The New England Journal of Medicine

ENDOLUMINAL BETA-RADIATION THERAPY FOR THE PREVENTION OF CORONARY RESTENOSIS AFTER BALLOON ANGIOPLASTY

VITALI VERIN, M.D., YOURI POPOWSKI, M.D., BERNARD DE BRUYNE, M.D., DIETRICH BAUMGART, M.D., WOLFGANG SAUERWEIN, M.D., MARKUS LINS, M.D., GYÖRGY KOVACS, M.D., MARTYN THOMAS, M.D., FRANCIS CALMAN, M.D., CLEMENS DISCO, M.SC., PATRICK W. SERRUYS, M.D., AND WILLIAM WIJNS, M.D., FOR THE DOSE-FINDING STUDY GROUP*

ABSTRACT

Background　Beta radiation is effective in reducing vascular neointimal proliferation in animals after injury caused by balloon angioplasty. However, the lowest dose that can prevent restenosis after coronary angioplasty has yet to be determined.

Methods　After successful balloon angioplasty of a previously untreated coronary stenosis, 181 patients were randomly assigned to receive 9, 12, 15, or 18 Gy of radiation delivered by a centered yttrium-90 source. Adjunctive stenting was required in 28 percent of the patients. The primary end point was the minimal luminal diameter six months after treatment, as a function of the delivered dose of radiation.

Results　At the time of follow-up coronary angiography, the mean minimal luminal diameter was 1.67 mm in the 9-Gy group, 1.76 mm in the 12-Gy group, 1.83 mm in the 15-Gy group, and 1.97 mm in the 18-Gy group (P=0.06 for the comparison of 9 Gy with 18 Gy), resulting in restenosis rates of 29 percent, 21 percent, 16 percent, and 15 percent, respectively (P=0.14 for the comparison of 9 Gy with 18 Gy). At that time, 86 percent of the patients had had no serious cardiac events. In 130 patients treated with balloon angioplasty without a stent, restenosis rates were 28 percent, 17 percent, 16 percent, and 4 percent, respectively (P=0.02 for the comparison of 9 Gy with 18 Gy). Among these patients, there was a dose-dependent enlargement of the lumen in 28 percent, 50 percent, 45 percent, and 74 percent of patients, respectively (P<0.001 for the comparison of 9 Gy with 18 Gy). The rate of repeated revascularization was 18 percent with 9 Gy and 6 percent with 18 Gy (P=0.26).

Conclusions　Intracoronary beta-radiation therapy produces a significant dose-dependent decrease in the rate of restenosis after angioplasty. An 18-Gy dose not only prevents the renarrowing of the lumen typically observed after successful balloon angioplasty, but actually induces luminal enlargement. (N Engl J Med 2001;344:243-9.)
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ARTERIAL renarrowing after angioplasty, or restenosis, occurs in 30 to 40 percent of patients and results from neointimal proliferation and constrictive remodeling of the injured artery.[1] A number of trials that took pharmacologic approaches to the prevention of restenosis have evaluated more than 20 candidate drugs, but the results so far have been disappointing.[2] Coronary stenting has led to a 30 to 50 percent decrease in the rate of restenosis, primarily by preventing the constrictive remodeling of the artery, but at the cost of an increase in neointimal proliferation.[3-5] Thus, a new technique for treatment that could prevent both neointimal hyperplasia and constrictive remodeling would be of great clinical benefit.

Experimental evaluation of beta and gamma radiation in animals has shown an inhibitory effect on neointimal proliferation as well as on constrictive remodeling.[6-9] Researchers applied a recently developed technique of treatment with endovascular beta radiation from an endoluminally centered, pure metallic yttrium-90 source.[10-13] In hypercholesterolemic rabbits, the delivery of a 9-Gy dose of radiation 1 mm below the surface of the tissue markedly inhibited neointimal hyperplasia.[7] However, in a study of safety and feasibility, the same dose used in 15 patients did not have a beneficial effect on restenosis.[14] We hypothesized

that higher doses of radiation were necessary, since the arterial wall in humans is thicker than that in rabbits. Thus, the primary objective of the present study was to determine the effect of 9, 12, 15, and 18 Gy of beta radiation at a tissue depth of 1 mm on the rate of restenosis after a first coronary angioplasty procedure. Secondary objectives were to evaluate the safety of the procedure and to assess the technical performance of the yttrium-90 system for intracoronary beta-radiation therapy.

