Radiation and the Stent: Results From Catheter - Based Radiation And Radioactive Stenting

Straling en de Stent
Resultaten van Catheter Gebaseerde Bestraling
en Radioactieve Stent Implantatie

PROEFSCHRIFT

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To Wendy, Brittany and Ethan. For giving me the freedom to pursue this goal and for providing me with such support and joy.

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INTRODUCTION AND OVERVIEW OF THIS THESIS

Angiographic restenosis occurs in up to 60% of cases after balloon angioplasty (BA). Restenosis after BA occurs due to elastic recoil of the artery, vascular remodeling with vessel shrinkage and neointimal hyperplasia. Neointimal hyperplasia develops by migration and proliferation of smooth muscle cells (SMCs) and myofibroblasts after balloon-induced trauma of the arterial wall and by deposition of an extracellular matrix by the SMCs. By preventing elastic recoil and negative remodeling stent implantation has resolved many of the problems created by balloon angioplasty. However, a new problem has been created – that of in-stent restenosis, which is caused by neointimal hyperplasia. This entity occurs in 9-30% of cases after stent implantation. In the USA this equates to some 125,000 cases per year. Conventional treatment for in-stent restenosis (balloon angioplasty and debulking) has been unsuccessful with 50-80% of cases suffering from further restenosis.

Alternative treatment modalities were clearly required. Since radiotherapy had proven to be effective in treating the exuberant fibroelasticity of keloid scar formation and other non-malignant process such as ocular pterygia, it was assumed that this adjunctive therapy may also inhibit coronary restenosis.

Principles of radiation

In the process of radioactive decay or disintegration atomic nuclei change their configuration and energy content to reach a stable state. This process is usually associated with the emission of α or β radiation. Alpha particles are heavyweight charged particles that can travel very short distances within tissue. Beta particles are lightweight high-energy electrons with either a positive or negative charge. A third type of emission originates 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 a stable state is to capture an electron orbiting just outside the nucleus. This process called electron capture makes the outer shell where the electrons are orbiting unstable. To fill the void of captured electrons other electrons from nearby orbits jump to the innermost orbit which leads to the emission of photons, called X-rays, which take the form of electromagnetic waves. Gamma and X-rays are high - energy photons without charge or mass. The only distinction between gamma and X-rays lies in their origins: 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 γ radiation. Only a few isotopes, for example ^{32}P, emit only β-particles, without γ-radiation.

The process of radioactive decay is a spontaneous random event. In a sample with a large number of atoms the decay follows exponential behaviour. 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 bequerel (Bq)=disintegration per second
1 curie (Ci)=$3.7*10^{10}$ Bq
1 millicurie=$3.7*10^{7}$ 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:
$A(t)=A(0)e^{-0.693*t/T1/2}$ where A(0) is the known activity at time zero; A(t) is the activity remaining at time t and $T^{1/2}$ is the half-life.

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 indirectly damage a critical target by interacting with other molecules to produce free radicles, which will subsequently damage the critical target. Approximately 80% of the radiation damage is caused by these free radicles. The most critical target that could be damaged by radiation is DNA. The consequence of this is chromosomal damage, where the cell loses the ability to proliferate, which will ultimately lead to its death. This mode of cell death leads to a dose – response relationship where the fraction of cells surviving (S) is a linear-quadratic function of the dose (D):
$S = e^{-\alpha D - \beta * D2}$ where α and β are constants that are a characteristic of a given cell type. At low doses the linear component dominates, but at higher doses (such as the single doses that are used in catheter – based radiation) the quadratic dominates. Theoretically a single acute dose of 12 to 20 Gy would result in a depopulation of SMCs of about 10^{-3} to 10^{-6}. These surviving cells would need to double between 12 to 20 times to produce sufficient progeny to block the artery. Considering that SMCs are not malignant and therefore do not have the capacity to proliferate indefinitely, it may be that a dose of this magnitude will result in a permanent inhibition of restenosis.

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. The effect of radiation on myofibroblast proliferation in the adventitia as well as on vessel remodeling has been recently reported. Endovascular radiation after balloon overstretch injury of porcine arteries significantly reduced the number of proliferating cells in the adventitia and medial wall compared to controls at a dose of 14 to 28 Gy prescribed at 2 mm into the vessel wall. The 28Gy dose resulted in a much greater inhibition of cell proliferation in the adventitia compared to 14Gy. In the same study a significant reduction in the extent of adventitial α-actin staining was observed in the irradiated cells compared to controls. This suggests an inhibition of adventitial fibrosis by the irradiation treatment, leading to a significant increase in the

vessel perimeter (inhibition of constrictive vascular remodeling). These findings support the concept that the adventitia is the target tissue of intracoronary radiotherapy.

Radiation Therapy Systems

Radiation therapy can be delivered to the coronary arteries by external beam radiation, by brachytherapy methods using catheter – based systems or by radiaoactive stents. This thesis focuses on the latter two modalities only. Catheter – based systems can use both β or γ emitters, which can deliver the prescribed dose at either a high or a low dose rate.

Table: Isotopes currently used for intraluminal brachytherapy:

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

Radioactive stents

The radioactive stent was first conceptualized in the late 1980s. Animal experiments followed in the early and mid 1990s, demonstrating efficacy in the porcine and rabbit model at activities as low as 0.14μCi. Human trials followed.

Radioactive stents utilize mainly β-emitters at a low dose rate. Low-dose beta-particle radiation inhibits smooth-muscle proliferation and migration through the stent struts. This process has been described as an 'electron beam fence'.

The dosimetry of the ^{32}P stent has been previously described. Janicki characterized the near field dose of a 1.0μCi 15mm length Palmaz –Schatz using a modification of the dose-point-kernel method. Modification of the dose-distribution around a uniform cylinder of P32 to account for the geometry of a tubular slotted Palmaz – Schatz stent with mathematical modeling allowed construction of 3-D dose maps. For a 1.0μCi 15mm length ^{32}P stent at a distance of 0.1mm dose values of 2500cGy are delivered at the strut wires (peaks) and 800 cGy between the wires (valleys) over one half-life (14.3 days). The non-uniformity of dosing reflective of the stent geometry decreases at distances of 1 – 2mm from the surface. The dosimetry predicted by the dose calculations correlated well with measured dose using photochromic film. While these data provide an in-vitro analysis of dosing from a radioactive stent the actual dose distribution will be affected by variations in atherosclerotic plaque morphology and the symmetry of stent expansion.

This thesis evaluates the results of two modalities of intracoronary radiation: catheter – based radiation and radioactive stenting. In part I important predictors of restenosis after conventional stenting are evaluated. Part II considers methodological issues important in the assessment of lesions that have undergone intracoronary radiation. These include relocation of the minimum lumen diameter and geographical miss. In Part III we discuss the evolution of radioactive stents through their initial human trials to later studies describing different stent configurations. Part IV explores aspects common to both radioactive stenting and catheter – based stenting and radiation. This includes a mechanistic approach to evaluating remodeling and restenosis using very powerful 3-dimensional IVUS technology. In part V we analyze the complications and interesting observations made during the application of this technology.

Part I

Important predictors of restenosis

Chapter 1

Periprocedural quantitative coronary angiography after Palmaz-Schatz stent implantation predicts the restenosis rate at six months: results of a meta-analysis of the BElgian NEtherlands Stent study (BENESTENT) I, BENESTENT II Pilot, BENESTENT II and MUSIC trials.

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Periprocedural Quantitative Coronary Angiography After Palmaz-Schatz Stent Implantation Predicts the Restenosis Rate at Six Months

Results of a Meta-analysis of the Belgian Netherlands Stent Study (BENESTENT) I, BENESTENT II Pilot, BENESTENT II and MUSIC Trials

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OBJECTIVES We aimed to identify periprocedural quantitative coronary angiographic (QCA) variables that have predictive value on long-term angiographic results and to construct multivariate models using these variables for postprocedural prognosis.

BACKGROUND Coronary stent implantation has reduced the restenosis rate significantly as compared with balloon angioplasty in short de novo lesions in coronary arteries >3 mm in size. Although the postprocedural minimal luminal diameter (MLD) is known to have significant bearing on long-term angiographic results, no practically useful model exists for prediction of angiographic outcome based on the periprocedural QCA variables.

METHODS The QCA data from patients who underwent Palmaz-Schatz stent implantation for short (<15 mm) de novo lesions in coronary arteries >3 mm and completed six months of angiographic follow-up in the four prospective clinical trials (BENESTENT I, BENESTENT II pilot, BENESTENT II and MUSIC) were pooled. Multiple models were constructed using multivariate analysis. The Hosmer-Lemeshow goodness-of-fit test was used to identify the model of best fit, and this model was used to construct a reference chart for prediction of angiographic outcome on the basis of periprocedural QCA variables.

RESULTS Univariate analysis performed using QCA variables revealed that vessel size, MLD before and after the procedure, reference area before and after the procedure, minimal luminal cross-sectional area before and after the procedure, diameter stenosis after the procedure, area of plaque after the procedure and area stenosis after the procedure were significant predictors of angiographic outcome. Using multivariate analysis, the Hosmer-Lemeshow goodness-of-fit test showed that the model containing percent diameter stenosis after the procedure and vessel size best fit the data. A reference chart was then developed to calculate the expected restenosis rate.

CONCLUSIONS Restenosis rate after stent implantation for short lesions can be predicted using the variables percent diameter stenosis after the procedure and vessel size. This meta-analysis indicates that the concept of "the bigger the better" holds true for coronary stent implantation. Applicability of the model beyond short lesions should be tested. (J Am Coll Cardiol 1999;34:1067–74) © 1999 by the American College of Cardiology

Introduction of coronary stenting into the armamentarium of interventional cardiology marks a distinct milestone in the history of coronary angioplasty. Although first conceptualized by Charles Dotter in 1964 (1), it became a reality when Jacques Puel (2), followed shortly by Ulrich Sigwart (3), performed the first human implantations in 1986. The initial multicenter study by Schatz et al. (4) demonstrated the safety and efficacy of the implantation of the Palmaz-Schatz (P-S) coronary stent. This was soon followed by two randomized trials: BElgian NEtherlands STENT study (BENESTENT I) (5) and STent REStenosis Study (STRESS) (6) that compared the P-S stent with balloon angioplasty. Since the landmark BENESTENT I trial we

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Abbreviations and Acronyms

AVID	= Angiography Versus Intravascular Ultrasound Directed Coronary Stent Placement
BENESTENT	= BElgian NEtherlands STENT study
CAAS II	= Cardiovascular Angiography Analysis System II
CI	= confidence interval
DS	= diameter stenosis
IVUS	= intravascular ultrasound
MLD	= minimal lumen diameter
MUSIC	= Multicenter Ultrasound Stent In Coronaries study
P-S	= Palmaz-Schatz
QCA	= quantitative coronary angiography, angiographic
RD	= reference diameter
STRESS	= STent REStenosis Study

have accumulated enormous data on the use of the P-S intracoronary stent. Over the years the practice of coronary stenting has evolved progressively through improvements in stent design and characteristics as well as in techniques of optimal deployment. The postprocedural management has also improved and the problem of stent thrombosis has been solved to a great extent. However, the problem of restenosis, although reduced, still exists despite this evolution. Various factors like use of multiple stents (7–9), stenting of long lesions (10), total occlusions (7) and small vessels <3 mm (7,8), diabetes mellitus (9) and stenting of restenotic lesions (7,11) have been considered to be the predictors of restenosis. We hypothesized that in the cohort of BENESTENT type lesions, the periprocedural quantitative coronary angioplasty (QCA) variables alone, after implantation of the P-S stent, could predict the restenosis rate at six months. This meta-analysis of the BENESTENT I, BENESTENT II pilot, BENESTENT II and Multicenter Ultrasound Stent In Coronaries (MUSIC) trials was done to verify this idea.

The aims of this analysis were to

1. identify periprocedural QCA variables that have a predictive value on long-term angiographic results, specifically the restenosis rate based on a categoric criterion of diameter stenosis (DS) >50%;
2. construct a variety of multivariate models using these variables for the prediction of long-term angiographic outcome;
3. select the model with best fit based on the Hosmer-Lemeshow goodness-of-fit test; and
4. obtain the most practical model for periprocedural guidance or for postprocedural prognosis, or both.

These trials have been considered together because their angiographic outcomes have been analyzed using identical methods of analysis and definitions of the variables in the same core laboratory.

METHODS

Four clinical trials (BENESTENT I [5], BENESTENT II pilot [12], BENESTENT II [13,14] and MUSIC [15]) that used the P-S intracoronary stent over a period of seven years were considered for this meta-analysis. These four studies were considered together because of their common design features. Of the four studies, two were prospective randomized studies and two were prospective observational studies for new treatment strategies. Only patients with stable angina pectoris were enrolled in the BENESTENT I and MUSIC studies, whereas the BENESTENT II pilot and BENESTENT II trials also recruited patients with unstable angina. Coronary angioplasty was performed with stent implantation of native coronary artery lesions <15 mm in length (only BENESTENT II included lesions <18 mm) in vessels >3 mm that supplied viable myocardium. Patients with an ostial lesion, a bifurcation lesion or a lesion in a previously grafted vessel were excluded. Balloon angioplasty followed by stent implantation was performed according to standard clinical practice by the femoral approach. The post-stenting anticoagulation regimen varied as a result of changes in concepts over time, but all patients received aspirin after stenting. Use of on-line quantitative angiography to optimize stent placement was encouraged in the BENESTENT II pilot study, and the use increased progressively during the course of the study. In the MUSIC study, systematic use of intravascular ultrasound (IVUS) guidance was undertaken to optimize the results. All patients had clinical follow-up after one, three and six months and a follow-up angiogram was obtained at six months.

Angiographic analysis. Three angiograms were obtained per patient, one immediately before the intervention, one immediately after and one at follow-up. The off-line analysis of all angiograms was done at the core laboratory (Cardialysis, Rotterdam, The Netherlands) using the Cardiovascular Angiography Analysis System II (CAAS II) (Pie Medical, Maastricht, The Netherlands), which has been validated previously (16). For each patient, multiple matched angiographic views were acquired after intracoronary administration of nitrates. Patients with an unsuccessful procedure or without angiographic follow-up were excluded from the final analysis. For patients having multilesion percutaneous transluminal coronary angioplasty, all lesions were analyzed and each was considered independent. To standardize the method of data acquisition and to ensure exact reproducibility of the angiograms performed after the intervention and at follow-up, measurements were made as described earlier (17). The catheter calibration was based on dimensions of the catheters not filled with contrast medium (18). A dual type of quantitative analysis was used: vessel analysis and stent analysis (12). Vessel analysis was applied to the segment located between two side branches, and stent analysis was applied to the part actually stented. This was considered necessary, because most of the vessels

Table 1. Baseline Patient Characteristics

	BENESTENT I	BENESTENT II Pilot	BENESTENT II	MUSIC
Age (yr)	57 ± 9	58 ± 10	59 ± 11	60 ± 9
Male gender (%)	80	84	77	82
CCS class III or IV angina (%)	54	46	24	43
Diabetes mellitus (%)	7	8	13	11
Previous MI (%)	20	23	25	25
Previous CABG (%)	0	3	2	2
Previous PTCA (%)	2	6	7	9

BENESTENT = BElgian NEtherlands STENT study; CABG = coronary artery bypass graft surgery; CCS = Canadian Cardiovascular Society; MI = myocardial infarction; MUSIC = Multicenter Ultrasound Stent In Coronaries study; PTCA = percutaneous transluminal coronary angioplasty.

taper and as a consequence minimal luminal diameter (MLD) was found out of the stented area. In each analyzed segment, mean diameter, MLD and reference interpolated diameter were determined. New lesions that developed in the vessel beyond the stented segments were excluded from the analysis.

Definitions. The reference diameter (RD) was the diameter obtained by an interpolated method, and the lesion length was defined by the curvature analysis (19,20). Diameter stenosis after stenting was defined as the MLD within the stent related to the interpolated diameter measured over the length of the stent. Plaque area was derived from the reconstructed boundaries. The luminal area measurements were obtained by a videodensitometric method (21,22) and included minimal luminal cross-sectional area and percent area stenosis. To describe negative stenosis where it was present, mean stent diameter was expressed relative to the interpolated RD.

Statistical methods. The statistical analysis was done using the SAS software package (SAS Institute, Cary, North Carolina). Continuous variables were compared using the Student *t* test and the categoric variables by the Fisher exact test. Multiple QCA variables were tested using univariate analysis to determine the predictors of long-term angiographic outcome. Using multivariate analysis, multiple models containing the QCA variables relating to long-term angiographic outcome were constructed. Considering this pragmatic approach indexes such as acute gain and late loss were not included in the models. Also variables accounting for the differences in the studies were not included in the models. The models were then tested using the Hosmer-Lemeshow goodness-of-fit test to choose the most appropriate model. In the Hosmer-Lemeshow goodness-of-fit test, an estimated event probability is calculated from the observations using a model. These observations are then sorted in order of their estimated event probability and divided in approximately 10 groups (g) of about equal size. The Hosmer-Lemeshow goodness-of-fit statistic is obtained by calculating the Pearson chi-square test from the $2 \times g$ table of the observed and the expected frequencies. The greater the p value (smaller the chi-square number) the better the model fits the data.

Ethical issues. The study was carried out according to the principles of the declaration of Helsinki. Written informed consent according to local practice was obtained from every patient.

RESULTS

A total of 775 patients who underwent coronary angioplasty with P-S stent implantation and who completed six-month angiographic follow-up were considered for the meta-analysis. The baseline characteristics of these patients are summarized in Table 1. The length of stent used was 15 mm except in BENESTENT II study where 10-mm and 20-mm stents were also used. The stents implanted in the BENESTENT II pilot and BENESTENT II studies were heparin-coated. The pharmacotherapy after stenting consisted of oral vitamin-K antagonist with aspirin in BENESTENT I and the first three phases of BENESTENT II pilot trial. In phase IV of the BENESTENT II pilot and BENESTENT II main study, all patients were treated with a combination of aspirin and ticlopidine, whereas in the MUSIC study patients meeting the IVUS criteria of optimal stent deployment received only aspirin. Online QCA was not used in the BENESTENT I trial. During the BENESTENT II pilot trial, its use increased progressively from 53% to 68% from phase I to phase IV. In addition IVUS guidance for stenting was also used in a minority of the patients in BENESTENT II (12%, 8%, 20% and 8% in phase I to IV, respectively). In the BENESTENT II main study, on-line QCA was performed for 57% of lesions. In the MUSIC trial, systematic use of IVUS guidance was made to optimize stent deployment. The mean balloon pressure used for final stent deployment was 10 ± 8 atm in BENESTENT I. Inflation pressures >12 atm for dilation after stenting were applied in 43%, 71%, 67% and 82% of patients, respectively, from phase I to IV of the BENESTENT II pilot study. The mean pressures used for final stent deployment in the BENESTENT II and MUSIC studies were 15 ± 3 and 15.8 ± 3.3 atm, respectively. The pooled mean RD was

Table 2. Quantitative Coronary Angiographic Results by Edge-Detection Method

	BENESTENT I	BENESTENT II—Pilot	BENESTENT II	MUSIC	Pooled Mean Value	25th Percentile	75th Percentile	Median Value
RD pre (mm)	2.99	3.16	2.96	3.09	3.04	2.72	3.33	2.99
Length (mm)	7.03	8.37	8.20	8.19	7.89	6.25	9.22	7.66
MLD pre (mm)	1.08	1.12	1.08	1.13	1.10	0.91	1.27	1.06
MLD post (mm)	2.49	2.77	2.69	2.90	2.69	2.42	2.97	2.68
DS pre (%)	64	64	63	63	63.6	58.0	70.00	64.00
DS post (%)	21	18	16	15	17.7	12.50	22.00	16.6
Stent-artery ratio (%)	—	−1.26	−3.82	−6.08	−3.52	−10.02	3.58	−2.69
Restenosis rate (%)	21	12	16	10	—	—	—	—

Columns 2 to 5 show the mean value of each variable in the individual study. Column 6 represents the pooled mean for each variable. Column 9 shows the median value for each variable in the pooled data. Negative values for stent-artery ratio indicate greater mean stent diameter than reference diameter.
DS = diameter stenosis; MLD = minimal lumen diameter; RD = reference diameter; pre = before procedure; post = after procedure; other abbreviations as in Table 1.

3.04 mm and the mean RD in the individual trials ranged from 2.99 mm (BENESTENT I) to 3.16 mm (BENESTENT II pilot). The mean length of the lesions dilated was 8.19 mm. Preprocedural MLD measured 1.10 mm, and the preprocedural DS was 63.6%. The mean MLD immediately after the procedure increased to 2.69 mm and DS decreased to 17.7%. The comparative data from the individual trials and the pooled mean values are presented in Table 2. The corresponding measurements calculated by videodensitometry are shown in the Table 3. Mean area stenosis decreased from 85% to 7%, and the mean minimal luminal area improved from 1.15 to 6.28 mm^2. The maximal nominal balloon size used increased gradually (3.40 ± 0.40 mm in BENESTENT I to 3.65 ± 0.37 mm in MUSIC), as did the maximal inflation pressures (10.0 ± 8.0 atm in BENESTENT I to 15.8 ± 3.3 atm in MUSIC).

The mean MLD achieved after the procedure progressively improved from smallest in BENESTENT I to largest in MUSIC (2.49 mm vs. 2.90 mm, respectively). A corresponding fall in the restenosis rate from 21% to 10% was observed in these trials. When the mean MLD was compared with the restenosis rate in each trial, a potential linear relation between the two variables emerged (Fig. 1). Univariate analysis performed using the angiographic variables to determine the predictor(s) of restenosis revealed that vessel size, MLD before and after the procedure, reference area before and after the procedure, minimal luminal cross-sectional area before and after the procedure, DS after the procedure, area of plaque before the procedure and area stenosis after the procedure were significant predictors of restenosis (Table 4). However, left anterior descending coronary artery location, stent-artery ratio, maximal balloon inflation pressure, lesion length, area stenosis and DS before the procedure were not related significantly to long-term angiographic outcome. Multiple models were constructed using the QCA variables in multivariate analysis (Table 5). Using the Hosmer-Lemeshow goodness-of-fit test, two appropriate models emerged—one with one variable (MLD after the procedure) and the other with two variables (vessel size and percent DS after the procedure) (Table 5). As MLD after the procedure is a more direct and practical measurement than percent DS after the procedure, a third model was constructed replacing percent stenosis with MLD after the procedure in model II. When tested using the Hosmer-Lemeshow goodness-of-fit test, this model showed a lower probability value than the second model, thereby indicating its inferiority. The observed and expected restenosis rate on the basis of model II is depicted in Figure 2.

Reference chart. Using the best fit model of DS after the procedure and vessel size (model II), a chart was developed

Table 3. Quantitative Coronary Angiographic Results by Videodensitometry

	BENESTENT I	BENESTENT II Pilot	BENESTENT II	MUSIC	Pooled Mean Value	25th Percentile	75th Percentile	Median Value
RA pre (mm^2)	7.21	8.00	7.11	7.72	7.47	5.87	8.76	7.06
RA post (mm^2)	8.03	9.12	8.13	9.25	8.55	6.93	9.88	8.35
MLCA pre (mm^2)	0.87	1.37	1.13	1.32	1.15	0.55	1.59	0.93
MLCA post (mm^2)	4.72	7.07	6.54	7.41	6.28	4.80	7.61	6.10
AS pre (%)	88.0	83.0	84.0	82.0	84.7	79.00	92.00	86.50
AS post (%)	41.0	23.0	20.0	20.0	27.2	15.3	37.5	25.00

Columns 2 to 5 show the mean value of each variable in the individual study. Column 6 represents the pooled mean value for each variable. Column 9 shows the median value for each variable in the pooled data.
AS = area stenosis; MLCA = minimal lumen cross-sectional area; RA = reference area; other abbreviations as in Tables 1 and 2.

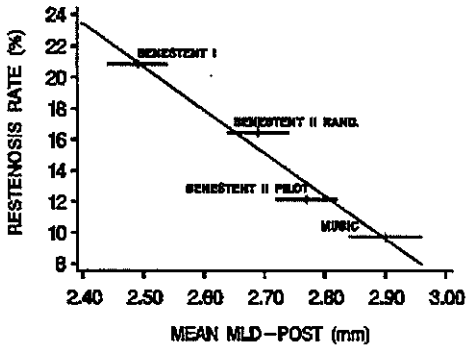

Figure 1. Potential linear relation between MLD after the procedure and observed restenosis rate in the four trials.

(Table 6 and Fig. 3) that can be used as a ready reference to estimate expected restenosis rates using immediate postprocedure angiographic variables. The range of the two variables was divided into 10 groups each. The expected restenosis rate using model II for the median value of each range was calculated along with the 95% confidence intervals (CIs) for this particular value. The expected restenosis rate is given at the top in each cell, and the CI is indicated at the bottom. For example, for a vessel size of 1.83 to 2.14 mm and postprocedural percent DS of 19.1% to 23.5%, the expected restenosis rate is 0.44% or 44% (95% CI 32% to 56%). The cells in the chart marked by an asterisk and figures in italics indicate that there were no observations in that range in the actual data set, and the figures mentioned there are calculated by extrapolation from the model.

Table 4. Quantitative Coronary Angiographic Variables—Univariate Analysis of Predictors for Long-Term Outcome

Variable	p Value
Vessel size	< 0.001
MLD post	< 0.001
RA pre	< 0.001
RA post	< 0.001
MLCA post	< 0.001
MLCA pre	0.001
MLD pre	0.002
DS post	0.006
Plaque area pre	0.015
AS post	0.035
LAD location	0.160
Stent-artery ratio	0.172
Lesion length	0.220
Plaque area post	0.452
Maximal balloon inflation pressure	0.474
AS pre	0.812
DS pre	0.917

LAD = left anterior descending coronary artery; RA = reference area; other abbreviations as in Tables 2 and 3.

Table 5. Multivariate Models Using Quantitative Coronary Angiographic Variables

Variable	Coefficient	SE	p Value
Model I			
Intercept	2.67		
MLD post	−1.68	0.28	<0.001
Hosmer-Lemeshow goodness-of-fit statistic 10.328; p = 0.243.			
Model II			
Intercept	1.32		
Vessel size	−1.34	0.25	<0.001
% DS post	0.05	0.001	<0.001
Hosmer-Lemeshow goodness-of-fit statistic 8.705; p = 0.368.			
Model III			
Intercept	3.45		
Vessel size	−0.59	0.26	0.025
MLD post	−1.31	0.30	<0.001
Hosmer-Lemeshow goodness-of-fit statistic 13.970; p = 0.083.			

SE = standard error; other abbreviations as in Table 2.

Caution must be exercised while using the reference chart in these ranges.

DISCUSSION

The multivariate analysis of QCA variables pooled from the four trials of P-S stent implantation for short de novo lesions in coronary arteries >3.0 mm revealed that MLD after the procedure, vessel size and percent DS after the procedure procedure were the strongest predictors of the long-term angiographic outcome. The model containing vessel size and percent DS after the procedure provide the best fit to the data, thus highlighting the importance of early results.

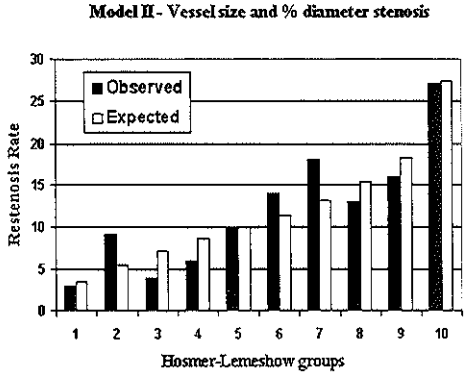

Figure 2. Observed and expected restenosis rate calculated using model II in the 10 patient groups on the basis of the Hosmer-Lemeshow goodness-of-fit test.

Table 6. Reference Chart Generated Using Model II

Vessel size (mm)	Percent Diameter Stenosis After Procedure									
	1.5–5.9	5.9–10.3	10.3–14.7	14.7–19.1	19.1–23.5	23.5–27.9	27.9–32.3	32.3–36.7	36.7–41.1	41.1–45.5
1.83–2.14	*0.24**	**0.28**	**0.33**	**0.38**	**0.44**	**0.49**	**0.55**	**0.61**	*0.66**	*0.71**
	0.15–0.36	0.19–0.40	0.23–0.45	0.28–0.50	0.32–0.56	0.37–0.62	0.41–0.69	0.44–0.75	*0.48–0.80*	*0.51–0.85*
2.14–2.45	**0.17**	**0.21**	**0.25**	**0.29**	**0.34**	**0.39**	**0.45**	**0.50**	**0.56**	*0.62**
	0.11–0.26	0.14–0.28	0.18–0.32	0.22–0.37	0.26–0.42	0.30–0.49	0.34–0.57	0.37–0.64	0.40–0.71	*0.43–0.78*
2.45–2.76	**0.12**	**0.15**	**0.18**	**0.21**	**0.25**	**0.30**	**0.35**	**0.40**	**0.46**	*0.51**
	0.08–0.18	0.11–0.20	0.14–0.22	0.17–0.26	0.21–0.30	0.24–0.37	0.27–0.44	0.29–0.52	0.32–0.61	*0.35–0.68*
2.76–3.07	**0.08**	**0.10**	**0.12**	0.15	**0.18**	**0.22**	**0.26**	**0.31**	**0.36**	**0.41**
	0.05–0.12	0.07–0.14	0.10–0.16	0.13–0.18	0.15–0.22	0.18–0.27	0.20–0.33	0.22–0.41	0.24–0.49	0.26–0.58
3.07–3.38	**0.06**	**0.07**	**0.09**	**0.11**	**0.13**	**0.16**	**0.19**	**0.23**	**0.27**	**0.32**
	0.03–0.09	0.05–0.10	0.06–0.11	0.08–0.13	0.10–0.16	0.12–0.20	0.14–0.25	0.15–0.32	0.17–0.39	0.19–0.48
3.38–3.69	**0.04**	**0.05**	**0.06**	**0.07**	**0.09**	**0.11**	**0.13**	**0.16**	**0.20**	**0.23**
	0.02–0.07	0.03–0.07	0.04–0.09	0.05–0.10	0.06–0.12	0.08–0.15	0.09–0.19	0.10–0.25	0.12–0.31	0.13–0.38
3.69–4.00	**0.03**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.09**	**0.11**	**0.14**	**0.17**
	0.01–0.05	0.02–0.06	0.02–0.07	0.03–0.08	0.04–0.10	0.05–0.12	0.05–0.15	0.06–0.19	0.07–0.24	0.08–0.30
4.00–4.31	*0.02**	**0.02**	**0.03**	**0.03**	**0.04**	**0.05**	**0.06**	**0.08**	*0.10**	*0.12**
	0.01–0.04	0.01–0.04	0.01–0.05	0.02–0.06	0.02–0.08	0.03–0.09	0.03–0.12	0.04–0.15	*0.05–0.19*	*0.05–0.24*
4.31–4.62	*0.01**	*0.01**	*0.02**	*0.02**	**0.03**	**0.03**	**0.04**	*0.05**	*0.07**	*0.08**
	0.00–0.03	*0.01–0.03*	*0.01–0.04*	*0.01–0.05*	0.01–0.06	0.02–0.07	0.02–0.09	*0.02–0.12*	*0.03–0.15*	*0.03–0.19*
4.62–4.93	*0.01**	*0.01**	*0.01**	*0.01**	**0.02**	*0.02**	*0.03**	*0.04**	*0.04**	*0.05**
	0.00–0.02	*0.00–0.03*	*0.00–0.03*	*0.01–0.04*	0.01–0.05	*0.01–0.06*	*0.01–0.07*	*0.01–0.09*	*0.02–0.11*	*0.02–0.15*

The cells marked with numbers in italics and an asterisk indicate the range without actual observations in the data set. Cells with bold numbers indicate the range with actual observations.

