Delivered Dose and Vascular Response After β-Radiation for In-Stent Restenosis
Retrospective Dosimetry and Volumetric Intravascular Ultrasound Analysis

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Background—Observations from previous intracoronary radiation therapy trials noted a considerable discrepancy between the prescribed radiation dose and the dose actually delivered. The aims of this study were to investigate the effect of actual delivered dose on vascular changes and to test the appropriateness of the current dose prescription.

Methods and Results—Serial volumetric intravascular ultrasound (IVUS) analysis was performed in 30 in-stent restenosis cases treated with a 40-mm 90Sr/Y source train. The fixed dose was prescribed at 2 mm from the centerline of the source train (18.4 Gy at 2 mm for reference diameter ≤3.35 mm and 23 Gy for diameter ≥3.36 mm). Only stent segments with full radiation coverage and device injury were enrolled and divided into 2-mm-long subsegments (n=202). DS90 EEM (the minimum dose absorbed by 90% of the external elastic membrane surface) was calculated as the delivered dose corresponding to each segment, assuming that the radiation catheter occupied the same position in the vessel as the IVUS catheter. Mean DS90 EEM of 23.5±5.82 Gy (range 12.3 to 41.7 Gy) was delivered to these subsegments. Overall, intimal hyperplasia volume remained constant from postintervention to follow-up (2.23±1.10 to 2.32±1.09 mm3/m; P=NS). Regression analysis revealed there was no correlation between delivered dose intensity and changes in intimal hyperplasia volume. No particular dose-dependent complications were appreciated in this delivered dose range.

Conclusions—The current dose-prescription protocol of 90Sr/Y radiation to native in-stent restenosis lesions may provide substantial inhibition of neointimal reproliferation regardless of the actual delivered dose intensity. (Circulation. 2002; 106:2334-2339.)

Key Words: restenosis ■ radioisotopes ■ stents ■ coronary disease

Presently, stenting represents the primary strategy used for percutaneous coronary intervention. As a result, the incidence of in-stent restenosis (ISR) poses a significant challenge for today’s interventionist. Although several aggressive strategies for ISR treatment, such as dilation and debulking, have altered late outcomes, the actual recurrent restenosis rates remain high.1,2 Recently, intravascular brachytherapy (IVBT), as a potential antiproliferative treatment, has been applied to ISR and has demonstrated a striking reduction in recurrent restenosis.3,5 This new technology has been approved and is currently being used worldwide.

Optimal dose delivery is fundamentally necessary for maximal IVBT effectiveness and to minimize relevant complications. The prescribed dose positively correlated with inhibition of neointimal proliferation in animal studies6,7 and in human pilot trials8,9. As a result, current dose-prescription protocols were organized in reference to these initial studies. However, when the actual delivered dose to the target tissues was simulated, a considerable discrepancy was appreciated between the prescribed and delivered dose,10 which necessitates precise investigations of vascular responses that are based on the actual delivered dose. Thus, the aims of the present study were to (1) investigate the relationship between the delivered dose and vascular changes individually by volumetric intravascular ultrasound (IVUS) analysis and (2) test the appropriateness of the current dose prescription.

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of the current dose-prescription protocol for $^{90}$Sr/Y radiation to native ISR lesions.

**Methods**

**Patients**

The study population consisted of patients enrolled in the STent And Radiation Therapy (START) 40/20 trial, a prospective, multicenter registry designed to evaluate the safety and effectiveness of intravascular β-radiation for the prevention of intimal hyperplasia in patients with initial ISR in native coronary vessels. The Beta-Cath System (Novoste Corporation) with a 40-mm $^{90}$Strontium/Yttrium ($^{90}$Sr/Y) radioactive source train was exclusively used for this trial. The lesion needed to be suitable for treatment with up to a 40-mm radiation train after treatment with a 20-mm balloon, with an existing margin of 10 mm on each end, and had to be located in reference vessels with maximum angiographic reference diameter of 2.7 to 4.0 mm by visual inspection. All patients received aspirin and clopidogrel for a minimum of 90 days.