METHODS

Study Design and Objectives

The study was designed as a prospective, randomized, multicenter, dose-finding trial. Between October 1997 and February 1999, 183 patients were enrolled in the trial at five European centers and randomly assigned by computer, over the telephone, to receive 9 Gy, 12 Gy, 15 Gy, or 18 Gy of radiation. Patients more than 50 years old who had angina pectoris or silent ischemia were enrolled if they were suitable candidates for the dilation of a previously untreated native coronary stenosis. For the enrollment criteria to be met, the diameter of the vessel had to be between 2.5 and 4.0 mm, and the stenosis had to be shorter than 15 mm. Patients also had to be eligible for angiographic and clinical follow-up at six months. Patients were deemed ineligible if they had had a recent myocardial infarction with abnormal base-line levels of cardiac enzymes, had a life expectancy of less than six months, were pregnant, had had cancer within the previous five years, had previously received mediastinal irradiation, or were currently participating in another trial. Written informed consent was obtained from all participating patients.

Irradiation was performed after the completion of the balloon angioplasty. The physicians performing the angioplasty were discouraged from using multiple balloon inflations and balloon displacements, so that the length of the vessel segment injured would be limited. Beta irradiation was not performed if there was an urgent need for stent implantation, if glycoprotein IIb/IIIa–receptor blockers had been administered, or if there was abrupt vessel closure that remained unresolved. Complementary stent implantation was allowed in cases in which there were extensive dissections, symptomatic reductions in blood flow, or both. Initially, ticlopidine and aspirin were given for two months after the procedure; starting in November 1998, the duration of treatment with these drugs was extended to seven months.

The primary end point of the study was the minimal luminal diameter at six months within the vessel treated by balloon angioplasty, as measured by quantitative coronary angiography, as a function of the delivered dose of beta radiation. The secondary end points were the incidences in the entire study population of the following serious cardiac events: death, myocardial infarction, percutaneous intervention in the target vessel (defined as any additional intervention within the treated vessel), and coronary-artery bypass grafting. Myocardial infarction was diagnosed when two of the following occurred: chest discomfort lasting at least 30 minutes, the development of abnormal new Q waves, and an increase in the level of creatine kinase or MB isoenzymes to more than twice the upper limit of normal.

Procedure for Radiation Therapy

The system used for intraarterial beta-radiation therapy has been described previously[10-13]; it consists of the yttrium-90 beta-ray–emitting source (half-life, 64 hours; maximal energy, 2.284 MeV), a centering balloon, and an automated delivery device. The radioactive source consists of a 29-mm-long, flexible coil, secured at the end of a 0.035-cm thrust wire between distal and proximal 6-mm-long, radiopaque tungsten markers, which allow precise localization of the source under fluoroscopy. The effective length of the vessel segment being irradiated (the 90 percent isodose line) is 24 mm. The centering balloon, consisting of four interconnect-ed compartments, is designed to position the source wire centrally inside the coronary lumen, thereby contributing to a more homogeneous distribution of the dose of radiation along the vessel wall. Three radiopaque markers are located between the balloon compartments and allow the device to be positioned, with the use of fluoroscopy, at the exact site of the previous angioplasty. The centering balloon is inflated with 5 ml of carbon dioxide up to a maximal pressure of 4 atm. As compared with the use of contrast medium, the use of carbon dioxide permits faster inflation and deflation of the balloon and a shorter treatment time (because there is less attenuation of the radiation).[11,12]

The use of an automated delivery device ensured the safe storage of the source, its easy insertion and withdrawal, its accurate positioning, and the instantaneous calculation and delivery of the dose. At the end of each treatment, a printed report was automatically generated. After the completion of balloon angioplasty, the centering balloon, which had the same diameter as the angioplasty balloon, was positioned so that it would cover fully the site dilated by the angioplasty balloon. After the successful advancement and retrieval of a nonradioactive test wire, the yttrium-90 source was automatically advanced to the same site. This procedure was performed by a team composed of a cardiologist, an oncologist, and a medical physicist, who collaborated according to local practices and regulations. All teams applied the measures normally used in the interventional suite for protection from radiation.[14]

