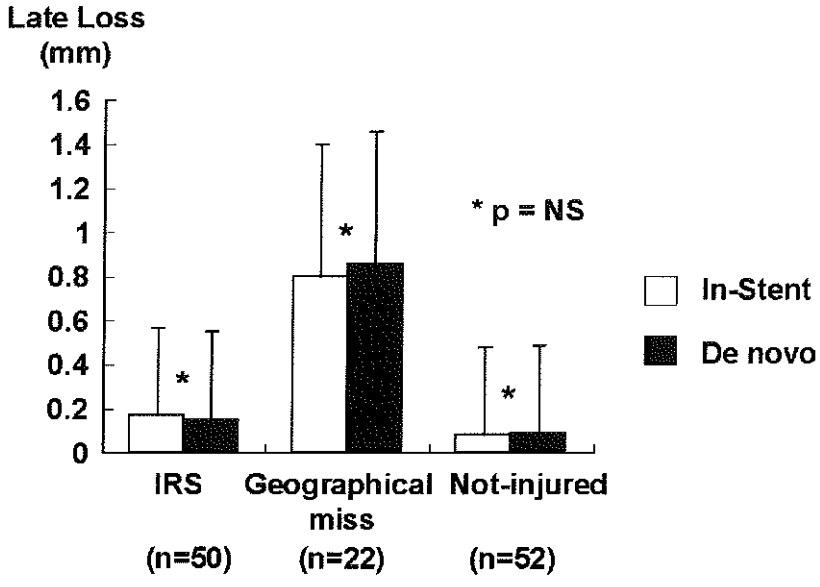


Figure 2. Difference in late loss between irradiated segment, geographical miss edges and not-injured edges. Both *de novo* lesions and in-stent restenosis demonstrated the same degree of late loss between the 3 different segments analysed.



Part V

Clinical Trials

Chapter 11

Beta particle emitting radioactive stent implantation. A safety and feasibility study.

(Circulation 1999;100:1684-1689)

β-Particle–Emitting Radioactive Stent Implantation

A Safety and Feasibility Study

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Background—This study represents the Heart Center Rotterdam's contribution to the Isostents for Restenosis Intervention Study, a nonrandomized multicenter trial evaluating the safety and feasibility of the radioactive Isostent in patients with single coronary artery disease. Restenosis after stent implantation is primarily caused by neointimal hyperplasia. In animal studies, β-particle–emitting radioactive stents decrease neointimal hyperplasia by inhibiting smooth muscle cell proliferation.

Methods and Results—The radioisotope ^{32}P, a β-particle emitter with a half-life of 14.3 days, was directly embedded into the Isostent. The calculated range of radioactivity was 0.75 to 1.5 μCi. Quantitative coronary angiography measurements were performed before and after the procedure and at 6-month follow-up. A total of 31 radioactive stents were used in 26 patients; 30 (97%) were successfully implanted, and 1 was embolized. Treated lesions were in the left anterior descending coronary artery (n=12), the right coronary artery (n=8), or the left circumflex coronary artery (n=6). Five patients received additional, nonradioactive stents. Treated lesion lengths were 13±4 mm, with a reference diameter of 2.93±0.47 mm. Minimum lumen diameter increased from 0.87±0.28 mm preprocedure to 2.84±0.35 mm postprocedure. No in-hospital adverse cardiac events occurred. All patients received aspirin indefinitely and ticlopidine for 4 weeks. Twenty-three patients (88%) returned for 6-month angiographic follow-up; 17% of them had in-stent restenosis, and 13% had repeat revascularization. No restenosis was observed at the stent edges. Minimum lumen diameter at follow-up averaged 1.85±0.69 mm, which resulted in a late loss of 0.99±0.59 mm and a late loss index of 0.53±0.35. No other major cardiac events occurred during the 6-month follow-up.

Conclusions—The use of radioactive stents with an activity of 0.75 to 1.5 μCi is safe and feasible. (***Circulation.* 1999;100:1684-1689.**)

Key Words: β-rays ■ angioplasty ■ radioactive isotopes ■ restenosis ■ stents

Percutaneous transluminal coronary angioplasty (PTCA) is an accepted treatment for coronary artery disease.[1] However, angiographic restenosis is reported in 40% to 60% of patients after a successful PTCA.[1,2] The main mechanisms of restenosis include late constriction of the arterial wall (vascular shrinkage) and neointimal hyperplasia,[3–6] which are due to the migration and proliferation of smooth muscle cells and myofibroblasts after balloon-induced trauma of the arterial wall and the deposition of an extracellular matrix by the smooth muscle cells.[6–9] Stent implantation reduces the restenosis rate[10,11] by preventing elastic recoil and late constrictive remodeling.[12] However, the occurrence of restenosis after stent implantation remains unresolved, especially in small vessels and long lesions, in which it may occur in >30% of cases.[13] Restenosis is primarily caused by neointimal hyperplasia, which occurs due to trauma of the arterial wall by the stent struts.[5]

Irradiation is used to decrease neointimal proliferation because the actively proliferating cells have an increased sensitivity to the lethal effects of radiation, which inhibits benign hyperplastic reactions such as keloid formation and heterotopic ossification.[14,15] Several experimental and clinical trials showed that brachytherapy with a radioactive source after PTCA or stent implantation can reduce restenosis by inhibiting neointimal hyperplasia,[16–19] and several animal studies demonstrated a dose-related reduction of in-stent restenosis with the use of radioactive stents.[20–22] Furthermore, a dose-dependent delay in the endothelialization of the stent occurred, which increased the chance of subacute thrombosis.[20,23]

This study evaluated the safety and feasibility of radioactive stent implantation (activity level, 0.75 to 1.5 μCi) in single-lesion, native coronary artery disease.

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TABLE 1. Balloon Inflation and Stent Deployment Data

Patient	Type of Stent	Predilatation			Stent Deployment		Postdilatation			Lesion Length, mm
		Diam, mm	Atm	Length, mm	Diam, mm	Atm	Diam, mm	Atm	Length, mm	
1	PS‡	3.0	6	20	3.0	10	3.5	16	30	17
2	PS	3.0	8	20	3.5	8	3.0	16	15	11
3	PS	3.5	14	30	3.5	10	3.5	16	13	10
4	PS	3.5	8	30	3.5	12	ND	ND	ND	15
5	BX*	2.5	14	20	3.0	12	3.5	16	13	15
6	BX	3.5	6	20	3.5	10	4.0	12	13	12
7	PS	3.0	10	20	3.0	12	3.5	10	13	11
8	BX	4.0	6	15	3.5	12	4.5	16	15	10
9	BX	2.5	6	15	3.5	16	2.5	12	15	14
10	BX	3.5	10	20	3.5	11	4.0	18	13	19
11	BX*	3.0	12	13	3.5	11	4.0	18	13	8
12	BX†*	3.0	10	20	3.0	12	3.0	18	20	17
13	BX*	3.0	10	20	3.0	8	3.5	16	13	17
14	BX	3.0	8	15	3.5	12	ND	ND	ND	14
15	BX	3.0	12	13	3.0	10	4.0	14	13	7
16	BX	3.0	12	13	3.0	10	4.0	16	13	10
17	BX	3.5	12	20	3.5	8	4.0	16	13	12
18	BX†	3.0	8	20	3.0	10	4.0	18	20	23
19	BX	3.5	7	20	3.5	7	4.0	14	13	10
20	BX†	3.0	14	29	3.0	18	3.5	16	29	15
21	BX	3.5	8	20	3.5	8	ND	ND	ND	12
22	BX	3.5	8	15	3.5	8	4.0	12	13	10
23	BX†	3.0	10	20	3.5	10	4.0	16	20	16
Mean		3.2	10	19	3.3	11	3.7	15	16	13
SD		0.4	3	5	0.2	3	0.5	2	5	4

Atm indicates maximum atmospheres; Diam, maximum diameter; ND, not done; PS, Palmaz-Schatz.
*1 additional nonradioactive stent implanted; †2 BX stents implanted; ‡2 additional nonradioactive stents implanted.

Methods

Patient Population

The Isostents for Restenosis Intervention Study (IRIS) is a nonrandomized, multicenter trial evaluating the safety and feasibility of radioactive stents. The data presented here represent the experience of the Heart Center Rotterdam. Patients who had single coronary lesions with a maximum lesion length of 28 mm (maximum, 2 radioactive stents of 15 mm implanted in tandem position) and objective evidence of ischemia were eligible. Exclusion criteria included the following: a recent myocardial infarction (MI; creatine kinase [CK] isoenzyme containing M and B subunits [MB] >3 times the upper limit of normal within 5 days of the intervention); left ventricular ejection fraction <40%; allergy or contraindication to aspirin, ticlopidine, or stainless steel; and lesions located in the left main artery or at the ostium of the right coronary artery. The Medical Ethical Committee of the University Hospital Rotterdam approved the study. All patients provided written, informed consent before the procedure.

Radioactive Stent, Dosimetry, and Safety Issues

Two types of stents were implanted in this study: the Palmaz-Schatz (Cordis Corp, Johnson and Johnson Interventional Systems Co) and BX stent (Isostent Inc). Phosphorus-32 (^{32}P), a pure β-emitter with a half-life of 14.3 days, was produced by neutron irradiation of red amorphous ^{31}P for 10 days to achieve a concentration of 20×10^{-6} $^{32}P/^{31}P$ (100 mCi). The irradiated phosphorus was then placed into a mass separator, ionized, and accelerated. A dipole magnet separated the ^{32}P and ^{31}P. Subsequently, ^{32}P was directly implanted into the metal stent surface.[21] The calculated radioactivity of the stents at implantation was 0.75 to 1.5 μCi, and the dose delivered over 100 days at 1 mm from the stent surface was calculated for each stent. All personnel were trained in the appropriate handling of radioactive materials. During implantation, the lucite shield enclosing the stent and the sheathed introduction system prevented exposure of the operator to the radiation of the stent. Background measurements of radioactivity were made by means of a Geiger counter (Model 14c, Ludlum Measurements Inc). All disposable materials that were in contact with the stent were immediately disposed of in a plexiglas container, and radioactivity measurements were made by the radiation technician.

Quantitative Coronary Angiography

Quantitative coronary angiography (QCA) was performed preprocedure, postprocedure, and at 6-month follow-up. Coronary angiography was performed after intracoronary administration of nitrates. The off-line analysis of $\geq$2 orthogonal projections was performed by the CAAS II analysis system (Pie Medical BV). Calibration of the system was based on dimensions of the catheters not filled with contrast medium. This method of analysis has been extensively validated and applied in numerous clinical trials.[24–26] The following measurements were obtained in each projection: minimum lumen diameter (MLD), reference diameter, percent diameter stenosis (%DS), and lesion length. Lesion length was user-defined.[26] Procedural success was defined as <20% DS as measured by online QCA. Short-term gain was defined as MLD postprocedure minus MLD

preprocedure. Late loss was defined as MLD postprocedure minus MLD at follow-up. Late loss index was defined as short-term gain divided by late loss.[27] Restenosis was defined as >50% DS at follow-up located within the stent or ≤5 mm from the stent edges. The latter represents an area where tissue is subjected both to balloon-induced trauma and to a lower dose of radiation,[21] which may stimulate restenosis. This edge-effect phenomenon has recently been described in patients and called the "candy-wrapper effect."[28] To quantify an edge effect, a QCA segmental analysis was performed. At both postprocedure and follow-up, the treated vessels were first divided into segments ≈5 mm in length; then, the mean diameter of the 5-mm segments distal and proximal to the stent edges were calculated using the CAAS II analysis system. Careful comparison of the proximal and distal edges was performed postprocedure and at follow-up.