**Radiation Protocol**

Immediately after successful intervention, the Beta-Cath System was inserted into the target artery. The 40-mm radioactive source train (RST) was then hydraulically delivered from the transfer device to the treatment site, optimizing longitudinal position of the train to cover the device-injury segment, referenced by gold markers on each end. The dose was prescribed at 2 mm from the centerline of the axis of the RST and then divided into 2 different dose-prescription protocols, as determined by visual angiographic reference diameter (18.4 Gy for reference diameter of $\geq2.7$ to $\leq3.35$ mm and 23 Gy for that of $\geq3.36$ but $\leq4.0$ mm).

**IVUS Imaging**

IVUS was documented at baseline (prerradiation) and 8-month follow-up. All patients received 10 000 IU of heparin before the procedures. After administration of 200 μg of intracoronary nitroglycerin, the imaging catheter was advanced distally under fluoroscopic guidance. Automated pullback (0.5 mm/s) was used to record ultrasound images on 0.5-in Super-VHS videotape for offline quantitative analysis. Automated pullback (0.5 mm/s) was used to record ultrasound images on 0.5-in Super-VHS videotape for offline quantitative analysis. In the cases selected for this IVUS subanalysis, a commercially available imaging system (3.2F 30-MHz; Boston Scientific) was used.

**Quantitative IVUS Analysis**

All recorded tapes were sent to an independent IVUS core laboratory (Cardiovascular Core Analysis Laboratory, Stanford, Calif). All measurements were performed by 2 experienced physicians blinded to any clinical or angiographic information. Three-dimensional reconstruction of IVUS images was performed with a commercially available quantitative analysis system that runs on an Intel Pentium-based PC system with Windows NT (EchoPlaque, Indec Systems, Inc). After digitization of IVUS recordings, lumen, stent, and external elastic membrane (EEM) areas were manually traced at 16 frame intervals (30 frames=1 mm), and the interpolated measurements of the remaining frames were automatically generated. Simpson’s method was used to calculate EEM volume, stent volume, and lumen volume, and these were adjusted by length as volume index (EEMVI, stent volume index [SVI], and lumen volume index [LVI], in mm$^3$/mm). Intimal hyperplasia volume index (IHVI, in mm$^3$/mm) was calculated as SVI−LVI.

**Lesion Segmentation: Radiated Zone and Injured Zone**

The longitudinal positions of RST and injury zone relative to the stents were determined by an independent angiographic core laboratory (Cardiovascular Research Foundation, New York, NY). These angiographic data sets were converted into IVUS on the assumption that both stent centers were geographically identical. A stent length ratio (IVUS:angiogram) was multiplied by total angiographic length, which converted it into IVUS length. A fully radiated zone was defined as each 18-mm segment from the RST center, because the longitudinal distance of the 100% isodose is nearly equal to 36 mm of the 40-mm-long RST. For this IVUS substudy, lesions that were fully radiated and had device injury inside the stent segment were used, with each divided into 2-mm-long subsegments.

**Retrospective IVUS-Based Dosimetry**

The simulated dose received by either intima plus media (I+M) volume or EEM surface was computed retrospectively by means of dose-volume histograms or dose-surface histograms with validated treatment planning software (iPlan, Emory University) on a PC-based platform. Dose-volume histograms summarize the dose-distribution information for a region of interest and identify characteristics such as dose uniformity and hot or cold spots. To calculate a dose-volume histogram, the dose-distribution data must be available for the given region of interest. The histogram is a plot diagram of the accumulated volume of those elements that receive a dose in a specified dose interval versus a set of equally spaced dose intervals. Dose-surface histograms are computed for the surface area of various target regions. The lumen surface and the EEM were outlined on images at 0.67-mm spacing (3 frames for 2 mm) throughout the segment (Extract, Indec Systems). The x, y, and z coordinates of the points that composed the luminal surface and EEM on each contoured image were then determined. An ASCII file of this information was exported to iPlan for subsequent dose calculation. The radiation catheter was assumed to occupy the same position in the vessel as the IVUS catheter. For the dose at the I+M level, the minimum dose absorbed by 90% of I+M ($D_{90,I+M}$) was calculated. For the adventitial dose level, the minimum dose absorbed by 90% of the EEM surface ($D_{90,EEM}$) was computed. These dose calculations were performed for each 2-mm-long subsegment for all patients.