The difference between BENESTENT I and MUSIC. The most conspicuous observation emerging from these trials is the improvement in MLD after the procedure (2.49 mm in BENESTENT I and 2.90 mm in MUSIC) and the reduction in the restenosis rate from 21% in BENESTENT I to 10% in MUSIC, thus supporting the concept "the bigger the better" in a very homogeneous population treated with intracoronary stent implantation. Introduction of on-line QCA and IVUS guidance are potentially responsible for this improvement. Heparin coating of the stents was tried in the BENESTENT II pilot and the BENESTENT II study to circumvent the problem of subacute stent thrombosis, which emerged as the main hurdle to overcome in coronary stent implantation since the BENESTENT I and STRESS studies. Analysis of both these studies made it clear that although heparin coating did reduce the subacute thrombosis rate significantly, it had no effect on long-term outcome and restenosis rate (12,14).

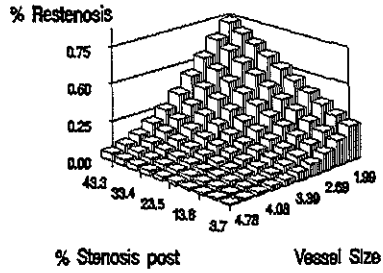

Figure 3. Three-dimensional bar diagram representing the reference chart. The lower the vessel size and the higher the DS after the procedure, the higher the expected restenosis rate.

Applicability of "the bigger the better." Kuntz et al. (23) first introduced this concept and demonstrated that it holds true irrespective of the device used for coronary angioplasty (24). They also suggested that a variety of other factors independently modulate restenosis superimposed on the platform of early results. However, there is significant evidence suggesting that this concept is device-specific and does not hold true for debulking techniques such as directional coronary atherectomy and excimer laser therapy (25,26).

Reasons for the difference. Three factors may have led to superior results, including the use of online QCA, high pressure dilation and IVUS guidance. Online digital automated edge detection QCA systems decrease measurement variability in comparison with visual assessment of coronary artery dimensions or hand-held callipers (27,28). Accurate

assessment of dimensions is important to guide sizing of balloon and other devices. Note that online QCA was not used during the BENESTENT I study but was used increasingly during the course of the BENESTENT II pilot study.

The concept of optimal stent deployment using high pressure dilation was proposed by Colombo et al. (29–33). Using IVUS they demonstrated that most of the angiographically satisfactory stent deployments were in fact far from being optimal and proposed the use of high pressure intrastent dilation and the use of IVUS to optimize stent placement. It was also noted that high pressure dilation with an appropriately sized balloon was better than using an oversized balloon, because the rate of complications like coronary rupture was higher with oversized balloons. The stent deployment strategy used in the BENESTENT I trial was according to the strategy in vogue (4), and only moderate pressure inflations were used for postdilation of the stents. The use of high pressure intrastent dilations became routine during subsequent trials. Although the debate about benefits of high pressure intrastent dilations has continued (34), a recent retrospective study by Goldberg et al. (33) has shown that the aggressive stent implantation techniques were not associated with increased late loss or restenosis and the above meta-analysis confirms this. Bauters et al. (35) have also demonstrated that high pressure inflation in the P-S stent was an independent predictor of lower late lumen loss. The results of this meta-analysis indicate that in the MUSIC study high pressure dilation was one of the factors associated with a reduction in the restenosis rate.

The role of IVUS imaging in the era of high pressure stent deployment remains to be clearly established. A recent study by Akiyama et al. (36) showed that, despite high pressure dilation, 33% of the lesions required additional treatment when assessed by IVUS. The preliminary results of the Angiography Versus Intravascular Ultrasound Directed Coronary Stent Placement (AVID) study (37) also support this; however, the long-term implications of this finding have yet to be established. The present study indicates that IVUS-guided optimal stent deployment was one of the important factors responsible for the improved results.

Left anterior descending coronary artery location. Phillips et al. (38) and Wong et al. (39) have demonstrated that stent implantation in the proximal left anterior descending coronary artery is associated with a greater reduction in the restenosis rate as compared with implantation elsewhere in the coronary tree. In contrast, Bauters et al. (35) and the current univariate analysis support the notion that after stent implantation, left anterior descending coronary artery location ceases to be a predictor of restenosis.

Can we equate the results of off-line QCA with on-line QCA? In the present study the results of offline QCA were used to construct the multivariate models, whereas the best-fit model, which was used to build the reference chart, used the variables of percent DS after the procedure and vessel size. Previous studies (40) have demonstrated that the geometric variables of MLD and obstruction diameter, as measured by off-line and on-line QCA systems, respectively, show good correlation. The correlation between interpolated and relative variables, like interpolated RD and percent DS, although acceptable, was lower ($r = 0.76$) than that of the geometric variables. The difference in the derived variables was due to the fact that the two systems use different definitions to calculate the relative variables. Availability of second-generation QCA systems like CAAS II, which can be used both online and offline, should resolve this problem. Other second-generation QCA systems like CMS, QANSAD, AWOS, Cardio 500 and Angioimage have been shown to be more precise than the first-generation systems and were validated in vitro by Hausleiter et al. (41). However, intersystem variability needs to be established before these results from CAAS II can be extrapolated to other systems.

Can the results be generalized? The multivariate models were developed using the data obtained by the use of the P-S stent, and the applicability of the same to other stents is not clear. Several ongoing or recently completed multicenter randomized trials comparing stents like GR II (42) (second-generation), AVE Micro (43) (SMART [Study of AVE Micro Stent ability to limit Restenosis Trial]), Cardiocoil (RACE), ACS Multilink (ASCENT [ACS Multilink Clinical Equivalence Trial]), NIR (NIRVANA [NIR vs. Palmaz-Schatz]), Radius (SCORES [Stent Comparative Restenosis Trial]) and Wallstent to the P-S stent will tell us about the equivalence of these stents to the P-S stent. Meanwhile, it would be interesting to apply the reference chart to the data from the WEST (Western European Stent Trial) I (44) and WEST II (45) trials (MULTI-LINK stent implanted under IVUS guidance) to find out the applicability of this type of reference chart. The current model is based on the implantation of stents in short de novo lesions in native coronary arteries >3 mm in diameter, and its applicability remains to be tested in cohorts outside this restricted framework.

Acknowledgments

This study would not have been possible without the clinical collaborations of multiple centers throughout Europe that participated in BENESTENT I, BENESTENT II pilot, BENESTENT II and MUSIC trials, as well as the reliable QCA analysis and data base management at the angiographic core laboratory at Cardialysis, Rotterdam, The Netherlands. Thanks also to Jille Kootstra and Rein Melkert, Biostatistics Division of Cardialysis for their invaluable assistance in the statistical analysis.

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Part II

Methodological issues in coronary brachytherapy

Chapter 2

Methodological and clinical implications of the relocation of the minimal luminal diameter after intracoronary radiation therapy. Dose Finding Study Group.

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Methodological and Clinical Implications of the Relocation of the Minimal Luminal Diameter After Intracoronary Radiation Therapy

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

BACKGROUND Luminal diameter of coronary lesions may increase over time following angioplasty and irradiatation. As a result, the MLD at follow-up may be relocated from its location preintervention, 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, four 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 (78.5% vs. 26.3%; $p < 0.0001$). The rate of >50% diameter stenosis differed among the four predefined 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 of the results of radiation clinical trials. (J Am Coll Cardiol 2000;36:1536–41) © 2000 by the American College of Cardiology

During the past 10 years the efficacy of percutaneous interventions in preventing restenosis 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; in addition, it possesses a better inter- and intra-observer 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 (IRS) (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 nonradiation studies unfair. This study was intended to 1) determine the incidence of the relocation of the MLD after beta-radiation therapy following successful BA and 2) to describe a new methodological approach to analyze and report accurately 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 beta-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

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Abbreviations and Acronyms

BA = balloon angioplasty
Gy = gray
INS = injured segment
IRS = irradiated segment
IVUS = intravascular ultrasound
MLD = minimal luminal diameter
QCA = quantitative coronary angiography
TS = target segment
VS = vessel segment

beta-emitting ^{90}Y, and patients were randomized to receive doses of 9, 12, 15 or 18 gray (Gy) at 1 mm 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 four interconnected compartments and which allows the source lumen to be centered relative to the arterial lumen; and 3) a computerized afterloader that allows automated advancement and positioning of either the dummy or the active source (14).

QCA analysis and definitions. The QCA analysis was performed off-line by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands). All angiograms were evaluated after intracoronary administration of nitrates. 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 preintervention, positions of angioplasty balloon and radiation source can be displayed simultaneously on the screen using the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands). The electrocardiographic (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 side branches that encompassed the original lesion, angioplasty balloon and radiation source. This segment was defined as the "vessel segment" (VS) (Fig. 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

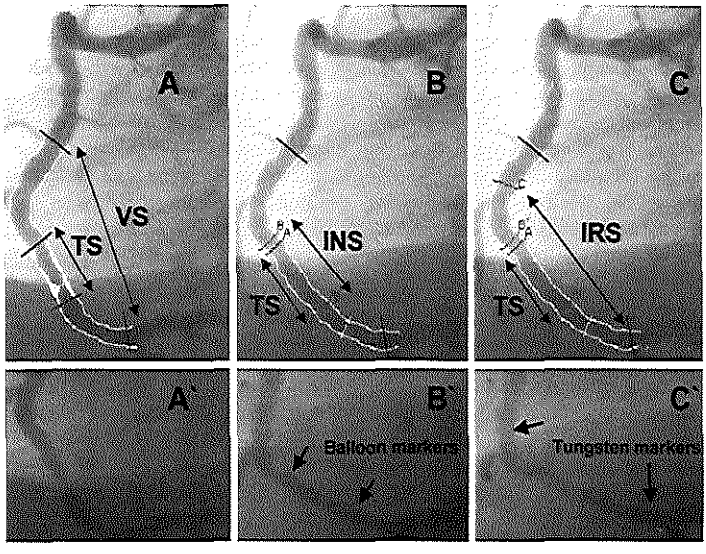

Figure 1. (A) Target segment (TS) is between proximal and distal margin of the target lesion, automatically defined by the quantitative coronary angiography system. Vessel segment (VS) is bordered by visible side branches, which encompass the target segment (TS) and the position of the angioplasty balloon 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 two 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.

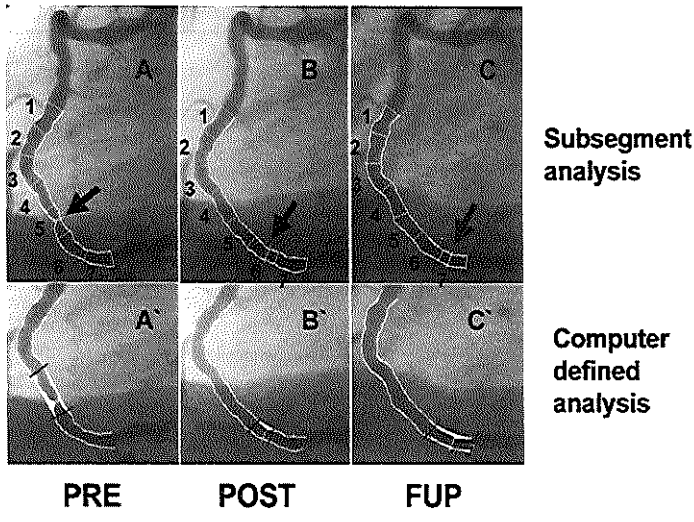

Figure 2. (A) Subsegmental analysis before procedure. Vessel segment (VS) was automatically divided into 5-mm subsegments by the CAAS II system. The original lesion is located at segment No. 5 preprocedure as the arrow indicates. (A') Computer defined analysis preprocedure. (B) Subsegmental analysis at postprocedure. Minimum lumen diameter is located at segment No. 6 (arrow). (B') Computer-defined analysis postprocedure. (C) Subsegmental analysis at follow-up. Minimum lumen diameter is located at segment No. 7 (arrow). (C') Computer-defined analysis at follow-up.

were filmed in the same projections as performed previously. The proximal side branch within the VS was used as an index anatomical landmark. The CAAS software computed 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. 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 two tungsten markers defined the IRS (Fig. 1). All regions of interest were superimposed on the pre-, post-procedural and follow-up angiograms. "Geographical miss" was defined for those cases in which the entire length of the INS was not fully covered by the IRS (17).

Using the software 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 this enabled relocation of the MLD to be defined (Fig. 2). "Relocation pre-post" was defined as those cases in which the MLD of the VS post-treatment was located in a different subsegment in the two orthogonal projections from that of the index procedure. "Relocation post-fup" was defined as those cases in which the MLD of the VS at follow-up was located in a different subsegment in the two orthogonal projections from that of the post-procedure. "Relocation pre-fup" was defined as those cases in which the MLD of the VS at follow-up was located in a different segment in the two orthogonal projections from that of the index procedure (Fig. 2).

Additionally, the analyst computed the MLD in every region of interest and calculated the acute gain, the late loss and the frequency of >50% diameter stenosis on a regional basis. "Acute gain" was defined as MLD posttreatment minus MLD preintervention. "Late loss" was defined as MLD posttreatment 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) and presenting with matched views and correct angiographic documentation was used as the control group. The VS, TS, and relocation of the MLD were defined in this cohort as described above.

Statistical analysis. Data are presented as mean ± SD or proportions. To compare qualitative variables, the chi-square test was carried out. To compare quantitative variables, the Student *t* 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 beta-radiation were eligible for the study. By comparing the technician worksheet with the angiograms recorded, the analyst was able to identify those patients for whom all balloon inflations and source positioning were filmed and all target views matched. Using this

Table 1. Baseline Characteristics

	Dose-Finding Group (n = 65)	Control Group (n = 179)
Age (yrs)	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 = gray.

systematic approach, 65 patients who did not accomplish these technical requirements for performing 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 prescribed (9, 12, 15, or 18 Gy at 1 mm 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 Table 1. No differences were observed between the two 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 patients (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 was defined 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 two 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 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).

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 = injured segment; IRS = irradiated segment.

Methodological implications of the relocation of the MLD. The QCA data derived from the analysis of the predefined regions are shown in 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 treated with "plain old balloon" angioplasty also demonstrated a notable incidence of relocation. This phenomenon was noted after radiation was witnessed in previous studies showing that the restenosis process affected the entire vessel segment, which was dilated, and not just the obstructed segment (19,20). To overcome this problem, the Total Occlusion Study of Canada (TOSCA) group devised the concept of "target lesion work length," defined as the length of contiguous target segment exposed to balloon inflation (21). In addition, the relocation of the MLD may explain the mismatch between good angiographic results of

Table 3. QCA Data From the Four Predefined 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

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

previous radiation trials and the poor clinical outcome (i.e., high target vessel revascularization rates) observed in these studies (22).

Further, because changes in the reference diameter may occur during the follow-up period, the use of the percent diameter stenosis measurements is questionable as an accurate estimate of lesion severity (19,20). In this regard, two thirds of our study population demonstrated an increase in the value of the preintervention 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 IVUS observations demonstrated that the vessel wall enlarges after catheter-based radiation therapy either following conventional BA or stent implantation (12,23). 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 preexisting plaques that became angiographically apparent or that progressed after the treatment and tapering of the vessel may have accounted for the relocation of the MLD. In addition to 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 predefined 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 that was injured by the 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 under optimal conditions. On the other side 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 the restenosis process after BA (24–27). This traditional approach is driven by the concern that hemodynamic effects (i.e., flow-limiting lesion), symptoms, and outcomes are likely related to the location of the new MLD, irrespective of precise anatomic concordance with its location preintervention. The meticulous analyses proposed are likely to yield new insights on the pathophysiology of this new therapy, and we believe that these are highly recommended during feasibility in vivo and in vitro studies. In clinical radiation trials, the traditional VS approach should be the common angiographic end point, and further analyses of the above-defined regions of interest may complement the results of the study. In this regard, the efficacy of the therapy itself would be determined by the results at the TS, whereas the effectiveness of the radiation therapy would be defined for the entire VS, which includes both the desired (i.e., lumen enlargement) and the side effects (i.e., edge restenosis).

Study limitations. The definition of relocation of the MLD depends decisively on the accurate documentation of all steps followed during the procedure. This was accomplished in only 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 be useful to determine both the potentialities and the limitations of this new technique.

APPENDIX

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

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

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

Data monitoring. Thomas Thaler, MD (Boston, Scientific).

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Chapter 3

Geographic miss: a cause of treatment failure in radio-oncology applied to intracoronary radiation therapy.

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Geographic Miss

A Cause of Treatment Failure in Radio-Oncology Applied to Intracoronary Radiation Therapy

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Background—A recognized limitation of endovascular β-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 precursor of this phenomenon. We translated the radio-oncological concept of "geographic miss" to define cases in which the radiation source did not fully cover the injured area. The aims of the study were to determine the incidence and causes of geographic miss and evaluate the impact of this inadequate treatment on the outcome of patients treated with intracoronary β-radiation.

Methods and Results—We analyzed 50 consecutive patients treated with β-radiation after percutaneous coronary intervention. The prescribed dose ranged between 12 and 20 Gy at 2 mm from the source axis. By means of quantitative coronary angiography, the irradiated segment (IRS) and both edges were studied before and after intervention and at 6-month follow-up. Edges that were injured during the procedure constituted the geographic miss edges. Twenty-two edges were injured during the intervention, mainly because of procedural complications that extended the treatment beyond the margins of the IRS. Late loss was significantly higher in geographic miss edges than in IRSs and uninjured edges (0.84±0.6 versus 0.15±0.4 and 0.09±0.4 mm, respectively; $P<0.0001$). Similarly, restenosis rate was significantly higher in the injured edges (10% within IRS, 40.9% in geographic miss edges, and 1.9% in uninjured edges; $P<0.001$).

Conclusions—These data support the hypothesis that the combination of injury and low-dose β-radiation induces deleterious outcome. **(*Circulation*. 2000;101:2467-2471.)**

Key Words: geographic miss ■ radioisotopes ■ balloon ■ angioplasty ■ stents ■ angiography ■ restenosis

Endovascular radiation therapy is a novel technique aimed at preventing 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 (IRS). This so-called "edge effect" was originally described after high-activity (>3 μCi) 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] concomitant with 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 "geographic 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 that were injured but received low-dose radiation. Typically, this phenomenon occurs when the edges of the IRS, where, by definition, the dose is rather low, are injured.

The aims of the study were (1) to determine the incidence and causes of geographic miss in the treatment of patients with intracoronary β-radiation by use of 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 β-radiation by means of the Beta-Cath system (Novoste Corp). Patients included in the radiation protocol were those with objective signs of ischemia and presence of

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significant de novo lesions (n=39) or recurrent in-stent restenosis (n=11). A 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 radiopaque markers separated by 30 mm.[14]

Procedure

The medical ethics committee of our institution approved the investigational use of β-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 patients who also received stent implantation, ticlopidine was initiated and continued for ≥15 days after the procedure. The radiation dose was prescribed at 2 mm from the source axis. The prescribed dose for the treatment of de novo lesions was randomly assigned to 12, 14, or 16 Gy for protocol requirements. For the treatment of in-stent restenotic lesions, the prescribed dose was 16 or 20 Gy if the reference diameter, by quantitative coronary angiography (QCA), measured ≤3.25 mm or >3.25 mm, respectively. The mean dwell time to deliver these doses was 143±44 seconds.

Definitions

The 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 to the angiographic location of the gold markers. The edges that were touched by the angioplasty balloon or received new stent implantation during the procedure were defined as geographic miss edges, because they represent injured segments receiving low-dose radiation. Uninjured edges were those that 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 was filmed in the same projection, as was the radiation source. This approach allowed us the correct matching of the cine films in the offline analysis. Either cine loop showing balloon inflation, stent implantation, and radiation source may be displayed simultaneously on the screen with the Rubo DICOM Viewer (Rubo Medical Imaging). ECG tracing is also displayed in either cine loop. 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 before and after intervention and at 6-month follow-up. All angiograms were evaluated after intracoronary administration of nitrates. The offline analysis of 2 orthogonal projections was performed by means of 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 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 after treatment minus MLD before intervention. Late loss was defined as MLD after 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, geographic miss edges, and uninjured edges, 1-way 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 geographic miss edges and between patients in whom the geographic miss was induced by balloon dilatation or stent implantation. To compare the binary restenosis between groups, the χ^2 test was performed. All tests were 2-tailed, and a value of $P<0.05$ 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 excluded because of the ostial location of the proximal end of the source in the right coronary artery (n=12) or overlapping of 1 of the edges with side branches (n=14). Thus, finally, 74 edge areas and 50 IRSs were studied. Mean age was 55.3±9 years, 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 diabetic. The left anterior descending coronary artery was treated in 21 patients, the left circumflex in 10, the right coronary artery in 18, and a saphenous vein graft in 1. Twelve patients received a stent in a bailout situation.

Incidence and Causes of Geographic Miss

Geographic 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 uninjured edges. The location of the geographic miss was in the proximal edge in 11 patients (50%) and in the distal margin in 11 patients (50%). The following reasons were responsible for this phenomenon: (1) development of procedural complications that extended the treatment beyond the margins of the IRS (unexpected geographic miss, n=9); (2) lack of availability of a longer radiation source (>30 mm) in patients with diffuse recurrent in-stent restenosis in whom radiation was given on a compassionate-use basis (n=8); and (3) lack of accurate matching; ie, the injured segment from previous balloon inflations was not appropriately covered by the source (n=5). An example of a patient with geographic miss induced by a balloon dilatation in the proximal margin is depicted in Figure 1.

QCA Analysis

QCA data are presented in the Table. As expected, IRSs demonstrated, on average, a higher acute gain than both injured and uninjured edges. However, geographic 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 geographic miss edges, and in 1 case (1.9%) in the uninjured edges ($P<0.001$). No difference in the pattern of the late loss between the 3 areas was observed in de novo lesions compared with recurrent in-stent restenotic lesions (Figure 2). In the geographic miss edges, 4 edge restenoses (44%) were located at the proximal edges, whereas the other 5 (56%)

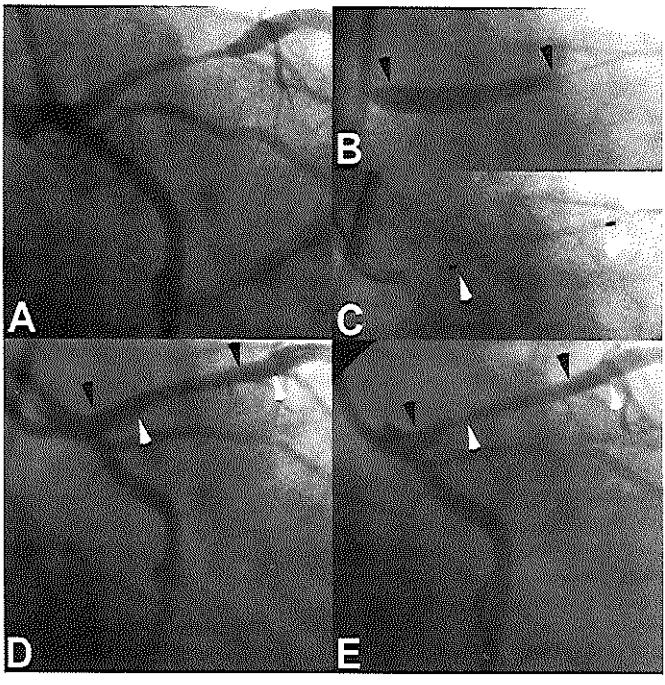

Figure 1. Geographic miss induced by balloon dilatation. A, Lesion located in proximal segment of left anterior descending coronary artery. B, Balloon dilatation performed during intervention (black arrowheads indicate area injured by balloon). C, Radiation source train in place. Irradiated area is delimited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

were located at the distal edges. Mean relative late loss was comparable between those edges, with geographic miss located proximal or distal to the IRS (0.31±0.2 versus 0.34±0.2, respectively; P=NS). Those edges in which the geographic 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 geographic miss (0.95±0.9 mm and 0.36±0.3, respectively, after stent versus 0.77±0.3 mm 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 β-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 patients presented with the predefined technical error, called geographic miss. This concept requires the concurrence of 2 conditions: low-dose radiation and injury. Any other clinical situations that do not include both conditions cannot be called geographic miss. For instance, (1) the effect of injury on coronary segments not being irradiated (proximal or distal to an IRS but in areas in which the calculated dose is almost 0) should fall into the category of normal restenotic process; (2) the effect of low-dose radiation in areas that have not been injured may be defined as the pure radiation edge effect, because in intracoronary radiation, the

QCA Data

	IRS (n=50)	Geographic Miss Edges (n=22)	Uninjured Edges (n=52)	P
MLD before intervention, mm	1.20±0.3	2.02±0.6	2.10±0.6	<0.0001
MLD after 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 before intervention, %	54.9±13	19.8±14	17.9±11	<0.0001
%DS after 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

%DS indicates diameter stenosis. Data are mean±SD.

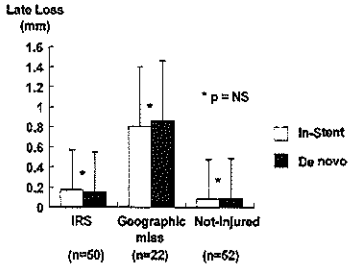

Figure 2. Difference in late loss between IRS, geographic miss edges, and uninjured edges. De novo lesions and in-stent restenosis demonstrated same degree of late loss between 3 groups.

edges of any IRS will always receive low-dose radiation; and (3) finally, the effect of a full prescribed dose on segments presenting with or without injury is the situation in which the physician may be able to irradiate (with full dose) the entire injured segment and include some uninjured margin. A key issue in the definition of geographic miss is to define those segments receiving a low dose. These may vary between systems and sources used. With the Beta-Cath system, the longitudinal distance of the 100% isodose is 26 mm. Because the β-emitting $^{90}Sr/^{90}Y$ has an acute falloff of dose related to the distance,[19] the last 2 mm within the markers of the source should be considered as having received a lower than 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). At 3 mm, 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 a lower than prescribed dose (up to 60% of the prescribed dose). By this definition, late loss and restenosis rate were significantly lower than those of the injured edges (analyzed from the inner part of the gold marker). Furthermore, 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 the edge effect after the edges had probably been injured during the procedure, especially when a 20-mm-long balloon was used. Thus, the region receiving a low dose may be defined, for this system and source, as the 5-mm-long segment located 2 mm farther from 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 (26 mm) 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 5 mm) must be considered to be at 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 in 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 because of procedural complications. Equally, the use of online QCA in the decision-making would avoid appreciation errors due to visual assessment of the target area and subsequent underestimation or overestimation of balloon lengths. Finally, the selection of the most suitable fluoroscopic projections (eg, less foreshortening, no overlapping) would avoid errors in the quantification of the region of interest.

The facts that the locations of most of the restenoses were in geographic miss edges and that late loss in those areas was unexpectedly high must raise an 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 after either BA or stent implantation[20,21] and higher than that demonstrated in the uninjured edges. Balloon overstretch 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.[10,22,23] The stimulatory effect of low-dose radiation after BA on smooth muscle cell proliferation has been reported previously.[11] In the low-dose radiation group of this swine model (10 Gy), neointima was composed of smooth muscle cells, with a marked increase in inflammatory cells and less medial and intimal fibrosis than in the higher-dose groups (15 and 20 Gy) and the control group. It was suggested that at low dose, inadequate fibrosis was induced to prevent effective smooth muscle cell 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, neointimal hyperplasia was significantly greater than that after nonradioactive control stents.[12] If ongoing intravascular studies reveal that edge restenosis is mainly due to plaque increase, the former hypothesis that at a low dose, inadequate medial and intimal fibrosis to avoid migration and proliferation predominates may become a plausible explanation. Conversely, 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 predilatation and postdilatation of the radioactive stent. In this regard, a higher balloon-to-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 after either radioactive stent– or catheter-based systems.

Study Limitations

In this study, only 1 type of radiation delivery catheter using the β-source $^{90}Sr/^{90}Y$ was evaluated. Thus, the effect of either other catheter-based systems using centering balloons and different sources or the γ-radiotherapy on the geographic miss edges cannot be extrapolated from our results.

The actual dose at the margins of the radiation source has not been calculated. A low dose at these edges was assumed because the isotope $^{90}Sr/^{90}Y$ demonstrates an acute falloff related to the distance from the 100% isodose boundary.[19]

This angiographic study was aimed at defining the concept and the clinical implications of the geographic 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 a 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 the cardiac cycle, cannot be completely ruled out.

This study was not placebo-controlled. Thus, the effect of the sham source on the balloon-injured coronary segments has not been determined.

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Part III

Radioactive stents

Chapter 4

β-Particle-emitting radioactive stent implantation. A safety and feasibility study.