Procedure and Follow-Up

Patients received 250 mg of aspirin and 10 000 IU of heparin at the start of the procedure. The activation clotting time was maintained at >300 s. After balloon predilatation, the radioactive stent was implanted at a nominal deployment pressure of 8 to 10 atm. If needed, stent deployment was optimized using shorter postdilatation balloons of longer diameters to higher pressures (Table 1). Extreme care was taken to avoid inflating the balloon outside the edges of the stent. Because of the poor radiopacity of the Palmaz-Schatz and the BX stents, the best angiographic view was selected, and images were filmed in a magnified field (5 inch) with digital zoom enhancement to optimize stent visualization. All patients received ticlopidine 250 mg BID for 4 weeks after stent implantation and aspirin 80 mg daily indefinitely. CK and CK-MB measurements were made, and the ECG was recorded at 6 and 12 to 18 hours postprocedure in all patients.

Patients returned for 1- and 6-month clinical follow-up. An ECG was performed at each visit. The 30-day and 6-month clinical end points were death, Q-wave MI (using the Minnesota code criteria[29]), non Q-wave MI (CK-MB rise >2 times normal upper limit), bypass surgery, target segment revascularization, sustained abrupt closure, or subacute thrombosis of the target vessel.

At the 6-month visit, an exercise stress test was performed. Target vessel revascularization was performed on the basis of clinical symptoms and/or evidence of ischemia on exercise testing.

Statistical Analysis

Data are presented as mean±SD. Continuous data were compared by 2-tailed Student's *t* test or linear regression when appropriate.

Results

Baseline Characteristics

Baseline demographics, anginal status, and lesion characteristics are shown in Table 2.

Procedural Success

A total of 30 of the 31 stents (97%) were successfully implanted (26 were BX Isostent and 4 were Palmaz-Schatz) in 26 patients. One stent (BX) was lost in the peripheral circulation without clinical sequelae. Eighteen patients were successfully treated with a single radioactive stent, and 4 required a second radioactive stent to cover lesions >15 mm. Five patients received additional nonradioactive stents: 2 due to procedural dissection not covered by the radioactive stent, 2 because a second radioactive stent was not available, and 1 because a second radioactive stent became dislodged when trying to implant it distal to the first radioactive stent. All procedures were successful, and no complications occurred.

TABLE 2. Patient Demographics

Sex, male/female	18/8 (69/31%)
Age, y	
Average	60
Range	43–74
Risk factors	
Diabetes mellitus	1 (4%)
Hypercholesterolaemia	16 (62%)
Hypertension	11 (42%)
Smoking	15 (58%)
Family history	11 (42%)
AP CCS	
2	3 (12%)
3	10 (38%)
4	13 (50%)
Lesion type, AHA/ACC	
B1	8 (31%)
B2	18 (69%)

Data are *n* (%) unless otherwise indicated. AHA indicates American Heart Association, and ACC, American College of Cardiology.

Follow-Up

The mean hospital stay was 1.8 days. All patients were angina-free at hospital discharge. At 30-day follow-up, no clinical end points had occurred: 24 patients (92%) were asymptomatic, and 2 patients (8%) had recurrent angina pectoris (AP) of Canadian Cardiovascular Society Classification (CCS) 1 (n=1) and CCS 2 (n=1). All 26 patients returned for 6-month clinical follow-up. Twenty-one (81%) were asymptomatic, and 5 patients (19%) had AP CCS 1 (n=1), CCS 2 (n=2), CCS 3 (n=1), or CCS 4 (n=1).

Six-month angiographic follow-up was performed in 23 patients (88%). The remaining 3 patients (12%) refused: 2 of them were asymptomatic, and the third had AP CCS 1. Four patients had angiographic restenosis (17%). All restenotic lesions were diffuse (located throughout the entire length of the stent). One of the 4 restenoses occurred in a patient with a single radioactive stent, 1 restenosis was in a patient receiving 2 radioactive stents in combination with a nonradioactive stent, and 2 restenoses were observed in patients receiving a combination of 1 radioactive and 1 nonradioactive stent. In the restenotic patients who received an additional nonradioactive stent, restenosis occurred in both the radioactive and the nonradioactive stent. On QCA, no discernible differences existed between the patterns of proliferation between the Palmaz-Schatz and BX stents. No cases of restenosis at the stent edges were noted. Two of the 4 restenotic patients underwent a re-PTCA. One was referred for bypass surgery for in-stent restenosis in the proximal left anterior descending coronary artery and progression of a previously nonsignificant lesion in the proximal left circumflex artery (main stem equivalent). One was treated medically; this patient was asymptomatic, with a negative stress test. No other clinical end points existed at 6-month follow-up.

TABLE 3. Dosimetry and QCA Analyses

Patient	Type of Stent	Activity, μCi	Dose, cGy	Artery	Lesion Length, mm	Preintervention			Postintervention			Follow-Up			Acute Gain	Late Loss	LLI
						MLD	DS	RD	MLD	DS	RD	MLD	DS	RD			
1	PS‡	1.07	712	RCA	17	0.65	76	2.64	2.48	19	3.04	1.74	30	2.51	1.83	0.74	0.40
2	PS	1.07	712	LAD	11	1.02	52	2.12	2.56	8	2.78	0.54	77	2.39	1.54	2.02	1.31
3	PS	0.97	647	LCX	10	0.46	85	3.05	2.93	15	3.41	2.77	18	3.36	2.47	0.16	0.06
4	PS	0.97	647	RCA	15	0.75	79	3.50	2.91	22	3.73	1.60	47	3.01	2.16	1.31	0.61
5	BX*	1.07	712	LAD	15	0.90	59	2.22	2.80	9	3.07	0.47	87	3.61	1.90	2.33	1.23
6	BX	1.50	1000	RCA	12	1.64	53	3.49	3.06	15	3.59	2.45	23	3.18	1.42	0.61	0.43
7	PS	0.75	500	LAD	11	0.67	75	2.67	2.64	15	3.12	1.58	39	2.58	1.97	1.07	0.54
8	BX	1.24	824	RCX	10	0.99	74	3.65	3.51	19	4.31	2.76	44	4.20	2.52	0.75	0.30
9	BX	1.12	748	RCX	14	0.50	77	2.08	1.92	12	2.19	1.77	26	2.39	1.43	0.16	0.11
10	BX	1.73	1157	LAD	19	0.99	71	3.31	3.18	18	3.87	2.39	16	2.82	2.19	0.79	0.36
11	BX*	0.88	587	LAD	8	0.59	79	2.73	3.42	17	4.11	2.65	20	3.32	2.83	0.77	0.27
12	BX†*	1.24	827	LAD	17	1.00	58	2.37	2.36	16	2.81	0.86	55	1.90	1.37	1.51	1.10
13	BX*	1.36	908	LAD	17	0.69	72	2.45	2.48	14	2.87	1.73	11	1.94	1.80	0.76	0.42
14	BX	1.12	748	LAD	14	0.62	79	2.96	2.75	12	3.12	1.61	44	2.86	2.13	1.15	0.54
15	BX	1.02	678	RCX	7	0.49	83	2.81	3.03	16	3.59	2.20	25	2.91	2.54	0.83	0.33
16	BX	1.06	712	LAD	10	1.10	67	3.36	3.27	10	3.63	1.87	34	2.81	2.17	1.41	0.65
17	BX	1.43	953	RCA	12	0.85	75	3.44	2.92	9	3.19	0.83	70	3.29	2.07	2.09	1.01
18	BX†	1.00	678	RCA	23	0.83	73	3.08	2.99	5	3.07	2.51	28	3.47	2.15	0.48	0.22
19	BX	1.02	677	RCX	10	0.96	71	3.28	2.90	17	3.50	2.87	17	3.46	1.94	0.03	0.02
20	BX†	0.75	500	LAD	15	1.13	60	2.81	2.81	17	2.81	1.97	39	3.23	1.69	0.84	0.50
21	BX	1.43	953	RCX	12	1.23	62	3.31	2.89	21	3.61	2.03	39	3.34	1.66	0.85	0.51
22	BX	1.06	700	RCA	10	1.16	66	3.37	2.91	9	3.18	1.72	45	3.12	1.75	1.20	0.68
23	BX†	0.75	500	RCA	16	0.90	68	2.75	2.66	23	3.45	1.73	42	2.99	1.76	0.93	0.53
Mean		1.10	743		13	0.87	70	2.93	2.84	15	3.31	1.85	38	2.99	1.97	0.99	0.53
SD		0.25	165		4	0.28	9	0.47	0.35	5	0.48	0.69	20	0.54	0.39	0.59	0.35

Dose indicates dose over 100 days at 1 mm from the stent surface; DS, percentage diameter stenoses; LAD, left anterior descending artery; LCX, left circumflex artery; LLI, late loss index; PS, Palmaz-Schatz stent; RCA, right coronary artery; and RD, reference diameter. QCA measurements are in mm.

*1 additional nonradioactive stent implanted; †2 BX stents implanted; ‡2 additional nonradioactive stents implanted.

QCA Measurements

QCA and procedural data are presented in Table 3. MLD increased from 0.87±0.28 mm preprocedure to 2.84±0.35 mm postprocedure ($P<0.0001$). MLD at follow-up was 1.85±0.69 mm ($P<0.0001$ relative to postprocedure), resulting in a late loss index of 0.53±0.35. Segmental analysis of the mean diameter of the 5-mm segments distal and proximal to the stent edges showed significant changes. The proximal diameter decreased from 3.19±0.42 mm postprocedure to 2.78±0.62 mm at follow-up ($P=0.006$). The distal diameter decreased from 2.69±0.49 mm postprocedure to 2.45±0.50 mm at follow-up ($P=0.0167$).

Radiation Doses

Stent activity level and the cumulative dose over 100 days that was delivered to a 1 mm depth outside the stent are presented in Table 3. No correlation existed between stent activity or delivered dose and MLD or late loss index at follow-up. No additional environmental radiation was measured during the procedure.

Discussion

This nonrandomized study illustrates that β-particle–emitting radioactive stent implantation is safe and feasible, with no subacute or 30-day clinical events recorded. Subacute thrombosis was not seen, despite the concern regarding delay in endothelialization, as previously reported in animal studies.[20,23] The embolization of the radioactive stent had no clinical sequelae at this level of activity. When stents with higher levels of radioactivity are implanted, this may not remain true. Detecting an embolized radioactive stent is a problem because (1) the β-radiation of the stent is not measurable outside the body and (2) the stents have a relatively low radiopacity. Clearly, there is room to increase the radiopacity or to add markers to the stents.

Using a multivariate model constructed from the data of the Benestent trials that was based on similar lesions, vessel size, and short-term result, a predicted restenosis rate of 12% and an MLD at follow-up of 2.05 mm was calculated.[30,31] Thus, the actual results achieved are somewhat less favorable; however, in such a small patient cohort, no definite conclusions can be drawn except that the late results are within the

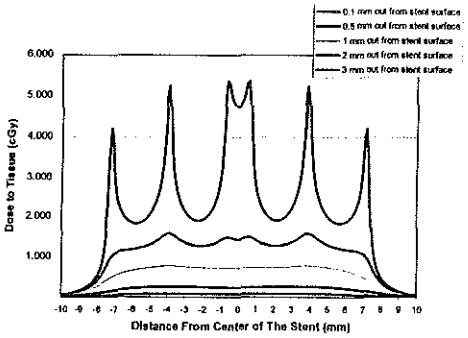

Figure 1. Two-dimensional dose representation for 1-μCi ^{32}P Palmaz-Schatz stent. Cumulative dose given over 100 days is shown (source, Isostent Inc).