Angiographic Analysis

Coronary angiograms were obtained in multiple views after patients had received an intracoronary injection of nitrates. An independent core laboratory (Cardialysis, Rotterdam, the Netherlands), whose personnel were unaware of the dose of radiation associated with each angiogram, analyzed the angiograms quantitatively using edge-detection techniques.[15] Coronary luminal diameter and degree of stenosis (as a percentage of the diameter) were measured before dilation, at the end of the procedure, and during follow-up angiography six months later (or earlier if there were recurrent symptoms). Restenosis was defined as the presence of stenosis of more than 50 percent of the luminal diameter. The loss in luminal diameter was calculated as the difference between the luminal diameter measured immediately after the procedure and that measured at six months. The entire irradiated segment of the vessel (24 mm long) and the edges of that segment (5 to 6 mm on each side of the segment) were analyzed. The resulting segment (34 to 36 mm long) encompassed the initial site of stenosis, the 20-mm segment injured by the angioplasty device, the 30-mm area affected by the centering balloon, and the immediately adjacent proximal and distal segments of the vessel (each 2 to 3 mm long). This method of analysis has been used in previous trials of vascular brachytherapy.[15]

Statistical Analysis

For a study with a power ($1-\beta$) of 90 percent, a one-sided type I error (α) of 0.05, and an expected minimal luminal diameter at follow-up of 1.67 mm (that achieved in the Benestent II trial[5] among patients who underwent balloon angioplasty alone), with a standard deviation of 27.5 percent, we calculated that we had to enroll 34 patients in each group in order to detect a 20 percent improvement in the minimal luminal diameter at six months (2.00 vs. 1.67 mm). In order to account for an expected 30 percent rate of stent implantation, we increased the study population to 180 patients (45 in each of four groups).

For the comparison of binary variables, a Fisher's exact test for two groups was used, or the chi-square test was used when applicable. For the comparison of continuous variables, two-tailed Student's t-tests were used. The data are expressed as means ±SE.

RESULTS

Patient Population

Of 183 patients who underwent randomization, 181 (mean age, 64±0.6 years; 74 percent male) received

the prescribed doses of beta radiation: 45 received 9 Gy, 45 received 12 Gy, 46 received 15 Gy, and 45 received 18 Gy. Radiation therapy was not administered in two cases (in one due to a technical failure, and in one because the angioplasty was unsuccessful). There were no significant differences among the dose groups in terms of the demographic characteristics of the patients or the characteristics of the lesions (Table 1). Balloon angioplasty alone was performed in 130 patients (72 percent). Stent implantation following brachytherapy was required in 51 patients (in 47 percent of these patients because of residual stenosis of more than 50 percent of luminal diameter, and in the remainder because of major dissection).

Angiographic Results

The mean degree of stenosis before the angioplasty procedure, expressed as a percentage of the vessel diameter, was 65±1.5, 64±1.6, 66±1.3, and 65±1.7 in the 9-Gy, 12-Gy, 15-Gy, and 18-Gy groups, respectively. There were no significant differences among the groups in the mean degree of residual stenosis after balloon angioplasty or in the postprocedural minimal luminal diameter (Table 2). The mean duration of radiation treatment was 1.81±0.10, 2.55±0.20, 3.01±0.16, and 3.17±0.19 minutes, respectively, in the four groups. Ten patients who were asymptomatic at six months declined to undergo a second catheterization; one patient died after having an acute myocardial infarction; and lung cancer was diagnosed in another patient. The full complement of angiograms was thus available for analysis in 169 patients; all three angiograms — preprocedural, postprocedural, and follow-up — were suitable for quantitative analysis in 168 of these patients.

The largest loss in minimal luminal diameter (from the postprocedural result to follow-up) occurred within the irradiated segment of the vessel (Fig. 1). Six months after balloon angioplasty, a significant dose-dependent benefit of beta radiation was evident in the minimal luminal diameter (P=0.006 for the comparison of 9 Gy with 18 Gy); the mean diameter for patients who had balloon angioplasty alone was 1.67± 0.09, 1.82±0.13, 1.80±0.11, and 2.10±0.12 mm,