**Relative IVUS Parameters**

The following relative IVUS parameters were investigated in the present study to examine the relationship between delivered dose and vascular changes. $\%\Delta$EEMVI and $\%\Delta$VI could be calculated as $[(\text{follow-up }−\text{postintervention})/\text{postintervention}]\times100$. Change in IHVI was divided by postintervention SVI rather than by postintervention IHVI [$\%\Delta$IHVI = (follow-up IHVI−postintervention IHVI)/ postintervention SVI$\times100$]. Two different dose histograms, $D_{90,I+M}$ and $D_{90,EEM}$, were applied to perform simple linear regression analysis with these IVUS relative parameters.

**Statistical Analysis**

Continuous data are presented as mean±SD, and categorical data are presented as frequencies. Continuous variables were compared by use of paired or unpaired Student’s t tests. Categorical variables were compared by $\chi^2$ statistics and Fisher’s exact test. Significance was assumed at a value of $P<0.05$.

**Results**

**Patient Selection and Characteristics**

Of 207 patients enrolled in the overall trial, 77 had completed serial IVUS acquisitions. Forty cases were excluded from 3D analysis because of inadequate automated/manual pullback (n=23) or poor image quality (n=17) caused by considerable air bubble artifact or nonuniform rotation distortion. Two cases were rejected because of lack of angiographic information for the determination of radiated/injured zone. Five cases demonstrating a difference in stent length $>5$% between 2 IVUS sequences were not enrolled because of the difficulty in subsegment identification. As a result, 30 patients, with a mean age of 60.4±12.9 years, met the strict inclusion criteria. Clinical and procedural characteristics among this sample are shown in Table 1.
A total of 226 subsegments were identified with injured and fully irradiated in-stent segments in the present cohort. Twenty-four subsegments (10.6%) were excluded from the final analysis because of either regional severe calcified plaque that precluded accurate EEM border detection or a mismatch of stent volume due to the abrupt change by the influx of side branches or stent overlap. Ultimately, the study sample comprised 202 subsegments.

At 8-month follow-up, target-lesion revascularization was performed in 5 patients (16.7%), and no thrombotic complication (<30 days) was observed in this population, which was not statistically different from the overall START 40/20 study cohort (target-lesion revascularization 11.1%, thrombus <30 days 0%, $P=$NS for both).

### Delivered Dose and Vascular Changes
Simple linear regression plots regarding the relationship between $D_{\text{90}}$EEM and IVUS relative parameters are shown in Figure 5. No correlation was observed for either $D_{\text{90}}$EEM and %IHVI ($P=$NS) or $D_{\text{90}}$EEM and %LVI ($P=$NS). On the other hand, a weak positive correlation was observed between %EEMVI and $D_{\text{90}}$EEM ($P<0.0001, r=0.28$). Identical results were seen when the relationships between $D_{\text{90}}$I+M and the same IVUS parameters were examined.

The delivered dose of 1 patient with late stent incomplete apposition was investigated. The dose absorbed in this

### Dosimetry
Nineteen patients received 18.4 Gy and 11 received 23 Gy 2 mm from the centerline of the axis of the RST (mean prescribed dose 20.1±2.22 Gy). The calculated $D_{\text{90}}$I+M and $D_{\text{90}}$EEM were 27.6±6.36 and 23.5±5.82 Gy, respectively. Figure 2 displays the frequency distribution of $D_{\text{90}}$I+M and $D_{\text{90}}$EEM, revealing a wide range of the delivered dose (15.2 to 48.0 Gy in $D_{\text{90}}$I+M, 12.3 to 41.7 Gy in $D_{\text{90}}$EEM). There was a strong positive correlation between $D_{\text{90}}$I+M and $D_{\text{90}}$EEM ($P<0.0001, r=0.999, y=0.91x-1.61$) $D_{\text{90}}$EEM was 23.5±5.89 Gy in cases receiving the prescribed dose of 18.4 Gy and 23.5±5.79 Gy in those receiving 23 Gy ($P=$NS; Figure 4). Nearly identical dose delivery was achieved by setting 2 different dose prescriptions of either 18.4 or 23 Gy on the threshold of angiographic diameter of 3.35 mm.