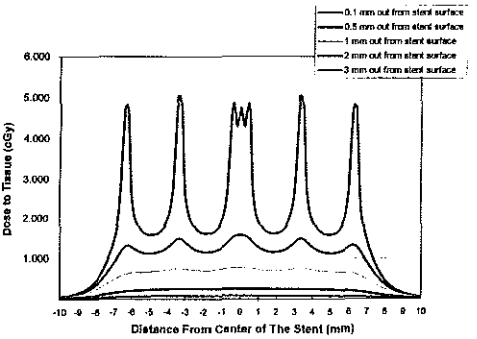

Figure 2. Two-dimensional dose representation for 1-μCi ^{32}P BX stent. Cumulative dose given over 100 days is shown (source, Isostent Inc).

acceptable limits for safety and feasibility of this stent. It must be noted that 3 of the 4 patients who had in-stent restenosis had multiple stents implanted, which increases the risk of restenosis; in the group of 18 patients who had a single radioactive stent implanted, only 1 had restenosis. Overall, these 6-month clinical and angiographic results are similar to the published results of nonradioactive stents.[10,11]

The Milan group was the first to report restenosis within the stent and at the edges of the stent (the candy-wrapper phenomenon); this restenosis was possibly caused by increased balloon injury (barotrauma) and the lower radiation dose at the stent edges.[21,28] In the Rotterdam series, particular attention was paid to avoiding balloon injury outside the stent to minimize the edge effect. No cases of edge restenosis were seen in this cohort; however, the proximal and distal mean diameter at the stent edges, measured postprocedure and at follow-up, decreased significantly. Because extreme care was taken to avoid inflating the balloon outside the stent edges, this edge effect may be caused by the lower radiation dose.

Dosimetry

Previous work by Janicki et al[32] on the 1.0-μCi Palmaz-Schatz stent demonstrated the nonuniformity of dosing in areas adjacent to stent strut wires and those areas between the wires. Models showed that for a ^{32}P stent of 1.0 μCi that was 15 mm in length, at a distance of 0.1 mm, dose values of 2500 cGy were delivered at the strut wires (peaks) and 800 cGy between the wires (valleys) over 1 half-life (14.3 days). The nonuniformity of dosing, reflective of stent geometry, decreased at distances 1 to 2 mm from the stent surface. Although these data provide an in-vitro analysis of dosing from a radioactive stent, the actual dose distribution is probably affected by variations in atherosclerotic plaque morphology and the symmetry of the lesion and stent expansion. The 2D dosimetry representation of the Palmaz-Schatz and BX stent were done using the Janicki model[32] (Figures 1 and 2).

Currently, dose-finding studies examining restenosis after implantation of ^{32}P BX stents in patients with lesion morphology similar to that described in this study are underway. It is possible that increased doses will decrease in-stent restenosis, as has been described in animal studies.[21–23] Therefore, a European Dose Response trial has been started with activities ranging from 1.5 to 3, 3 to 6, 6 to 12, and 12 to 20 μCi.

Conclusion

This study reports that the implantation of β-particle–emitting radioactive stents with an activity of 0.75 to 1.5 μCi is safe and feasible.

Acknowledgments

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Chapter 12

Compassionate use of intracoronary beta-irradiation for treatment of recurrent in-stent restenosis.

(J Invas Card 1999 11:582-588)

Compassionate Use of Intracoronary Beta-Irradiation for Treatment of Recurrent In-Stent Restenosis

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ABSTRACT: Recurrent in-stent restenosis after balloon angioplasty poses a serious management problem. Previously γ-radiation has been shown to be effective in patients with in-stent restenosis. The aim of the study was to determine the feasibility and safety of β-radiation in patients with recurrent in-stent restenosis. From May 1997 to December 1998, 18 patients were treated with balloon angioplasty (n = 8) or laser (n = 10), followed by intracoronary β-radiation at a prescribed dose of 16 Gray at 2 mm from the source, for reference diameters by quantitative coronary angiography < 3.25 mm or 20 Gray for reference diameters ≥ 3.25 mm. Vessels treated were as follows: left anterior descending: (n = 5); circumflex: (n = 4); right coronary artery: (n = 6); saphenous vein graft: (n = 3). Average recurrence rate was 2.4 ± 0.7 and the restenotic length was 16 ± 7 mm. β-radiation was successfully delivered in all patients. Two patients presented complications related to laser debulking: a non-Q wave myocardial infarction in one and a re-angioplasty due to uncovered distal dissection in another. Geographical miss, defined as an area which has been injured but not covered by the radiation source, was demonstrated in 8 patients. Seventeen patients (94%) completed the 6-month angiographic follow-up. Restenosis (> 50% Diameter Stenosis) was observed in 9 patients (53%), leading to target lesion revascularization in 8 patients (47%). Six of the 9 restenoses were located in areas with geographical miss. Intracoronary β-radiation for recurrent in-stent restenosis appears to be a safe and feasible management strategy. However, the mismatch between injured and irradiated area may lead to failure of this therapy.

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Key words: balloon angioplasty, geographical miss, in-stent restenosis, laser debulking, radiation therapy

The long-term results of balloon angioplasty are limited by the occurrence of restenosis in 30–60% of all cases.[1,2] Mechanisms involved in the restenotic process include acute recoil, neointimal proliferation and late vessel constriction.[3-6] Stent implantation demonstrated a beneficial effect by preventing both the acute recoil and the late negative remodeling of the vessel.[7,8] However, the restenosis after stent implantation, which is caused by neointimal hyperplasia, occurs in 15–20% of the cases.[7,8] Treatment of in-stent restenosis is rather disappointing, with recurrence rates of 38–50%,[9-11] which increase with the number of re-interventions.[12] Radiation therapy appears to be a novel therapy to inhibit the proliferative response after balloon-injury.[13-16] Three randomized trials have demonstrated the efficacy of gamma-radiation in the treatment of in-stent restenosis.[17-19] A non-randomized trial reported favorable results with the use of beta-radiation for the treatment

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Table 1. Baseline characteristics (n = 18)

Gender (male):	12 (67%)
Age (years):	62 ± 10
Coronary risk factors	
Smoking	5 (28%)
Dyslipidemia	11 (61%)
Systemic hypertension	8 (44%)
Diabetes mellitus	3 (17%)
Family history of coronary disease	8 (44%)
Treated vessel	
Left anterior descending	5 (28%)
Left circumflex	4 (22%)
Right coronary artery	6 (33%)
Saphenous vein graft	3 (17%)
Recurrence number	2.4 ± 0.7
Stable angina:	15 (83%)

Continuous data are presented as mean ± SD

of in-stent restenosis.[20] To date, no data exist regarding the efficacy of brachytherapy in the subgroup of patients with recurrent in-stent restenosis. Thus, we designed this pilot study to evaluate the feasibility and safety of beta-radiation therapy in patients with recurrent in-stent restenosis.

METHODS

Patient selection. Patients eligible for the study were those with recurrent in-stent restenosis with objective evidence of ischemia. The following inclusion criteria were required: the lesion treated involved the second episode of restenosis in the same stented segment; the lesion length had to measure < 25 mm and, the vessel size between 2.5 and 4.0 mm in diameter. Patients were excluded if they had received previous radiation therapy on the chest; had a left ventricle ejection fraction < 40%; suffered from a recent myocardial infarction (< 3 days), the target lesion would not withstand the source dwell time of > 3 minutes; the result after BA was unsuccessful as defined by diameter stenosis > 35% or minimal luminal diameter < 1.5 mm; and finally, an allergy or contraindication to aspirin. Female patients of child-bearing age required a negative pregnancy test and undertook not to get pregnant during the study.

Radiation delivery system. The Beta-Cath System™ (Novoste Corp., Norcross, Georgia) was used to deliver localized beta-radiation at the site of coronary intervention. The device consists of 3 components: 1) the transfer device which stores the radiation source train and allows the positioning of these sources within the catheter; 2) the delivery catheter, which is a 5 French (Fr) multilumen over-the-wire non-centered catheter which uses saline solution to send and return the radiation source train; and 3) the radiation source train consisting of a series of twelve independent cylindrical seeds which contain the radioisotope 90Sr/90Y sources and is bordered by 2 gold radiopaque markers separated by 30 mm.[21]

Procedure. The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, approved the

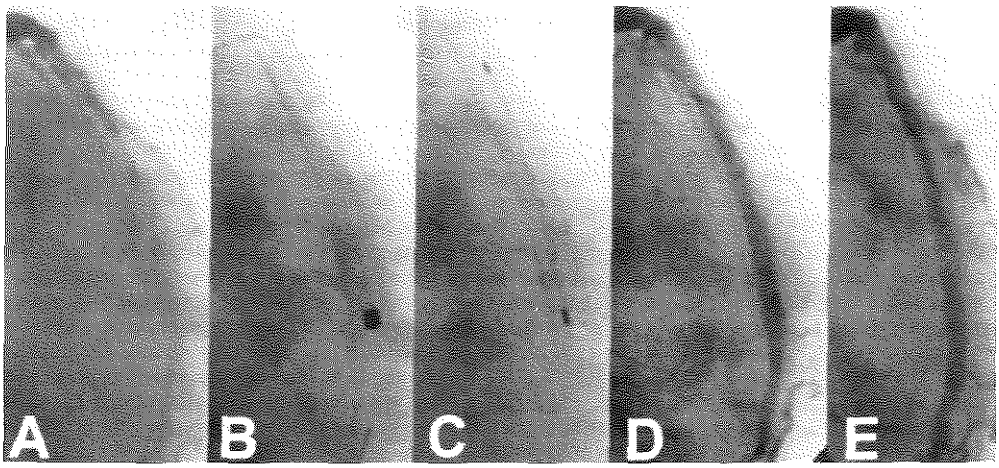

Figure 1. *(A) Coronary angiography of a severe in-stent restenosis in a Wallstent® in a saphenous venous bypass graft, (B) treated with concentric laser debulking, (C) followed by intracoronary radiation. (D) Angiographic result of the procedure. (E) No significant angiographic restenosis is observed at 6-month follow-up.*

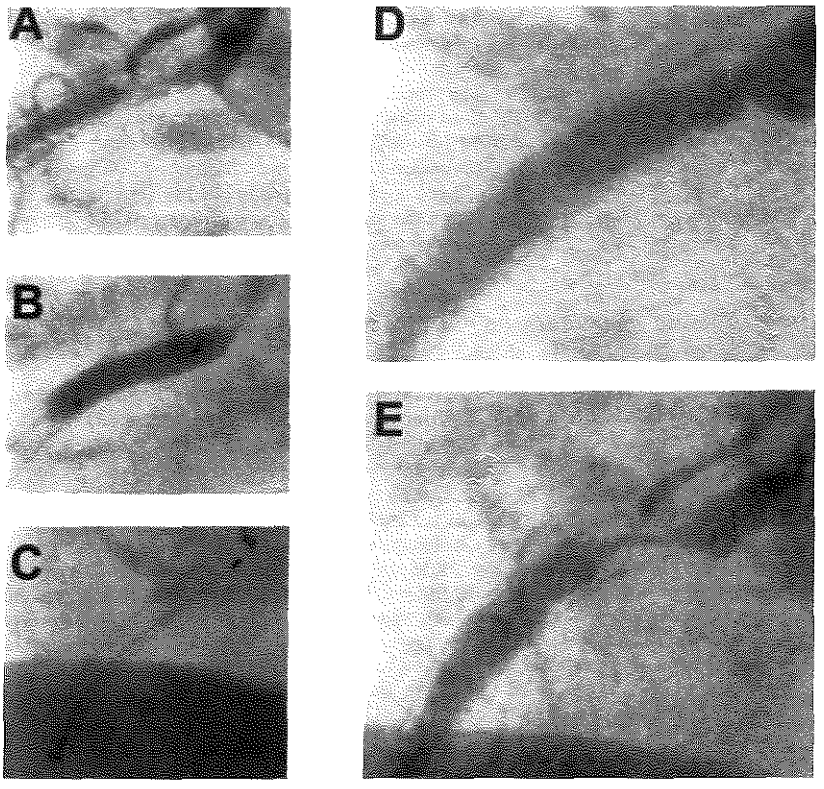

Figure 2. *(A) Coronary angiography of a severe in-stent restenosis in the right coronary artery, (B) treated with balloon angioplasty, (C) followed by intracoronary radiation. (D) Despite a good angiographic result, (E) a severe restenosis was observed at follow-up.*

study and all patients signed a written informed consent form. Patients received 250 mg aspirin and 10,000 IU heparin at the initiation of the procedure, and additional doses of heparin were administered to maintain the activated clotting time > 300 seconds. In diffuse restenosis, plaque debulking was performed by the use of Vitesse II® excimer laser catheters of 1.7 or 2.0 mm (Spectranetics International BV., Colorado Springs, Colorado) followed by balloon angioplasty according to standard clinical practice. In focal restenosis, treatment was performed only with balloon angioplasty. After successful treatment, the radiation delivery catheter was placed at the target site. The radioactive seeds remained in place during a dwell-time of 2.5 to 4.0 minutes to deliver a dose of 16 Gy or 20 Gy for lesions with a reference diameter by quantitative coronary angiography < 3.25 mm or ≥ 3.25 mm, respectively. The dose was prescribed at 2 mm from the source. Because of the low penetration force of beta-energy in tissue, no additional measures were taken to protect the patient or staff. The delivery of the radioactive seeds was carried out by a radiation oncologist.