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TABLE 1. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	9 Gy (N=45)	12 Gy (N=45)	15 Gy (N=46)	18 Gy (N=45)	TOTAL (N=181)
			mean ±SE		
Age — yr	64±1.2	65±1.2	64±1.3	63±1.4	64±0.6
			no. (%)		
Male sex	32 (71)	30 (67)	35 (76)	36 (80)	133 (73)
Medical history					
Previous infarction	15 (33)	20 (44)	18 (39)	16 (36)	69 (38)
Previous CABG	5 (11)	0	0	1 (2)	6 (3)
Previous PTCA	7 (16)	9 (20)	6 (13)	2 (4)	24 (13)
Family history of CAD	13 (29)	13 (29)	14 (30)	15 (33)	55 (30)
History of smoking	30 (67)	26 (58)	30 (65)	32 (71)	118 (65)
Current medical condition					
Unstable angina	16 (36)	15 (33)	17 (37)	13 (29)	61 (34)
Diabetes mellitus	5 (11)	6 (13)	4 (9)	7 (16)	22 (12)
Hypertension	23 (51)	21 (47)	20 (43)	20 (44)	84 (46)
Hypercholesterolemia	26 (58)	27 (60)	27 (59)	24 (53)	104 (57)
Treated vessel					
LAD	19 (42)	19 (42)	19 (41)	18 (40)	75 (41)
RCA	13 (29)	15 (33)	15 (33)	21 (47)	64 (35)
LCX	13 (29)	11 (24)	12 (26)	6 (13)	42 (23)
Lesion type†					
A	4 (9)	7 (16)	6 (13)	8 (18)	25 (14)
B1	17 (38)	12 (27)	18 (39)	17 (38)	64 (35)
B2	24 (53)	26 (58)	22 (48)	20 (44)	92 (51)
C	0	0	0	0	0
Single-vessel disease	36 (80)	34 (76)	36 (78)	32 (71)	138 (76)

*CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, CAD coronary artery disease, LAD left anterior descending artery, RCA right coronary artery, and LCX left circumflex coronary artery.

†The type of lesion was classified according to the American Heart Association–American College of Cardiology classification, with A denoting a short focal lesion, and C the most complex type of lesion.

TABLE 2. ANGIOGRAPHIC RESULTS IMMEDIATELY AFTER BALLOON ANGIOPLASTY AND AT SIX MONTHS.*

VARIABLE	9 Gy		12 Gy		15 Gy		18 Gy	
	AFTER ANGIOPLASTY	AT 6 MO	AFTER ANGIOPLASTY	AT 6 MO	AFTER ANGIOPLASTY	AT 6 MO	AFTER ANGIOPLASTY	AT 6 MO
All patients (no.)	45	42	45	42	46	44	45	40
Reference diameter (mm)	2.95±0.07	2.83±0.07	3.02±0.09	3.01±0.09	2.99±0.09	2.98±0.09	3.11±0.07	3.21±0.08
Minimal luminal diameter (mm)	2.04±0.06	1.67±0.08	2.01±0.08	1.76±0.12	2.04±0.07	1.83±0.10	2.15±0.06	1.97±0.13
Stenosis (% of luminal diameter)	30.9±1.28	41.5±2.33	33.4±1.24	41.3±3.48	31.9±1.13	38.6±2.70	30.5±1.37	38.4±3.77
Luminal loss (mm)		0.37±0.07		0.25±0.10		0.21±0.09		0.18±0.12
Rate of restenosis (% of patients)		28.6		21.4		15.9		15.0
Vessel occlusion (no. of patients)		2†		4†		2†		4†
Patients treated with angioplasty alone (no.)	33	32	33	30	33	31	30	26
Reference diameter (mm)	2.93±0.09	2.81±0.09	2.94±0.08	2.96±0.09	2.89±0.11	2.90±0.11	3.08±0.09	3.09±0.09
Minimal luminal diameter (mm)	1.98±0.07	1.67±0.09	1.94±0.07	1.82±0.13	1.89±0.07	1.80±0.11	2.06±0.07	2.10±0.12
Stenosis (% of luminal diameter)	32.6±1.22	41.0±2.17	33.7±1.45	38.1±3.73	34.3±1.16	37.7±3.10	33.2±1.45	32.4±3.01
Luminal loss (mm)		0.31±0.08		0.12±0.09		0.09±0.10		−0.04±0.1
Rate of restenosis (% of patients)		28.1		16.7		16.1		3.9
Vessel occlusion (no. of patients)		0		2		1†		1

*Plus−minus values are means ±SE. The P value for trend is 0.02 for the reference diameter at follow-up in all patients. The P value for trend is 0.07 for the minimal luminal diameter at follow-up and 0.08 for luminal loss in patients treated with balloon angioplasty alone. Follow-up data were available and suitable for quantitative analysis in 168 patients.