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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 ≥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.

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.

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.

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

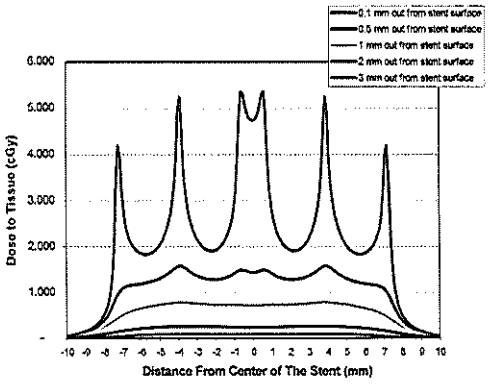

Figure 1. Two-dimensional dose representation for 1-μCi ^{32}P Palmaz-Schatz stent. Cumulative dose given over 100 days is shown (source, Isostent Inc).

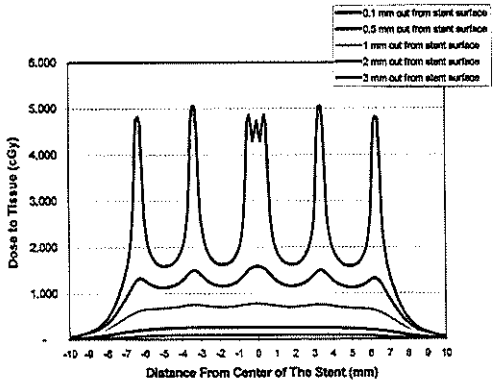

Figure 2. Two-dimensional dose representation for 1-μCi ^{32}P BX stent. Cumulative dose given over 100 days is shown (source, Isostent Inc).

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.

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Chapter 5

I like the candy, I hate the wrapper: the ^{32}P radioactive stent.

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I Like the Candy, I Hate the Wrapper

The ^{32}P Radioactive Stent

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United States patent 5059166, issued October 22, 1991, to Robert and Tim Fischell, described an "intraarterial stent with the capability to inhibit intimal hyperplasia."[1] The proponents of this patent went on to say in their proposal: "Since radiation from a radioisotope source is capable of selectively inhibiting the growth of hyperproliferating cells as compared with normal cells, a radioisotope material which forms part of the stent can be used to decrease the rate of arterial reclosure. The radioisotope could be placed inside the stent, alloyed into the metal from which the stent is made, or preferably, it can be coated onto the stent's exterior surface." So began the story of the radioactive stent. Eight years and several animal species later, we are becoming aware of the bright and dark sides of this treatment modality in the human model.

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The safety and efficacy study by Albiero and colleagues[2] describes the dose-related decrease noted at 6-month follow-up of intrastent neointimal hyperplasia after implantation of ^{32}P radioactive stents at activities of 0.75 to 12 μCi. Whereas in-stent restenosis was all but obliterated at higher doses of radiation, intralesion restenosis was high because of late lumen loss at the stent edges. Aptly, the authors coined the term "candy wrapper" to describe this new restenotic pattern. It is possible that the animal workers who implanted the first radioactive stents observed this phenomenon. Unfortunately, the significance of this finding may not have been immediately apparent.

Historical and Dosimetric Considerations

The study by Albiero and colleagues reflects the courage of the investigators who, despite indifferent and at times contradictory results from animal work, persisted in their endeavor to discover whether radioactive stent implantation would be effective in humans.

Previously, Hehrlein et al.[3,4] using the rabbit iliac model, polyisotopic ^{55}Co (elements ^{55}Co, ^{56}Co, ^{57}Co, ^{57}Ni, and ^{55}Fe) with activity levels of 17.5 and 35 μCi, and later ^{32}P stents (activity levels of 0.5, 4, 6, and 13 μCi), had demonstrated a dose-dependent effect of inhibition of neointimal hyperplasia within the stent. It had already been noted that lower activity levels were able to reduce neointimal hyperplasia, but the effect was lost at 12 weeks, particularly at the stent ends. Between struts and at stent ends, endothelialization occurred more rapidly and was dose-dependent.

In the porcine coronary restenosis model of Carter et al.[5] different activities of ^{32}P-containing stents were used. Mitchell[6] makes the following observation on these findings: "The doses delivered by the different activities of ^{32}P were divided into 3 categories: low (<2000 cGy), intermediate (4000 cGy) and high (>10 000 cGy). Based on these values, the average dose rates to the tissue over the 25-day period of the study were: low (3 cGy/h), intermediate (6 cGy/h), and high (15 cGy/h). It is interesting that both the high and low doses and dose rates were effective in reducing the extent of restenosis, whereas, the intermediate dose/dose rate was ineffective if not worse than the control. These findings do not conform to the findings that would be expected as dose and dose-rate are reduced. One might expect the high dose/dose rate to be effective and perhaps the intermediate and low dose/dose rate to be ineffective. The fact that the low dose/dose rate treatment was effective in this study suggests that perhaps an inverse dose-rate effect is operative over a narrow range of dose rates in this model." As suggested above, it is not only the total dose of irradiation delivered to the tissue that is important but also the dose-rate time interval in which radiation is delivered. This reflects the simultaneous processes of DNA repair, concurrent with the damage induced by radiation exposure. This is particularly important in comparisons of the high dose-rates of catheter-based techniques with those of radioactive stents that use low dose-rates. An increase in the dose-rate at which certain cell lines are irradiated in vitro demonstrates a killing effect that is most marked between 1 and 100 cGy/min.[4,7] However, at 0.6 cGy/min, there is more effective cell killing than at 0.2 or 2.6 cGy/min. This is due to cell cycle blockade. At this dose-rate, the cells are selectively blocked at G_2/mitosis, a more radiosensitive phase of the cell cycle. Once this occurs, the low-dose-rate treatment becomes much more efficient with respect to killing (inverse dose-rate effect).[6]

We previously made the following comment on these conflicting observations: "so far incremental doses have always resulted in more cell death or decreased cell proliferation. We cannot exclude that there is a U-shaped dose-response curve for endovascular radiation, but in view of all the earlier reports, this is unlikely."[8] Of course, it is possible that the European rabbit was more receptive to the effects of brachytherapy than the American pig. In general, the results derived from certain animal testing and the dose-finding

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effect in human series of Albiero et al appear logical and are in keeping with the general rule of brachytherapy: the more you irradiate, the more you inhibit proliferation, up to the point at which detrimental effects appear.

Recently, more information has become available on the delayed endothelialization of the radioactive stent,[9] with the consequent risk of late thrombosis. Albiero and colleagues endeavored to avoid the thrombotic sequelae of late endothelialization by using longer courses of antiplatelet agents. We are aware of only 1 episode of subacute thrombosis occurring in humans after radioactive stent implantation to date, in contrast to recent findings using the combination of conventional stents and catheter-based radiation.[10,11]

Not All Radioactive Stents Are Equal: Techniques of Stent Activation

The clinical effect of a radioactive stent may be modulated by use of radioisotopes with different half-lives, energy, activity, and penetration. Consequently, in the interpretation of results originating from different radioactive stent trials that used different isotopes, extrapolation between stents and isotopes may be inappropriate. The trials discussed above used 2 different techniques to make the stents radioactive: (1) direct ion implantation (that used by Isostent to create the ^{32}P stent) (Isostent Inc, Belmont, Calif, personal communication): phosphorus-containing ^{32}P isotope produced by neutron activation was inserted into the ion source of an implanter. Ionized ^{31}P and ^{32}P atoms were accelerated and separated by a magnet so that only the ^{32}P was implanted directly onto the stent surface. (2) Bombardment with charged particles (as used by Hehrlein et al)[3,4]: the stents were placed into a cyclotron and bombarded with deuterons. Metallic stent particles were transformed into several radioisotopes. Later, proton bombardment was used to reduce the high-energy γ-radiation emitted by the stents.

Other methods currently available include electrodeposition (a technique for the manufacture of a γ-radiation–emitting stent) and finally, isotope-emitting gold and phosphorylcholine stents. Clear advantages of 1 technique over another will be the subject of future consumer reports.

The ^{32}P Stent: An Antirestenotic Stent Using an Electron-Beam Fence

In our enthusiasm to control vessel recoil and remodeling after balloon angioplasty, 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 neointimal proliferation secondary to chronic vessel wall irritation, leading to in-stent restenosis.[12]

As a means of preventing neointimal proliferation, the idea of creating an electron-beam fence has been raised. Simply, the idea is to place radioactivity where it should be in the first place: at the endoluminal surface, generating a fence that should "fry" any smooth muscle cells or myofibroblasts trying to reach the endoluminal cavity created by the stent.[13] In this model, the concept of irradiating a target volume, as is desirable with cancer or catheter-based technologies, may not be relevant. Catheter-based brachytherapy involves the use of a single-hit, high-dose administration of intracoronary radiation. It seeks to target a volume of myofibroblasts and smooth muscle cells within the adventitia by irreversibly altering the DNA, such that on cell division, death will occur. This clearly decreases the reproductive capacity of the adventitia as a unit, and consequently, the potential for restenosis. Using the radioactive stent approach, we do not have to neutralize the huge reservoir of quiescent myofibroblasts lying dormant in the adventitia. Prevention of the migration and invasion of myofibroblasts occurs because of the continuous and low dose-rate, as witnessed by Albiero et al, adding credence to the concept of the electron-beam fence. This takes place regardless of the bulk of the atherosclerotic plaque and extent of penetration of the radiation. Equally, it occurs despite the eccentric placement of the radioactive stent within the vessel. In a preliminary report, the Milan group[14] demonstrated that a heterogeneous adventitial exposure (maximum dose, 4378±3078 cGy/14 d; minimum dose, 563±360 cGy/14 d; range, maximum dose, 644 to 12 210 cGy/14 d; range, minimum dose, 153 to 1461 cGy/14 d) still results in a homogeneous stent response with respect to the formation of neointimal hyperplasia.

Initially, basic scientists and radiotherapists perceived the concept of an electron-beam fence as being a fantasy created by cardiologists, objecting that it was not realistic. Ultimately, however, the proponents of the fence may just be correct.

Application of the concept of an electron-beam fence to the stent edge, however, makes one aware of its potential Achilles' heel. The range of the stent radioactivity is limited, and whereas those cells behind the stent struts may be well fenced at the doses discussed, cells proximal and distal to the extremity of the stent, in injured areas treated by the balloon (up to 3 mm outside the stent; personal communication, Isostent), may not be effectively covered by the range of the stent radiation. The latter phenomenon has been described in radiotherapeutic terms as "geographical miss": the mismatch between the irradiated and injured area[15] (Figure 1).

The Problem of the Candy Wrapper and Its Prevention: Is the Candy Wrapper Another Oculostenotic Illusion?

Stent-edge renarrowing occurs after conventional stent implantation.[16] This may not be angiographically visible, because the luminal ingrowth at the stent edges is in juxtaposition to the neointimal hyperplasia within the stent, producing a smooth contour on the luminogram. In contrast, after radioactive stenting, a visual gradient at the extremities becomes apparent, because nothing will grow within the stent, which makes all edge restenoses obvious.

In the study by Albiero et al, we note that lesions received a further percutaneous intervention on the basis of whether there was evidence of >50% intralesion angiographic stenosis. It may be that a word of caution is required in the assessment of the stent-edge lesion so as not to be seduced into believing that all such stenoses require treatment, given that the transition from the pristine stent lumen to the stent edge may appear great.

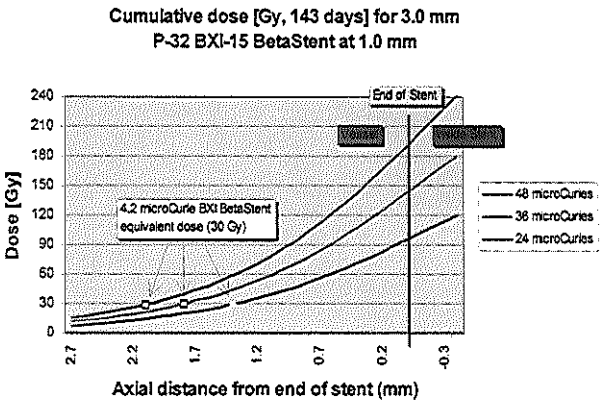

Figure 1. Dose representation for a 3.0-mm-diameter P-32 BX Isostent with activity level 4.2 μCi measured at 1 mm from stent struts. *y* axis: Total dose to tissue in Gy. *x* axis: Vertical line represents edge of stent. Area to right of vertical line is within stent. Area proximal (or distal) to stent is depicted to left of vertical line. Maximal balloon overhang is described to a total of 2.7 mm axially. Each isodose curve describes dose delivered to tissue by stents of different activity levels (24, 36, and 48 μCi), both within and proximal/distal to stent. Model assumes that a dose of 30 Gy is required to inhibit neointimal proliferation. Note that as stent activity decreases, dose delivered to tissue proximal/distal to stent is no longer sufficient to cover area injured by balloon.

The propensity for edge restenosis to occur at either the proximal, distal, or both edges also remains ill-defined. It is conceivable that after conventional stenting, stent-edge restenosis with luminal narrowing adjacent to a pristine stent lumen could result in a rheological condition with consequent alteration of shear stress, promoting what is finally viewed as a candy wrapper.

Identifying the mechanism by which the candy wrapper occurs may permit a more focused strategy concerning its treatment. Using intravascular ultrasound, the authors describe an increase in plaque/media in the region 1 to 3 mm immediately proximal and distal to the stent and a decrease in the external elastic membrane from 4 to 10 mm. To combat these identified vascular changes that induce stent-edge restenosis, various modifications to existing radioactive stent morphology could be proposed: (1) the square-shouldered balloon, (2) the cold-end stent, (3) the hot-end stent, (4) a hybrid radioactive stent/radioactive catheter–based system, (5) a self-expanding radioactive stent, and finally (6) the γ-stent.

The appropriateness of any one of these suggestions will depend on what underlies the change in plaque volume and/or shrinkage in vessel size. As usual in medicine, the problem is likely to be multifactorial, with confounding factors. At first sight, the elements may be portrayed schematically as in Figure 2.

Is the edge effect secondary to low-dose radiation at the margins of the stent, or due to balloon injury at the stent edges, or a combination of the 2? In this study, the univariate analysis suggests that those vessels with a higher final balloon-to-artery ratio, smaller reference lumen diameter, and smaller final minimum lumen diameter by angiography are most susceptible to adverse stent-edge morphological change.

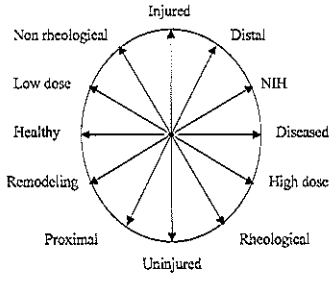

Figure 2. Multifaceted interaction that creates candy wrapper.

If the edge effect is the result of balloon-induced trauma and low-dose radiation (Figure 3A), then limiting the trauma outside the stent and expanding the irradiated area beyond the injured area should be attempted. Conceivably, the most practical approach may be to use a square-shouldered balloon (to minimize the injured area outside the stent) in combination with an extension of the area of irradiation beyond the injured area ("hot-end stent") (Figure 3B).

If the candy wrapper were purely the result of negative remodeling induced by low-dose radiation in an injured area, then the lengthening of the stent by a nonradioactive, cold-end stent would be a logical solution to prevent remodeling at the extremities (Figure 3C). If plaque constitutes a large percentage of the healing process manifested by the candy wrapper, then cold-end stent implantation is unlikely to work. Similarly, neointimal proliferation may occur at the edges of the radiation within the stent if this treatment modality is used.

A more elaborate, sophisticated approach would be the hybrid combination of a radioactive stent with the use of catheter-based radiation. The sources could be incorporated on the shaft of the balloon at the balloon extremities (Figure 3D). This approach would ensure that the injured area receives appropriate radiation.

If the candy wrapper is the result of an aberrant response by noninjured healthy or diseased tissue subjected to radiation, then this may suggest that low-dose radiation has a stimulatory effect on noninjured tissue.[17] This would be the worst possible scenario, because clearly, noninjured healthy or diseased tissue will always be irradiated at some stage.

In the event that excessive vascular remodeling is present after hot-ended or hybrid therapy, then a self-expanding nitinol radioactive stent may play a useful role (Figure 3E).

The γ-stent would have better tissue penetration than the β-emitting rivals. However, the energy generated by the former will be a drawback, with increased radiation exposure to patients, relatives, and personnel. It is conceivable that a low-energy, γ-radiation–emitting stent would minimize this

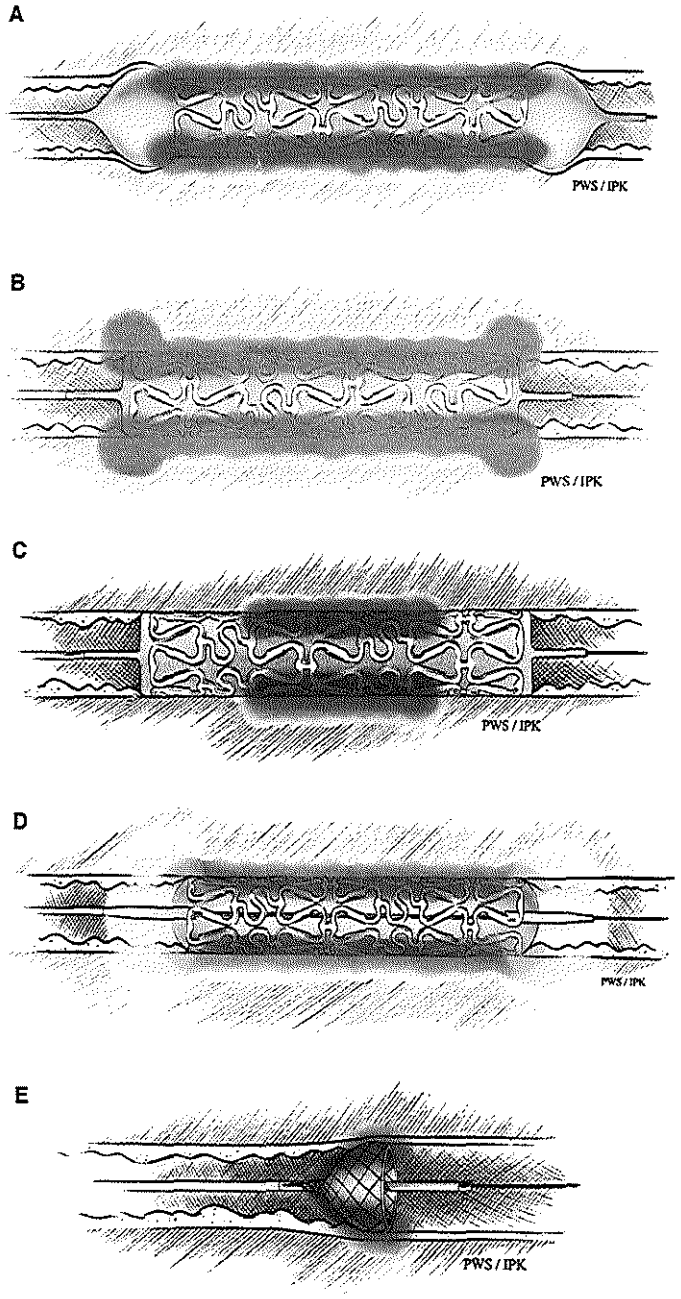

Figure 3. A, Illustration of a balloon-expandable BX stent. Radiation is depicted in orange. Note that trauma to vessel wall extends beyond that of radiation. B, Square-shouldered balloon limits area of injury, whereas radiation from hot-ended stent extends to normal/uninjured tissue. C, Cold-end stent with radiation limited to central area. D, Hybrid radioactive stent with catheter-based sources at each end to ensure that injured area receives adequate radiation coverage. E, Self-expanding radioactive nitinol stent.

environmental risk, yet provide adequate clinical effect. Further scientific exploration of this area is clearly justified.

Conclusions

Although a decade has elapsed since the inception of radioactive stenting, we are now beginning to understand that this treatment modality is indeed a double-edged sword. The path of evolution is clearly a slow one; meticulous work has been performed to clarify the efficacy of the radioactive stent. Albiero and colleagues have pointed us in a new direction, beyond the stent itself, and that is to carefully analyze the effect of injury and low-dose radiation on vessel healing at the stent edge. The true sweetness of the candy will only be appreciated once the pathophysiology of stent-edge restenosis is understood.

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KEY WORDS: Editorials ■ radioisotopes ■ stents ■ restenosis ■ coronary disease

Chapter 6

Clinical and angiographic follow-up after implantation of a 6.0-12.0μCi radioactive stent in patients with coronary artery disease.

European Heart Journal 22, 669-675, 2001.

Clinical and angiographical follow-up after implantation of a 6–12 μCi radioactive stent in patients with coronary artery disease

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Aims This study is the contribution by the Thoraxcenter, Rotterdam, to the European ^{32}P Dose Response Trial, a non-randomized multicentre trial to evaluate the safety and efficacy of the radioactive Isostent® in patients with single coronary artery disease.

Methods and Results The radioactivity of the stent at implantation was 6–12 μCi. All patients received aspirin indefinitely and either ticlopidine or clopidogrel for 3 months. Quantitative coronary angiography measurements of both the stent area and the target lesion (stent area and up to 5 mm proximal and distal to the stent edges) were performed pre- and post-procedure and at the 5-month follow-up. Forty-two radioactive stents were implanted in 40 patients. Treated vessels were the left anterior descending coronary artery (n=20), right coronary artery (n=10) or left circumflex artery (n=10). Eight patients received additional non-radioactive stents. Lesion length measured 10 ± 3 mm with a reference diameter of 3·07 ± 0·69 mm. Minimal lumen diameter increased from 0·98 ± 0·53 mm pre-procedure to 2·29 ± 0·52 mm (target lesion) and 2·57 ± 0·44 mm (stent area) post-procedure. There was one procedural non-Q wave myocardial infarction, due to transient thrombotic closure. Thirty-six patients returned for angiographical follow-up. Two patients had a total occlusion proximal to the radioactive stent. Of the patent vessels, none had in-stent restenosis. Edge restenosis was observed in 44%, occurring predominantly at the proximal edge. Target lesion revascularization was performed in 10 patients and target vessel revascularization in one patient. No additional clinical end-points occurred during follow-up. The minimal lumen diameter at follow-up averaged 1·66 ± 0·71 mm (target lesion) and 2·12 ± 0·72 (stent area); therefore late loss was 0·63 ± 0·69 (target lesion) and 0·46 ± 0·76 (stent area), resulting in a late loss index of 0·65 ± 1·15 (target lesion) and 0·30 ± 0·53 (stent area).

Conclusion These results indicate that the use of radioactive stents is safe and feasible, however, the high incidence of edge restenosis makes this technique currently clinically non-applicable.

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Key Words: β-particles, angioplasty, radioisotope, restenosis, stent.

See page 669 for the Editorial comment on this article

Introduction

In-stent restenosis is almost exclusively caused by neointimal hyperplasia formation, which occurs due to trauma of the arterial wall, caused primarily by the stent struts and balloon dilatations[1,2].

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Vascular brachytherapy with a radioactive source after PTCA or stent implantation has been shown, in several experimental and clinical trials, to be a promising treatment in reducing restenosis rates, by inhibiting the process of neointimal hyperplasia[3–6]. Several animal trials have demonstrated a dose-related reduction of in-stent restenosis, following radioactive stent implantation[7–9]. However, a dose-dependent delay in endothelialization of the stent has been shown, which increases the risk of subacute and late thrombotic occlusions[8,10]. Recently, a porcine coronary model indicated that continuous low-dose rate irradiation by

high-activity ^{32}P radioactive stents may promote an 'atheromatous' neointima by the 6-month follow-up[11]. Controversially, in normal canine coronary arteries, radioactive stents result in a larger fibrin-rich neointima at follow-up, as compared to a control group[12].

In patients treated with implantation of ^{32}P radioactive stents with activities ranging from 0·75 to 12 μCi, angiographic restenosis was reported in 43–62% of the cases, with the restenosis primarily located at the edges of the stent[13]. The edges represent an area where tissue is subjected both to balloon-induced trauma and a lower dose of radiation, which may stimulate edge restenosis[9,14]. Our group reported that the implantation of a radioactive stent with an activity of 0·75 to 1·5 μCi was feasible and safe, with an in-stent restenosis rate of 17% and no occurrence of edge restenosis[14].

The aim of this study was to evaluate the safety and efficacy of implantation of a radioactive stent, with an activity level of 6-12 μCi, in patients with single, native, coronary artery disease.

Methods

Patient population

The European ^{32}P Dose Response Trial was a non-randomized multicentre trial to evaluate the safety and efficacy of radioactive stent implantation, with activities ranging from 1·5–3·0, 3–6 and 6–12 μCi. The data presented here is the experience of the Thoraxcenter Rotterdam.

Patients with single, native, coronary lesions, with a maximum lesion length of 28 mm (treatable with a maximum of two radioactive stents, implanted in tandem position), and objective evidence of ischaemia were eligible. Exclusion criteria were: recent myocardial infarction (creatine kinase-MB >three times the upper limit of normal, within 5 days of the intervention); left ventricular ejection fraction <40%; allergy or contraindication to aspirin, ticlopidine, clopidogrel or nickel; lesions located in the left main.

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

The BX® Isostent (Isostent® Inc., San Carlos, CA, U.S.A.) was implanted in this trial. It was 15 mm in length and available in diameters of 3·0 and 3·5 mm. The BX® Isostent was made radioactive by Phosphorus-32 (^{32}P)[9]. The initial activity of the stents was measured and thereafter the date at which the radioactivity should have decreased to 6–12 μCi (radioactivity level suitable for implantation) was calculated. The dose delivered over 100 days at 1 mm from the stent surface was calculated for each implanted 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. All disposable materials, which were in contact with the stent, were immediately disposed of in a plexiglas container.

Quantitative coronary angiography

Quantitative coronary angiography was performed pre-procedure, post-procedure, and at the 6-month follow-up. Coronary angiography was performed after intracoronary administration of nitrates. The off-line analysis of at least two orthogonal projections was performed by means of the CAAS II (Cardiovascular Angiographical Analysis System, Version II) (Pie Medical B.V., Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters not filled with contrast medium, which has been extensively validated and applied in numerous clinical trials[15–17]. The following measurements were obtained in each projection for the target lesion: minimal luminal diameter, reference diameter, diameter stenosis and lesion length. Lesion length was measured by means of a computer algorithm[17]. Procedural success was defined as %diameter stenosis <20%, measured by on-line quantitative coronary angiography. Acute gain was defined as minimal luminal diameter post-procedure minus minimal luminal diameter pre-procedure. Late loss was defined as minimal luminal diameter post-procedure minus minimal luminal diameter at follow-up. The late loss index was defined as late loss divided by acute gain[18]. For analytical purposes, three regions of interest were defined: (1) stent area, (2) target lesion and (3) target vessel. The stent area was defined as the segment which included only the radioactive stent(s). The target lesion was defined as the stent area and 5 mm proximal and 5 mm distal to the edge of the radioactive stent. The target vessel was defined as the target lesion and the remaining segments of the treated vessel. Target lesion restenosis was defined as >50% diameter stenosis at follow-up, located within the target lesion. Edge restenosis was defined as >50% diameter stenosis at follow-up, located at the proximal and/or distal edge. In order to quantify an edge effect, a quantitative coronary angiography subsegmental analysis was performed in 30 patients, excluding patients with ostial lesions or occlusions pre-procedure or at follow-up. Target vessel stenosis was defined as >50% diameter stenosis at follow-up, located on any segment of the treated vessel. Quantitative coronary angiography measurements were performed by means of the CAAS II analysis system. Careful matching of the segments, encompassing the proximal and distal edges and the stent area, was performed pre-, post-procedure and at follow-up (see also Fig. 1).

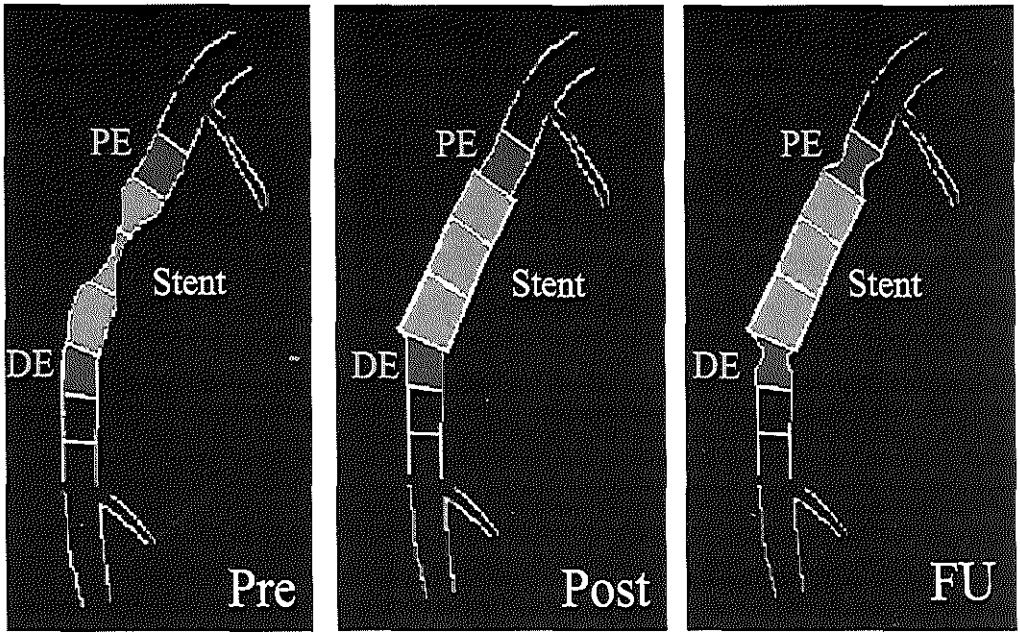

Figure 1 **Quantitative coronary angiography methodology. Quantitative coronary angiography measurements were performed at pre-procedure, post-procedure and follow-up. First, the Ref. diam. was measured from side-branch to side-branch (blue lines). Subsequently, the vessel was subdivided in segments of approximately 5 mm in length. Minimal lumen diameter, mean diameter and diameter stenosis were measured for the proximal edge, stent area and distal edge. DE=distal edge; FU=follow-up; PE=proximal edge; Pre=pre-procedure; Post=post-procedure; Stent=stent area.**

Procedure and follow-up

Patients received 250 mg aspirin and 10 000 international units heparin at the initiation of the procedure. The activation clotting time was maintained at >300 s. After balloon pre-dilatation, the radioactive stent was implanted at a nominal deployment pressure of 6–18 atmospheres. Extreme care was taken to minimize the trauma at both edges by taking the following, previously published[14], precautions: the best angiographic view to optimize stent visualization was chosen and the diaphragm was used to further enhance stent imaging. If needed, stent deployment was optimized using shorter post-dilatation balloons of larger diameter, to higher pressures. All post-dilatation balloons had a radiopaque marker at each end. Images were filmed in a magnified field (5 inch), using digital zoom enhancement (3 inch) in order to avoid inflating the balloon outside the stent edges (see Table 1). All patients received either ticlopidine 250 mg twice daily or clopidogrel 75 mg daily for 3 months after stent implantation and aspirin 80 mg daily indefinitely. Creatinine kinase and creatine kinase-MB measurements were made and the electrocardiogram was recorded at 6 and 12–18 h post procedure in all patients.