Follow-up. Patients returned for 6-month clinical and angiographic follow-up. A control ECG was performed at the time of the visit. The following clinical endpoints were defined at 6 months: death, Q-wave myocardial infarction (using the Minnesota code criteria),[30] bypass surgery, and target lesion revascularization.

Definitions. *In-stent restenosis* was defined as focal when the restenotic segment measured < 10 mm and diffuse when it measured ≥ 10 mm. *Procedural success* was defined as < 35% diameter stenosis post-procedure without acute complications (coronary dissection, acute myocardial infarction or death). *Geographical miss* is the term used in radio-oncology to define a cause of failure of the treatment due to low-dosage. In such cases, a small part of the treatment zone has either escaped radiation or been inadequately irradiated because the total volume of the tumor was not appreciated and hence an insufficient margin was taken.[23] This concept is translated in interventional cardiology for those cases where the radiation source cannot fully cover the injured area. Basically, two reasons may account for this phenomenon: coronary

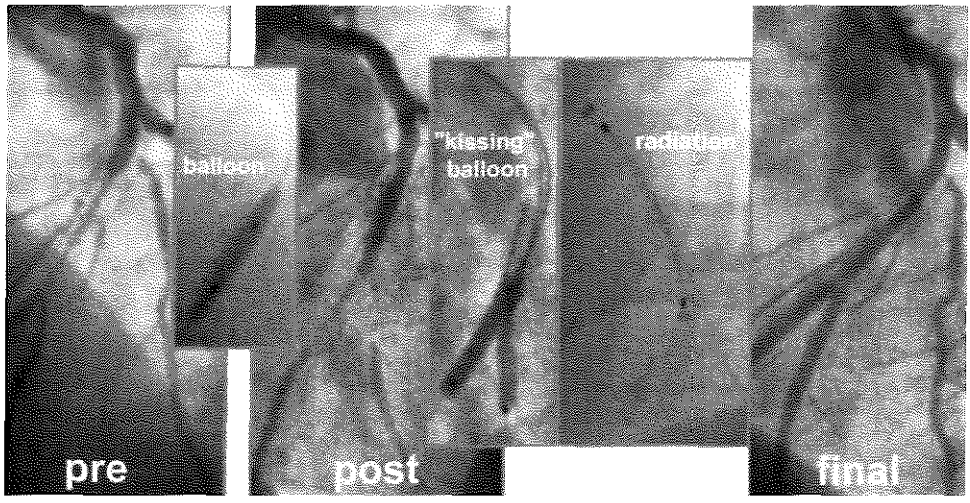

Figure 3. *Serial coronary angiograms showing a coronary dissection following balloon angioplasty which involved the distal segment of the left anterior descending and the second diagonal. Additional kissing balloon and stent implantation were performed. The radiation source could cover only the original restenotic area (geographical miss). At follow-up, a diffuse restenosis at the site of the geographical miss was demonstrated.*

dissection extended to the edges of the radiation source which leads to an additional treatment or source shorter than the targeted and injured area. Overall, there exist traumatized areas receiving low dose which is potentially not able to prevent either neointimal proliferation or vessel shrinkage. To identify those areas with geographical miss these steps were followed: during the procedure all balloon inflation and laser passes were filmed in the same projection as was the radiation source. This approach allowed us the correct matching of the cinefilms in the off-line analysis. By the use of the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands), either of the cineloops showing balloon inflation, laser passes and radiation source may be displayed simultaneously on the screen. By selecting those frames in the same part of the cardiac cycle, we were able to define whether the radiation source completely covered the injured area.

Quantitative coronary angiography. Quantitative coronary angiography was performed prior and after intervention, and at 6-month follow-up. All angiograms were analyzed after intracoronary administration of nitrates. The off-line analysis of at least two orthogonal projections was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters not filled with contrast medium. This method of analysis has been previously validated.[24-26] The following measures were obtained in each projection: minimal luminal diameter, reference diameter, percent diameter stenosis and lesion length. Lesion length was user defined and not done by an algorithm using curvature analysis of the diameter function.[25] Reference diameter was obtained by an interpolated method.[24-26] Diameter stenosis post stent implantation and at follow-up was defined as the minimal luminal diameter within the injured segment related to the interpolated diameter measured over the length of the stent. Acute gain was defined as minimal luminal diameter measured after treatment minus minimal luminal diameter pre-intervention. Late loss was defined as minimal luminal diameter post-intervention minus minimal luminal diameter at follow-up. Late loss index was defined as late loss divided by acute gain.[26] Restenosis was defined as > 50% diameter stenosis at follow up and located in the mediated area on either of the edges.

Statistical analysis. Data are presented as mean ± standard deviation or proportions. To compare continuous data in patients treated with and without laser the unpaired two-tailed Student's t-test was performed. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics. From May 1997 to February 1999, 18 patients were treated according to the above protocol. Baseline characteristics of the study population are presented in Table 1. Number of

Table 2. Lesion and quantitative coronary angiography data

Pat. no.	Laser	Stent Type	Stent Length	Lesion Length	Pre procedure MLD	DS%	RD	Post procedure MLD	DS%	RD	Follow up MLD	DS%	RD	Acute Gain	Late loss Index
1	yes	Wallstent	39	26	0.45	80	2.28	1.80	30	2.58	1.89	29	2.66	1.35	-0.07
2	yes	BARD	19	19	0.82	68	2.51	1.62	36	2.54	1.63	26	2.21	0.80	-0.01
3	no	Wallstent	24	24	0.93	52	1.92	1.4	25	1.92	0.00	100	—	0.51	2.82
4	yes	Wallstent	34	6	0.70	70	2.37	1.77	28	2.46	1.38	43	2.41	1.07	0.36
5	yes	Wallstent	34	26	0.07	97	1.87	1.35	23	1.76	0.70	69	2.24	1.29	0.51
6	no	AVE	39	16	0.95	66	2.76	2.02	30	2.90	1.58	41	2.67	1.07	0.41
7	no	NIR	9	9	0.00	100	2.51	1.95	21	2.47	0.35	85	2.35	1.95	0.82
8	no	Wallstent	24	14	0.82	70	2.77	1.98	26	2.67	1.79	29	2.54	1.16	0.16
9	yes	Multilink	35	21	1.49	48	2.86	2.48	25	3.31	2.29	41	3.85	0.99	0.19
10	yes	NIR	16	5	0.91	63	2.49	2.01	19	2.48	1.05	57	2.47	1.10	0.87
11	no	Wallstent	34	7	0.55	74	2.14	2.25	38	3.61	0.80	80	4.00	1.70	0.85
12	no	Multilink	25	23	1.18	51	2.39	1.77	33	2.66	2.30	16	2.74	0.59	-0.89
13	yes	BARD	19	23	0.92	56	2.10	1.81	31	2.62	0.88	59	2.13	0.89	1.04
14	yes	Crown	22	19	1.04	46	1.93	1.59	19	1.97	NA	NA	NA	0.55	NA
15	yes	Naevius	15	10	0.53	85	3.48	2.64	25	3.51	1.67	45	3.03	2.11	0.46
16	no	NIR	16	16	1.28	56	2.88	2.76	10	3.06	1.34	52	2.80	1.48	0.96
17	no	Bestent	25	9	1.08	47	2.03	1.49	19	1.85	0.81	54	1.76	0.41	1.65
18	yes	Biodyvisio	15	15	0.70	75	2.79	2.16	17	2.60	0.61	78	2.77	1.46	1.06
Mean			19	16	0.80	67	2.45	1.94	25	2.61	1.25	53	2.68	1.14	0.64
SD			4	7	0.38	16	0.42	0.40	7	0.53	0.68	24	0.60	0.48	0.82

MLD = minimal lumen diameter; DS = diameter stenosis; RD = reference diameter; NA = not available

recurrences of restenoses were 2 in 10 patients (55%), 3 in 7 patients (39%) and 4 in 1 patient (6%).

Procedural data. Lesion characteristics and QCA data are presented in Table 2. Laser debulking was performed in 10 patients. Lesion length showed a trend to be longer in patients pre-treated with laser as compared to patients treated only with balloon angioplasty (17 ± 7 mm vs. 12 ± 3 mm, respectively; $p = 0.06$). Examples of patients treated either with laser debulking or balloon angioplasty alone prior to radiation are depicted in Figures 1 and 2. Procedural success was achieved in 16 patients (89%). In two cases the procedure was complicated by a dissection secondary to laser debulking leading to a transient occlusion of the vessel: a non-Q wave infarction occurred in one case and a re-angioplasty in a distal segment was performed in the other patient. Radiation was successfully delivered in all cases. The prescribed dose at 2 mm from the source was 16 Gy in 16 patients and 20 Gy in 2 patients. Retrospective analysis of the angiograms revealed that geographical miss occurred in 8 cases: distal dissection in which additional stents were implanted distal to the irradiated area (n = 3) and area injured by the balloon but not covered by the radiation source (n = 5). An example of the outcome of a patient with geographical miss is depicted in Figure 3. All patients were discharged asymptomatic.

Follow-up. Seventeen patients (94%) returned for angiographic follow-up. One patient refused. Follow-up QCA data are presented in Table 2. Restenosis was observed in 9 patients (53%). In 7 patients, the location of the restenosis was at the edge of the irradiated area, whereas in 2 patients it was within the irradiated area. The number of recurrences of restenoses were comparable between restenotic and non-restenotic patients. Six of the 7 edge restenoses were in areas with geographical miss. There were neither deaths nor Q-wave myocardial infarctions observed at 6-month follow-up. Total lesion revascularization was performed in 8 patients (47%): 3 patients were referred for bypass surgery and 5 underwent re-PTCA. Progression of atherosclerosis was also observed in the non-irradiated vessels in the 3 patients referred for surgery. Acute gain, late loss and late loss index were similar between patients pre-treated with and without laser debulking (p = NS).