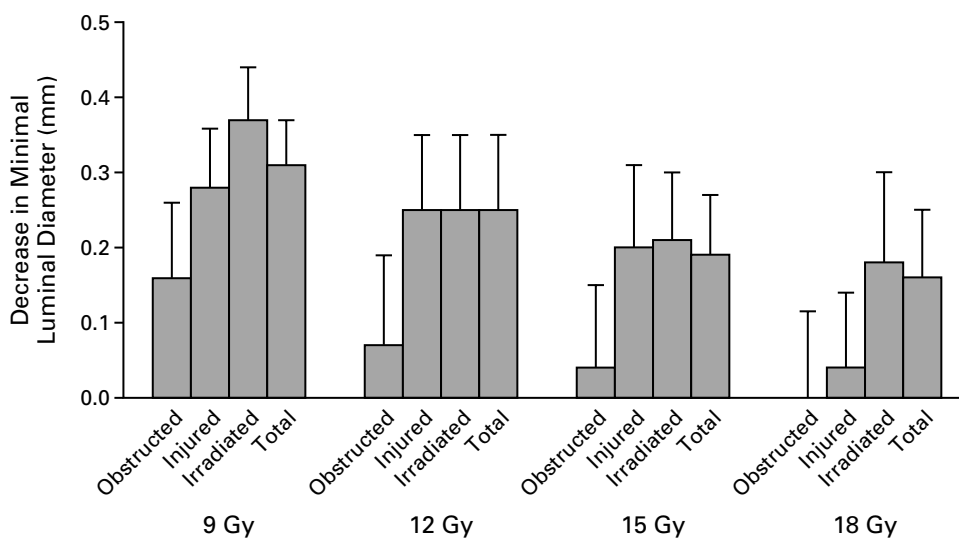†One of these patients had subacute thrombosis.

Figure 1. Loss in Minimal Luminal Diameter per Vessel Segment from Immediately after Angioplasty to Follow-up in the 168 Patients for Whom Angiographic Follow-up Data Were Available at Six Months.

The mean (+SE) loss in minimal luminal diameter is shown for all patients in the four dose groups. The length of the vessel segment analyzed was progressively increased from the obstructed segment to include the injured segment, the irradiated segment plus the edges, and finally to the entire vessel (total). The loss decreased in a dose-dependent manner, and the greatest loss occurred in the irradiated area. P=0.06 for the loss in the injured segment (9 Gy vs. 18 Gy).

respectively (Table 2). The loss in luminal diameter was 0.31±0.08 mm in the 9-Gy group, 0.12±0.09 mm in the 12-Gy group, and 0.09±0.10 mm in the 15-Gy group (Fig. 2). After irradiation at the 18-Gy dose, the luminal diameter actually increased by 0.04± 0.10 mm (P=0.008 for the comparison of 9 Gy with 18 Gy). Luminal enlargement occurred in 28 percent,

50 percent, 45 percent, and 74 percent of the patients in the 9-Gy, 12-Gy, 15-Gy, and 18-Gy groups, respectively (P<0.001 for the comparison of 9 Gy with 18 Gy). On follow-up angiographic examination, there was occlusion of the vessel in 4 of the 120 patients who had had balloon angioplasty alone (3.3 percent) and in 7 of the 49 who had also required stents
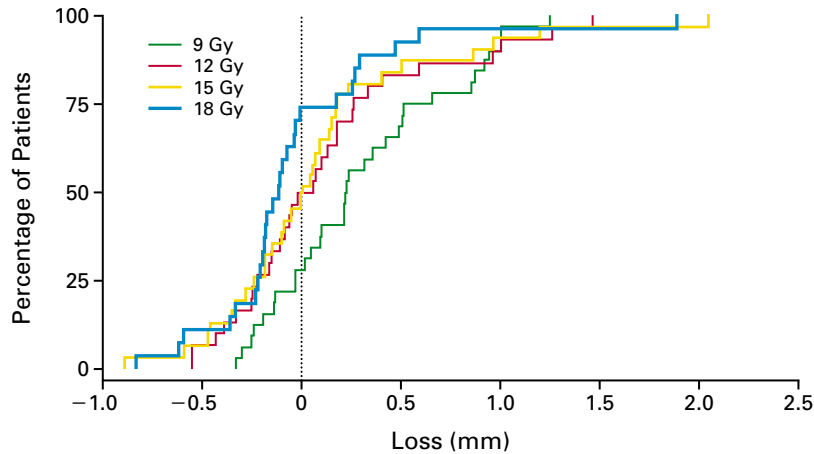
Figure 2. Cumulative Frequency Distribution of the Loss in Minimal Luminal Diameter from Immediately after Angioplasty to Follow-up at Six Months in Patients Treated with Angioplasty and Irradiation with 9, 12, 15, and 18 Gy of Beta Radiation.