### Qualitative and Quantitative Results
Qualitatively, there was no evidence of distinct thrombus formation in these subsegments. One case revealed late stent incomplete apposition at follow-up (Figure 1). This phenomenon was seen in the healthy part of the vascular wall, similar to previous reports. Quantitative coronary angiography and 3D IVUS parameters are summarized in Table 2. On average, stent volume did not change between the 2 sequences (SVI 7.57±2.10 to 7.55±1.83 mm$^3$/m, $P=$NS). Intimal hyperplasia remained constant in these subsegments (IHVI 2.23±1.10 to 2.32±1.09 mm$^3$/m, $P=$NS), with maintenance of the luminal volume (LVI 5.34±1.57 to 5.24±1.49 mm$^3$/m, $P=$NS). No significant change was observed in average EEM volume (EEMVI 15.4±4.12 to 15.5±4.22 mm$^3$/m, $P=$NS).

### Table 2. Overall Quantitative Results

<table>
<thead>
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<th></th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>$P$</th>
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<tbody>
<tr>
<td><strong>Quantitative coronary angiography</strong></td>
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<tr>
<td>Minimal lumen diameter, mm</td>
<td>2.09±0.33</td>
<td>2.00±0.41</td>
<td>NS</td>
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<tr>
<td>% Diameter stenosis</td>
<td>23.2±15.8</td>
<td>24.8±15.4</td>
<td>NS</td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
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<td>2.69±0.40</td>
<td>NS</td>
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<tr>
<td><strong>3D IVUS</strong></td>
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</tr>
<tr>
<td>EEMVI, mm$^3$/m</td>
<td>15.4±4.12</td>
<td>15.5±4.22</td>
<td>NS</td>
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<tr>
<td>SVI, mm$^3$/m</td>
<td>7.57±2.10</td>
<td>7.55±1.83</td>
<td>NS</td>
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<tr>
<td>LVI, mm$^3$/m</td>
<td>5.34±1.57</td>
<td>5.24±1.49</td>
<td>NS</td>
</tr>
<tr>
<td>IHVI, mm$^3$/m</td>
<td>2.23±1.10</td>
<td>2.32±1.09</td>
<td>NS</td>
</tr>
</tbody>
</table>

n=30 patients.

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**Figure 1.** Corresponding IVUS cross sections of case with late stent incomplete apposition at postradiation and 8-month follow-up. Some stent struts were "floated" from enlarged vessel surface (arrows), filling with blood speckle signals at 8-month follow-up.
specific segment was calculated as $D_{90\text{EEM}}$ of 31.9 Gy and $D_{V90\text{I/M}}$ of 35.5 Gy for the entire circumference.

Restenosis-Positive Versus Restenosis-Negative Cases

Of 5 cases counted as positive for target-lesion revascularization, 2 underwent CABG surgery despite no evidence of recurrent restenosis (angiographic percent diameter stenosis $<40\%$ and minimal lumen area $>4.5$ mm$^2$). Therefore, we carefully examined the remaining 3 cases whose target-lesion revascularization was due to “true” recurrent ISR, which was essential for a dose-response study. Delivered dosage to 24 subsegments of these 3 cases (restenosis-positive group) was $D_{90\text{EEM}}$ of 28.2±6.47 (range 19.3 to 41.7) Gy and $D_{V90\text{I/M}}$ of 33.0±6.98 (range 23.8 to 48.0) Gy, which was significantly higher than that of the restenosis-negative group (22.9±5.47 and 26.9±5.95 Gy, respectively; $P<0.0001$ for both comparisons). However, intimal hyperplasia volume increased significantly in the positive group compared with the negative group (%ΔIHVI 12.1% versus 2.0%, $P<0.0003$), and lumen volume decreased significantly in the positive group (%ΔLVI −19.1% versus 0.7%, $P<0.0001$). On careful scrutiny, we found no distinctive features in clinical, lesion, or procedural characteristics in these 3 cases.