DISCUSSION

This study describes the use of beta-radiation therapy for the treatment of recurrent in-stent restenosis. Although this treatment modality is feasible and safe, the observed restenosis rate in this small cohort of patients remains rather high (53%), and is comparable to conventional treatment either with balloon angioplasty or debulking techniques.[10,11] The main finding was that the vast majority of the restenosis were located in areas with geographical miss. To date, three randomized placebo-controlled trials have been carried

out to evaluate the efficacy of gamma-radiation in patients with restenosis.[17,19] Teirstein et al,[17] randomized 55 patients to receive a 0.030" ribbon containing 192 Ir sealed sources or a ribbon containing placebo seeds (Best Industries, Springfield, Virginia). Thirty-five patients were treated due to in-stent restenosis. The dosimetry was calculated based on intravascular ultrasound measurement in a range of 8–30 Gray to the internal elastic membrane. The placebo group showed a restenosis rate of 70%, as compared to 14% in the irradiated group (p = 0.0006). This beneficial effect was sustained at 2-year follow-up.[27] Waksman et al,[18] evaluated 130 patients who had developed in-stent restenosis up to 47 mm in the Washington Radiation for In-Stent restenosis Trial (WRIST). These patients were randomized to radiation using a 192 Ir ribbon versus a non-radioactive ribbon delivered into a non-centered closed-end lumen catheter (Medtronic, Minneapolis, Minnesota). The prescribed dose was 15 Gray to a distance of 2 mm from the center of the source for a vessel size of 3.0–4.0 mm, and to a distance of 2.4 mm from the center of the source for vessel diameter of 4.0–5.0 mm. At 6-month follow-up, the irradiated group showed a reduction of 67% in the restenosis rate, 79% in total lesion revascularization and 63% in major adverse cardiac events. Similarly, the multicenter randomized GAMMA-1 trial demonstrated a reduction of 58% in the restenosis rate within the stent. When considering the edges of the source, the reduction in the restenosis rate was 43%.[19] Using beta-radiation therapy, the non-randomized Beta-WRIST trial demonstrated a reduction in target vessel revascularization of 47% when compared to a matched group from the placebo arm of the WRIST trial.[20] Although easier to implement in the catheterization laboratory, the use of beta-radiation presents the potential drawback of the steep dose fall-off, which might lead to inhomogeneity of the prescribed dose to the vessel wall.[28] This phenomenon may be more pronounced when non-centered devices are used, where the dose reaching the predefined adventitial volume might be as less as 30% of the prescribed dose.[28] Considering these beta-radiation characteristics, we hypothesize that areas with geographical miss may have received a very low dose which has not been able to inhibit either proliferation or vessel shrinkage. The importance of low-dose radiation in injured areas will be addressed in further ongoing randomized studies (START trial/ INHIBIT trial).

Limitations. This was a non-randomized, non-placebo-controlled study with a relatively small number of patients included. Thus, no conclusions regarding effectiveness of the beta-radiation for treatment of this challenging population with restenosis can be drawn. In this regard, the main cause associated to the restenosis in this cohort was the presence of injured areas not covered by the radiation source. This limitation may be solved with the use of the recently developed longer radiation sources (up to 40 mm).

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Chapter 13

European Clinical Trials

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24. EUROPEAN CLINICAL TRIALS

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The pioneering work in the field of intravascular radiation therapy was originally carried out in Europe. In 1992. Liermann et al performed the first four cases of brachytherapy after femoral percutaneous angioplasty.[1] Subsequently, animal experiments carried out in the USA[2,3] and Europe[4] demonstrated the reduction of neointimal hyperplasia after endovascular radiotherapy. The insertion of a radioactive delivery catheter in human coronary arteries was performed for the first time by Condado et al in Venezuela.[5] As a result of these pioneering investigations, the first clinical trials were reported in 1997: in the USA, Teirstein et al demonstrated the effectiveness of gamma therapy for the treatment of in-stent restenosis,[6] whilst in Europe, Verin et al reported the feasibility of using beta sources after balloon angioplasty.[7]

In Europe, most of the trials have been carried out using beta-radiation sources, either with catheter-based systems or radioactive stents. Overall, the initial target has been the treatment of de novo coronary stenosis. However, recent design trials have included patients with restenotic lesions. This chapter summarizes the clinical trials carried out in Europe either as a part of larger trials designed in the USA or primarily designed in Europe.

Intracoronary radiation clinical trials using catheter-based systems

The clinical trials with catheter-based systems are summarized in Table 24.1. Initially, these trials were aimed at demonstrating the safety and feasibility of beta emitters in coronary arteries. Currently, results from the dose-finding and placebo-controlled trials are pending.

The GENEVA pilot clinical experience

This was the first feasibility study performed in Europe (Geneva, Switzerland) and also the first in the world to use intracoronary beta-radiation in humans.[7] A pure ^{90}Y beta-emitter source delivered via a centering catheter (Schneider Endovascular Radiation System, Schneider Worldwide, Büllach, Switzerland) was used to deliver 18 Gy at the surface of the balloon in 15 patients with de novo coronary stenoses treated with balloon angioplasty. At follow-up the restenosis rate was 40%. The investigators considered these to be unfavorable results owing to an insufficient dose administered at the adventitia (< 4 Gy).

Table 24.1 Intracoronary radiation clinical trials using catheter-based systems

Study (principal investigator)	*Design*	*Radiation system*	*Source*	*Prescribed dose*
GENEVA pilot study (V Venn/ Y Popowski)	Prospective, open- label	Schneider intravascular radiation system	^{90}Y wire (29 mm)	18 Gy to the inner arterial surface
Boston Scientific/ Schneider Dose-Finding Study (W Wijns)	Prospective, multi-center, randomized, dose-finding	Boston Scientific/Schneider intravascular radiation system	^{90}Y wire (29 mm)	9, 12, 15, and 18 Gy at 1 mm from the balloon surface
BERT 1.5 – European arm (PW Serruys)	Prospective, uncontrolled	Novoste system	^{90}Sr/^{90}Y seeds (30 mm)	Randomized 12, 14, 16 Gy at 2 mm from the source
Beta Cath (RE Kuntz)	Prospective, randomized, placebo-controlled, triple-masked	Novoste system	^{90}Sr/^{90}Y seeds (30 mm)	Randomized placebo or radiation (14 Gy in vessels ≥ 2.7 ≤ 3.35 mm and 18 Gy in vessels > 3.35 ≤ 4.0 mm) at 2 mm from the source
BRIE (PW Serruys)	Prospective, uncontrolled	Novoste system	^{90}Sr/^{90}Y seeds (30 and 40 mm)	14 Gy (≥ 2.5 ≤ 3.25 mm) or 18 Gy (> 3.25– ≤ 4.0 mm) at 2 mm from the source
START (JJ Popma)	Prospective, randomized, placebo-controlled triple-masked	Novoste system	^{90}Sr/^{90}Y seeds (30 mm)	Randomized placebo or radiation (16 Gy in vessels ≥ 2.7 ≤ 3.35 mm and 20 Gy in vessels > 3.35 ≤ 4.0 mm) at 2 mm from the source
START 40-20 (JJ Popma)	Prospective, control group of START will be used as control	Novoste system	^{90}Sr/^{90}Y seeds (40 mm)	16 Gy in vessels ≥ 2.7 ≤ 3.35 mm and 20 Gy in vessels > 3.35 ≤ 4.0 mm at 2 mm from the source
RENO (P Urban)	Prospective, surveillance registry	Novoste system	^{90}Sr/^{90}Y seeds (30 and 40 mm)	14–20 Gy after balloon, 16–22 Gy in stented pts, at 2 mm from the source
PREVENT (A Raizner)	Prospective, randomized, blind	Guidant intravascular radiotherapy system/Nucleotron (afterloader)	^{32}P wire (27 mm)	Randomized 0, 28, 35, 42 Gy, at 0.5 mm into the vessel wall

Inclusion	Population/ number of centers	Period	Primary end-point	Status/ results
De novo lesions	15 pts/1 center in Switzerland	June 1995–November 1995	Feasibility and safety at 6 months	Completed — demonstrated safety and feasibility
De novo lesions	181 pts/ 5 centers in Europe	September 1997–September 1999	Angiographic criteria at 6 months	Interim results: dose-dependent reduction in the restenosis rate
De novo lesions	31 pts/ Rotterdam	April 1997–June 1998	Safety, feasibility and angiographic restenosis at 6 months	Completed — demonstrated safety and feasibility
De novo or restenotic lesions without a stent	1450 pts/55 sites in USA and 3 sites in Europe	July 1997–June 2000	TVR and MACE at 8 months	Enrollment phase
De novo or restenotic lesions without a stent in up to two vessels	350 pts (150 pts with single lesions and 100 with 2-vessel disease)/20 sites in Europe	July 1997–June 2000	TVR and MACE at 1 month and 6 months and 1 year. Angiographic criteria, aneurysm formation at 6 months	Enrollment phase
In-stent restenotic lesions	476 pts/49 sites in USA and 2 sites in Europe	September 1998–December 1999	TVR and MACE at 8 months	Follow-up phase
In-stent restenotic lesions	200 pts/25 sites in USA and 1 site in Europe	August 1999–August 2000	TVR and MACE at 8, 12, and 24 months and angiographic restenosis at 8 months	Enrollment phase
De novo or restenotic lesions up to three vessels	1000 pts/50 sites in Europe	April 1999	MACE at 6 months	Enrollment phase
De novo and restenotic lesions	50 pts/site in USA and 35 pts/site in Europe	February 1998–2000	Feasibility, safety and MACE at 1 and 6 months	Enrollment completed; follow-up phase

Continued

Table 24.1 continued

Study (principal investigator)	Design	Radiation system	Source	Prescribed dose
INHIBIT (R Waksman)	Prospective, randomized, double-blind, sham-controlled	Guidant intravascular radiotherapy system/Nucletron (afterloader)	^{32}P wire (27 mm)	Randomized 0 or 20 Gy, at 1 mm into the vessel wall
DURABLE (PW Serruys)	Prospective, randomized, controlled, double-blind	Guidant intravascular radiotherapy system/Nucletron (afterloader)	^{32}P wire (27 mm)	16 Gy at 0.5 times reference diameter + 1 mm distance from the source
MARS (De Scheerder)	Prospective, registry	Mallinckrodt system	^{188}Re liquid-filled balloon (25 mm)	20 Gy at 0.5 mm into the vessel wall
GRANITE (PW Serruys)	Prospective, uncontrolled	Cordis gamma IRT™ delivery system	^{192}Ir seeds (23, 39, 55 mm)	14 Gy at 2 mm from the source

Intracoronary beta-radiation following PTCA for reduction of restenosis using the Boston Scientific/Schneider system: Dose-Finding Study

This multi-center, prospective, randomized, non-controlled study aimed to determine the effect of four different doses of beta-radiation, using the ^{90}Y pure beta-emitting source via a centering catheter (Schneider Irradiation Therapy System, Büllach, Switzerland) on coronary stenosis. In five European centers, 181 patients were randomized to receive 9, 12, 15, or 18 Gy at 1 mm tissue depth. The preliminary analysis demonstrated a dose-dependent reduction in angiographic restenosis with an extremely low restenosis rate in the 18 Gy arm: 8.3% in all patients (stented and treated with balloon alone) and 4.2% in patients treated with balloon alone (V Verin, personal communication, Congress of the European Society of Cardiology Barcelona, August 1999). Final results will be available by November 1999.