Patients returned for a 1- and 5-month clinical follow-up. An electrocardiogram was recorded at each visit. Clinical end-points were: death, Q wave myocardial infarction (using the Minnesota code criteria[19]), non-Q wave myocardial infarction (creatine kinase-MB rise >twice normal upper limit), target lesion revascularization (reintervention of the stent area and/or revascularization of the proximal and distal edge), target vessel revascularization (revascularization of any segment of the treated vessel), non target vessel revascularization, subacute[20] and late[21] thrombotic occlusion of the target vessel. At the 5-month visit an exercise stress test was performed. Revascularization was performed on the basis of clinical symptoms and/or evidence of ischaemia on exercise testing.

Table 1 Balloon inflation and stent deployment data

	Pre-dilatation	Stent deployment	Post-dilatation
Nom. size balloon	3·09 ± 0·43	3·28 ± 0·25	3·51 ± 0·50
Balloon length	16 ± 3		14 ± 2*
Stent length		16 ± 3*	
Pressure	9 ± 4	10 ± 3	16 ± 2
Balloon artery ratio	1·06:1		1·17:1
Stent artery ratio		1·11:1	

*38 patients with one Isostent, two patients with two Isostents.

Table 2 Baseline patient demographics and anginal status

Gender	
Male	30 (75%)
Female	10 (25%)
Age (years)	
Average	58
Range	38–75
Risk factors	
Previous MI	20 (50%)
Diabetes mellitus	4 (10%)
Hyperlipidaemia	29 (73%)
Hypertension	18 (45%)
Smoking	14 (35%)
Family history	13 (33%)
Anginal class	
CCS 2	11 (27·5%)
CCS 3	23 (57·5%)
CCS 4	6 (15%)

MI=myocardial infarction; CCS=Canadian Cardiovascular Society.

Table 3 Baseline lesion characteristics

Treated vessel	
LAD	20 (50%)
LCx	10 (25%)
RCA	10 (25%)
Lesion type	
A	5 (12·5%)
B1	13 (32·5%)
B2	18 (45%)
C	4 (10%)
Ostial lesions	5 (12·5%)
Total occlusions	3 (8%)
Instent restenosis	2 (5%)
Lesion length	10 ± 3 mm

LAD=Left anterior descending coronary artery; LCx=left circumflex artery; RCA=right coronary artery.

Statistical analysis

Data are presented as mean ± standard deviation. Continuous data was compared by means of the two-tailed Student's t-test or linear regression when appropriate.

Results

Baseline characteristics

Baseline demographics and anginal state are shown in Table 2, lesion characteristics in Table 3.

Procedural data

All 42 stents were successfully implanted in 40 patients. Thirty-eight patients were successfully treated with a single radioactive stent, two required a second radioactive stent to cover lesions >15 mm. Eight patients received additional non-radioactive stents due to procedural dissections. There were three transient thrombotic occlusions during the procedure, two due to dissections and one due to a combination of a dissection with a low activation clotting time. Treatment was with Reopro in one patient and a combination of ReoPro and rtPA in the other two patients. Despite the Reopro and rtPA, one non-Q wave myocardial infarction occurred, leading to a maximum creatinine kinase of 673 IU $.l^{-1}$ (normal upper limit 190 IU $.l^{-1}$) and an MB of 78 (normal upper limit 24 IU $.l^{-1}$). All further procedures were uncomplicated. A good final angiographical result was achieved in all patients.

Table 4 Five-month clinical follow-up

Angina free	26 (65%)
Target lesion revascularization	10 (25%)
PTCA	9 (22·5%)
CABG	1 (2·5%)
Target vessel revascularization	11 (28%)
Non-target vessel revascularization	1 (2·5%)
Late occlusion	2 (5%)
Myocardial infarction	1 (3%)
Death	0 (0%)

Follow-up

The mean hospital stay was 1·7 days. All patients were angina free at hospital discharge. At the 30-day follow-up no clinical end-points had occurred. Thirty-two (80%) patients were asymptomatic, whereas eight (20%) patients had recurrent angina pectoris. All 40 patients returned for the 5-month clinical follow-up (see Table 4). Twenty-six (65%) were asymptomatic and 14 (35%) patients had angina pectoris: Canadian Cardiovascular Society 1 (n=4), 2 (n=7), 3 (n=2) and 4 (n=1). The patient in angina Canadian Cardiovascular Society 4 had chest pain with ST-elevation, during his protocol-required 5-month exercise stress test. This was treated by primary angioplasty of a non-target vessel. Creatinine kinase rose to a maximum level of 257 IU $.l^{-1}$ (normal upper limit 190 IU $.l^{-1}$) with an MB of 30 IU $.l^{-1}$ (normal upper limit 24 IU $.l^{-1}$). Since there was neither a creatinine kinase rise of more than twice the upper limit of normal, nor new Q wave formation on the electrocardiogram, this was, by definition according to the protocol, not considered as a myocardial infarction.

A 5-month angiographic follow-up was performed in 36 (90%) patients. The remaining four (10%) patients refused; three were asymptomatic and the fourth had angina pectoris, Canadian Cardiovascular Society 3. Two late occlusions were noted, which were both proximal to the stent at angiographic follow-up. These two patients had recurrent angina >3 months after the index

Table 5 Quantitative coronary angiography analysis of the target lesion and stent area (n=36)*

	Pre	Post		Follow-up	
		Lesion	Stent	Lesion	Stent
MLD	0·98 ± 0·53	2·29 ± 0·52	2·57 ± 0·44	1·66 ± 0·71	2·12 ± 0·72
%DS	68 ± 15	28 ± 11	18 ± 11	46 ± 21	30 ± 21
Ref. diam.	3·07 ± 0·69	3·17 ± 0·53		3·03 ± 0·46	
Acute gain		1·31 ± 0·65	1·60 ± 0·59		
Late loss				0·63 ± 0·69	0·46 ± 0·76
LLI				0·65 ± 1·15	0·30 ± 0·53
Restenosis, n (%)				16 (44%)	0 (0%)

*Results of all 36 patients, who returned for angiographic follow-up, four patients refused.
%DS=% diameter stenosis; FU=follow-up; Lesion=target lesion (stent area and up to 5 mm proximal and distal to the stent edge); LLI=late loss index; MLD=minimal lumen diameter; Pre=pre-procedure; Post=post-procedure; Ref. diam.=reference diameter; Stent=stent area.
Quantitative coronary angiography measurements are in mm.

procedure, more specifically: within 1 week of discontinuation of the clopidogrel, without any signs of a myocardial infarction. Sixteen (44%) patients (including the two total occlusions) had angiographic edge restenosis. There was no in-stent restenosis in the 34 patent vessels. Ten of the 16 restenoses occurred in patients treated with a single radioactive stent, two restenoses were in patients receiving two radioactive stents, four restenoses were observed in patients receiving a combination of one radioactive and one non-radioactive stent. Examining the four restenotic patients who had an additional non-radioactive stent implanted at the baseline procedure, one had a total occlusion proximal to the Isostent, therefore it cannot be established whether the BX-Isostent and the distally placed non-radioactive stent were patent. Of the remaining three patients, the restenoses all occurred at the edge, located contralateral to the non-radioactive stent (one implanted proximal and two implanted distal to the Isostent), whereas the non-radioactive stent had no restenosis. One of the two patients, treated with a radioactive stent for in-stent restenosis, had a restenosis at follow-up. This restenosis was located at the proximal edge. In the three patients treated initially for a total occlusion, one restenosis and one reocclusion occurred. Nine of the 16 restenotic patients underwent a target lesion re-PTCA, one patient was referred to bypass surgery because it was the third in-stent restenosis in this patient, the remaining six were treated medically since these patients were both asymptomatic and had a negative stress test.

Quantitative coronary angiography measurements

Quantitative coronary angiography data, as measured for the target lesion and stent area, are presented in Table 5. Results of the subsegmental analysis of the stent area and the edges in a subgroup of 30 patients are shown in Table 6. Location of the restenosis is summarized in Table 7. Restenosis was observed to occur more often at the proximal edge compared to the distal edge (P=0·02).

Table 6 Subsegmental analysis of the stent area and edges (subgroup of 30 patients)*

	Prox. edge	Stent area	Dist. edge
MLD			
Pre	2·52 ± 0·81	1·09 ± 0·48	2·33 ± 0·70
Post	2·81 ± 0·53	2·57 ± 0·46	2·37 ± 0·63
FU	2·05 ± 0·71	2·26 ± 0·52	2·07 ± 0·63
%DS			
Pre	17 ± 10	55 ± 16	13 ± 6
Post	9 ± 4	17 ± 8	13 ± 8
FU	22 ± 13	22 ± 12	16 ± 12
Mean. diam.			
Pre	2·99 ± 0·79	2·45 ± 0·78	2·68 ± 0·80
Post	3·09 ± 0·55	3·10 ± 0·43	2·70 ± 0·58
FU	2·57 ± 0·60	2·89 ± 0·58	2·44 ± 0·57
Acute gain	0·29 ± 0·69	1·47 ± 0·52	0·04 ± 0·61
Late loss	0·76 ± 0·66	0·31 ± 0·56	0·30 ± 0·66
LLI	NA	0·23 ± 0·46	NA
Restenosis rate, n (%)	10 (33%)	0 (0%)	5 (17%)

*Excluded from subsegmental analysis were two patients with ostial lesions, one patient with a total occlusion pre-procedure and three patients with total occlusions at follow-up.
%DS=% diameter stenosis; Dist. edge=distal edge; FU=follow-up; LLI=late loss index; Mean. diam.=mean diameter; MLD=minimal lumen diameter; NA=not applicable; Prox. edge=proximal edge; Pre=pre-procedure; Post=post-procedure.
QCA measurements are in mm.

Table 7 Location of the restenosis (n=16)

Proximal edge	9 (56%)
Distal edge	4 (25%)
Proximal and distal edges	1 (6%)
Stent area	0 (0%)
Unknown (proximal occlusion)	2 (13%)

Radiation doses

Stent activity level was 8·6 ± 1·6 μCi at implantation, resulting in a calculated cumulative dose given over 100 days delivered to a 1 mm depth from the stent surface of 58 ± 10 Gy. There was no correlation between stent activity or delivered dose and minimal luminal diameter or late loss index at follow-up.

Discussion

This non-randomized study illustrates that the implantation of a 6–12 μCi β-particle emitting radioactive stent is safe and feasible, with one procedural non-Q wave myocardial infarction and no subacute or 30-day clinical events recorded. Subacute thrombosis was not seen despite the concern of delay in endothelialization, as previously reported in animal studies[8,10]. Two late occlusions were seen, which were probably late thrombotic stent occlusions, since both patients had recurrent angina, within 1 week of discontinuation of the clopidogrel. However, since both occlusions were proximal to the stent, and stent patency could not be observed at angiography, severe edge restenosis cannot be fully excluded. Therefore, it may be desirable to give patients at least 6 months of clopidogrel following radioactive stent implantation.

The Milan group has previously reported restenosis not only within the stent, but also at the edges of the stent[13], possibly caused by a combination of balloon injury (barotrauma) and lower radiation dose at the stent edges[9,14]. In this series particular attention was paid to avoid balloon injury outside the stent, in order to minimize barotrauma at the edges. Despite these precautions, edge restenosis was seen in 44%, occurring predominantly at the proximal edge. The commonly occurring narrowing observed proximal to the edge of the stent may, in combination with a complete inhibition of neointimal proliferation inside the stent, create unfavourable rheological conditions, such as a diverging flow pattern, which in itself will self-perpetuate the neointimal proliferation[22]. Careful shear stress analysis could elucidate the cause of restenosis at the proximal edge[23].

Since in all cases the pre-dilatation was performed with a balloon longer than the BX-Isostent and the balloon used for stent deployment extended outside the edges of the stent, geographical 'miss' occurred in 100% of the cases. Since geographical miss has been shown to be one of the determinants of edge restenosis[24], future therapies will concentrate on the prevention of geographical miss by minimizing trauma and/or increasing radiation dose at the edges. Several new therapies are currently under investigation. Direct stenting will prevent trauma caused by pre-dilatation with balloons longer than the radioactive stent. Square shouldered balloons, used for stent deployment, in which the entire balloon remains within the stent, will minimize barotrauma at the proximal and distal edges. Cold end stents, in which the centre of the stent is made radioactive, while the proximal and distal 5 mm of the stent edges are non-radioactive may prevent edge restenosis, if this restenosis is caused by negative remodelling. The final therapeutic option is the implantation of hot end stents, in which the stent edges are made more radioactive compared to the centre of the stent. This strategy increases the dose delivered to the traumatized proximal and distal edge, thereby decreasing the chance of geographical miss[22].

Conclusion

These results indicate that the use of radioactive stents, with an activity of 6–12 μCi, is safe and feasible; however, the high incidence of edge restenosis makes this technique currently clinically non-applicable.

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Chapter 7

Radioactive stents delay but do not prevent in-stent neointimal hyperplasia.

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Radioactive Stents Delay but Do Not Prevent In-Stent Neointimal Hyperplasia

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Background—Restenosis after conventional stenting is almost exclusively caused by neointimal hyperplasia. β-Particle–emitting radioactive stents decrease in-stent neointimal hyperplasia at 6-month follow-up. The purpose of this study was to evaluate the 1-year outcome of ^{32}P radioactive stents with an initial activity of 6 to 12 μCi using serial quantitative coronary angiography and volumetric ECG-gated 3D intravascular ultrasound (IVUS).

Methods and Results—Of 40 patients undergoing initial stent implantation, 26 were event-free after the 6-month follow-up period and 22 underwent repeat catheterization and IVUS at 1 year; they comprised half of the study population. Significant luminal deterioration was observed within the stents between 6 months and 1 year, as evidenced by a decrease in the angiographic minimum lumen diameter (−0.43±0.56 mm; $P=0.028$) and in the mean lumen diameter in the stent (−0.55±0.63 mm; $P=0.001$); a significant increase in in-stent neointimal hyperplasia by IVUS (18.16±12.59 mm^3 at 6 months to 27.75±11.99 mm^3 at 1 year; $P=0.001$) was also observed. Target vessel revascularization was performed in 5 patients (23%). No patient experienced late occlusion, myocardial infarction, or death. By 1 year, 21 of the initial 40 patients (65%) remained event-free.

Conclusions—Neointimal proliferation is delayed rather than prevented by radioactive stent implantation. Clinical outcome 1 year after the implantation of stents with an initial activity of 6 to 12 μCi is not favorable when compared with conventional stenting. ***(Circulation.* 2001;103:14-17.)**

Key Words: radioisotopes ■ restenosis ■ stents ■ angiography

Implantation of ^{32}P radioactive stents with activities ranging from 3.0 to 12 μCi in coronary artery lesions has been reported to inhibit neointimal hyperplasia within the stent at 6-month follow-up.[1,2] The major limitation of this therapy is significant renarrowing at the stent edges, which is called the "candy wrapper" or "edge effect."[1] Catheter-based radiation significantly reduces the recurrence of restenosis 6 months after percutaneous transluminal coronary angioplasty for in-stent restenosis, but 3-year follow-up reveals greater luminal deterioration in γ-radiation–treated patients.[3,4] Such findings indicate the need for longer follow-up beyond the traditional 6 months in patients treated with intracoronary radiation. The purpose of this study was to assess late results after the implantation of radioactive stents using repeat catheterization with quantitative coronary angiography and 3D intravascular ultrasound (IVUS) at 1 year.

Methods

Patient Population

The European ^{32}P Dose-Response Trial was a nonrandomized multicenter trial evaluating the safety and efficacy of implanting radioactive stents with activity levels of 3 to 12 μCi in single, native coronary artery lesions. All stents were implanted in de novo lesions, except for 1 case of in-stent restenosis. For the purposes of this analysis, this case was excluded. Other inclusion and exclusion criteria, as well as immediate and 6-month results, were previously reported.[1,2] Only patients undergoing 6-month angiographic and IVUS follow-up who did not experience major adverse cardiac events during the first 6 months were included. The study was performed in accordance with the Declaration of Helsinki and the European Guidelines for Good Clinical Practice. Ethical approval was provided by the Medical Ethical Committee of the University Hospital Rotterdam. All patients gave written, informed consent.

Radioactive Stent

The BX Isostent (^{32}P) (Isostent Inc), which is 15 mm in length and 3.0 or 3.5 mm in diameter, was used. The initial activity of the stents was measured and, thereafter, the date at which the radioactivity would have decreased to 6 to 12 μCi was calculated.

Procedure and Clinical Follow-Up

Procedural details have been published previously.[5] All patients received either 250 mg of ticlopidine BID or 75 mg of clopidogrel per day for 3 months after stent implantation and 80 mg of aspirin per day indefinitely. Revascularization was performed on the basis of clinical symptoms and/or evidence of ischemia on exercise testing. Clinical end points were death, Q-wave myocardial infarction, non–Q-wave myocardial infarction (creatine kinase-MB rise >2

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TABLE 1. Baseline Characteristics of the 22 Patients Studied

Male sex	20 (91)
Age, y	57 (38–73)
Risk factors	
Previous MI	12 (55)
Diabetes mellitus	3 (14)
Hyperlipidemia	18 (82)
Hypertension	9 (41)
Smoking	8 (36)
Family history	7 (32)
CCS class 3/4	15 (68)
Treated vessel	
LAD	12 (55)
LCx	5 (22.5)
RCA	5 (22.5)
Lesion type	
A	2 (9)
B1	10 (45.5)
B2	8 (36.5)
C	2 (9)
Lesion length, mm	10±3

Values are n (%), mean (range), or mean±SD. MI indicates myocardial infarction; CCS, Canadian Cardiovascular Society; LAD, left anterior descending coronary artery; LCx, left circumflex artery; and RCA, right coronary artery.

times normal upper limit), target vessel revascularization, non–target vessel revascularization, and early and late thrombotic occlusion of the target vessel.

Angiographic and IVUS Procedures

Angiography in multiple projections was performed before the procedure, after stenting, and at 6-month and 1-year follow-up. The stented vessel segments were examined with quantitative coronary angiography (CAAS II analysis system,[6,7] Pie Medical BV) and mechanical IVUS (CardioVascular Imaging System). IVUS images were acquired to coincide with the peak of the R wave by using an ECG-triggered pullback device with a stepping motor at 0.2 mm/step. This system eliminates the artifacts caused by the movement of the heart during the cardiac cycle.[8] The ECG-gated image acquisition and digitization was performed by a workstation designed for 3D reconstruction (EchoScan, Tomtec). A Microsoft Windows-based contour detection program was used for the volumetric 3D analysis.[8]

Core Laboratory Analysis Procedures

Quantitative coronary angiography using at least 2 orthogonal projections was performed. For analytical purposes, the following 3 regions of interest were defined: (1) stent, (2) target lesion, and (3) target vessel. The stent included only the radioactive stent. The target lesion was defined as the stent and 5 mm proximal and 5 mm distal to the edge. The target vessel was defined as the target lesion and the remaining segments of the treated vessel. Target lesion restenosis was defined as >50% diameter stenosis, located within the target lesion, at follow-up.[9] Edge restenosis was defined as >50% diameter stenosis, located at the proximal and/or distal edge, at follow-up.

Quantitative IVUS analysis of the stent and 5 mm proximal and distal to the stent was performed. Lumen and stent boundaries were detected using a minimum cost algorithm. Total stent and lumen volumes were calculated as previously described.[8] Neointimal volume was calculated as stent volume minus luminal volume. Feasibility, reproducibility, and interobserver and intraobserver variability of this system have been validated in vitro and in vivo.[8]

Statistical Analysis

Data are presented as mean±SD. Continuous data were compared using repeated measures ANOVA or a 2-tailed Student's *t* test as appropriate.

Results

Baseline demographics and lesion characteristics are shown in Table 1. Between 6 months and 1 year, target lesion revascularization and target vessel revascularization were performed in 4 patients (18%) and 5 patients (23%), respectively. No late occlusion was seen. No patient died or experienced myocardial infarction. In total, 21 of 40 patients (53%) were event-free through the 1-year follow-up.

Quantitative Coronary Angiography and IVUS Measurements

Quantitative coronary angiography data, presented as a subsegmental analysis of the stent area and the edges, are shown in Table 2. A significant decrease in the minimum and mean lumen diameters was noted between 6 months and 1 year ($P=0.028$ and $P=0.001$, respectively) compared with both edges. The late loss of mean lumen diameter was significantly larger after 6 months than before 6 months. Furthermore, in 11 patients (50%), the minimum lumen diameter at the edge at 6 months was detected within the stent at 1 year ("migration" from the stent edge to within the stent). Lesion progres-

TABLE 2. Subsegmental Quantitative Coronary Angiography Analysis

				Late Loss			
	Baseline	6 Months	1 Year	Baseline to 6 Months	6 Months to 1 Year	Total	*P* Between Periods
Minimum lumen diameter, mm							
Proximal edge	2.92±0.53	2.23±0.73*	2.08±0.50	0.69±0.80†	0.15±0.51‡	0.84	0.060
Stent	2.50±0.47	2.36±0.47*	1.93±0.52*	0.14±0.52†	0.43±0.56‡	0.57	0.16
Distal edge	2.29±0.61	2.17±0.58	2.08±0.49	0.36±0.49†	0.09±0.49‡	0.45	0.9
Mean lumen diameter, mm							
Proximal edge	3.19±0.56	2.73±0.57*	2.50±0.40*	0.39±0.62§	0.22±0.51‖	0.61	0.33
Stent	3.12±0.42	3.09±0.58	2.54±0.41*	0.03±0.62§	0.55±0.63‖	0.68	0.041
Distal edge	2.64±0.56	2.51±0.56	2.36±0.50	0.12±0.49§	0.16±0.52‖	0.28	0.9

*$P<0.05$, †$P=0.0041$, ‡$P=0.025$, §$P=0.028$, ‖$P=0.001$ by ANOVA.

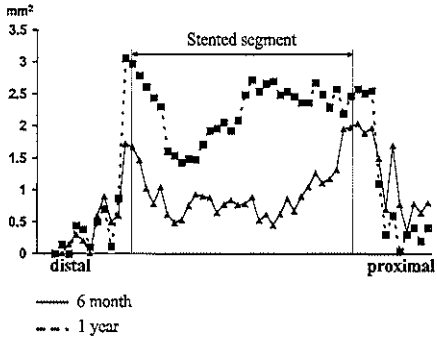

Figure 1. Mean neointimal area in stent at 6 months (■) and 1 year (▲) using IVUS.

sion to >50% diameter stenosis was observed in 5 patients. This was due to a progression of in-stent restenosis in 4 patients and a progression of a proximal stent-edge lesion in the other.

IVUS was completed in 19 patients; omissions were due to equipment failure[2] or patient clinical instability.[1] IVUS analysis demonstrated a significant increase in neointimal hyperplasia between 6 months and 1 year (18.16±12.59 mm^3 to 27.75±11.99 mm^3; increase of 52.8%; P=0.001), mainly in the mid and distal portions of the stent (Figure 1). An increase in neointimal hyperplasia >25% (range, 25% to 360%) occurred in 12 cases (63%), as shown in Figure 2. No change in lumen volume was noted at the stent edges between 6 months and 1 year.

Radiation Doses

The radioactive stents had a mean activity of 8.6±1.6 μCi at implantation and delivered 58±10 Gy to a depth of 1 mm from the stent at 100 days, with a dose rate of >15cGy/h. There was no correlation between stent activity or delivered dose and changes in minimum or mean lumen diameter at 6-month or 1-year follow-up.

Discussion

A worrying late progression of in-stent neointimal hyperplasia was observed between 6 months and 1 year after the implantation of radioactive stents, leading to target vessel or lesion reintervention in 5 of 26 patients (19%) who had been event-free at 6 months. The event-free rate at 1 year after the implantation of 6 to 12 μCi radioactive stents was 21 of 40 patients (53%), which compares poorly to the expected outcome after the implantation of a nonradioactive stent.[10]

In contrast to the tissue growth seen in malignancy, the DNA synthesis that occurs after nonradioactive stenting in experimental models terminates after 6 weeks.[11] At this time point, the activity of the radioactive stent used in this study would have been sufficient to inhibit cellular proliferation. Thereafter, the majority of lumen deterioration occurs in the first 3 months after conventional stent implantation, with minimal change between 6 months and 1 year,[12–14] and actual regression of neointimal hyperplasia between 1 and 3 years after stenting.[15] This latter phenomenon has been attributed to a reduction in the proteoglycan content of hyperplastic tissue.[16] Accordingly, the findings reported here of "breakthrough" or "rebound" hyperplasia causing further lumen deterioration between 6 months and 1 year must be interpreted as being specific to the effects of radioactivity, presumably due to a fall- off in radiation levels. The observation that the radioactive stent may provide a substrate for atherosclerosis may well have been predicted by Carter et al's porcine model.[17]

Because no significant stenosis progression was observed at the stent edges among our patients, the candy wrapper effect may be considered a short-term healing response to vessel wall injury beyond the stented vessel segment combined with the effects of low-dose radiation.[18,19]

Unexpected late luminal deterioration has also been reported between 6 months and 3 years among patients treated by catheter-based γ-radiation after repeat intervention for in-stent restenosis (mean loss of 0.37 mm with 4 of 17 patients [26%] progressing to restenosis [diameter stenosis >50%]), compared with no major changes in the placebo group.[4] The difference in the time frame of this virtual "rebound hyperplasia" between radioactive stenting and catheter-based γ-radiation therapy may be a function of the biological effects of and response to the type and dosage of radiation administered. Alternatively, late loss may also have

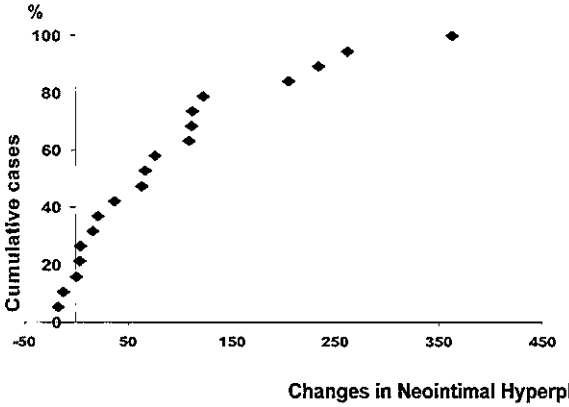

Figure 2. Cumulative distribution curve of percent changes in late neointimal growth after 6 months, as measured by IVUS.

occurred between 6 months and 1 year and remained subclinical in the catheter-based study.

Conclusions

Neointimal hyperplasia is delayed rather than prevented by radioactive stent implantation. The combination of this phenomenon of rebound hyperplasia with the established phenomenon of edge restenosis calls into question the clinical applicability of radioactive stenting using current approaches.

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Chapter 8

Angiographic follow-up after ^{32}P β-emitting radioactive "Cold-ends" isostent implantation. Results from Aalst, Milan and Rotterdam.

Submitted

Angiographic follow-up after 32P β-emitting radioactive "Cold Ends" Isostent implantation. Results from Aalst, Milan and Rotterdam.

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MINI ABSTRACT

The problem after radioactive stent implantation is edge restenosis due to neointimal hyperplasia and vessel remodeling. The aim of this trial was to evaluate whether extending the radioactive stent with non-radioactive Cold Ends might diminish this edge restenosis by preventing remodeling at the injured extremities. The 25 mm in length (15 mm radioactive center segment & 5 mm non-radioactive ends) "Cold Ends" Isostents were preferably implanted by direct stenting. A total of 43 stents were implanted in 43 pts with de novo native coronary artery disease. There were 2 procedural & 1 subacute stent thrombosis. One late (3.5 months) stent thrombosis occurred after discontinuation of antiplatelett therapy. QCA results showed that the restenosis occurred at the transition zone from radioactive to non-radioactive. The overall in-stent restenosis rate of 22% was relatively low, compared to other radioactive stents. Edge restenosis is mainly caused by a proliferative response, induced by a combination of low dose radiation and balloon injury.

ABSTRACT

Aims. ^{32}P β-emitting stents with an activity of 3-24 μCi have shown >40% edge restenosis due to neointimal hyperplasia and vessel remodeling. The aim of this trial was to evaluate whether extending the radioactive stent with non-radioactive Cold Ends might diminish this edge restenosis by preventing remodeling at the injured extremities.
Methods and results. The 25 mm in length (15 mm radioactive center segment & 5 mm non-radioactive ends) "Cold Ends" Isostents had an activity of 6-24 μCi at implantation. When possible, direct stenting was performed. A total of 43 stents were implanted in 43 pts with de novo native coronary artery disease. Treated vessels were LAD (n=20), RCA (n=15) and LCx (n=8). QCA measurements were done pre-, post-procedure and at 6-mo FU.
There were 2 procedural & 1 subacute stent thrombosis. One late (3.5 months) stent thrombosis occurred after discontinuation of antiplatelett therapy. QCA results are available for 37 pts. Eight in-stent restenoses were located in the non-radioactive (Cold Ends) segments, and 5 restenoses were both at the radioactive segment and at a Cold End.
Conclusion. Restenosis of the radioactive segment occurred in 15%, all occurring at the transition zone from radioactive to non-radioactive. The overall in-stent restenosis rate was 22%. Cold Ends stents therefore have a relatively low restenosis rate compared to other radioactive stents. Edge restenosis is mainly caused by a proliferative response, induced by a combination of low dose radiation and balloon injury.