As uniformly observed with any coronary intervention used in the past, the distribution curve at follow-up after irradiation at the 9-Gy level is shifted to the right, indicating a progressive loss in the initial luminal gain ($P<0.001$ for the comparison with 0 on the x axis [no change]). However, after irradiation with 18 Gy, the distribution curve is shifted to the left (showing a negative loss), which is indicative of luminal expansion between the postprocedural result and follow-up. The loss curves for the 12-Gy and 15-Gy groups show an intermediate response.

(14.3 percent). Of the patients with occlusion, four (one treated with balloon angioplasty alone and three who received stents) presented with acute symptoms (at 7 days and at 10, 11, and 12 weeks after irradiation). None of these patients were receiving long-term ticlopidine treatment. As a consequence of the absence of ticlopidine therapy, the rates of angiographic restenosis in the patients who required stents were exceedingly high: 30 percent, 33 percent, 15 percent, and 38 percent, respectively (22 percent, 20 percent, 8 percent, and 20 percent, respectively, after the exclusion of the patients with stent thrombosis).

Clinical Results

The incidence of serious cardiac events was within the range of reported values and did not differ significantly among the dose groups (Table 3). The overall incidence of myocardial infarction was 3.3 percent. In addition, three patients had an isolated rise in the creatine phosphokinase level. Repeated percutaneous revascularization of the target vessel was required in 12 percent of the patients treated with balloon angioplasty alone and in 17.6 percent of the patients who required stents.

DISCUSSION

This dose-finding study demonstrates a marked reduction in the rate of restenosis in nonstented arteries after beta-radiation therapy at the 18-Gy level (at a tissue depth of 1 mm). No device or pharmaceutical approach has yielded similarly low rates of restenosis

TABLE 3. INCIDENCE OF SERIOUS CARDIAC EVENTS AT 210 DAYS.*

EVENT	9 Gy (N=45)	12 Gy (N=45)	15 Gy (N=46)	18 Gy (N=45)	TOTAL (N=181)
			no.		no. (%)
Death	0	0	0	1†	1 (0.6)
Myocardial infarction	1	2	0	2	5 (2.8)
Q-wave	0	1	0	1	2 (1.1)
Non−Q-wave	1	1	0	1	3 (1.7)
Target-vessel revascularization					
CABG	0	1	0	0	1 (0.6)
PTCA	6	3	5	5	19 (10.5)
None	38	39	41	37	155 (85.6)

*Only the most severe event in a given patient is shown. Periprocedural creatine kinase values were elevated in three additional patients (2.5, 3.2, and 3.6 times the upper limit of normal). CABG denotes coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

†Death from cardiac causes after acute infarction occurred six months after radiation and stent implantation in a 59-year-old patient who had had recurrent angina three weeks earlier.

after balloon angioplasty alone. The lowest rate of restenosis reported in the context of a randomized trial was 16 percent at six months with the use of coronary stents,[5] which are currently implanted during more than 60 percent of coronary interventions.[16] With the use of beta radiation, a restenosis rate of less than 5 percent was achieved in patients who had had good

angiographic results after balloon angioplasty alone, suggesting that beta-radiation therapy should be evaluated as a first-line adjunct to angioplasty. The effect observed in our study results from the effect of irradiation on both remodeling and the formation of neointima, as suggested by intravascular ultrasound imaging.[17,18]

Several systems for endovascular irradiation with sources of gamma or beta radiation have been developed. Gamma radiation was shown to decrease the rates of restenosis after the percutaneous treatment of restenotic lesions, but its effectiveness at the time of the first angioplasty has not been evaluated.[19-21] Moreover, the use of gamma radiation is less practical than that of beta radiation in the environment of a catheterization laboratory, because the medical staff must be exposed to greater radiation and the treatment times must be longer.