BERT 1.5 (Beta Energy Restenosis Trial—1.5): the Rotterdam experience

BERT 1.5 stands for the European arm of the BERT trial. This trial was conducted at the Thoraxcenter in Rotterdam in 31 patients from April 1997 to June 1998. This feasibility study was designed to test the ^{90}Sr/^{90}Y source in

Inclusion	Population/ number of centers	Period	Primary end-point	Status/ results
In-stent restenotic lesions	360 pts/USA and Europe	August 1998	TLR death or Q-MI at 9 months	Enrollment phase
De novo or restenotic lesions (≥ 1 lesion)	900 pts/9 centers in The Netherlands	October 1999	MACE at 1 year	Approval phase
De novo lesions	35 pts/2 centers (Belgium, The Netherlands)	November 1998-March 1999	Feasibility and safety at 6 months	Enrollment completed
In-stent restenotic lesions	120 pts/11 sites in Europe and 1 in Australia	June 1999-February 2003	Angiographic criteria, MACE safety at 6 and 36 months	Enrollment phase

a hydraulic system (Beta-Cath™ system, Novoste Corporation, Norcross, GA, USA). The dose was randomized to 12, 14 or 16 Gy prescribed at 2-mm depth from the source axis. Twenty-three patients were treated with balloon angioplasty, whereas eight patients received a stent after radiation. Delivery of radiation was successful in all patients but one. At 6 months, the restenosis rate was 28% and target vessel revascularization 23%. Two thrombotic occlusions in patients receiving a stent after radiation were observed at the 2.5- and 10-month follow-up.[14]

Beta-Cath Trial

This prospective, randomized, placebo-controlled trial aims to evaluate the safety and effectiveness of the $^{90}Sr/^{90}Y$ source (Beta-Cath™ system) versus placebo in de novo and restenotic lesions of native coronary arteries. Three centers in Europe are participating in this trial. Complete 8-month follow-up data will be available in 2000.

BRIE Trial (Beta Radiation in Europe)

This non-randomized trial is designed to evaluate the safety and performance of the $^{90}Sr/^{90}Y$ source (BetaCath™ system) in de novo and restenotic lesions of native coronary arteries up to two vessels. This study is being carried out only in Europe (20 sites). Complete 8-month follow-up data will be available in 2000.

START Trial (STents And Radiation Therapy)
This prospective, randomized, placebo-controlled trial aims to evaluate the safety and performance of the $^{90}Sr/^{90}Y$ source (Beta-Cath™ system) in the treatment of in-stent restenosis of native coronary arteries. Two sites in Europe are involved in this study. The enrollment phase will be completed by the end of 1999. One site in Europe will be involved in the START 40-20 Trial, which is designed to assess the feasibility and efficacy of the 40-mm long $^{90}Sr/^{90}Y$ source for the treatment of in-stent restenotic lesions.

RENO Trial (European surveillance Registry with the Novoste Beta-Cath™ system)
This prospective multi-center, multi-national surveillance registry is designed to assess the clinical event rate of $^{90}Sr/^{90}Y$ source (Beta-Cath™ system) combined with approved PTCA techniques (balloon angioplasty, rotablator, laser, and stenting) in patients with coronary artery disease (native or bypass grafts). This study is being carried out only in Europe (50 sites) and multi-vessel treatment up to three vessels is allowed.

PREVENT (Proliferation REduction with Vascular ENergy Trial)
Prospective, randomized, blinded, multi-center study aimed to determine the safety of the Guidant (Santa Clara, CA) beta-radiation system in human coronary arteries following PTCA or stent implantation. The system consists of a ^{32}P 27-mm source wire, a centering spiral balloon and an automatic computerized afterloader (Nucletron BV, Waardgelder, Veenendaal, The Netherlands). The enrollment phase has been completed in Europe and 6-month angiographic and clinical follow-up data are expected by the first quarter of 2000.

INHIBIT (INtimal Hyperplasia Inhibition with Beta In-stent Trial)
A randomized, multi-center, double-blind, sham-controlled study started in the USA and Europe to demonstrate the clinical safety and efficacy of the Guidant beta-radiation system for treatment of in-stent restenosis. The enrollment phase will be completed by the end of 1999 and 9-month angiographic and clinical follow-up will be available by the end of 2000.

DURABLE Trial (DUtch RAndomized Brachytherapy study for Long-term evaluation of Efficacy)
This randomized, placebo-controlled, double-blind study is aimed to assess the effect of brachytherapy by means of the Guidant intravascular brachytherapy system, after optimal balloon angioplasty (stenosis diameter < 35%), elective stenting, and indicated stenting (bail-out and suboptimal result) in patients with multi-vessel stentable lesions (up to two vessels) with

respect to MACE-free survival at 1 year. Nine hundred patients will be randomized in nine centers in The Netherlands. The enrollment phase started in October 1999.

MARS (Mallinckrodt Angioplasty Radiation Study)
This is the first European prospective registry to assess the feasibility and safety of the ^{186}Re liquid-filled balloon (Mallinckrodt System) for the treatment of de novo coronary lesions. Results at the 6-month follow-up will be available by the end of 1999.

The GRANITE Study (Gamma-Radiation to Atheromatous Neointima using Intracoronary Therapy in Europe)
This is the first trial utilizing gamma-radiation for the treatment of coronary in-stent restenosis in Europe. Patients will be followed up for 3 years at 11 sites in Europe including France, Germany, Italy, and The Netherlands, as well as one site in Australia. The radiation system (Gamma IRT™ Delivery System, Cordis, Miami, FL) consists of a ribbon of radioactive ^{192}Ir seeds (up to 55 mm in length) that will be delivered to the target lesion via a delivery catheter with a closed end lumen and using a hand-cranked containment/delivery device. The radioactive ribbon will be left at the angioplasty site for between 15 and 25 min to deliver the prescribed dose.

Intracoronary radiation clinical trials using radioactive stents

The clinical trials utilizing radioactive stents have demonstrated safety and effectiveness in preventing neointimal proliferation in a dose-related manner. However, a new phenomenon has become evident: restenosis at the edges of the high activity radioactive stent, coined the 'candy wrapper' effect.[8] The clinical trials using radioactive stents are summarized in Table 24.2.

IRIS Trial (Isostent for Restenosis Intervention Study)
This feasibility registry involved three centers in Europe in which 40 radioactive stents with an activity of 0.75–1.5 μCi were implanted. This trial demonstrated feasibility and safety with a restenosis rate that ranged between 17% (Rotterdam)[9] and 50% (Milan).[10]

European ^{32}P Dose–Response Study
This dose-finding study is being conducted in five centers in Europe. Radioactive stents of four ranges of activity have been utilized: 1.5–3.0;

Table 24.2 Intracoronary radiation clinical trials using radioactive stents

Study (principal investigator)	*Design*	*Radiation system*	*Source*	*Prescribed dose*
IRIS Trial Europe (J Moses)	Prospective, non-randomized	Isostent	^{32}P impregnated Palmaz-Schatz or BX stents (15 mm)	0.75–1.5 μCi
European ^{32}P Dose–Response Study (J Moses)	Prospective, non-randomized	Isostent	^{32}P 15-mm Fischell BX stent	1.5–3.0 μCi, 3.0–6.0 μCi, 6.0–12 μCi, and 12–20 μCi
Cold End Study (J Moses)	Prospective, non-randomized	Isostent	^{32}P 25-mm Fischell BX stent	3–24 μCi in mid 15.9 mm; cold ends 5.7 mm both edges
Hot End Study (J Moses)	Prospective, non-randomized	Isostent	^{32}P 18-mm Fischell BX stent	4.5–9 μCi total activity in mid 14 mm; 2-mm hot ends; 1.3–2.6 μCi/mm

3.0–6.0; 6.0–12; and 12–20 μCi. The Milan group (n = 82 patients) reported a suppression of the neointimal hyperplasia in a dose-related manner (between 1.5 and 12 μCi). Edge restenosis ('candy wrapper') was observed in 36% for 1.5–3.0 μCi, 38% for 3.0–6.0 μCi, and 50% for 6.0–12-μCi activity levels.[10] Currently, the Milan group is evaluating the use of stent activities up to 20 μCi.,The Heidelberg group enrolled 11 patients for radioactive stent implantation of activity levels between 1.5 and 3.0 μCi. Target vessel revascularization was 36%, mainly at the articulation of the Palmaz–Schatz stent.[11] In Rotterdam, 40 patients have been evaluated after 6.0–12.0-μCi radioactive stent implantation. To date, 18 patients have returned for angiographic follow-up. No restenosis (> 50% diameter stenosis) was observed within the stent. However, at the edges of the stent the restenosis rate reached 55%, leading to target vessel revascularization in 30% of the patients (AJ Wardeh, personal communication). Data from the Vienna experience will be available at the end of 1999.

Two trials have been designed to address the problem of edge restenosis. The **Cold End Study** is aimed to determine the efficacy and safety of the ^{32}P 25-mm Fischell BX stent, of which both 5-mm ends are inactive ('cold

Inclusion	Population/ number of centers	Period	Primary end-point	Status/ results
De novo or restenotic lesions	40 pts/3 centers (Milan, Rotterdam, Hanover)	September 1997–October 1998	Safety and efficacy on prevention of restenosis at 4–6 months	Completed: demonstrated feasibility and safety
De novo or restenotic lesions	200 pts/5 centers (Milan, Heidelberg, Rotterdam, Aalst, Vienna)	June 1997–ongoing	Safety and efficacy on prevention of restenosis at 4–6 months	Reduction of pure intra-stent restenosis in dose–response manner. Stent edge restenosis ≥ 3 μCi
De novo or restenotic lesions	38 pts/3 centers (Rotterdam, Milan, Aalst)	May 1999–ongoing	Safety and efficacy on prevention of restenosis in-stent and at edges at 6 months	Enrollment phase
De novo or restenotic lesions	60 pts/4 centers (Rotterdam, Milan (2 sites), Vienna)	August 1999–ongoing	Safety and efficacy on prevention of restenosis in-stent and at edges at 6 months	Enrollment phase

ends'). Conversely, the **Hot End Study** is aimed to determine the efficacy and safety of the ^{32}P 18-mm Fischell BX stent, of which both 2-mm ends present with higher activity ('hot ends') as compared with the inner 14 mm, which has a total activity ranging from 4.5 to 9 μCi. These two studies are still in the enrollment phase.

Conclusions and future perspective

The use of endovascular beta-radiotherapy in Europe demonstrated that this therapy is safe and feasible. Furthermore, preliminary results of a dose-finding study with the Boston Scientific/Schneider system have been very promising (V Verin, personal communication). This beneficial effect of radiation in preventing restenosis may be explained partially by the positive influence of brachytherapy on the remodeling process.[12,13] However, some detrimental clinical consequences of intracoronary radiation may also be recognized from the European experience. The edge effect, also named 'candy wrapper effect', was

reported by Albiero et al after radioactive stent implantation.[10] Further, the occurrence of late coronary thrombosis has been associated with radiotherapy.[14] This phenomenon may be the consequence of delayed endothelialization, persisting dissections[15] or the inability of tubular stents to follow vessel enlargement promoted by radiation leading to late stent malapposition.[16]

Potential solutions for these problems include the use of new designs of radioactive stents or hybrid techniques (catheter-based + radioactive stent)[17] in addition to the use of prolonged antithrombotic therapy. Also, the avoidance of conventional stent implantation may be considered in the setting of catheter-based endovascular radiotherapy.

There are still several unanswered questions which should be resolved before determining the potential of this new technique. First, the use of beta or gamma sources or a combination of both. Secondly, the use of centering or non-centering devices. Further, to determine the best vehicle for radiation: solid (wire or train of seeds), liquid (filled-balloon) or gaseous. Equally, the clinical effect of the dose-rate (radioactive stent—low dose-rate versus catheter-based radiation—high dose-rate). Finally, the target tissue must be defined, as well as the minimal effective dose to be delivered. Hopefully, after the completion of ongoing trials in Europe, as well as in the USA, many of these issues will be answered.

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Vascular brachytherapy is the technically most innovative and exciting recent development in Interventional Cardiology.