Key words β-particles • angioplasty • radioisotope • restenosis • stent

Abbreviations

ACT: Activation Clotting Time
CK: Creatinine Kinase
ECG: Electrocardiogram
MI: Myocardial Infarction

INTRODUCTION

Vascular brachytherapy with a radioactive source after PTCA or stent implantation has been shown, in several clinical trials, to inhibit the process of neointimal hyperplasia and thereby in-stent restenosis [1-4]. Several animal trials have demonstrated a dose-related reduction of in-stent restenosis, following radioactive stent implantation [5-7]. However, a dose-dependent delay in endothelialization of the stent was shown, thereby increasing the risk of subacute and late thrombotic occlusions [6,8].

In patients treated with implantation of ^{32}P radioactive stents with activities ranging from 0.75 to 12 μCi, angiographic restenosis was reported in 43-62% of the cases with the restenosis being primarily located at the edges of the stent and caused by neointimal hyperplasia and/or vessel remodeling.[9]. These edges represent an area where tissue is subjected both to balloon-induced trauma and a lower dose of radiation, which may stimulate edge restenosis [7,10]. The aim of this trial was to evaluate whether extending the radioactive stent with non-radioactive Cold Ends might diminish this edge restenosis by preventing remodeling at the injured extremities.

METHODS

Patient Population.

The ^{32}P radioactive "Cold Ends" stent trial was a non-randomized multi-center trial to evaluate the safety and efficacy of radioactive "Cold Ends" stent implantation, with activities ranging from 6-24 μCi. The data presented here represents all patients treated with "Cold Ends" stents, and were treated at the centers in Aalst, Milan, and Rotterdam.

Patients with single, de novo, native, coronary lesions, with a maximum lesion length of 15 mm (treated with a 25 mm Cold Ends stent), and objective evidence of ischemia were eligible. Exclusion criteria were: recent MI (CK-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, clopidogrel or nickel; lesions located in the left main coronary artery.

The Medical Ethical Committees of the enrolling centers approved the study. All patients provided written informed consent before the procedure. The trial was conducted according to the GCP guidelines.

Radioactive stent, dosimetry and safety issues.

The BXI™ Betastent (Isostent™ Inc., San Carlos, CA, USA) was investigated in this trial. It was 25 mm in length and available in diameters of 3.0 & 3.5 mm. The 15 mm center segment was made radioactive by Phosphorus-32, whereas both 5 mm edges (the Cold Ends) were kept non-radioactive [7]. The initial activity of the stents was measured and thereafter the date at which the radioactivity had decreased to 6-24 μCi (radioactivity level suitable for implantation) was calculated. 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. All disposable materials, which were in contact with the stent, were immediately disposed of in a plexiglas container.

Quantitative coronary angiography.
Quantitative coronary angiography (QCA) was performed pre-procedure, post-procedure, and at 6-month follow-up. Coronary angiography was performed 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 B.V., Maastricht, The Netherlands) by the Thoraxcenter Rotterdam angiographic corelab. Calibration of the system was based on dimensions of the catheters not filled with contrast medium [11-13]. Lesion length was measured by means of a computer algorithm [13]. Procedural success was defined as %DS <30%, measured by on-line QCA. Acute gain was defined as MLD post-procedure minus MLD pre-procedure. Late loss was defined as MLD post-procedure minus MLD at follow-up. Late loss index was defined as late loss divided by acute gain [14]. For analytical purposes, 3 regions of interest were defined: 1) target vessel, 2) target lesion (total stent) and 3) radioactive area. The radioactive area was defined as the segment, which included only the radioactive segment of the stent, 15 mm in length. The target lesion was defined as the total stent area, consisting of the radioactive segment and both Cold Ends, being 25 mm in length. The target vessel was defined as the target lesion and the remaining segments of the treated vessel.

QCA Methodology

First, the minimum lumen diameter (MLD), reference diameter (RD) and diameter stenosis (DS) were measured from side-branch to side-branch for the target vessel. Subsequently, the MLD, mean diameter (MD) and DS were measured for the total stent (approximately 25 mm in length). Finally, the MLD, MD and DS were measured for the radioactive segment (approximately 15 mm in length), First the total stent (approximately 25 mm in length) was delineated as the region of interest, by means of a proximal and distal cursor. Thereafter, by moving the cursors 1/5 of the total stent length (approximately 5 mm) away from the proximal and distal stent edges towards the center of the stent, the radioactive segment (approximately 15 mm) was identified. Target lesion restenosis was defined as >50% DS at follow up, located within the target lesion. Cold Ends restenosis was defined as >50% DS at follow up, located at the proximal and/or distal Cold Ends segment of the stent.
Procedure and follow-up.
Patients received 250 mg aspirin and 10000 international units heparin at the initiation of the procedure. The ACT was maintained at >300 seconds. Preferably direct stenting was performed. The radioactive stent was implanted at a nominal deployment pressure

of 8-18 atmospheres. Also, post-dilatation was avoided to minimize balloon trauma. The radioactive segment of the stent had to completely cover the original lesion length. Extreme care was taken to minimize the trauma at both edges by taking the following, previously published [10], precautions: The best angiographic view to optimize stent visualization was chosen and the diaphragm was used to further enhance stent imaging. If needed, stent deployment was optimized using shorter post-dilatation balloons of larger diameter, to higher pressures. All post-dilatation balloons had 1 radio-opaque marker at both extremities. (see Table 1 for balloon inflation and stent deployment data). All patients received either ticlopidine 250 mg BID or clopidogrel 75 mg daily for 6-7 months after stent implantation and aspirin ≥80 mg daily indefinitely. CK and CK-MB measurements were made and the ECG was recorded at 6 and 12-18 hours post procedure in all patients.

Patients returned for 1 and 6-month clinical follow-up. An ECG was recorded at each visit. Clinical endpoints were: death, Q-wave MI (using the Minnesota code criteria [15]), non Q-wave MI (CK-MB rise >2 times normal upper limit), target lesion revascularization (reintervention inside the stent area), target vessel revascularization (revascularization of any segment of the treated vessel), non-target vessel revascularization, subacute[16] and late[17] thrombotic occlusion of the target vessel.

At the 6-month visit an exercise stress test was performed. Revascularization was performed on the basis of clinical symptoms and/or objective evidence of ischemia.

Statistical analysis

Data is presented as mean ± standard deviation. Continuous data was compared by means of the two-tailed Student's t-test or linear regression when appropriate.

Table 1. Balloon inflation & stent deployment data, measured by quantitative coronary angiography.

	Predilatation	Stent Deployment	Postdilatation
Nom. Size Balloon, mm	2.68±0.51	3.21±0.37	3.48±0.56
Balloon Length, mm	18±4		20±5
Stent Length, mm		25±3	
Balloon Artery ratio	0.90:1		1.16:1
Stent Artery ratio		1.07:1	
Direct stenting		16 (37%)	
No post-dilatation			10 (23%)

RESULTS

Baseline characteristics

Baseline demographics and anginal state are shown in Table 2, lesion characteristics in Table 3.
Procedural data.
All 43 stents were successfully implanted in 43 patients. All patients were successfully treated with a single Cold Ends radioactive stent. Five patients received additional non-radioactive stents due to procedural dissections. There were 3 transient stent occlusions: 2 procedural & 1 subacute stent thrombosis. The last occurring during an IVUS evaluation of the stent performed 1 day post procedure for logistic reasons. None of these stent thrombosis lead to a myocardial infarction. All other procedures were uncomplicated. Procedural success was achieved in all, but 2, patients. These 2 patients had a DS of 33 and 30%.
Follow-up.
All patients were angina free at hospital discharge. At 30-day follow-up no other subacute stent thrombosis occurred. Thirty-nine (91%) patients remained angina free, whereas 4 (9%) patients had recurrent AP. One late (3.5 months) stent thrombosis, without total occlusion, occurred after discontinuation of all antiplatelet therapy by the patient himself, leading to a non-Q-wave MI, for which a primary target lesion revascularization was performed. All 43 patients returned for 6-month clinical follow-up (see Table 4). Thirty-three (77%) were asymptomatic and 10 (23%) patients had Angina Pectoris Class: CCS 1 (n=1), CCS 2 (n=6), CCS 3 (n=1) and CCS 4 (n=2, including the above mentioned MI). Six-month angiographic follow-up was performed in 37 (86%) patients. The remaining 6 (14%) patients refused; 5 were asymptomatic and 1 had AP CCS 2. No additional late occlusions were observed during the 6-month follow-up. Eight (22%) patients had angiographic restenosis (see Table 5). Nine (21%) patients underwent a target lesion re-PTCA: 7 due to binary restenosis (DS >50%), 2 patients were treated for recurrent angina with a DS <50%: 1 patient had recurrent angina and an MLD of 1.71, while the other was the one with the late stent thrombosis, leading to an acute MI (see above), with an MLD of 1.69 mm. One restenotic patient was treated medically since this patient was both asymptomatic and had a negative stress test. There were 2 additional repeat PTCAs: 1 because of progression of atherosclerosis in the target vessel and 1 because of progression of atherosclerosis in a non-target vessel.
QCA measurements.
QCA data are presented in Table 5. Location of the restenosis is summarized in Table 6. Stents implanted by direct stenting followed by post-dilatation or direct stenting without post-dilatation have a significantly worse late loss index at follow-up compared to stents implanted after balloon predilatation (see Figure 1). Cold Ends stents showed only in 1 patient (3%) a diffuse restenosis (both diffuse throughout the radioactive segment and proximal Cold End) restenosis, while other non-radioactive stents have the tendency to be more diffuse restenotic. For a patient example see Figure 2.

Table 2. Baseline patient demographics and anginal status.

Gender	Male	34	(79%)
	Female	9	21%)
Age	Average	58	
	Range	41-80	
Risk Factors	Previous MI	20	(47%)
	Diabetes Mellitus	3	(7%)
	Hyperlipidemia	32	(74%)
	Hypertension	16	(37%)
	Smoking	16	(37%)
	Family History	19	(44%)
Anginal Pectoris	Stable	32	(74%)
	Unstable	11	(26%)

Table 3. Baseline lesion characteristics.

Treated vessel	LAD	20 (46.5%)
	LCx	8 (19%)
	RCA	15 (34.5%)
Lesion type	A	15 (35%)
	B	26 (60%)
	C	2 (5%)
Total occlusions		2 (5%)
Lesion length		10±4 mm

Table 4. Six-month clinical follow-up.

Angina Free	33 (77%)
Target Lesion Revascularization (TLR)	9 (21%)
PTCA	9 (21%)
CABG	0 (0%)
Target Vessel Revascularization (incl. TLR)	10 (23%)
Non Target Vessel Revascularization	1 (2%)
Late Occlusion	1 (2%)
Myocardial Infarction	1 (1%)
Death	0 (0%)
Total MACE	11 (26%)

Table 5. QCA Analysis (n=37).

	Pre		**Post**			**Follow-up**	
		Radioactive	***Total Stent***	***Vessel***	***Radioactive***	***Total Stent***	***Vessel***
MLD	1.03±0.44	2.68±0.46	2.57±0.43	2.14±0.44	2.04±0.53	1.79±0.56	1.66±0.49
%DS	66±13	10±12	13±13	28±11	28±17	37±19	42±16
RD or *MD*	2.99±0.60	*3.00±0.45*	*3.03±0.45*	3.00±0.52	*2.66±0.51*	*2.56±0.49*	2.87±0.51
Acute Gain		1.66±0.57	1.55±0.55	1.11±0.54			
Late Loss					0.65±0.57	0.79±0.58	0.49±0.49
LLI					0.42±0.41	0.60±0.64	0.55±0.83
Restenosis, n (%)					5 (14%)	8 (22%)8 (22%)	

*results of all 37 patients, who returned for angiographic follow-up, 6 patients refused.

%DS = % diameter stenosis, FU = follow-up, LLI = late loss index, MLD = minimum lumen diameter, MD = mean diameter, Pre = pre-procedure, Post = post-procedure, Radioactive = radioactive segment (15mm in length), RD = reference diameter, Total Stent = radioactive segment and both Cold Ends (25mm in length), Vessel = Total vessel (sidebranch to sidebranch). MLD, MD, RD., Acute Gain and Late Loss measurements are in mm.

Table 6. Location of the Restenosis (n=8).

Proximal Stent Segment	5 (14%)
Distal Stent Segment	1 (3%)
Prox. & Distal Stent Segment	2 (5%)

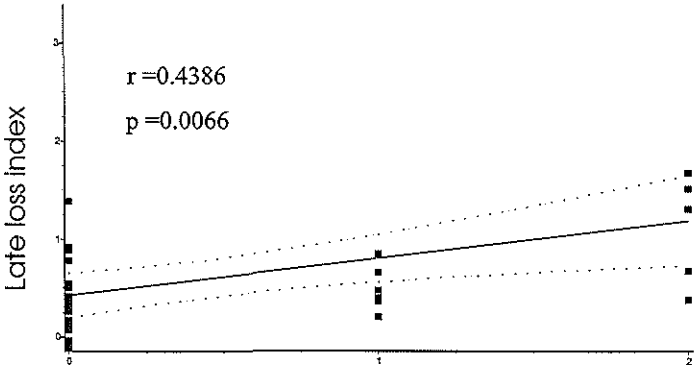

Figure 1.
Late loss index at follow-up versus direct stenting of the radioactive stent with and without postdilatation.
Stents implanted by direct stenting followed by post-dilatation or direct stenting without post-dilatation have a significantly worse late loss index at follow-up compared to stents implanted after balloon predilatation (p=0.0066). 0=predilatation followed by stenting, 1=direct stenting & post-dilatation, 2=direct stenting without post-dilatation.

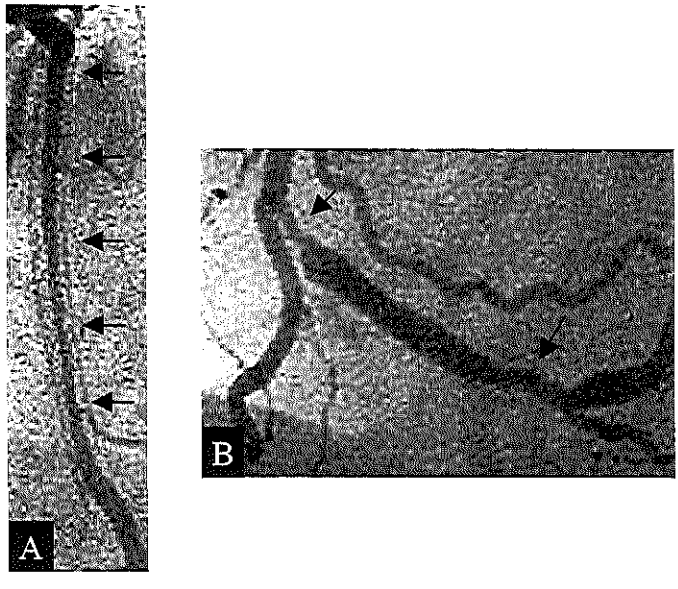

Figure 2.
Example of a patient at 6-month angiographic follow-up.
The Wallstent (4.5 long), implanted in the ramus circumflexus, had a diffuse in-stent restenosis (see yellow arrows in Figure A), while the Cold Ends stent, implanted in the right coronary artery, showed a good result in the radioactive segment, with Cold Ends restenosis (see yellow arrows in Figure B).

Radiation doses

Stent activity level was 7.58±2.78 μCi at implantation. There was no significant correlation between stent activity and late loss or late loss index at follow-up.

DISCUSSION

The results of this non-randomized study show that the implantation of a 6-24 μCi β-radioactive "Cold Ends" stent is safe and feasible, with a total MACE rate of 26% at 6-month follow-up.

This trial was conducted to investigate whether edge restenosis [9], occurring in more than 40% of the cases, treated with an isodose radioactive stent [18] and possibly caused by a combination of balloon injury (barotrauma) and lower radiation dose at the stent-edges [7,10], can be diminished by using Cold Ends radioactive stents. Using IVUS analysis, edge restenosis seemed to be caused both by negative remodeling and neointimal hyperplasia [19-21]. Therefore, it was hypothesized that edge restenosis could be reduced if the remodeling component of the edge restenosis phenomenon could be attenuated by the scaffolding properties of Cold Ends stents. The Cold Ends stents were manufactured as 15 mm isodose radioactive stents, extended with 5 mm non-radioactive Cold Ends segments. Furthermore, in order to control the extent of the barotrauma caused by predilatation outside the stent area, direct stenting was performed whenever possible. Also, post-dilatation of the stent was only performed, when necessary, and strictly inside the stent.

What was observed in this trial was a shift of the restenosis, usually occurring at the edges of the isodose radioactive stent, into the Cold Ends segment. More specifically, the most severe restenosis occurred at the transition zone from radioactive to non-radioactive segments, a region located in dose fall off. This phenomenon has also been recently demonstrated, by the group of the Thoraxcenter, in an experimental setup in which a half radioactive/half non-radioactive stent was implanted in coronary arteries of pigs. It was clearly demonstrated that the peak level of neointimal hyperplasia was observed specifically in front of the last radioactive strut, thus in the region of dose fall-off. This strongly suggested that the combination of low dose radiation in association with chronic injury by the stent, implanted in non-atherosclerotic tissue, is the main determinant of neointimal hyperplasia [22]. Other trials also noted that low dose radiation has a stimulatory effect, compared to higher dose radiation [23-25]. All these trials give support to the hypothesis that a combination of low-radiation dose and balloon injury, actually stimulates neointimal hyperplasia. Edge restenosis was relatively low with overall 22% restenosis compared to the other radioactive stent trials, despite the fact that the Cold Ends stents were 25 mm in length, while the other radioactive stents were 15 mm in length. The deleterious effects of the negative remodeling, seen at the stent edges in previous radioactive stent trials, were prevented at the Cold Ends segments.

Interestingly, patients after direct stenting have a higher late loss compared to patient with predilatation followed by stenting. Even more surprisingly, the patients with a combination of direct stenting and no post-dilatation have the highest late loss during follow-up. This may support the hypothesis that edge restenosis is mainly caused by low dose radiation, rather than the degree of injury. One of the other options to reduce edge injury, currently under investigation, is the use of square shouldered balloons: They are used for radioactive stent implantation, in which the entire balloon remains within the stent during stent deployment, thereby minimizing barotrauma at the proximal and distal edges. If edge restenosis is not diminished in that trial, it will give support to the hypothesis that the low dose radiation, or dose fall-off in itself, is the main contributor of edge restenosis.

CONCLUSION

The implantation of Cold Ends radioactive stents is feasible and safe. In 14% instent restenosis of the transition zone of the radioactive to non-radioactive Cold Ends segment was observed. A pure proximal and/or distal Cold Ends restenosis was noted in 8%. Cold Ends stents therefore have a relatively low restenosis rate compared to other radioactive stents, despite the use of a longer stent. This favorable effect was obtained by preventing negative remodeling at the edges. Edge restenosis is mainly caused by the proliferative response, induced by a combination of low dose radiation and balloon injury.

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Chapter 9

The pattern of restenosis and vascular remodeling after cold-end radioactive stent implantation.

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The pattern of restenosis and vascular remodelling after cold-end radioactive stent implantation

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Background Edge restenosis is a major problem after radioactive stenting. The cold-end stent has a radioactive mid-segment (15·9 mm) and non-radioactive proximal and distal 5·7 mm segments. Conceptually this may negate the impact of negative vascular remodelling at the edge of the radiation.

Method and Results ECG-gated intravascular ultrasound with three-dimensional reconstruction was performed post-stent implantation and at the 6-month follow-up to assess restenosis within the margins of the stent and at the stent edges in 16 patients. Angiographic restenosis was witnessed in four patients, all in the proximal in-stent position. By intravascular ultrasound in-stent neointimal hyperplasia, with a >50% stented cross-sectional area, was seen in eight patients. This was witnessed proximally (n=2), distally (n=2) and in both segments (n=4). Echolucent tissue, dubbed the 'black hole' was seen as a significant component of neointimal hyperplasia in six out of the eight cases of restenosis. Neointimal hyperplasia was inhibited in the area of radiation: Δ neointimal hyperplasia=3·72 mm^3 (8·6%); in-stent at the edges of radiation proximally and distally Δ neointimal hyperplasia was 7·9 mm^3 (19·0%) and 11·4 mm^3 (25·6%), respectively (P=0·017). At the stent edges there was no significant change in lumen volume.

Conclusions Cold-end stenting results in increased neointimal hyperplasia in in-stent non-radioactive segments.

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Key Words: Stents, remodelling, radioisotopes, angioplasty, ultrasonics.

See page 1245 for the Editorial comment on this article

Introduction

Conventional stenting has eliminated recoil and negative remodelling as components of the restenotic process. However, this has been at the cost of exacerbating neointimal 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 balloon angioplasty and stent implantation. Studies recently performed in humans demonstrated a dose-dependent inhibition of neointimal hyperplasia at the 6-month follow-up in stents with activity levels >3 μCi[3,4]. However, a significant increase in neointimal hyperplasia was noted at the extremes of the stent and at the edges. Edge restenosis was mainly due to an increase in plaque and to a lesser extent, remodelling of the native vessel wall[4,5]. A fall-off in radiation in areas receiving vascular injury was proposed as a possible stimulatory mechanism. In order to minimize the effect of vascular remodelling on stent-edge restenosis, the stent design was modified. The 'cold-end' stent (Isostent® Inc., San Carlos, CA, U.S.A.) was rendered radioactive in its mid-portion (15·9 mm in length); the edges (5·7 mm each) were non-radioactive (Fig. 1).

We aimed to analyse tissue growth within the stent and at its edges and to define the segments that had the greatest propensity to restenosis after the implantation of a cold-end stent.

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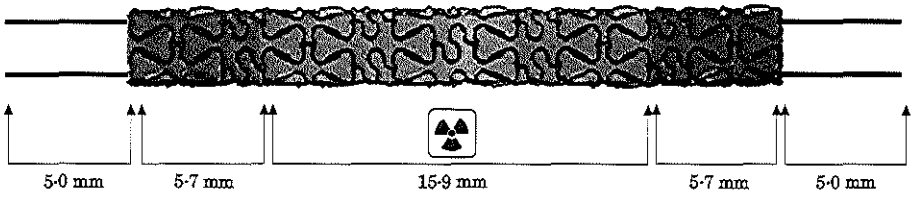

Figure 1 **A cold-end stent with a central radioactive segment and proximal and distal non-radioactive segments. Analysis of each segment was performed individually to assess neointimal hyperplasia. This included neointimal hyperplasia over the length of the stent and edges.**

Methods

Patient selection

We analysed neointimal hyperplasia and vascular remodelling in 16 patients who had completed a 6-month angiographic follow-up with intravascular ultrasound analysis. All patients had single native vessel coronary artery disease, normal left ventricular function and objective evidence of ischaemia.

Implantation technique

Pre-dilation of the lesion was performed where necessary followed by stent implantation High-pressure balloon inflation to ensure good strut apposition to the vessel wall was then performed at the operator's discretion. 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[3]. Intravascular ultrasound was used to ensure optimal stent deployment.

Medication

Patients received 250 mg aspirin and 10 000 international units of heparin at the initiation of the procedure and the activated clotting time was maintained at >300 s. All patients received aspirin 80 mg daily indefinitely and clopidogrel 75 mg daily for 6 months.

Radioactive stent

The stent was 27·3 mm in length and available in diameters of 3·0 and 3·5 mm. It was made radioactive in its central portion by phosphorus-32 (^{32}P)[3]. The 5·7 mm edges were shielded from radiation. The initial activity of the stents was measured and thereafter it was calculated at what date the activity had decreased to 3·0–12·0 μCi, suitable for implantation.

Intravascular ultrasound image acquisition analysis

After the final balloon inflation and administration of intracoronary nitrates, ECG-gated intravascular ultrasound pullback was performed. This was repeated at the 6 month follow-up. The segment was subjected to three-dimensional reconstruction and examined with a mechanical intravascular ultrasound system (Clearview, CardioVascular Imaging System, Sunnyvale, CA, U.S.A.) with a sheath-based intravascular ultrasound catheter incorporating a 30 MHz single-element transducer rotating at 1800 rpm. The intravascular ultrasound transducer was withdrawn through the stationary imaging sheath by an ECG-triggered pullback device with a stepping motor[6]. Intravascular ultrasound images were acquired, 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 0·2 mm to acquire the next image coincident with the R-wave. By definition, this permits acquisition of five slices per mm, enabling the operator to easily define the stent margins. By increasing the frequency of sampling this approach may also decrease error due to regression to the mean created by the use of greater step sizes and non-ECG-gating[7,8].

ECG-gated image acquisition and digitation was performed using a workstation designed for three-dimensional reconstruction of echocardiographic images[6] (EchoScan, Tomtec, Munich, Germany). A Microsoft Windows®-based contour detection program, developed at the Thoraxcenter, was used for automated three-dimensional analysis of up to 200 intravascular ultrasound images[9]. 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 intra-observer variability of this system have been previously described in clinical protocols[5,9].

Quantitative intravascular ultrasound 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, stent volume, neointimal hyperplasia, and lumen volumes were obtained. The

neointimal hyperplasia presented was a value measured at follow-up (stent volume–lumen volume).

The assessment of total vessel volume in stented patients has previously been reported[5,10]. In our study the delineation of the total vessel volume boundary was possible in all stented patients. When the total vessel volume 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 three-dimensional reconstruction with multiple longitudinal views, facilitates the visualization of vessel structures outside the stent.

Definitions and segments of analysis

Stent edges were defined as those volumes axially 5 mm proximal and distal to the final stent strut. In addition, segments in-stent proximally and distally were analysed separately to assess neointimal hyperplasia in areas which were subject to injury and received stent implantation. Effectively, these were segments which received a fall-off in radiation. Finally the in-stent radioactive segment was analysed (see Fig. 1). To facilitate comparison between the non-radioactive in-stent segments (5·7 mm) and the central radioactive segment (15·9 mm), lengths were normalized to a standard length (5 mm) and appropriate comparisons made. Restenosis was defined as an angiographic restenosis >50% at 6-month follow-up, by off-line quantitative coronary angiography.

Statistical analysis

Quantitative data are presented as mean ± standard deviation. Volumetric data derived from the three-dimensional reconstruction of the intravascular ultrasound image were compared immediately after treatment and at follow-up using the two-tailed paired Student's t-test. ANOVA was used to compare multiple variables. 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 provided written informed consent before the procedure.

Results

Baseline clinical and procedural characteristics are described in Tables 1 and 2. Table 3 describes quantitative coronary angiography data pre- and post-intervention and at the 6-month follow-up.

In-stent radioactive segment

Neointimal hyperplasia measured within the margins of the stent is presented in Fig. 2. Intra-stent neointimal hyperplasia was significantly decreased in the radioactive mid-segment of the stent: 3·72 ± 3·3 mm^3 (8·6%). compared with the proximal: 7·90 ± 7·2 mm^3 (19·0%) and distal: 11·42 ± 10·5 mm^3 (25·6%) in-stent segments. Over the entire stent length there was a 30·48 mm^3 (14%) increase in neointimal hyperplasia. No evidence of remodelling was seen behind the stent with the total vessel volume remaining unchanged.

Table 1 Clinical characteristics

Age (mean)	52 (41–78)
Male (%)	69
Prior MI (%)	75
Unstable angina (%)	40
Smoking (%)	56
Hypercholesterolaemia (%)	69
Family history (%)	56
Hypertension (%)	40
Diabetes (%)	0

Table 2 Procedural characteristics

Vessel	
LAD	6
LCx	7
RCA	3
Lesion length (mm)	11·2 ± 4·5
Balloon length-post (mm)	15·6 ± 5·7
Final balloon size (mm)	3·9 ± 0·5
Max inflation pressure[1] (atms)	10 ± 4·0
Max inflation pressure[2] (atms)	16 ± 2·2
Balloon-to-artery ratio	1·12

Max inflation pressure[1]=balloon at time of stent implantation.
Max inflation pressure[2]=balloon inflation within stent.
LAD=left anterior descending coronary artery; LCx=left circumflex artery; RCA=right coronary artery.

Table 3 Angiographic data

	Pre	Post	FU
MLD	0·98 ± 0·40	2·26 ± 0·40	1·67 ± 0·48
DS	67 ± 14	26 ± 8	42 ± 13
RD	2·97 ± 0·46	3·06 ± 0·41	2·82 ± 0·43
Acute gain		1·28 ± 0·46	
Late loss			0·59 ± 0·49
Late loss index			0·57 ± 0·56

FU=6-month follow-up.
MLD=minimum lumen diameter; DS=diameter stenosis; RD=reference diameter.

In-stent non-radioactive segment

Significant neointimal in-growth was noted distally and proximally from 2–3 mm within the radioactive segment and extended on average to the extremities (non-radioactive) of the stent (see Fig. 3). Four individuals experienced angiographic restenosis in the proximal

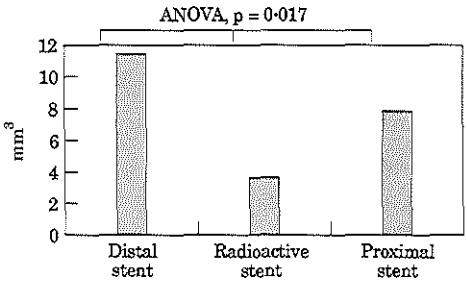

Figure 2 **Neointimal hyperplasia (mm^3) in the three in-stent segments. Each segment is standardized to a 5 mm length for comparison.**

portion of the stent. However, the greatest mean volume of tissue growth as quantified by intravascular ultrasound was seen in the distal stent. Neointimal hyperplasia, with a >50% stented cross-sectional area, was seen in eight patients. This was witnessed proximally (n=2), distally (n=2) and in both segments (n=4). Tissue growth in-stent was due to a combination of conventional neointimal hyperplasia and echolucent, hypodense material, described by this group as the 'black hole' (P. W. Serruys, personal communication, Rotterdam, 1999). This was witnessed (Fig. 4) in the non-radioactive proximal and distal in-stent segments in six out of the eight patients.