Results with other systems of beta radiation have not been as encouraging as our results. The initial analysis of the Beta Energy Restenosis Trial (BERT), which used a noncentered strontium-90–yttrium-90 source, found a 15 percent rate of restenosis when the angiographic analysis was limited to the stenotic segment.[22] However, more recent reports using either strontium-90–yttrium-90 or phosphorus-32 found higher rates of restenosis (as high as 25 percent) when a longer segment of the vessel was analyzed, as in our study.[23]

Our data also indicate that caution should be exercised when combining radiation therapy with the implantation of stents. Historically, the occurrence of subacute stent thrombosis was reduced from 25 percent to less than 2 percent when patients received treatment with aspirin and ticlopidine for four weeks after implantation.[24-26] After irradiation, there was abrupt thrombosis or late occlusion of vessels in 14.3 percent of patients with stents, a finding that is consistent with other reports.[27,28] By delaying endothelialization after the implantation of a stent, radiation therapy may extend the risk of stent thrombosis beyond four weeks. Further studies addressing the safety of combining radiation therapy with stenting are necessary; the long-term use of antiplatelet drugs will presumably be required.

The use of radiation therapy for the treatment of a nonmalignant disease may cause concern about several potential problems. One is radiation-induced arteriopathy, an arterial narrowing that occurs after external fractionated radiation treatment for malignant diseases. This complication occurs after a mean of 16 years, and it occurs more frequently in younger patients in whom large volumes of tissue have been irradiated.[29] It is unknown whether this adverse effect can occur several years after the irradiation of a small volume of coronary artery. Another concern is that remodeling of the vessel might ultimately result in the formation of coronary aneurysms. Despite experimental[30] and clinical[31] evidence that radiation may induce aneurysms, we did not observe this phenomenon. We believe that the aneurysmal dilatations observed in earlier studies were related to high-dose gamma radiation of large volumes of tissue,[32] but longer follow-up is certainly warranted.

Another reason for concern is that radiation may induce a soft-tissue sarcoma in the arterial wall or the myocardium. Previous experience with radiation therapy for breast cancer[33] suggests that the maximal risk of carcinogenesis during the 10-year period after intravascular radiation therapy is in the range of 1 case per 1 million patients treated, given the small volume of irradiated tissue. Radiation-induced cancers were not found in large groups of patients who had received radiation treatment for keloids or pterygia with focused doses of 12 and 18 Gy.[34,35]

Our principal findings have important implications for the field of interventional cardiology. Current practice follows the "bigger is better" paradigm, which holds that the bigger the luminal diameter achieved by angioplasty, the better the long-term result.[36] A larger lumen can indeed be achieved safely and reliably with the implantation of a stent. In this respect, stents are superior to balloons, although they do not inhibit the neointimal proliferation that causes restenosis. Intracoronary beta radiation has the potential to change this treatment paradigm, not only because it reduces neointimal proliferation but also because of its beneficial effect on the healing process in the arterial wall. In a similar fashion to its effect on the healing surgical wound,[37,38] beta radiation decreases chronic arterial constriction and induces luminal enlargement, as we have shown. Further randomized trials should therefore test the clinical efficacy of the combination of beta-radiation therapy and balloon angioplasty, as compared with the implantation of coronary stents, in improving long-term, event-free survival after percutaneous revascularization.

APPENDIX

Other institutions and investigators that participated in the Dose-Finding Study Group are as follows (the numbers of patients enrolled are given in parentheses): University Hospital, Geneva (57) — I. Papirov, A. Sergey, P. Debruyne, and J. Ramos de Olival; Cardiovascular Center, Onze-Lieve-Vrouw Ziekenhuis, Aalst, Belgium (54) — G. Heyndrickx, L. Verbeke, and J. De Jans; University Hospital, Essen, Germany (26) — M. Haude, D. Flühs, U. Quast, A. Müller, K. Hidgeghty, and C. von Birgelen; University Hospital, Kiel, Germany (22) — M. Thomas, G. Herrmann, R. Wilhelm, and P. Kohl; King's College Hospital, London (22) — N. Lewis; Study Coordination (Boston Scientific) — T. Thaler; Critical Events Committee — J. Dekkers; Angiographic Core Laboratory and Data Analysis — Y. Teunissen, A. Spierings, C. van der Wiel, and G. Kloek.

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