The **part I** of this thesis, reports on the structural and functional changes that intracoronary beta-radiation therapy induces in coronary tissue when delivered either by catheter-based systems or radioactive stent. After plain balloon angioplasty catheter-based radiotherapy induces vessel enlargement which is able to accommodate the increase in plaque volume that occurs after this coronary intervention (Chapter 1). Furthermore, the use of conventional stent before or immediately after brachytherapy does not preclude the development of this positive remodeling of the vessel wall.(Chapter 2 and 3) Potentially, this phenomenon may lead the stent to become malapposed during the follow-up period which may account for the development of late thrombotic occlusion as witnessed in excess in this population (Chapter 8). This vessel enlargement may be explained by inhibition of migration but not of cellular proliferation that occurs at low dose of radiation. Further, the production of α-actin by the adventitial myofibroblasts is decreased after brachytherapy. Therefore, cells may remain in situ unable to migrate but able to grow in the presence of positive vascular remodeling. After one week, the effect of radiation diminishes and cellular proliferation as a reaction to the presence of the stent, occurs behind the stent in the context of positive remodeling. In stark contrast to what is observed after catheter-based radiotherapy, vessel enlargement is not seen after radioactive stent implantation. (Chapter 3) In such cases, it is hypothesized that the continuous and low dose rate provided by the stent creates a "radioactive fence" which prevent the migration and invasion of myofibroblasts from the adventitia through the stent struts and into the lumen. Thus, adventitial cells remain intact without upregulation of growth factors and inhibition of contractile proteins.

Another important structural finding demonstrated during the follow-up in patients who received either catheter-based radiation or high activity radioactive stent is the development of the so-called "edge effect". (Chapter 1 and 3) The combination of increase in plaque volume and absence of vessel enlargement or even vessel shrinkage was the common structural change observed at the edge of the irradiated coronary segment.

Finally, irradiated coronary segments were functionally tested at 6-month follow-up after plain balloon angioplasty. The endothelium-dependent vasodilator acetylcholine was selectively infused in the coronary segments of patients in stable condition formerly irradiated by means of catheter-based system. A vasodilatory response was observed in most of these patients which was indicative of restoration of the endothelial function. This favorable functional response

may play an important role in the potential beneficial effect of the radiation therapy on the restenosis process.

The **part II** of this manuscript reports on dosimetry calculated from intravascular ultrasound studies performed in patients treated with catheter-based brachytherapy systems (Chapters 5 and 6). The first main finding demonstrated in those studies is the inhomogeneity of the radiation dose demonstrated when non-centered devices are used. Further, the effective dose to be delivered to the adventitia volume, as considered to be the target volume in intracoronary radiotherapy, has been determined to range between 4 and 6 Gy. However, this optimal radiation dose was delivered in less than 50% of the irradiated coronary segments. In addition to these findings, residual plaque burden, delivered dose and tissue composition have been identified as independent predictors of plaque volume at 6-month follow-up, as assessed by intravascular ultrasound. (Chapter 5) All the above mentioned factors have to be taken into account when intracoronary radiation treatment is planned.

The **part III** of the thesis describes a new methodological approach based on quantitative coronary angiography, in order to homogenize the interpretation of results from clinical studies aimed to define the effectiveness of brachytherapy. Since vessel enlargement frequently occurs at the site of the previous target lesion, minimal luminal diameter may be relocated at follow-up in a different coronary subsegment. As a result, discrepant results may be obtained depending on the region subject to the analysis. The definition and identification of the target segment, irradiated segment, injured segment and vessel segment, may be helpful to understand the mechanism of action of this new treatment modality. (Chapter 7)

The **part IV** of this manuscript reports on the potential complications derived from the use of beta-radiation therapy. The development of late thrombotic occlusion occurs in excess either after plain balloon angioplasty or after stent implantation in the context of catheter-based brachytherapy system. (Chapter 8) The use of double antiplatelet regimen (aspirin and clopidrogrel) for long-term may reduce this undesirable effect. Several mechanisms are hypothesized to be involved in this phenomenon: first, a delay in stent re-endothelisation may occur after brachytherapy. Furthermore, balloon-induced coronary artery dissections may not be resolved during the follow-up period as witnessed in a great proportion of patients treated with balloon angioplasty and catheter-based radiation therapy. (Chapter 9) Finally, as discussed in previous chapters, the vessel enlargement may induce late stent malapposition which is a well known subtract for stent thrombosis.

Another complication which may be linked to the development of the "edge effect" is the occurrence of geographical miss. This concept has been genuinely used in radio-oncology to define that cause of treatment failure due to low dose radiation. Radiation dose at the edge of the source is rather low due to the steep decay of beta radio-isotopes. This feature when combined with the stimulus of the injury (balloon or stent-induced injury) has been demonstrated to provoke a higher-than-expected late loss as compared to those non-injured edges. (Chapter 10)

The knowledge of all the above sources of complications may help to improve the performance and safety of intracoronary radiation therapy.

In the **part V** of the thesis the results of some clinical trials performed by this new therapy are described. The implantation of low activity radioactive stent has been demonstrated to be safe and feasible. However, the restenosis rate was comparable to conventional stent implantation. (Chapter 11) The use of catheter-based beta radiation is also feasible in recurrent in-stent restenosis. Nevertheless, the occurrence of restenosis in this cohort of patients appeared to be rather high probably due to the presence of geographical miss. (Chapter 12). Finally, a summary of the trials currently under way in Europe is described in the Chapter 13.

FUTURE DIRECTIONS.- There are still several unanswered questions which should be defined before determining the potential of this new technique. First, the use of ß- or γ- sources or a combination of both. Secondly, the use of centering or non-centering devices. Further, to determine the best vehicle for radiation: solid (wire or train of seeds), liquid (filled-balloon) or gaseous. Equally, the clinical effect of the dose-rate (radioactive stent-low dose-rate versus catheter-based radiation-high dose-rate). And, finally, to define the subgroup of patients which will benefit most from this new technique.

Vasculaire brachytherapie is de meest vernieuwende en veelbelovende recente technische ontwikkeling in interventie cardiologie.

In het **eerste deel** van dit proefschrift vermelden we de structurele en functionele veranderingen die ontstaan in coronair weefsel, na bestraling door middel van intracoronaire katheters of radioactieve stents. Na klassieke ballonangioplastiek induceert radiotherapie een vergroting van het lumen waardoor de toename in plaquevolume na coronaire interventie geneutraliseerd wordt ('positive remodeling'). (Hoofdstuk 1) Verder verhindert het gebruik van een conventionele stent voor of onmiddellijk na brachytherapie deze 'positive remodeling' van de vaatwand niet (hoofdstuk 2 en 3). Dit fenomeen zou kunnen leiden tot malappositie van de stent tijdens follow-up, wat de oorzaak kan zijn van late thrombotische occlusie, zoals veelvuldig beschreven in deze populatie. (Hoofdstuk 8). 'Positive remodeling' kan worden verklaard door het voorkomen van migratie van cellen, maar niet door de inhibitie van cellulaire proliferatie welke zich voordoet bij lage stralingsdoses. De productie van alfa-actine door de myofibroblasten in de adventitia neemt af na brachytherapie, waardoor cellen zich niet verplaatsen maar wel kunnen groeien tijdens de 'positive remodeling'. Na een week neemt het effect van de bestraling af en als reactie op de stent ontstaat celvermeerdering achter de stent, in samenhang met 'positive remodeling'. In tegenstelling tot eerdere observaties wordt 'positive remodeling' niet waargenomen na het implanteren van een radioactieve stent (Hoofdstuk 3). In dergelijke gevallen is het mogelijk dat een continue lage dosis bestraling vanuit de stent een 'radioactieve afrastering' vormt, die de migratie en het binnendringen van myofibroblasten in het lumen vanuit de adventitia door de stentstruts belemmert. Zo blijven adventitiacellen intact zonder stimulatie van groeifactoren en inhibitie van contractiele eiwitten.

Een andere belangrijke bevinding tijdens de follow-up van patiënten behandeld met brachytherapie, zowel door katheter systemen dan wel door radioactieve stent, is het zogenaamde 'edge'effect (Hoofdstuk 1 en 3). De combinatie van plaque toename en het uitblijven van vaatverwijding of zelfs het optreden van vaatvernauwing, was de meest voorkomende structurele verandering die werd geobserveerd.

Ook testten we de functie van de bestraalde coronaire segmenten 6 maanden na de klassieke ballonangioplastiek. Wanneer we acetylcholine (endotheel afhankelijke vasodilator) selectief infuseerden in de coronaire segmenten van stabiele patiënten, eerder behandeld met brachytherapie (katheter systemen), zagen we in de meeste gevallen vasodilatatie optreden, suggestief voor het herstel van de endotheelfunctie. Deze gunstige respons kan een belangrijke rol spelen in het potentieel positieve effect op het restenose proces.

In het **tweede deel** van dit proefschrift beschrijven we de dosimetrische berekeningen uit intravasculaire ultrageluid studies, bij patiënten behandeld met brachytherapie (hoofdstuk 5 en 6). De eerste belangrijke bevinding is dat de stralingsdoses bij gebruik van niet–gecentreerde katheter systemen niet homogeen zijn. Wij vonden dat de effectieve dosis die de adventitia, het doelwit van brachytherapie, dient te ontvangen, tussen 4 en 6 Gy bedraagt. Deze optimale dosis werd echter bij minder dan 50% van de bestraalde coronair segmenten toegediend. De hoeveelheid resterende plaque, de toegediende dosis en de samenstelling van het weefsel, zijn voorts onafhankelijke voorspellers van plaque volume bij 6 maanden follow-up zoals gezien bij intravasculair ultrageluid (hoofdstuk 5).

In het **derde deel** beschrijven wij een nieuwe methodologische benadering gebaseerd op kwantitatieve coronaire angiografie, teneinde een standaard interpretatie van studieresultaten van de effectiviteit van brachytherapie te verkrijgen. Omdat vaatverwijding vaak optreedt op de plaats van de behandelde stenose, zou bij een vervolgstudie een minimale lumendiameter gesitueerd kunnen worden in een ander coronair segment. Dit kan tot gevolg hebben dat er tegenstrijdige resultaten gevonden worden, afhankelijk van de geanalyseerde gebieden. Het definiëren en identificeren van het te behandelen segment, het bestraalde segment, het beschadigde segment en het vaatsegment kan behulpzaam zijn bij het begrijpen van de werkingsmechanismen van deze nieuwe behandelingsmethode (hoofdstuk 7).

In het **vierde deel** bespreken we de mogelijke complicaties die verband houden met het gebruik van bèta bestraling. De ontstaan van late thrombotische occlusie wordt frequent gezien na ballon angioplastiek of stent implantatie, gecombineerd met brachytherapie (hoofdstuk8). Het gebruik van een gecombineerd langdurig anti-plaatjesregime met aspirine en clopidogrel kan deze complicatie voorkomen. Verscheidene mechanismen kunnen bijdragen tot het optreden van late thrombotische occlusie: een vertraging in de stent re-endothelialisatie, persisterende dissectie 6 maanden na ballon angioplastiek in combinatie met brachytherapie (hoofdstuk 9) en het optreden van vaatverwijding met mogelijke stent malappositie. Een andere complicatie, die te maken kan hebben met het 'edge' effect is het optreden van 'geographical miss". Dit concept is oorspronkelijk gebruikt in de radio-oncologie, om het falen van een te lage stralingsdosis te beschrijven. De stralingsintensiteit aan de randen van de bron is laag, vanwege het hoge verval van bèta radio isotopen. Deze eigenschap is samen met de ballon- of stent geïnduceerde beschadiging verantwoordelijk voor de onverwacht grotere reduktie van lumen in vergelijking met de onbeschadigde randen. (hoofdstuk 10)

Kennis van boven beschreven complicaties kan helpen bij de verbetering en uitvoering van brachytherapie.