Total vessel volumes

No significant change in total vessel volumes or plaque behind the stent was seen between post-procedure and follow-up. No echolucent tissue was seen behind the stent.

Stent edge

Late lumen loss was seen at the stent edge without evidence of restenosis. On average, there was evidence of a decrease in total vessel volume, with little change in plaque as a cause of late lumen loss.

Stent activity

Mean stent activity at implantation was 6·9 ± 1·9 μCi.

Discussion

Dose-finding studies in humans have shown that in-stent neointimal hyperplasia is decreased in a dose-dependent manner after the implantation of stents with activity levels >3·0 μCi[3,4]. Unfortunately, stent edge restenosis was a side effect of this treatment modality at these activity levels. Because the stent edge is systematically

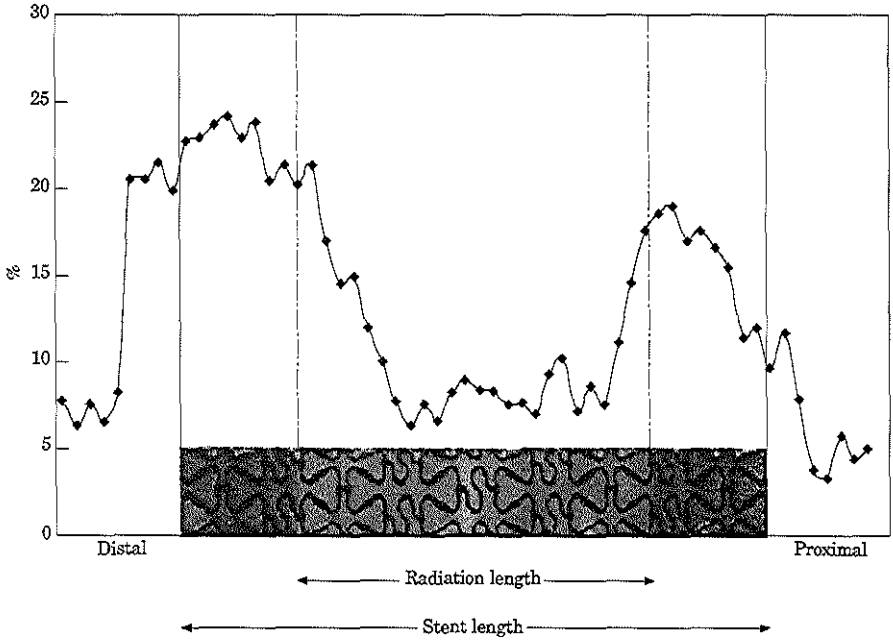

Figure 3 **Graph showing neointimal hyperplasia (% increase) over the length of the stent and edges. Note significant hyperplasia proximally and distally in-stent and the relative sparing of the radioactive mid-segment of the stent. Note also that significant in-growth begins within the radioactive segment of the stent and extends to the non-radioactive proximal and distal extremities of the stent.**

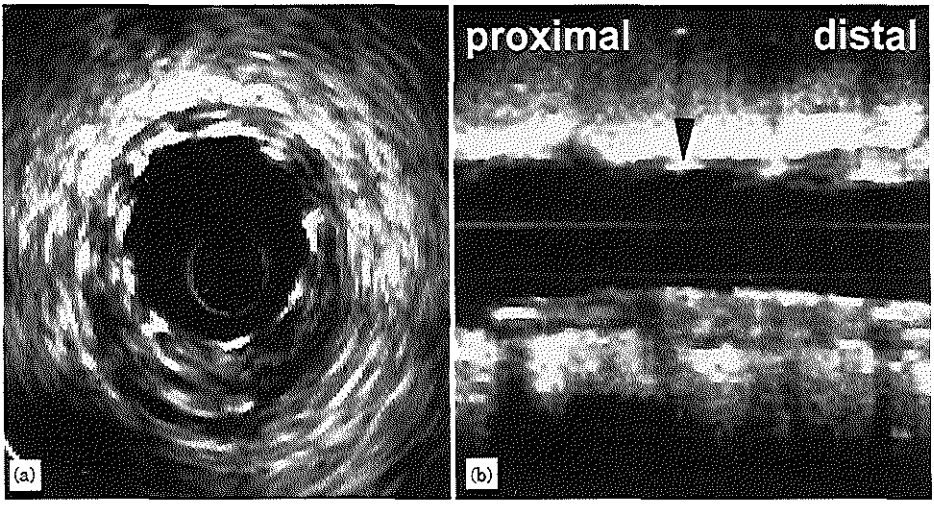

Figure 4 **Representative example of echolucent tissue ('black hole'). (a) A transverse section. A black hole is seen from 9 o'clock to 3 o'clock. (b) A longitudinal reconstruction. Arrowhead points to semi-circular echolucent tissue seen adjacent to the stent struts.**

damaged by barotrauma at the time of balloon expansion, a situation of geographical miss[11], in which the damaged edges receive low dose radiation, is germane to radioactive stenting in the absence of appropriately shaped balloons. Previously we have argued: 'If the candy wrapper (bilateral 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 candy wrapper then cold-end stent implantation is unlikely to work. Similarly neointimal proliferation may occur at the edges of the radiation within stent using this treatment modality'[12]. This prediction appears to have materialized in the current study, with migration of the restenotic edge from outside the stent to within the stent at the edges of radiation.

Neointimal hyperplasia

Neointimal hyperplasia in the true radioactive segment was suppressed at the 6-month follow-up to a degree similar to that noted in the ^{32}P radioactive stent dose-finding trial previously reported by this group (mean neointimal hyperplasia = 17·67 mm^3 (13·94%)), using a 15 mm stent[5]. Regrowth of tissue starting 1–2 mm within the radioactive extremes and extending out of the stent was noted in the ^{32}P radioactive stent dose finding trial, translating to significant stent-edge hyperplasia proximally. In the cold-end stent, neointimal hyperplasia was noted in the final millimetres of radiation and extended bilaterally. In the latter study, this left the true stent edges relatively, although not completely, spared as there remained evidence of tissue growth in three individuals, which started within the radioactive portion and continued to the true vessel lumen. No angiographic restenosis occurred in these three however. Again, we must assume that the position of such restenosis is caused by geographical miss. Why some individuals are affected and others not is unclear, but may be explained by an idiosyncratic individual response to healing, dose heterogeneity along the length of the stent, tissue type behind the stent, plaque burden and even strut apposition to the vessel wall.

Echolucent tissue

In nearly 50% of subjects, echolucent tissue was present within the stent at the distal or proximal (in-stent) edge of radiation and consituted on average 50% of neointimal ingrowth in areas of restenosis. These echolucent lesions had the following characteristics: a homogeneous black appearance without backscatter. Images with ring-down or other artefacts were excluded and no attenuation behind intraluminal echodense structures was seen. Exclusion of other causes of relative echolucency such as contrast[13], thrombus[14] or a lipid lake[15] was performed. Lesions were discrete and readily distinguishable from conventional neointimal hyperplasia. After radioactive stenting, all appeared to be juxtaposed to stent struts.

We have performed atherectomy on four such lesions detected at the 6-month follow-up after radioactive stenting and found that they contain a hypocellular matrix with areas of proteoglycan, similar to that seen in the animal model[16,17]. The mixture of neointimal hyperplasia and proteoglycan, which has a high water content, may explain the echolucent tissue adjacent to the stent struts noted in Fig. 5. Further pathological

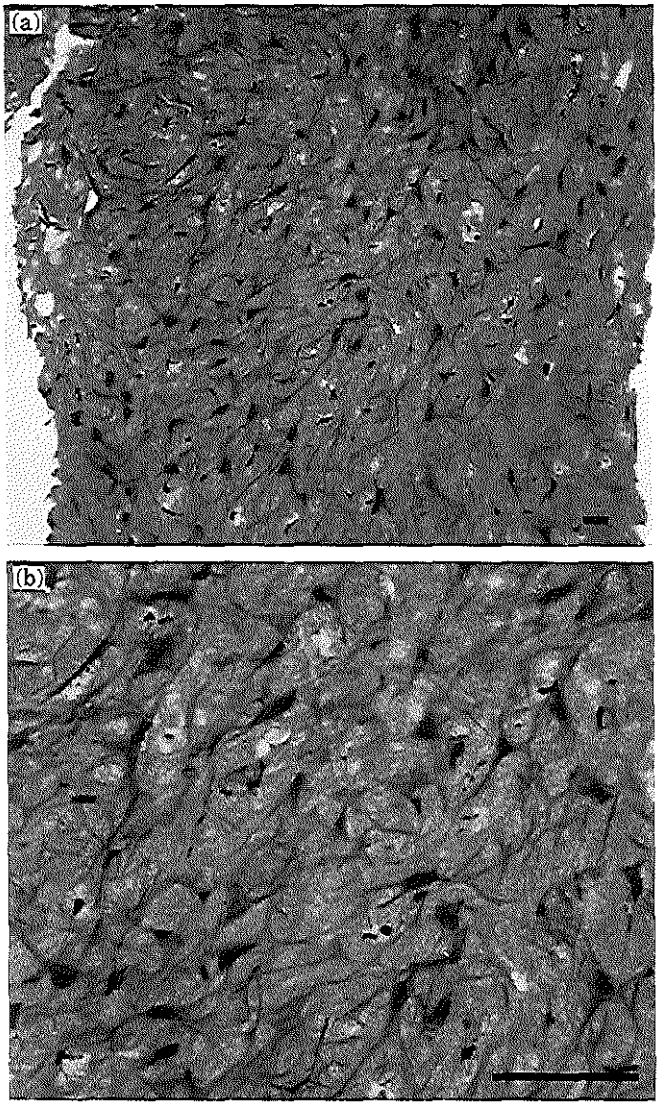

Figure 5 **Photomicrographs (a) and (b) show neointima consisting of arboryzing smooth muscle cells in a proteoglycan matrix. H&E stain; bars=50 μm.**

assessment is required before definitive comment can be made on this interesting observation. Equally, the long-term incidence of restenosis from such lesions is yet to be determined.

Edge remodelling

This was similar to that seen after non-radioactive stenting, whereby non-restenotic late lumen loss was due to negative remodelling[5,18].

Implications 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 to 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. A further therapeutic option is that of hybrid treatment with radioactive stent implantation followed by catheter-based therapy localized to the stent edges only.

Conclusion

Cold-end stent implantation, a strategy devised to prevent edge restenosis after radioactive stenting results in migration of the restenotic edge from outside the stent to within the stent at the edges of radiation. This adds credence to the hypothesis that injury and low-dose radiation stimulate neointimal hyperplasia[19].

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Chapter 10

Edge Restenosis After Implantation of "Hot Ends" 32P Radioactive ß-Emitting Stents. The Milan and Rotterdam Experience.

Submitted

Edge Restenosis After Implantation of "Hot Ends" ^{32}P Radioactive ß-Emitting Stents The Milan and Rotterdam Experience

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ABSTRACT

Background—A high restenosis rate has been reported at the edges ("edge restenosis") of ^{32}P radioactive stents with an initial activity level up to 21 µCi. This edge effect might be due the systematic balloon injury in the first 2 mm outside the stent margins in combination with a sub-therapeutic level of radiation at the stent edges. The aim of this study was to evaluate whether an increased activity at the proximal and distal end of the stent ("hot ends") might diminish the problem of "edge restenosis", by extending the area of irradiation beyond this injured area.

Methods and Results— The "hot ends" ^{32}P radioactive ß-particle-emitting stent has a length of 18 mm. The initial radioactivity level is 2.6 µCi/mm in the proximal and distal 2 mm of the stent, and 0.57 µCi/mm in the central 14 mm of the stent. The initial total radioactivity of the stent is ~ 18.5 µCi. From July until Nov 1999, 53 patients (pts) with 56 lesions were treated in Milan (36 patients with 39 lesions) and Rotterdam (17 patients with 17 lesions) by implantation of 56 "hot ends" ^{32}P radioactive stents. There were no procedural events. At the 6-month angiographic follow-up, performed in 51 patients with 54 lesions (96%), intralesion binary restenosis was 33% (19% at the proximal edge, 7% at the distal edge, and 7% at both edges).

Conclusions—Radioactive ^{32}P "hot ends" stents did not solve the problem of edge restenosis.

CONDENSED ABSTRACT

Restenosis at the edges of ^{32}P radioactive stents of 3-12 μCi activity was possibly explained by the lower dose of radiation delivered in the balloon injured arterial segment at the stent ends. We evaluated whether an increased radioactivity at both stent edges ("hot ends") might diminish "edge restenosis", by extending the area of irradiation beyond the balloon injured area. Six months after stenting, there were no deaths, or stent occlusions. Only one patient had an AMI. However, intralesion binary restenosis was 33%. Radioactive ^{32}P "hot ends" stents did not solve the problem of edge restenosis.

Key words: **radioisotopes, restenosis, stents, ultrasonics**

In patients with coronary artery disease treated with ^{32}P radioactive ß-emitting stents with an initial activity of 3 to 21 μCi, intrastent restenosis at the 6-month angiographic follow-up was ≤4% [1-3]. However, the intralesion restenosis rate was >30% due to restenosis at the stent edges ("edge restenosis") [1-3]. This edge effect might be due to the systematic balloon injury in the first 2 mm outside the stent margins in combination with a sub-therapeutic level of radiation at the stent edges [4]. The purpose of this study was to evaluate whether ^{32}P radioactive stents with an increased activity at the proximal and distal end of the stent ("hot ends") could solve the problem of "edge restenosis", by extending the area of irradiation beyond this injured area.

METHODS

Patient Population

Inclusion criteria for enrollment in this study were previously reported [1]. From July until Nov 1999, 53 patients with 56 lesions were treated in Milan (36 patients with 39 lesions) and Rotterdam (17 patients with 17 lesions) by implantation of 56 radioactive ^{32}P BX "hot ends"stents.

Radioactive Stent

The radioactive ^{32}P BX "hot ends" stent had a length of 18 mm. The initial radioactivity level (at a pre-specified date) was 2.6 μCi/mm in the proximal and distal 2 mm of the stent, and 0.57 μCi/mm in the central 14 mm of the stent. The initial total radioactivity of the stent was ~18.5 μCi. The activity reported in this study was that calculated at the date of implantation. The stent was mounted on a 20-mm-long balloon. The characteristic of the isotope (^{32}P) used in this study was previously described [1].

Procedure and Clinical Follow-Up

The technique used to implant a radioactive stent was previously reported [1]. The "hot ends"stents were implanted predilating the lesions with a nonoversized balloon, deploying the stent at 8 to 10 atm, and postdilating using a shorter balloon inflated at high pressure (>12 atm) inside the stent. After stenting, patients received long-term treatment with aspirin (325 mg daily) plus ticlopidine (250 mg twice daily) or clopidogrel (75 mg daily) for ≥3 months. Death, myocardial infarction, stent thrombosis, and target lesion revascularization (TLR) were defined as previously reported. [1,5-7]. TLR was performed on the basis of clinical symptoms and/or evidence of ischemia on exercise testing.

Angiographic and intravascular ultrasound (IVUS) analyses

The methods used for angiographic analysis and IVUS imaging, and the definitions of intrastent and intralesion restenosis were previously reported [1,5-7].

Quantitative IVUS analysis was performed by a Core Laboratory (Intravascular Ultrasound Imaging and Cardiac Catheterization Laboratories, Washington Hospital Center, Washington, DC). Validation of IVUS measurements and reproducibility of sequential IVUS mesurements in the Washington Hospital Laboratory have been previously reported [8]. The image cross sections (1 mm apart) of the stent and of 5 mm proximal and distal to the stent were analyzed measuring postintervention (PI) and follow-up (FU) external elastic membrane (EEM), lumen, stent, and plaque (EEM minus lumen) cross sectional areas (CSA). Calculation and analysis of late lumen loss (PI-FU lumen CSA), tissue growth at the stent edges (FU-PI plaque CSA) and inside the stent (stent-lumen CSA), and remodeling (PI-FU EEM CSA) were performed in the 18 lesions with a complete serial IVUS evaluation treated by a single "hot end" stent without additional nonradioactive stents.

Statistical Analysis

Continuous variables were presented as mean±SD and categorical variables as number and percentage.

RESULTS

Patient characteristics are shown in Table 1. Angiographic and procedural characteristics are shown in Table 2. Most of the treated lesions (90%) were de novo lesions. A single stent ("hot ends") was implanted in 82% of the lesions, while an additional non-radioactive stent was required to treat a dissection in 10 lesions (18%).

Clinical Events

At 30-day follow-up no subacute stent thrombosis occurred. At 6 months, no late occlusion was seen. No patient died and only one patient experienced myocardial infarction. TLR was performed in 13/54 (24%) lesions.

Table 1. Clinical Characteristics of the 53 Patients Studied

Male sex	40 (75)
Age, y	60.1± 9.6 (36–85)
Risk factors	
Diabetes mellitus	6 (11)
Hyperlipidemia	30 (57)
Hypertension	30 (57)
Smoking	7 (13)
Family history	21 (40)

Values are n (%) or mean±SD (range)

Table 2. Angiographic and Procedural Characteristics

No. of lesions	56
Radioactivity, μCi	14.0 ± 2.6 (9.5-18.5)
De novo lesions, n (%)	37 (90)
Vessel: - LAD	30 (54)
- LCx	12 (21)
- RCA	14 (25)
Final balloon size, mm	3.42±0.47
Final balloon length, mm	14.8±4.0
Final inflation pressure, atm	14.3±3.0
Final Balloon-to-artery ratio	1.16±0.17
No. stents/lesion	1.07±0.26
Lesions treated by a single stent	46 (82)

LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery;

RCA, right coronary artery; Values are mean±SD (range) or number (%) of lesions.

Table 3. Quantitative Angiographic Results

Preintervention	n=56
Reference diameter, mm	3.00 ± 0.61
MLD, mm	0.95 ± 0.51
Lesion length, mm	13.9 ± 4.8
Postintervention	n=56
Reference diameter, mm	3.25 ± 0.51
MLD, mm	2.95 ± 0.57
Follow-up	n=54
Reference diameter, mm	3.01 ± 0.49
MLD, mm	2.12 ± 0.94
Intralesion Restenosis, n (%)	18 (33)
- proximal edge	10 (19)
- proximal + distal edge	4 (7)
- distal edge	4 (7)

Values are mean±SD or number (%) of lesions

Quantitative Angiographic and IVUS Analysis

Table 3 summarizes the quantitative angiographic results. Intralesion restenosis rate was 33%, mainly located at the proximal edge, Moreover, it occurred in 50% (5/10) of the lesions treated by an additional non-radioactive stent. There was only one case (2%) of diffuse intrastent restenosis. An example of a patient with edge restenosis ("candy wrapper") 6 months after "hot ends" stent implantation is shown in Figure 1. Quantitative IVUS analysis in the 18 lesions with complete serial IVUS evaluation is shown in Figure 2: late lumen loss in the first 2 mm outside the proximal stent margin was mainly due to tissue growth, while late lumen loss ouside the distal stent margin was not higher than inside the stent.

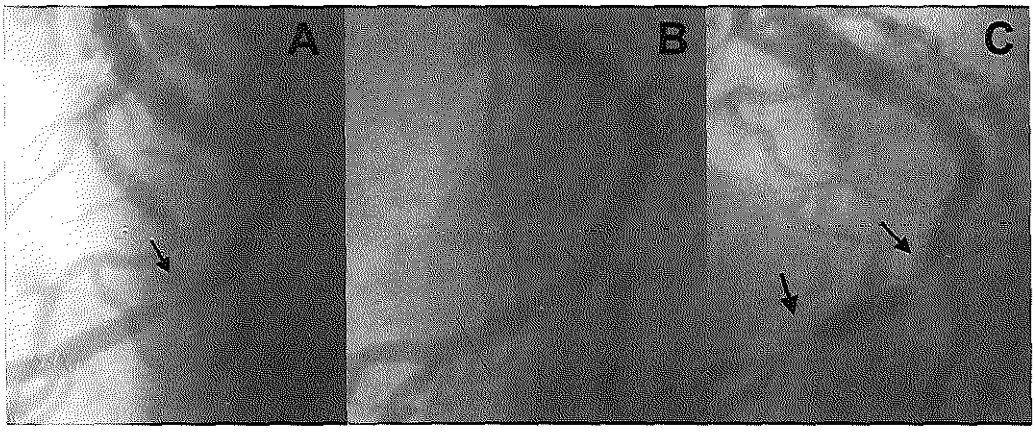

Figure 1.
Representative patient with "candy wrapper" edge effect 6 months after radioactive ^{32}P "hot ends" stent implantation. Baseline angiography (A) demonstrates a moderate 60% stenosis in the distal circumflex coronary artery. After implantation (B) of a 18-mm BX "hot ends" stent. At 6 month follow-up (C), there is absence of late loss inside stent but a tight stenosis at both stent edges. In this case, IVUS imaging demonstrated that edge restenosis was due to neointimal hyperplasia without negative remodeling.

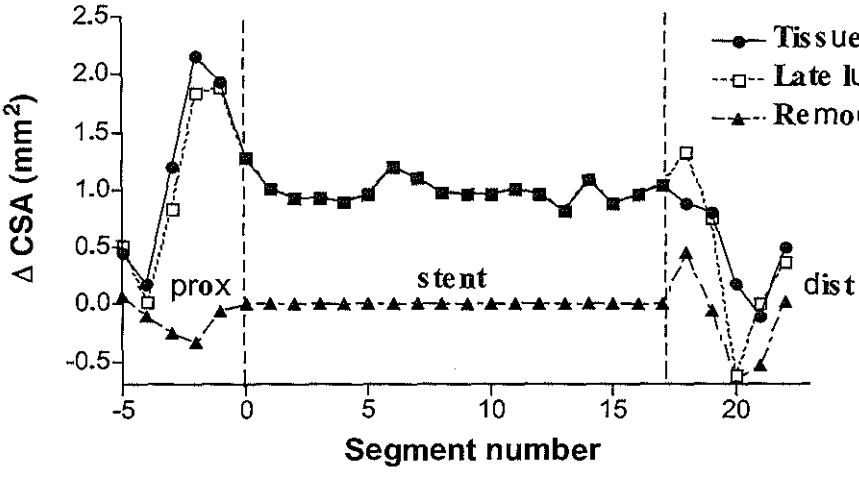

Figure 2.
Plot of mean of late lumen loss, tissue growth, and remodeling (in mm^2) in 18 lesions with complete serial IVUS evaluation treated by a single 18-mm BX "hot ends" stent. Point represents differences in CSA measured in slices 1 mm apart inside stent and in proximal and distal reference segments.

DISCUSSION

The results of this study confirm our prior observations [1-3] on the effectiveness of ^{32}P radioactive stents in inhibiting intrastent neointimal hyperplasia. However, the "hot-ends" stents, designed to prevent edge restenosis, by extending the area of irradiation beyond the balloon-injured area outside the stent margins, did not reach this goal.

Mechanism of edge restenosis

The edge effect may be considered a short-term healing response to vessel wall injury beyond the stented vessel segment combined with the effects of low-dose radiation [1-4]. In this study, restenosis occurred predominantly at the proximal edge. A reason for this result may be the tendency of the operator, in order to avoid distal dissection and guarantee a good proximal stent expansion, to postdilate the stent at high pressure positioning the balloon close to the proximal margin of the stent, with an increased risk of barotrauma at this site. Another possibile explanation for the proximal edge restenosis may be the edge shear stress created by the presence of a complete inhibition of neointimal proliferation inside the stent [9].

Conclusion

Single ^{32}P radioactive ß-emitting "hot ends" stents did not solve the problem of "edge restenosis.

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Part IV

Catheter-based radiation

Chapter 11

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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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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Background—Recent reports demonstrate that intracoronary radiation affects not only neointimal formation but also vascular remodeling. Radioactive stents and catheter-based techniques deliver radiation in different ways, suggesting that different patterns of remodeling after each technique may be expected.

Methods and Results—We analyzed remodeling in 18 patients after conventional stent implantation, 16 patients after low-activity radioactive stent implantation, 16 patients after higher activity radioactive stent implantation, and, finally, 17 patients who underwent catheter-based radiation followed by conventional stent implantation. Intravascular ultrasound with 3D reconstruction was used after stent implantation and at the 6-month follow-up to assess remodeling within the stent margins and at its edges. Preprocedural characteristics were similar between groups. In-stent neointimal hyperplasia (NIH) was inhibited by high-activity radioactive stent implantation (NIH 9.0 mm^3) and by catheter-based radiation followed by conventional stent implantation (NIH 6.9 mm^3) compared with low-activity radioactive stent implantation (NIH 21.2 mm^3) and conventional stent implantation (NIH 20.8 mm^3) (P=0.008). No difference in plaque or total vessel volume was seen behind the stent in the conventional, low-activity, or high-activity stent implantation groups. However, significant increases in plaque behind the stent (15%) and in total vessel volume (8%) were seen in the group that underwent catheter-based radiation followed by conventional stent implantation. All 4 groups demonstrated significant late lumen loss at the stent edges; however, edge restenosis was seen only in the group subjected to high-activity stent implantation and appeared to be due 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. (***Circulation.* 2000;102:1434-1439.**)

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

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 neointimal 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 using radioactive stents[3–7] and the other using 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, one may intuitively 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 has not been described. Preliminary studies have reported the effect at the stent edge after radioactive stent implantation.[4] However, these reports did not encompass the response behind the stent in the arterial wall.

The aim of the present study was to describe the response of the coronary artery to radiation and stenting by examining the stent and its edges after radioactive stent implantation and also after catheter-based radiation with stent implantation.

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TABLE 1. Clinical Characteristics

	Groups			
	C	LA	HA	CBS
Patients, n	18	16	15	17
Age, y	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
Hypercholesterolemia, %	60	62	65	55
Family history, %	33	42	30	40
Hypertension, %	40	42	30	33
Diabetes, %	5	5	10	6

Age values are mean (range). MI indicates myocardial infarction.

Methods

Patient Selection

We analyzed geometric vascular remodeling in 4 groups of patients: (1) LA group, those who had undergone implantation of ^{32}P-emitting radioactive stents at activity levels of 0.75 to 1.5 μCi (Isostent Inc); (2) HA group, those who had undergone implantation of ^{32}P radioactive stents at activity levels of 6.0 to 12 μCi (Isostent Inc); (3) CBS group, those who had undergone conventional stent implantation after suboptimal BA (clinically significant dissection or residual stenosis >30%) and catheter-based radiation; and (4) C group, 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. 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 intravascular ultrasound (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 with use of either a premounted stent or the Johnson & Johnson delivery system (Johnson & Johnson Interventional Systems Co). A balloon shorter than the stent was then selected, and high-pressure balloon inflation was performed within the stent to ensure good stent apposition. Intravascular ultrasound was used to ensure optimal stent deployment.

Medication

Patients received 250 mg aspirin and 10 000 IU heparin at the initiation of the procedure, and the activated clotting time was maintained at >300 seconds. All patients received aspirin (80 mg daily) indefinitely and ticlopidine (250 mg BID) for 2 weeks (C group) or clopidogrel (75 mg daily) for 12 weeks (LA, HA, and CBS groups) after stent implantation.

Radioactive Stents

The BX stent (Isostent Inc) was the only radioactive stent implanted in this trial. It was 15 mm in length and available in diameters of 3.0 and 3.5 mm. The BX stent was made radioactive by ^{32}P. The initial activity of the stents was measured; thereafter, it was calculated at the date on which the activity had decreased to 0.75 to 1.5 μCi or 6 to 12 μCi, levels suitable for implantation.

Catheter-Based Radiation Delivery System

The Beta-Cath System (Novoste Corp) was used to deliver localized β-radiation (^{90}Sr/^{90}Y) to a depth of 2 mm from the center of the

TABLE 2. Procedural Characteristics

	Groups			
	C	LA	HA	CBS
Vessels, n				
LAD	10	9	9	9
LCx	4	3	3	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 after implantation, mm	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

Values are mean±SD. LAD indicates left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; Max inflation pressure 1, balloon at time of stent implantation; and Max inflation pressure 2, balloon inflation within stent.

TABLE 3. Volumes for Edge Proximal and Distal to Stent (10-mm Length)

	Edge, mm^3					
	LV		TVV		Plaque	
Group	Post	F/UP	Post	F/UP	Post	F/UP
C	67.7±18.9	58.3±19.3*	124.4±32.6	116.5±34.1*	56.7±22.6	58.2±23.1
LA	75.2±39.0	67.3±34.4*	126.6±58.0	116.4±49.0*	51.4±24.5	49.1±21.0
HA	74.9±23.0	63.0±23.7*	126.2±44.9	117.6±46.2*	51.3±16.4	54.6±16.1
CBS	72.6±27.7	61.1±26.3*	133.2±48.5	138.9±46.5†	60.6±26.1	77.8±28.6*†

Values are mean±SD. Post indicates baseline; F/UP, follow-up.
*$P<0.05$ vs Post (within-group comparison); †$P<0.05$ for between-group comparison (ANOVA).

source at the site of coronary intervention. The device consisted of 3 components: (1) the transfer device that stored the radiation source train and allowed the positioning of these sources within the catheter; (2) the delivery catheter, which was a 5F multilumen over-the-wire noncentered catheter that used saline solution to send and return the radiation source train; and (3) the radiation source train, which consisted of a series of 12 independent cylindrical seeds that contained the radioisotope ^{90}Sr sources and was bordered 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 5 mm 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 that 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 the present 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 the 6-month follow-up.

The segment subjected to 3D reconstruction was examined with a mechanical IVUS system (ClearView, CVIS) 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 coinciding with the peak of the R wave, which eliminates the artifacts caused by the movement of the heart during the cardiac cycle, were acquired. After each image acquisition, the transducer was withdrawn 0.2 mm to acquire the next image coincident with the R wave. The ECG-gated image acquisition and digitization was performed by a workstation designed for the 3D reconstruction of echocardiographic images[12] (EchoScan, Tomtec). A Microsoft Windows–based contour detection program, developed at the Thoraxcenter, Rotterdam, was used for the automated 3D analysis of up to 200 IVUS images.[13] The feasibility, reproducibility, and interobserver and intraobserver variability of this system have been previously validated in clinical protocols.[13]

Quantitative IVUS Analysis

At the stent edges, the area encompassed by the lumen-intima and media-adventitia boundaries defined the luminal volume (LV) and the total vessel volume (TVV), respectively. The difference between LV and TVV defined the plaque volume. TVV, stent volume, neointimal hyperplasia (NIH), plaque behind the stent (TVV−stent volume), and LV were obtained within the axial boundaries of the stent.

The assessment of TVV in stented patients has previously been reported.[14] Although in the previous report the delineation of TVV was not possible in some patients because of stent shadowing, in the present study the delineation of the TVV boundary was possible in all stented patients. When the TVV boundary was not visible in a single cross-sectional view, the computer extrapolated it from the contours of the previous and subsequent cross sections. In addition, the use of 3D reconstruction with multiple longitudinal views facilitates the visualization of vessel structures outside the stent.

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 the 2-tailed paired Student *t* test. Comparison between groups was performed by 1-way ANOVA. 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 provided written informed consent before the procedure.

TABLE 4. Volumes for Stent

	Stent, mm^3						
	LV		TVV		PBS		
Group	Post	F/UP	Post	F/UP	Post	F/UP	NIH
C	113.9±29.7	92.8±28.7*	256.1±73.2	257.3±67.4	142.2±54.1	143.7±49.4	20.8±11.5
LA	127.3±42.6	105.5±40.1*	266.6±96.5	264.5±98.3	139.3±59.1	137.8±63.7	21.2±12.1
HA	122.4±20.0	111.7±24.3*	267.8±66.9	265.3±65.1	145.4±49.1	144.6±45.3	9.0±8.6†
CBS	128.6±41.3	121.8±41.6*	258.9±73.6	278.0±89.8*	130.3±34.2	149.3±49.8*	6.9±6.6†

Values are mean±SD. Post indicates baseline; F/UP, follow-up; and PBS, plaque behind the stent. No significant difference between groups was seen at baseline (Post).
*$P<0.05$ vs Post (within-group comparison); †$P<0.05$ for between-group comparison (ANOVA).

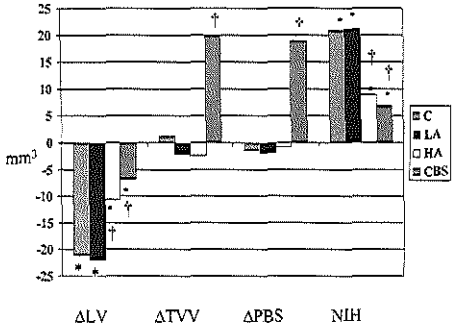

Figure 1. Remodeling within margins of stent. PBS indicates plaque behind the stent. *P<0.05 for values immediately after treatment vs follow-up; †P<0.05 for values between groups.

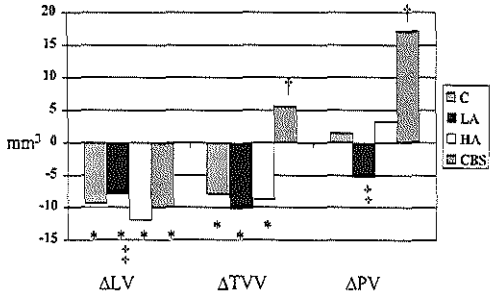

Figure 2. Changes in volumes at stent edge. PV indicates plaque volume. *P<0.05 for values immediately after treatment vs follow-up; †P<0.05 for values between groups; and ‡P=NS for ΔLV (all groups) and ΔPV (C, LA, and HA groups).

Results

Baseline Characteristics

Eighteen patients were enrolled in the conventional group (C group). 16 patients were enrolled in both the 0.75- to 1.5-μCi and the 6.0- to 12-μCi radioactive stent groups (LA and HA groups, respectively), and 17 patients were enrolled in the group subjected to catheter-based radiation plus a stent (CBS group). In the C group, 10 ACS Multi-Link (Guidant Corp) and 8 NIR (new intravascular rigid-flex stent; Boston Scientific/Scimed) stents were implanted, and in the CBS group, 8 NIR and 9 ACS Multi-Link stents were implanted. Baseline characteristics are similar between all groups and are described in Table 1. Lesion and procedural characteristics are described in Table 2. No statistically significant differences were seen between groups in the parameters described in Table 2. Comparisons of volumetric data measured at the stent edges and within the margins of the stent are presented in Tables 3 and 4.

In-Stent Inhibition of NIH

Intrastent NIH was decreased after high-activity radioactive stent implantation and catheter-based radiation followed by conventional stent implantation (P=0.008). Lower activity radioactive stents had an effect similar to that of conventional stent implantation (see Table 4 and Figure 1).

Behind Stent

The C, LA, and HA groups demonstrated an absence of remodeling behind the stent, with no significant changes in TVV or plaque volumes. This is in contrast to the CBS group, which demonstrated a significant increase in plaque (immediately after treatment versus follow-up, 15%; P=0.002) and an increase in TVV (after treatment versus follow-up, 8%; P=0.003). Intergroup comparison showed that this change was significant (Table 4, P=0.01). Further comparisons of changes within and between groups are demonstrated in Figure 1. No chronic recoil of the stent was seen in any group.

Stent Edge

No significant difference between groups was seen at baseline (after stent implantation). All groups demonstrated late lumen loss at the stent edges. At the stent edges, remodeling is similar in the C and LA groups. In these groups, there is evidence of a decrease in TVV, with little change in plaque as a cause of late lumen loss (Figure 2). In the HA group, a target segment restenosis (angiographically >50%) was observed in 7 patients at the stent edges. This was more common at the proximal edge (in 6 of 7 patients). The major mechanism of such a restenosis appears to be due to an increase in plaque at the stent edge. In nonrestenotic patients, the edge effect appears to be due to a decrease in TVV and, to a lesser degree, an increase in plaque (Figure 3).

In the CBS group, the edge effect is largely due to an increase in plaque, with no negative remodeling seen (P=0.045 for plaque increase in CBS versus LA, HA, and C groups). No patient 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 group) was 1.1±0.3 μCi. Mean stent activity at implantation (HA group) was 8.6±1.6 μCi. For the CBS group, the mean dose prescribed was 16.7±2.0 Gy.

Discussion

The development of NIH within the stent witnessed at the 6-month follow-up is well appreciated[15]; however, the

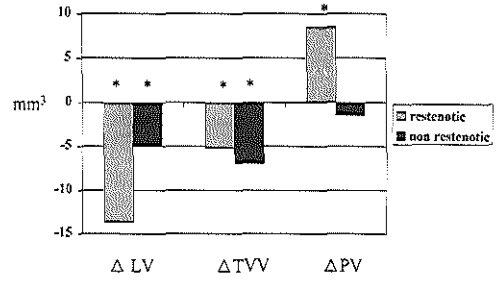

Figure 3. High-activity (6.0- to 12.0-μCi) stents. Restenotic edges are compared with nonrestenotic edges. Δ indicates change in volume (immediately after treatment vs follow-up). *P<0.05 for values immediately after treatment vs follow-up. Note greater lumen loss seen in restenotic group. This loss was caused by increase in plaque (P<0.05) and a less profound decrease in TVV (P<0.05). ΔTVV is similar in both groups.

changes that occur at the stent edges or indeed behind the stent struts have not been the focus of attention until recently.[4] The present study is the first to describe the difference in vascular remodeling seen after radioactive stent implantation and catheter-based radiation plus stenting with the use of modern conventional stents as a benchmark. The key findings are as follows: (1) The degree of inhibition of NIH was similar in the HA and CBS groups. (2) There was no significant remodeling behind the stent after conventional or radioactive stent implantation; however, the CBS group demonstrated an increase in plaque behind the stent and in TVV. (3) At the stent edge, 3 patterns of remodeling are seen at the 6-month follow-up: first, a shrinkage in TVV and LV was noted in the C and LA groups. These 2 subgroups were not associated with stent edge restenosis in this series. After high-activity stent implantation, a pattern similar to conventional and low-activity stent implantation is seen in those edges that remain nonrestenotic; however, in the restenotic edges, plaque increase is the major contributor to lumen loss. In the CBS group, a lumen loss similar to that found in the other groups is seen; however, this occurs secondary to a relatively greater increase in plaque, without loss in TVV.

Neointimal Hyperplasia

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

Mechanism of Remodeling Behind the Stent

Catheter-Based Radiation

After conventional and radioactive stent implantation, little positive or negative remodeling is witnessed behind the stent. In stark contrast to this is the increase in plaque behind the stent and TVV seen after catheter-based radiation and stenting. Part of the key to understanding this process may be acquired from understanding the healing process after BA. Wilcox and colleagues[17,18] 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 and colleagues hypothesize that the adventitial myofibroblasts constrict the artery at the angioplasty site in much the same way as 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.[19]

Radiation treatment of porcine coronary arteries after BA upregulates p21 synthesis in adventitial cells, especially myofibroblasts. Such induction is dose dependent and is sustained for at least 7 days after radiation. Additionally, radiation inhibits the expression of growth factors, reduces the proliferation of adventitial myofibroblasts, and decreases the production of α-actin by the adventitial myofibroblasts, preventing the formation of the myofibroblast scar around the angioplasty site and negative vascular remodeling.[17,20] Data from Fareh and et al [21] suggest that inhibition of migration but not of cellular proliferation may occur at lower doses of radiation. Therefore, cells may remain in situ, unable to migrate but able to grow in the presence of a weakened external elastic membrane. After 1 week, the effect of the radiation diminishes, and cellular proliferation, possibly as a reaction to the presence of the stent, continues 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.[22,23] A further concept to be explored is that relating to the sharp drop-off in radiation seen with the β-radiation source, which may cause underdosing deep in the adventitia and geographical miss[24] in a radial sense rather than the more commonly described longitudinal sense.

Radioactive Stent

The objective of using the radioactive stent is not to neutralize myofibroblasts in the adventitia; 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 by the continuous and low dose rate provided by the radioactive stent. Because of 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 at either activity level.

Edge Remodeling

Hoffmann et al[15] have previously described negative remodeling at the stent edge after conventional stent implantation. In the present study, we have been able to precisely describe the decrease in TVV as the dominant contributor to nonrestenotic lumen loss at the stent edge. Recent reports on radioactive stents 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] The contributing factors to radioactive stent edge restenosis have been discussed in detail recently by Serruys and Kay.[25]

It may be argued that stent-edge restenosis was not seen in the CBS group because no individuals with geographical miss were evaluated. However, our objective in the present study was to analyze the vascular response to appropriately applied catheter-based radiation, which necessitates the exclusion of all those in whom injury was not covered by radiation. Recent reports have suggested that the combination of suboptimal low-dose radiation and injury may make individuals with geographical miss vulnerable to edge restenosis.[26]

Study Limitations

This was a retrospective nonrandomized study of individuals who had completed 6 months of follow-up and in whom IVUS examination was possible. Individuals who had a total occlusion or in whom the IVUS catheter could not be passed under acceptable clinical circumstances were not included.

No edge restenosis was seen in the CBS group, unlike the HA group; however, both the CBS and the HA groups reflected the larger parent populations from which they were selected in all other features.

The dosimetry (catheter-based) described in the present study relates to prescribed doses only and does not necessarily reflect the dose delivered 2 mm from the source in the adventitia. Description of dosimetry is beyond the scope of the present study; however, previous work by the authors (Sabaté et al[27]), who used a similar radiation source and study population, suggests that delivered dose, residual plaque burden, and tissue composition play a fundamental role on the volumetric outcome at 6 months of follow-up after catheter-based β-radiation therapy and BA.

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 edge restenosis seen after higher activity radioactive stent implantation and positive remodeling behind the stent seen 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 at the adverse response of the artery to the combination of injury and radiation.

Acknowledgments

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Chapter 12

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

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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

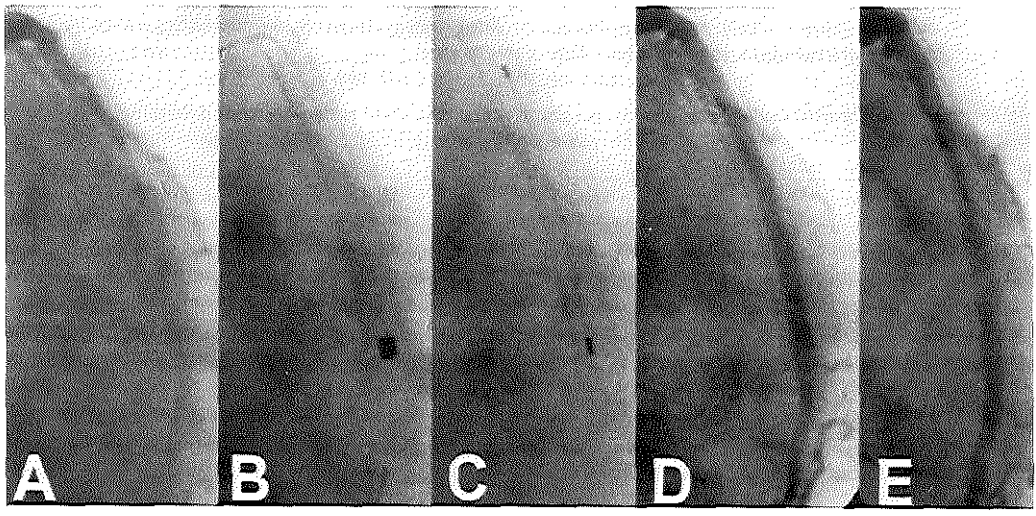

Figure 1. *(A) Coronary angiography of a severe in-stent restenosis in a Wallstent® in a saphenous venous bypass graft, (B) treated with concentric laser debulking, (C) followed by intracoronary radiation. (D) Angiographic result of the procedure. (E) No significant angiographic restenosis is observed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

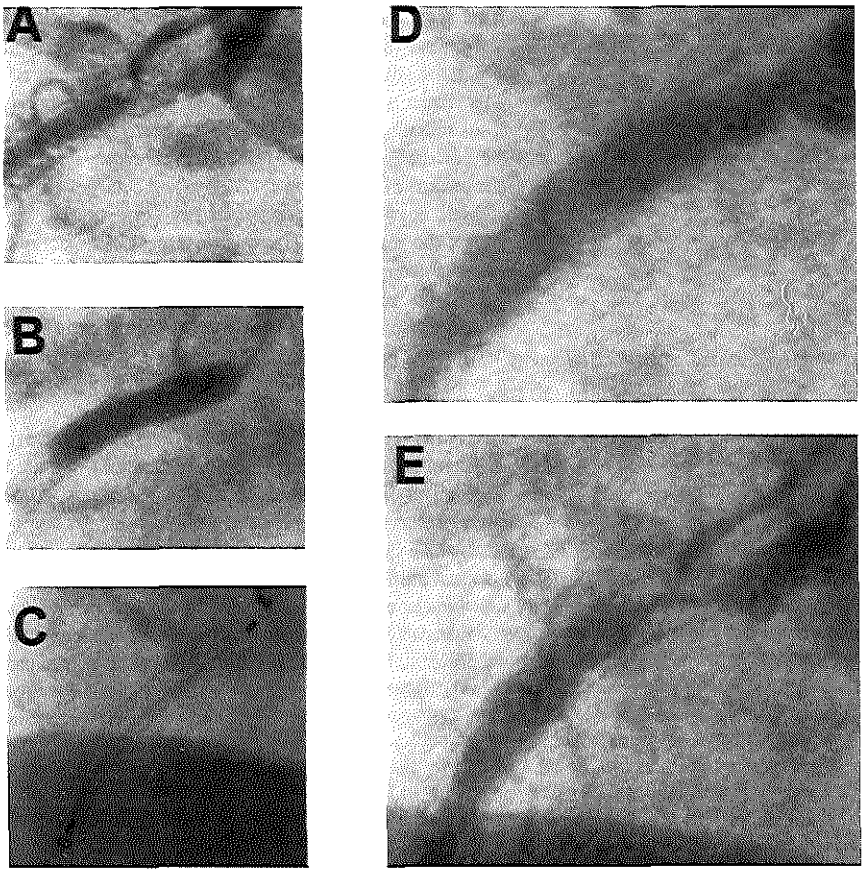

Figure 2. *(A) Coronary angiography of a severe in-stent restenosis in the right coronary artery, (B) treated with balloon angioplasty, (C) followed by intracoronary radiation. (D) Despite a good angiographic result, (E) a severe restenosis was observed at follow-up.*

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),[20] 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.[21] 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

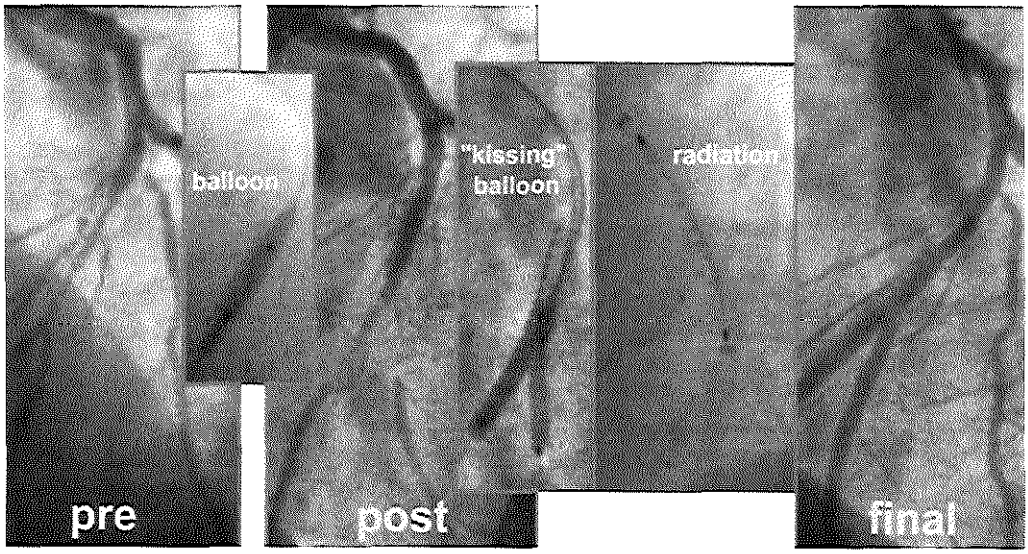

Figure 3. *Serial coronary angiograms showing a coronary dissection following balloon angioplasty which involved the distal segment of the left anterior descending and the second diagonal. Additional kissing balloon and stent implantation were performed. The radiation source could cover only the original 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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Part V

Complications and Interesting Observations

Chapter 13

Late coronary occlusion after intracoronary brachytherapy.

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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]

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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-

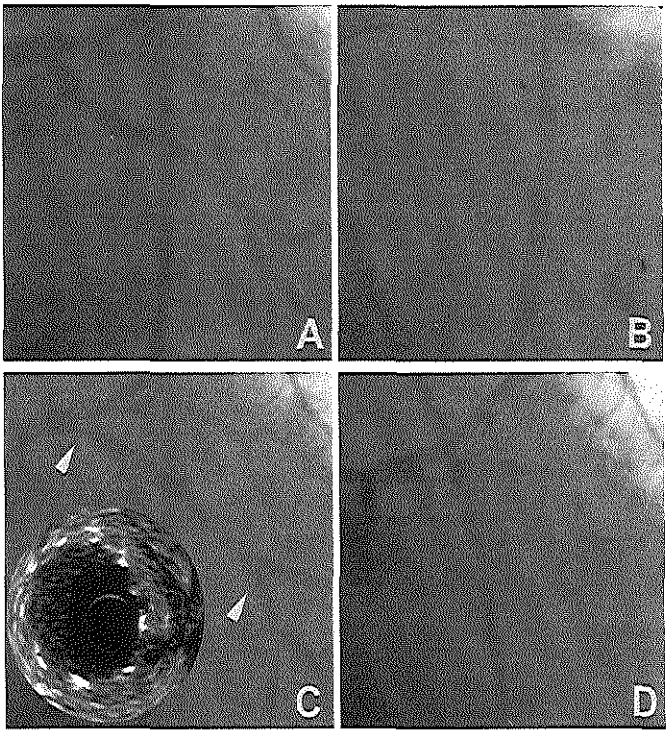

Figure 1. Patient 1. A, Preprocedure angiography shows a significant lesion in the mid-third of left circumflex artery. B, Radioactive source placed in treated site. C, Postprocedure angiography and IVUS images show an optimal result (arrowheads). D, At 2 months, the proximal part of stent appeared occluded.

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.

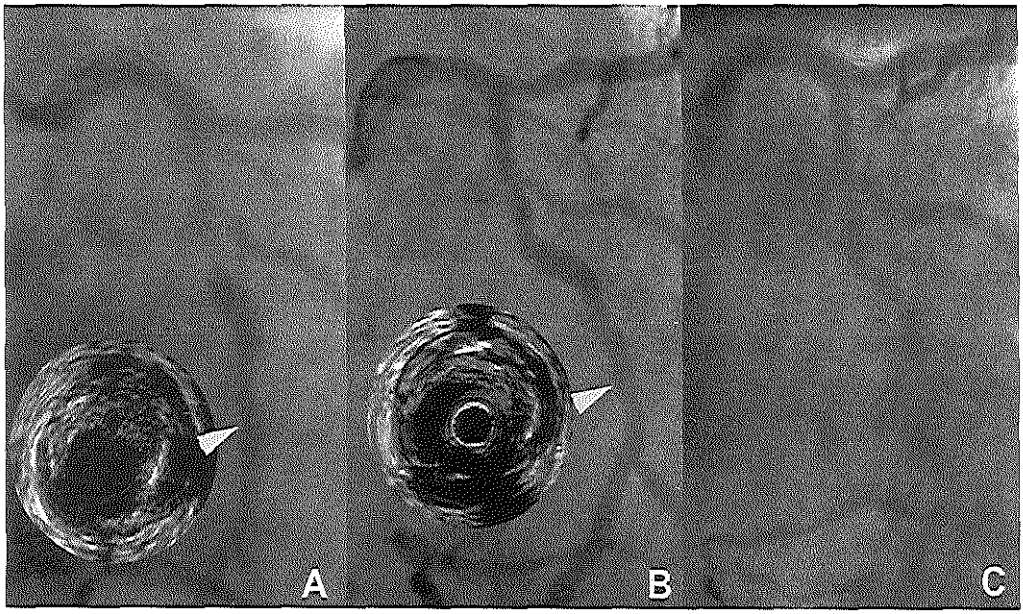

Figure 2. Patient 3. A, Postprocedure coronary dissection, demonstrated both on angiography and IVUS, did not compromise flow in treated area (arrowhead). B, This dissection persisted unhealed at 6-month control (arrowhead). C, At 15 months, irradiated segment appeared occluded.

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Chapter 14

Outcome from balloon induced coronary artery dissection after intracoronary beta radiation.

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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.

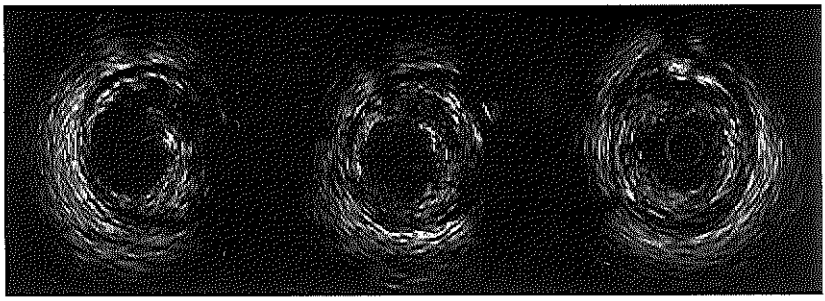

Figure 1 Intravascular ultrasound images (left and centre) showing a double lumen between 12 and 3 o'clock postintervention. The right image shows the same lesion at six month follow up with the unhealed false lumen seen between 11 and 2 o'clock.

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.

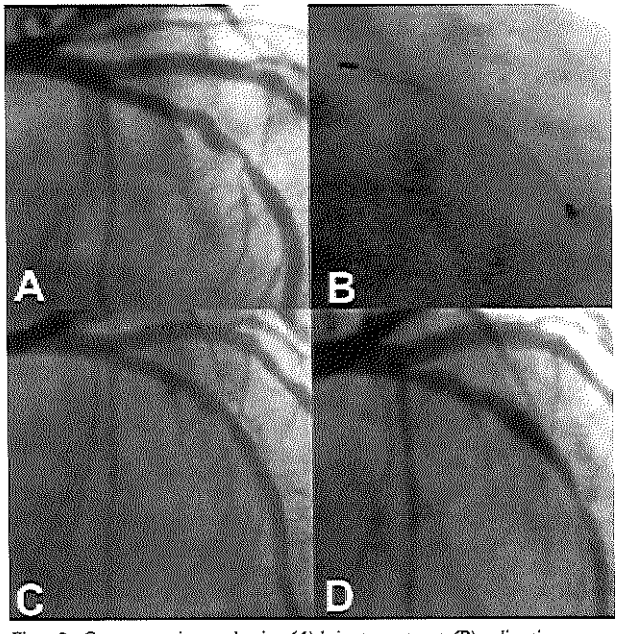

Figure 2 Coronary angiogram showing: (A) lesion pretreatment; (B) radioactive source in situ; (C) postintervention; and (D) the same lesion at six month follow up. Note the presence of an edge effect and absence of angiographic dissection at six month follow up.

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

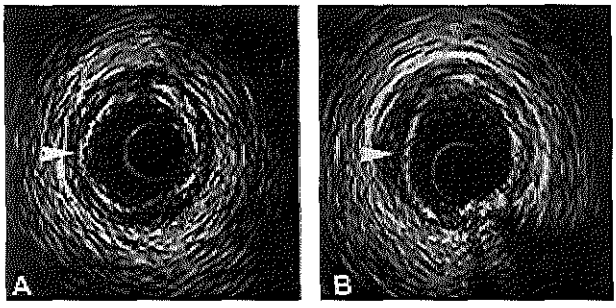

Figure 3 This IVUS image correlates with the angiogram in fig 2. The arrowheads show the presence of an intact lumen (A) and an unhealed flap (B), corresponding to the same area.

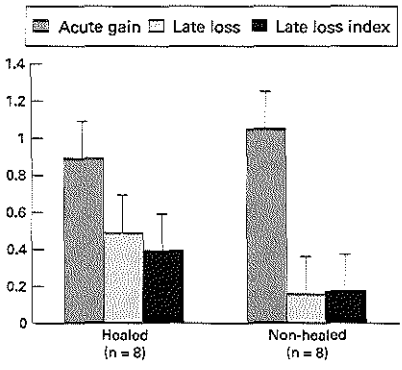

Figure 4 QCA analysis of healed versus non-healed dissection (p = NS).

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.[23] 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 15

The black hole: echo-lucent tissue observed following intracoronary radiation.

Submitted.

The black hole: echo-lucent tissue observed following intracoronary radiation

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ABSTRACT

Background Recent trials in humans have given us insight into some of the consequences of intracoronary radiation. We describe a new observation noted on intravascular ultrasound (IVUS): that of intraluminal echo-lucent tissue, dubbed the 'black hole', noted at 6-month follow-up.

Methods and Results We analyzed 128 consecutive patients enrolled in brachytherapy protocols. The control group (C) consisted of individuals who underwent PTCA with (n = 48) and without (n = 22) stent implantation. Radiation groups included those who underwent low activity (LA) (n = 18), high activity (HA) (n = 26) and cold – end (CE) (n = 18) radioactive stenting. The Novoste Betacath (n = 39) and Guidant (n = 27) catheter-based radiation systems were also employed. At 6 – month follow – up echo-lucent tissue was identified in a total of 28 cases (22%). Angiographic restenosis occurred in 17 cases (61%). Of those lesions with restenosis echo-lucent tissue comprised 50% of the neo-intimal hyperplasia. No echo-lucent tissue was seen in the control group or in the LA group. HA and CE radioactive stents were most commonly associated with echo-lucent tissue (incidence 35% and 39% respectively). All occurred at the proximal or distal edges of radiation. Echo-lucent tissue was seen in all groups treated with catheter-based radiation with and without stenting. Atherectomy was performed on 4 lesions. Pathology demonstrated smooth muscle cells scattered in extracellular matrix containing abundant proteoglycans and an absence of elastin and mature collagen.

Conclusions This paper is the first to describe atherectomy samples extracted from humans after radioactive stent implantation. Also it is the first to link the IVUS finding of echolucency noted after intracoronary radiation with tissue rich in proteoglycans while poor in mature collagen and elastin

CONDENSED ABSTRACT

Using IVUS we describe an echo-lucent 'black hole' following intracoronary radiation. Radiation groups (n=128) included those who underwent radioactive stenting and catheter-based radiation. In total 28 'black holes' (22%) were identified (radioactive stents (>6.0μCi) =37%, catheter-based radiation =17%). Angiographic restenosis was a feature in 61% of these cases. Of those lesions with restenosis echo-lucent tissue was on average responsible for 50% of NIH. Atherectomy was performed on 4 lesions. Pathology demonstrated smooth muscle cells scattered in extracellular matrix containing abundant proteoglycans and an absence of elastin and mature collagen.

Key words: ultrasonics, radiation , proteoglycan.

ABBREVIATIONS

IVUS - intravascular ultrasound
μCi – microCurie
NIH – neointimal hyperplasia
SMC – smooth muscle cell

Intracoronary radiation, a therapeutic modality aimed at decreasing restenosis, has been investigated in both animals and humans for several years. With the advent of human trials we have started to understand the consequences of this treatment. These include non - healing dissection[1], late occlusion[2] and positive remodeling[3]. We describe a further new finding: an echo-lucent area within the lumen of the coronary artery, noted using intravascular ultrasound (IVUS). This phenomenon has been dubbed the 'black hole'. We describe the finding in terms of IVUS characteristics and present data on its incidence in various subgroups treated conventionally and with radiation. Finally we describe the pathological findings of this entity.

METHODS

We analyzed 128 consecutive patients enrolled in brachytherapy protocols, who had completed 6 - month follow-up that included angiography with IVUS. These protocols included individuals who had undergone catheter – based radiation using the ^{90}Sr / ^{90}Y Betacath™ (Novoste, Norcross, Ga) and ^{32}P Guidant (Santa Clara, CA) systems. The radioactive stent group comprised those who received 0.75 – 1.5μCi (n = 18), 6.0 – 12.0μCi (n = 26) and 'cold – end' (n = 18) stents (Isostent™ Inc., San Carlos, CA, USA). The control group included individuals who underwent PTCA with (n=48) and without stent implantation (n=22).