In het **vijfde deel** beschrijven we de resultaten van een aantal klinische studies, met deze therapie. De implantatie van laag-actieve radioactieve stents is mogelijk en veilig gebleken. Het restenose percentage echter was te vergelijken, met dat van conventionele stentimplantatie. (Hoofdstuk 11). Het gebruik van brachytherapie is ook mogelijk bij recidiverende in-stent restenose. Desalniettemin blijft het percentage restenose in deze groep patiënten vrij hoog, waarschijnlijk ten gevolge van het optreden van 'geographical miss' (Hoofdstuk 12). In hoofdstuk 13 tenslotte, geven wij een overzicht van de lopende Europese studies op dit gebied.

TOEKOMSTVERWACHTINGEN.- Verscheidene vragen dienen te worden beantwoord, voordat het nut van deze techniek definitief kan worden vast gesteld: het gebruik van bèta- of gamma bronnen of een combinatie van beiden; gecentreerde versus niet-gecentreerde bronnen; het bepalen van het beste medium om de straling toe te dienen; vast (draad of een reeks van radioactieve zaden), vloeibaar (een met radioactieve vloeistof gevulde ballon), of in gasvorm; het klinische effect van de dosis (radioactieve stent met lage dosis ten opzichte van hoge dosis, toegediend met het kathetersysteem); de bepaling van de subgroep van patiënten die het meest gebaat zijn met deze nieuwe techniek.

I am sitting in front of a blank page trying to write probably the most difficult part of this manuscript. In few lines I have to explain my feelings from 2 years at the Thoraxcenter. So many things, so many people.... I must admit that I have read several Acknowledgement sections from some colleagues who previously defended their thesis, trying to find inspiration, and perhaps trying to find good paragraphs to be copied. But finally, I couldn't..... This section has to be something personal and original. So, I will start from the beginning in a chronological way:

Day 1: I arrived in Rotterdam on September the 30th, 1997. It was a foggy and a rainy day. You can imagine such a naive Spanish fellow asking to the taxi driver: is this weather quite common here? Some time later, I understood why he charged me with 50 gulden for a trip from Central Station to Boergoensevliet!!

Day 2: October the 1st, 1997, Wednesday, 8:00 a.m. Location Thoraxcenter. Jurgen Ligthart. I met him in the corridor, and he offered me een koppie koffie. At that time I did not know, but this was a very lucky day! Beste Jurg: You are one of the milestone of the Thoraxcenter. Your enthusiasm, knowledge, friendship, hard work and patience with fellows make our integration into the cath lab possible in a very smooth and easy way. In return, you normally receive from us work to be done for yesterday!: slides, figures, IVUS reconstructions, ... Most of the papers of this manuscript wouldn't have been possible in time without your help. I have to extend my gratitude to Mieke and Evelien Ligthart for helping me with my Dutch, and showing me that it exists something else outside the Thoraxcenter.

Day 2: October the 1st, 1997, Wednesday, 8:15 a.m. Location Thoraxcenter after the first koppie koffie in The Netherlands (it wouldn't be the last...). Jurgen introduced me to Dr.Pim J de Feyter. Beste Pim: it was a distinct privilege to work with you. You have always been friendly, supportive and critical (in your typical and humorous way) of my research work with IVUS. In any scenario, your opinion was always of great value. You used to face any clinical problem, research idea or just philosophical question from a different and unique angle.

Day 3: October the 2nd, 1997, Thursday, 8:00 a.m. Location Thoraxcenter-viewing room. My first meeting with Professor Patrick W. Serruys. Beste Patrick: much has been written or said by many other fellows and colleagues all over the world regarding your extreme capacity of work, high intelligence and exquisite dedication to the world of Interventional Cardiology. I had the privilege to experience all of these features. To summarize your philosophy of work I write

some of your favorite sentences: 1) In Interventional Cardiology, tell the truth, only the truth and nothing but the truth, 2) Nothing is impossible!, 3) PWS: You have an idea, put it in paper and come tonight to my place! I call Danielle!- MS: But you have just arrived from Japan, you must be tired!- PWS: OK! Lets play tennis first! At that point, I have to extend my gratitude to Danielle Serruys and to Olivia, Gregory and Michael for their repeated hospitality.

Day 3: October the 2nd, 1997, Thursday, 9:00 a.m. Location Thoraxcenter. After the film bespreking: I was introduced to Anja, the "secretaresse van de Professor". Beste Anja: behind a good professor, there is always an efficient secretary (and a good dancer...). You knew always where to find the fellows when the professor need them: waar is Manel? Roep Manel!

That day I met for the first time Michael Kutryk and Stephane Carlier the 2 other fellows in the cath lab. Dear Michael: you were always my reference, for your capacity of work and sacrifice (we always remember your famous: life is hell!!) and for your knowledge. Any question or doubt I could have regarding stenting was immediately solved with an exact and accurate answer. Dear Stephane: You helped me from the beginning, giving me some tips to survive: where and when the "lekker soupje" was ready, how to get to the library or to the dagbehandeling, what to do when we were on duty, ...

Also, I was introduced to the other "senioren", who were going to be responsible for my clinical training: Wim van der Giessen, Marcel van den Brand, David Foley and Jaap Hamburger. Beste Wim, beste co-promotor: It was a privilege to work with you inside the lab and also in research. I learned from you how to be calm and patience during the procedure and think twice before taking a decision. Outside the lab, you were a tough reviewer, but always pertinent and really constructive. I knew (and all fellows knew) that if you agreed with a paper, this was going to be a good one. Beste Marcel: Your expert opinion was always very helpful in any difficult case. Dear David: Your skills together with your Irish sense of humour made smooth and comfortable even the most difficult cases. Beste Jaap: I really learned working with you in "your typical chronic total occlusions" cases. Thanks for that.

At that point, I can extend my gratitude to the young generation of Interventional cardiologists at the Thoraxcenter: Peter Smits with whom we shared the 316 room for almost 1 year; Benno Rensing and Jeroen Vos.

During the first 2-3 days, I was introduced to the personnel of the cath lab: nurses, technicians, secretaries, managers, staff from the AVC-Thorax, computer group, dagbehandeling, CCU, 12 hondred and 3-zuid.I have to thank ALL of them for their help during these 2 years: with my

Dutch, with patients, with statistics, making slides, videotapes, computer connections, with cath lab bureaucracy, and thousand of small details which made me feel "thuis". As a matter of fact, you have been my family in the Netherlands. Everyone merits being in this section. But I am really afraid of forgetting some of you; thus, I prefer not to write any particular name. I'll keep all of you in my heart for the rest of my life (what a romantic paragraph!).

Further, I met for the first time two essential people at the Thoraxcenter: the study coordinators Alex Wardeh and Anthonie Gijzel and later on Marco Knook. Beste Alex, Anthonie and Marco: Your collaboration was very important since you were the necessary link between the international fellows and the patients during any clinical follow-up. Thanks for your help.

Also, I met Nico Bruining: Beste Nico, I have to thank you for your assistance with the 3D analysis and with some other computer softwares.

Day 8: October the 7th, 1997, Tuesday, 8:00 a.m. Still raining. Location Thoraxcenter-Brachytherapy day. That day I met Veronique Coen our radio-oncologist. We were going to share the same room and table (but not the chair) for almost 1 year. Beste Veronique: you helped me to understand what the effect of an electron was and stimulate my research in brachytherapy. Thank you for being my friend during my wife's pre-delivery days. She works together with Professor Peter C. Levendag and Hans Marijnissen. Beste Peter: You also guide my research in brachytherapy with stimulating discussions and brainstorms. Beste Hans: Your collaboration and help was crucial and your work great for the outcome of some of the studies of this thesis. Thanks for your effort.

Four months later. Still raining. Location Thoraxcenter. Almost fully integrated. After demonstrating that I could articulate some words in Dutch I started my clinical training. Another fellow arrived: Niteen V. Deshpande. The room 316 started to be crowded. Dear Niteen: You joined me with the research on IVUS. We had interesting clinical and also philosophical discussions. Because of you, I started appreciating more the Indian food with Dutch ingredients and you appreciate the Catalan and Spanish food with Dutch ingredients.

June 1998. Another fellow at the 316 room: Patrick Kay. Dear Pat, dear friend: We have got a fruitful collaboration during these 18 months. Next to you, my spanglish improved a little bit especially because of your ironical comments; *jauever*, it still needs some work to do. Thank you for your support during the depressive days and giving me the opportunity to visit the Rijksmuseum. I extend my gratitude to your nice family: Wendy, Brittany and Ethan (I'm sure that one day he will forgive and forget Marta).

Autumn 1998; one year later- Location Thoraxcenter: Two other fellows at the Marx brother's room: Mariano Albertal and Glenn van Langenhoven. Querido Mariano: Tú has sido el aire latino refrescante en ese mundo frío, cerrado y de ideas fijas. Gracias por estar ahí y por estimularnos con tus preguntas y discusiones científicas. Dear Glenn: although you worked in a different field you were always receptive and critical in our IVUS-brachytherapy evening discussions. Did you finally change the number plate of your car for a Dutch one?

January 1999- new year, new fellow: Marco Aurelio de Alvim Costa. Dear Marco, dear friend: Thank you for your friendship. It was a pleasure and a challenge to discuss with you any idea I might have. Many of the papers we both published started in a small an innocent discussion with a beer or two in our hands. This, together with your extraordinary enthusiasm and capacity of work made the rest. You really deserve what you have got during your stay at the Thoraxcenter. I have to extend my gratitude to your lovely and sacrificed wife, Erica, for making me feel like home during those long weekends in Rotterdam.

February 1999: a new fellow in town: Pavel Cervinka. Dear Pavel: You joined us with the research on IVUS. Thank you for your critical and pertinent comments.

March 1999: a new fellow, a new friend: Ken Kozuma. Dear Ken, dear friend: Europeans can not imagine how difficult is for a Japanese to communicate in English. You could really manage to do that. All your intelligent comments were of great value. I knew that if you finally agreed with any idea this was going to work. Thank you for being there.

I can not finish the acknowledgements section without saying anything from one of the persons who helped me most from a non-clinical point of view: Maria Elena. Querida Maria Elena: usted me daba la dosis necesaria de alegría diaria cuando venía a limpiar nuestro despacho. (Sobretodo los lunes por la mañana en que me informaba de los resultados de la liga de fútbol). Muchas gracias por todo su apoyo durante estos 2 años.

I am grateful to all project coordinators and analysts from the core lab in Cardialysis for their collaboration (and also for their Christmas box) and patience with our ideas and projects.

Finally, I am really grateful to Marianne Eichholtz for making the presentation of this thesis possible. Thank you for your help and for not allowing me any further delay in the schedule.

October 1999, my last month arrived. This was the end of the 2-year cycle. A new fellow arrived: Giorgios Sianos: he took my place in the crowded room. But this is no longer the 316 room but the 377ª. He is planning to stay also 2 years. Dear Giorgios: Life in Holland is hard but don't worry! I'm pretty sure that finally, you'll enjoy the Thoraxcenter as much as I did.

"Veel Success!"

CURRICULUM VITAE

Manel Sabaté was born in Barcelona, Spain, on October 23, 1966. He received his basic medical training at the Central University of Barcelona (Unitat Docent de Bellvitge), from which he graduated in June 1990. He got the position of Resident in Cardiology by the MIR examination in October 1990. From January 1991 to December 1995 he completed his Cardiology training as Resident of Cardiology at the Hospital Prínceps d'Espanya de Bellvitge, Barcelona, Spain. He got the degree of Cardiologist in December 1995. He worked as MAU at the Coronary Care Unit of the Cardiology Department and in the Catheterization Laboratory from January 1996 to September 1997. From October 1997 to October 1999, he was appointed as Research and Clinical Fellow at the Cath Lab, Thoraxcenter, Rotterdam, The Netherlands, under the supervision of Professor dr. Patrick W. Serruys. He is currently working at the Interventional Cardiology Department of the Hospital Clínico San Carlos, Madrid, Spain.

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