Catheter – based radiation

The Novoste Betacath and the ^{32}P Guidant β-radiation systems have been described in detail elsewhere [3,4]. We followed certain steps to ensure the correct identification and analysis of the irradiated segment post intervention and at 6 – month follow - up. First, an angiogram was performed after positioning the delivery catheter and the relationship between anatomical landmarks and the two gold markers were 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 motorized IVUS pullback, all side branches were counted and the guiding landmark was identified. The correct selection of the marker was confirmed by visualizing the position of the IVUS probe during a contrast injection. At follow-up, we selected the same region of interest and compared it with that after treatment.

Radioactive stent

The properties of low (0.75 – 1.5μCi) and higher activity (6.0 – 12.0μCi) radioactive stents and procedural characteristics specific to their implantation have been described elsewhere[5]. All stents were implanted with a stent to artery ratio of 1.1:1. 'Cold - end' stents were 27.3mm in length and available in diameters of 3.0 & 3.5 mm. The distal and proximal 5.7mm of the stent was non-radioactive, whereas the central 15.9mm had an activity of 3.0-24.0 μCi (see Figure 1).

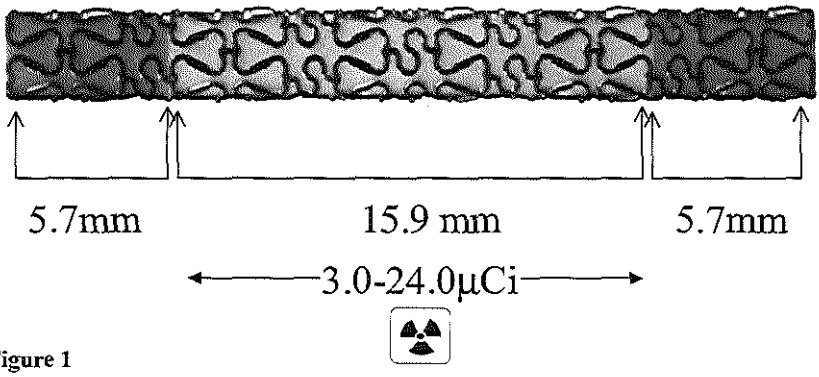

Figure 1
Cold-end stent with central radioactive segment and proximal and distal non-radioactive segments

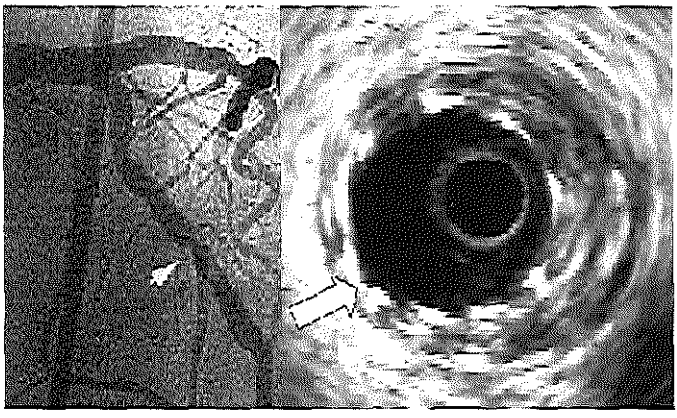

Figure 2
Left coronary angiogram performed at 6-month follow-up. Proximal in-stent restenosis is seen in a 6-12μCi stent implanted in the circumflex artery (left frame).
IVUS performed at 6 month follow-up demonstrating homogeneous black tissue from 6 to 1 o'clock (right frame).

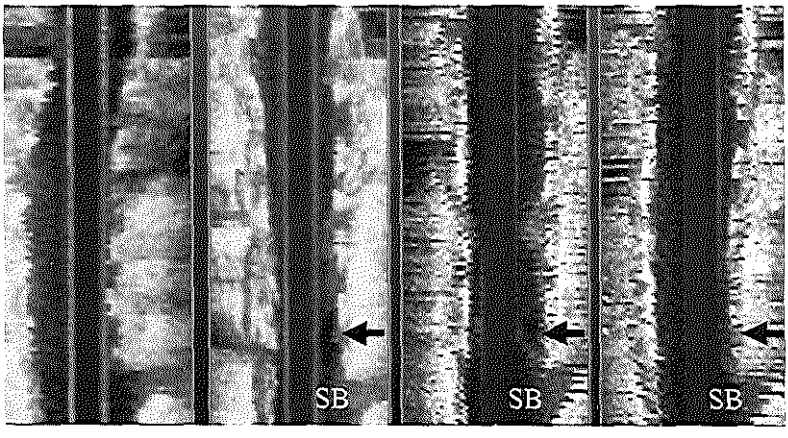

Figure 3
a. Baseline longitudinal IVUS reconstruction of freshly implanted stent.
b. Longitudinal reconstruction of the same transverse IVUS image seen in Fig 2. This

IVUS Acquisition

We used a mechanical 30MHz IVUS system (ClearView, CVIS, Sunnyvale, CA). Motorized pullback was performed at 0.5mm/sec. We examined the entire segment subjected to radiation, plus the associated 10mm proximal and distal edges. For radioactive stents this included 10mm proximal and distal to the final stent strut. Images were stored on S-VHS tape for later analysis. Findings were verified by 3 independent observers, who were blinded to whether images were from control or radiation cases.

IVUS definition of echo-lucent tissue

Lesions with the echo-lucent tissue had the following characteristics: a homogeneous black appearance without backscatter. Images with ring-down or other artefacts were excluded as were intraluminal echodense structures with associated attenuation. Exclusion of other causes of relative echolucency such as contrast[6], thrombus[7] or a lipid lake[8] was performed. Lesions were discrete and readily distinguishable from conventional neointimal hyperplasia (Fig. 2, 3). After radioactive stenting all lesions were observed adjacent to stent struts.

Definitions

The following dimensions were measured in each group: total vessel area (TVA), lumen area (LA), the area of echo-lucent tissue and the percentage of neointimal hyperplasia (NIH) caused by the echo-lucent tissue in the cross-section of greatest stensosis. Restenosis at 6–month follow-up was defined using standard angiographic criteria after off-line quantitative coronary angiography (diameter stenosis > 50%).

Medication

All patients received clopidogrel for between 1 month (conventional stenting) and 3-6 months (stenting plus catheter – based radiation or radioactive stenting), plus life-long aspirin.

Immunohistochemistry

For immunostaining, sections were preincubated with 0.3% hydrogen peroxide and Protein Block Serum-Free (X0909, Dako Corp, CA). A mouse monoclonal antibody against α-smooth muscle actin (1:5000 dilution, Dako) was used to identify smooth muscle cells. Polyclonal antibodies against biglycan (LF-51) and decorin (LF-122) were used for identification of proteoglycans (antibodies kindly provided as a gift from Larry Fisher, NIH, Bethesda, Maryland). Before incubating with proteoglycan antibodies, sections were first incubated with 1U/L chrondroitinase ABC (code #100332, Seikagaku Corp., Tokyo, Japan) for 15 minutes at 37°C to detach glycosaminoglycan side chains from the protein core; this procedure intensifies staining[9]. All primary antibodies were incubated overnight in a humidified chamber at 4°C. After rinsing in PBS, the primary antibody was labeled by a biotinylated link antibody directed against mouse using a

peroxidase based LSAB kit (Dako). Positive staining (brown reaction product) was visualized with a diaminobenzidine (Dako). After immunostaining, the sections were counterstained with Gill's hematoxylin, dehydrated in a graded series of alcohols, rinsed in xylene and mounted in Permount (Fisher Scientific).

RESULTS

At 6 – month follow - up 28 discrete areas of echo-lucent tissue ('black hole') (22%) were identified. No echo-lucent tissue was seen in the control group or in the low activity radioactive stent group. Angiographic restenosis was present in 61% of cases where echo-lucent tissue was present. Of those lesions with restenosis, echo-lucent tissue was on average responsible for 50% of neointimal hyperplasia. More severe stenosis was more frequently observed in the 6.0-12.0μCi and cold-end radioactive stent groups (mean stenosis = 63.1% ± 24.1) compared with catheter-based techniques (mean stenosis = 37.2% ± 20.5), p=0.005. Mean length of the echo-lucent tissue was 4.0mm ± 1.6mm (range 2-8mm).

Radioactive stent

Higher activity and cold-end radioactive stents were most commonly associated with echo-lucent tissue (Table 1). All occurred at the proximal and distal margins of radiation within the stent or at the stent edges. By definition this fall-off in radiation occurred in the final 1-2mm of 6.0-12.0μCi stents and in-stent for cold-end stents. Bilateral echo-lucent tissue was seen in 5 out of 7 cases that presented with restenosis 6 months after cold-end stent implantation. In four of theses cases the proximal edge was more severely affected.

Catheter-based

Echo-lucent tissue was seen in all groups treated with catheter-based radiation with and without stenting. These tended to be smaller lesions than those seen in the radioactive stent group (Table 1). After catheter-based radiation only one of the echo-lucent tissues described involved geographical miss (area of injury associated with a fall-off in radiation)[10].

Pathology features

Atherectomy was performed on 4 individuals (AtheroCath - Bantam™, DVI, Guidant, Temecula, CA, USA). Macroscopic assessment of the tissue samples showed two types of tissue: dark yellow, often containing pieces of stent strut and white more fibrotic appearing tissue (Fig. 4A). Microscopy revealed tissue containing smooth muscle cells in abundant extracellular matrix (myxoid change) with two distinct regions (Fig.4B, C) and containing abundant proteoglycans (Fig.4D). Region 1 (Fig 4E) was more cellular in nature, contained collagen and elastin (Fig 4C), and was not distinguishable from

	Location	% BHA of NIH	Restenosis (QCA)
Radioactive stent			
6-12 μCi (n=26)			
1	P edge	96	Y
2	P edge	100	Y
3	D edge	56	N
4	P edge	64	Y
5	P edge	100	Y
6	P edge	48	Y
7	D edge	71	Y
8	P edge	52	N
9	D edge	68	N
cold-end (n=18)			
10	P In stent*	100	Y
11	D In stent*	42	N
12	P In stent*	50	N
13	D In stent*	26	Y
14	P In stent*	48	Y
15	D In stent*	38	N
16	P In stent*	51	Y
Guidant CBS (n=16)			
17	In-stent	26	Y
18	In-stent	34	N
19	Out of stent	45	Y
Betacath CBS (n=18)			
20	In stent	48	N
21	In-stent	26	Y
22	In-stent	26	N
23	In-stent	56	N
Guidant: no stent (n=11)		%BHA of NIH	Restenosis
24		34	Y
25		90	N
Betacath: no stent (n=21)			
26		27	Y
27		16	Y
28		18	Y

CBS=catheter-based radiation plus stenting. P=proximal. D=distal. * at junction of radioactive and non radioactive segment of the stent. NIH=neointimal hyperplasia.

%BHA of NIH = % of NIH caused by echo-lucent tissue.

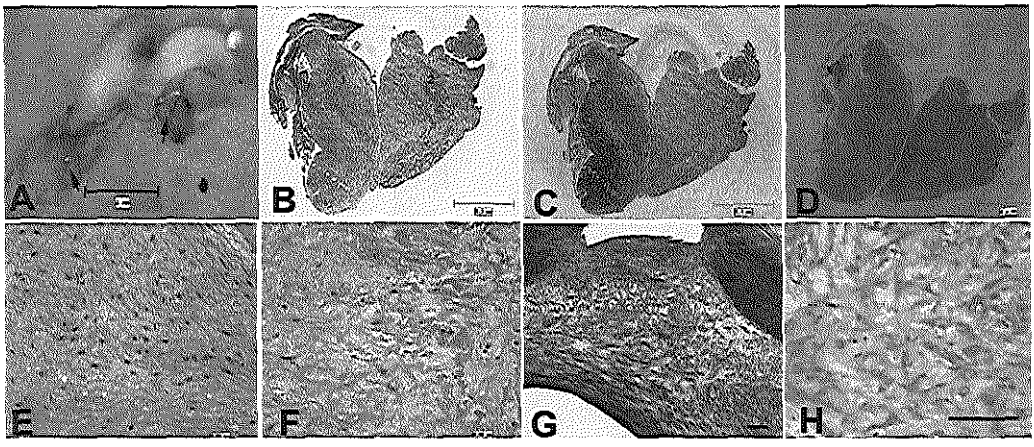

Figure 4

Fig. 4A Gross macroscopy of atherectomy specimen, showing that darker more yellow tissue overlies stent strut remnants (arrow), with a cover that is white in appearance.

Fig. 4B. Hematoxylin-Eosin stain showing two distinct regions; region 1 being more cellular than region 2.

Fig. 4C. Elastin stain, showing that region 1 consists of a more elastin and collagen rich tissue as compared to region 2.

Fig. 4D. Alcian Blue stain showing that the extracellular matrix contains large amounts of proteoglycans, most of which is hyaluronic acid (differential stain, not shown).

Fig. 4E. Detail of region 1, showing tissue that is similar in appearance to normal restenotic tissue.

Fig. 4F. Detail of region 2, showing sparse and pyknotic cells.

Fig 4G (Movat stain) and Fig 4H (H&E). Porcine model with 3μCi stent at 6 months. Extensive NIH consisting of SMCs in a proteoglycan matrix.

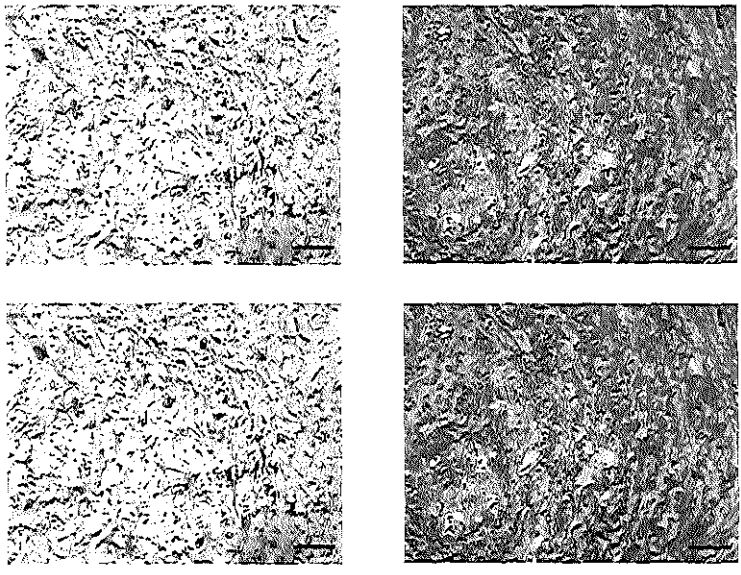

Figure 5

Fig 5A. Immunoperoxidase stained section showing a-actin positive smooth muscle cells.

Fig 5B. Immunoperoxidase stained section showing strong matrix positivity for biglycan.

normal restenotic tissue. Region 2 (Fig 4F) was more sparsely populated showing pyknotic nuclei, with some of the extracellular matrix having a coagulated or dense appearance (fibrinoid change). The latter was thought to be tissue constituting the echo-lucent tissue.

The area of the myxoid, proteoglycan rich matrix was thought to constitute the black hole. Three of the four biopsies were stained for a-actin (Fig 5A) to confirm presence of smooth muscle cells and for biglycan (Fig 5B), which is the dominant proteoglycan in restenotic lesions[9]. All three biopsies were strongly postive for biglycan and one biopsy stained for decorin was weakly positive.

DISCUSSION

Echo-lucent tissue ('black hole') noted at 6 – month follow-up was uniquely associated with intracoronary radiation. More common after radioactive stent (>6.0μCi) implantation, it was frequently located adjacent to the stent struts in areas of radiation fall-off, where it was associated with greater restenosis than the catheter-based techniques.

Echo-lucent tissue may be a dominant cause of restenosis as seen in 4 patients (1,2,5 and 10). Overall it appeared to contribute to approximately 50% of the restenotic burden associated with NIH seen at 6-month follow-up. The lesion may be missed on IVUS examination due to its echolucency, caused by tissue rich in proteoglycans and poor in mature collagen and elastin.

What is unclear is the cause of such lesions. Certainly irradiation is associated with proteoglycan accumulation in various tissues[11,12]. Hehrlein has noted that the increase in neointimal volume in arteries treated with external beam radiation (EBR) was predominantly due to enhanced extracellular matrix production. This study suggested that the accumulation of extracellular matrix after stent deployment was augmented by external beam radiation and that excessive matrix formation was a determinant of failure of radiation therapy to prevent restenosis. The atherectomy samples of the current paper reflect changes seen in Carter's porcine model[12] with radioactive stents (Fig 2G & H). Carter has reported myxoid changes in low, intermediate and high activity stents (30%, 60% and 37% respectively) while no myxoid change was seen in control stents (personal communication, 2000). This would indicate that the echo-lucent tissue is a general response to irradiation of damaged vascular tissue.

The matrix seen is rich in biglycan proteoglycan; biglycan secretion by smooth muscle cells in culture has been shown to be controlled by TGF-β[13,14]. Therefore it is likely that radiation may induce greater TGF-β production that results in excessive biglycan production and formation of echo-lucent tissue on IVUS.

O'Brien[15] and colleagues suggest that biglycan may bind apoE and apoB in atherosclerotic intima. They also raise the possibility that apoE may act as a bridging molecule that traps apoA-I-containing HDL in atherosclerotic intima. Taken together these findings

are consistent with the hypothesis that biglycan may contribute to the pathogenesis of atherosclerosis by trapping lipoproteins in the artery wall.
Atherectomy samples taken at points where echo-lucent tissue is seen on IVUS shows aberrant nuclear morphology, suggesting ongoing cell death. This process continues to take place long after stent radioactivity has decreased to background levels. This indicates that radiation indeed has long-term effects. The presence of fibrinoid change may also be indicative of delayed healing, as was also seen in Carter's report.
With time the echo-lucent tissue becomes more discernible on IVUS due to its echodense cap (Figure 3). This cap is also seen on pathology showing collagen and elastin - rich tissue. This may be in keeping with a phenotypic change in the SMCs, allowing them to produce collagen and elastin - rich matrix typical of mature NIH with a lack of proteoglycan.

Conclusion

This paper is the first to describe atherectomy samples extracted from humans after radioactive stent implantation. Also it is the first to link the IVUS finding of echolucency noted after intracoronary radiation in various modalities with tissue rich in proteoglycans while poor in mature collagen and elastin

Limitations

Atherectomy was only performed in 4 patients and the findings described here will need to be substantiated with greater numbers. The issue of radioaction dosimetry is complex and fundamental, however is beyond the scope of this report.

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One of the contributions of the radiation era that will persist long after the modality has been surpassed is the ability to clinically appraise the effects of any intervention, using the tools of the modern cath-lab. In this era a great contribution to the understanding of this new technology was made through the application of individuals working at the Thoraxcenter, Rotterdam.

Summery and Conclusions

This thesis assesses issues central to intracoronary radiation and stent implantation.

Part I addresses factors that affect the angiographic restenosis rate after stent implantation. The best predictors of restenosis were post-procedural stent diameter stenosis and vessel size. A simple reference chart was devised that defines the probability of angiographic restenosis at 6 months.

Part II considers methodological issues important to the assessment of lesions that have undergone intracoronary radiation. These include relocation of the minimum lumen diameter (MLD) and geographical miss. Both issues were applicable to radioactive stents and catheter-based radiation. Geographical miss was germane to all radioactive stenting due to the configuration of the balloon on the stent, which left injured areas at the stent edges insufficiently treated with radiation. After catheter-based radiation late loss was noted to be significantly greater in edges that had geographic miss, than in uninjured edges. Similarly the restenosis rate was greater in these edges.
Relocation of the MLD was more frequently observed in the catheter-based group. Since vessel enlargement frequently occurs at the site of the previous target lesion, the MLD may be relocated at follow-up to 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 in the understanding of the mechanism of action of this treatment modality.

In **Part III** we discuss the evolution of radioactive stents through their initial human trials to later studies describing different stent configurations. Low activity stents did not demonstrate a significant improvement over placebo – a fact verified by clinical, QCA and IVUS criteria. By increasing the activity of the stent (6.0-12.0 μCi), neointimal hyperplasia was decreased in-stent at 6-month follow-up, however probably due to a combination of sub optimal radiation and injury (geographical miss) there was evidence of a new entity described as the edge – effect witnessed at the stent edges in 50% of cases. This interesting finding was subsequently also described after catheter – based radiation, both with and without stenting. The implementation of cold-end radioactive

stents regrettably did not prevent the edge - effect. Instead of restenosis occurring outside of the stent at the edges of radiation it occurred in-stent at the edges of radiation. Similarly the implementation of hot-end radioactive stents was unsuccessful.
Although inhibition of neointimal hyperplasia was successful in-stent at 6 months at the activity level 6.0-12.0 μCi, this was not the case at 1 year. Here there was evidence of a late 'catch-up', which was unprecedented after conventional stenting. Consequently there was an excessive amount of patients who went onto late revascularization.

Part IV explores aspects common to both radioactive stenting and catheter – based stenting and radiation. Using 3- dimensional IVUS, positive geometric remodeling was described behind the stent after catheter – based radiation, but not after radioactive stenting at 0.75 – 12.0μCi. It remains unknown whether this increase in plaque became a nidus for subsequent restenosis. Equally one may hypothesize that this positive remodeling may leave the stent vulnerable to late thrombosis due to stent malapposition.
The mechanism of edge restenosis was also described – in conventional angioplasty there is almost always some degree of edge renarrowing after stenting. This rarely is significant and generally accounts for 10-15% of late lumen loss at the stent edges. Mechanistically this is due to negative remodeling at the stent edges with consequently a late lumen loss. In contrast the edge effect after radioactive stenting was due to a minor degree of negative remodeling and a major increase in plaque.

In **Part V** we discuss complications witnessed thusfar. The entity of late thrombotic occlusion is extremely important. It occurs more frequently than after conventional balloon angioplasty or stent implantation. Several mechanisms are hypothesized as being involved in the mechanism: first a delay in stent endothelialization may occur after brachytherapy. Furthermore balloon-induced coronary artery dissection may not be healed during the follow-up period as witnessed in a substantial proportion of patients treated with balloon angioplasty and catheter-based radiation. Finally as discussed in previous chapters vascular enlargement may induce late stent malapposition which is a well-known substrate for stent thrombosis.
Hypoechoic tissue, dubbed the 'black hole' was first described at 6-month follow-up after radioactive stenting. Such tissue was difficult to diagnose initially due to its echolucency. We were able to perform the first atherectomy procedures in humans. Theses demonstrated that the echolucent tissue was in fact predominantly proteoglycan with a paucity of collagenous tissue. Concern has been raised that such tissue may be the precursor of atherogenic tissue, explaining the late lumen loss (>6 month) in patients that have undergone radioactive stenting.

Future directions of this treatment modality are uncertain. Certainly radioactive stents do not appear to have a clinical application in their current format. Efficacy in preventing in-stent re-restenosis has been proven in 5 trials involving catheter-based gamma and beta radiation. This may be a niche for this treatment, pending the introduction of a more efficacious therapy.

Samenvatting en Conclusies

Dit proefschrift beschrijft onderwerpen met betrekking tot intracoronaire bestraling en stent implantatie.

Deel 1 beschrijft faktoren die de angiografische restenose percentage na stent implantatie beïnvloeden. De beste voorspellers van restenose waren stent lengte en in-stent minimale lumen oppervlakte na de index interventie. Een simpele referentietabel werd gemaakt, welke de waarschijnlijkheid van angiografische restenose na 6 maanden omschrijft.

Deel II beschouwt methodologische kwesties, welke belangrijk zijn voor de beoordeling van lesies, die een intracoronaire bestraling hebben ondergaan. Deze omvatten de relokatie van het minimale lumen diameter (MLD) en geografische mis. Beide zijn zowel van toepassing op radioactieve stents als catheter-gebaseerde bestraling. Geografische mis was obligaat bij alle radioactieve stent implantaties ten gevolge van de configuratie van de ballon, waarmee de stent geïmplanteerd werd, welke beschadigde gebieden aan de stent randen veroorzaaktten welke onvoldoende behandeld werd met bestraling. Na de catheter-gebaseerde bestraling bleek het late lumen verlies significant groter te zijn in randen met geografische mis, dan in onbeschadigde randen. Het restenose percentage was vergelijkbaar ook groter in deze randen.
Relokatie van de MLD werd meer frequent geobserveerd in de catheter-gebaseerde groep. Aangezien vergroting van het bloedvat vaker optreedt op de plaats van de vorige doellesie, kan de MLD bij controle verplaatst zijn naar een ander coronair subsegment. Hierdoor kunnen verschillende resultaten verkregen worden, afhankelijk welk gebied men in beschouwing nam voor de analyse. De definitie en indentificatie van het doel segment, bestraalde segment, beschadigde segment en bloedvatsegment kan nuttig zijn in het begrijpen van het mechanisme van werking van deze behandelingsmodaliteit.

In **Deel III** bespreken we de evolutie van radioactieve stents vanaf het eerste gebruik in patiëntenstudies tot latere studies met verschillende stent configuraties. Lage activiteit stents toonden geen significante verbetering ten opzichte van placebo – een feit bevestigt door klinische, QCA en IVUS criteria. Door de activiteit van de stent te verhogen (6-12 μCi), werd de in-stent neointimale hyperplasie verminderd bij de 6-maands controle, echter waarschijnlijk door een combinatie van suboptimale bestraling en beschadiging

(geografische mis) was er een nieuw fenomeen ontstaan, welke werd omschreven als randen-effect, welke in 50% van de casussen werd waargenomen aan de randen van de stent. Deze interessante bevinding werd vervolgens ook beschreven na catheter-gebaseerde bestraling, zowel met als zonder stent implantatie. De implantatie van Cold-Ends radioactieve stents konden helaas niet het randen effect voorkomen. In plaats van restenose aan de buitenkant van de stent bij de randen van de bestraling, kwam de restenose in de stent aan de randen van de bestraling. De implantatie van Hot-Ends stents waren vergelijkbaar onsuccesvol. Alhoewel de inhibitie van neointimale hyperplasie in de stent succesvol was 6 maanden na implantatie van een stent met een activiteit van 6-12 μCi, was dit niet het geval na 1 jaar. Er bleek sprake van een late "inhaalslag", welke na conventionele stent implantatie niet gezien wordt. Daardoor was een meer dan verwachte aantal patiënten, welke een late revascularisatie ondergingen.

Deel IV onderzocht aspekten gemeenschappelijk voor zowel radioactieve stents als stent implantatie gevolgd door catheter-gebaseerde bestraling. Met behulp van 3-dimensionele IVUS, werd positieve remodelering beschreven achter de stent na een catheter-gebaseerde bestraling, maar niet na implantatie van een radioactieve stent met een activiteit van 0.75-12 μCi. Het is onduidelijk of de geziene toename in plak een oorzaak was voor de dooropvolgende restenose. Tevens kan men veronderstellen dat deze positieve remodelering de stent vatbaar kan maken voor late thrombose ten gevolge van stent malappositie.
Het mechanisme van randen restenose was ook eerder beschreven – in conventionele angioplastiek was er vrijwel altijd enige vernauwing aan de randen na een stent implantatie. Dit is zelden significant en speelt een rol voor 10-15% van het late lumen verlies aan de stent randen. Mechanism gezien is dit ten gevolge van negatieve remodelering aan de randen met vervolgens een late lumen verlies. In contrast hiermee was het randen effect na de implantatie van radioactieve stents, welke ten gevolge van een kleine mate van negatieve remodelering is en een grote toename van de plak.

In **Deel V** worden de complicaties, welke tot nu toe geobserveerd zijn, besproken. Het verschijnsel van late thrombotische occlusie is extreem belangrijk. Het treedt vaker op dan na conventionele ballonangioplastiek of stent implantatie. Verschillende mechanisme worden verondersteld betrokken te zijn in het mechanisme: Ten eerste een vertraging in de stent endothelialisatie kan optreden na brachytherapie. Bovendien kunnen de door de ballon veroorzaakte cornaire dissecties niet goed genezen gedurende de controle periode. Dit is bij een substantiële portie van de patiënten waargenomen, welke behandeld zijn met een ballonangioplastiek gevolgd door een catheter-gebaseerde bestraling. Ten slotte, zoals in de vorige hoofdstukken is besproken, kan vatvergroting late stent maloppositie veroorzaken, welke een reeds bekende substraat is voor stent thrombose.

Hypoechogene weefsel, genaamd het "zwarte gat" werd als eerste beschreven bij de 6-maands controle na een radioactieve stentimplantatie. Zulk weefsel was in het begin moeilijk te diagnostiseren door het echolucente karakter van dit weefsel. Wij hebben voor het eerst dit weefsel vanuit coronairen van patiënten verkregen met behulp van atherectomie. Het verkregen materiaal toonde aan dat dit echolucente weefsel voornamelijk bestond uit proteoglycanen met een gebrek aan collageen weefsel. Er is bezorgdheid ontstaan dat dit weefsel de voorloper zijn kunnen zijn van atherogeen weefsel, welke het late lumen verlies (> 6 maanden) in patiënten na een radioactieve stent implantatie zou verklaren.

Toekomst verwachtigen van deze behandelingsmodaliteit blijven onzeker. Zeker radioactieve stent lijken geen klinische toepassing te hebben in hun huidige vorm. De effectiviteit in het voorkomen van in-stent re-restenose is aangetoond in 5 studies verricht met catheter-gebaseerde gamma en beta-bestraling. Dit zou de enige toepassing kunnen zijn voor deze behandeling, afhankelijk van de introductie van een meer effectieve behandeling.

Curriculum Vitae

Patrick Kay was born in London, England on December 19, 1963. He received his undergraduate medical training at The University of Otago, Dunedin, New Zealand between 1985 and 1989. He commenced advanced training in cardiology in 1994 and obtained his fellowship in 1997. During this period he worked in the catheterization laboratory of Dunedin Hospital as well as performing general cardiology duties. In 1998 he was appointed as a clinical and research fellow at the catheterization laboratory of the Thoraxcenter, Rotterdam, under the supervision of Professor Patrick W Serruys. He returned to New Zealand in June 2000 and has been working as an interventional cardiologist at Dunedin Hospital, New Zealand.