Discussion

To the best of our knowledge, this is the first report to investigate the relationship between delivered dose and vascular responses of ISR lesions under clinically applied dose prescriptions of $^{89}$Sr/Y radiation. This method of using dose-volume/surface histograms allows evaluation of the cumulative dose received by a certain specified tissue volume/surface and has recently been implemented in the field of IVBT as a tool for dosimetry.$^{12}$

Several animal studies have suggested that adventitial myofibroblasts contribute to cell proliferation/migration.$^{13,14}$ Furthermore, radiation may cause medial smooth muscle cell apoptosis and a resultant decrease of arterial wall cellular-
Accordingly, adventitia and media have been considered as the primary targets of intracoronary radiation. Because of difficulty in IVUS interpretation of adventitia or media volume, we used doses at the EEM surface (DS90 EEM) in the present study, where the border of these 2 vascular structures is visible. We found that the delivered dose to I/H11001 highly corresponds with that of the EEM (adventitia surface) under actual coronary geometry (1:1).

Despite a wide range of delivered dose, current dose-prescription protocols provide the following facts: (1) at a minimum, DS90 EEM of >12 Gy can be delivered to the EEM surface; (2) DS90 EEM was similar in the 2 different prescriptions (18.4 or 23 Gy) divided by the threshold of angiographic reference diameter of 3.35 mm; and (3) overall, substantial neointimal inhibition was achieved under the delivered dose range without apparent dose-dependent complications. These facts indicate that the current dose prescription appears to be reasonable for native ISR lesions. Importantly, the absolute delivered dose intensity to the restenosis-positive cases appeared to be high enough, which suggests that some ISR lesions may be less responsive to doses of radiation that are effective in other radiation lesions. This speculation may account for the mild recurrent ISR rates (15% to 25%) seen in the present trial and other human IVBT trials, the causes of which cannot be fully explained by the “geographic miss” theory. One potential treatment option may be to apply a higher-dose prescription for these lower responders. However, prediction of these specific patients before treatment is difficult, because potential associated factors are unknown at present.

A very weak positive correlation was observed between delivered dose intensity and changes in EEM volume in the present investigation. In ISR cases in which stents support the vascular wall from the inside, relatively high doses of radiation (estimated DS90 EEM >30 Gy; Figure 5) may cause slight enlargement of the EEM to nearly all segments, as seen frequently in irradiated, nonstented segments. Endovascular substructures have been hypothesized to fill the gap between the EEM and stent struts to accommodate EEM enlargement, including the extracellular proteoglycan matrix or fibrous compartment, rather than true cellular proliferation.

In the present study, 1 case revealed late incomplete stent apposition after β-radiation to the ISR lesion, which lends support to the possibility of EEM enlargement even in the ISR segment. However, this dose dependency remains unclear, because the dose delivered to this particular segment was not comparatively excessive (DS90 EEM of 31.9 Gy). In fact, 26 (12.9%) of 202 segments (9 patients) circumferentially received DS90 EEM >30 Gy, yet only 1 segment in 1 patient revealed this phenomenon. One potential explanation is that the noncentering radiation catheter might lie closer to the specific vascular wall, delivering a higher dose to that side of the normal vascular wall (although the IVUS catheter was located circumferentially opposite to this vascular wall at preradiation in this segment; Figure 1). The dose delivered to a specific “sector” will need to be calculated to investigate the actual relationship between dose intensity and this phenomenon in the future. However, when the existence of late incomplete stent apposition in the nonradiated ISR segment is considered, there may be unique lesion/procedural factors associated with resultant late incomplete stent apposition aside from absolute delivered dose intensity. To date, no dose-dependent complications or safety issues have been associated with this dose prescription.

Sabate et al demonstrated that a dose-dependent response was seen in lumen/plaque/vessel volume changes after 90Sr/Y radiation. In contrast, other than a very weak positive correlation in EEM volume changes, a dose-dependent response was not observed (reaching “plateau”) in the present study. This discrepancy may be due to a difference in target lesions (nonstented lesions versus ISR) and actual delivered dose intensity (5.5±2.5 [range 0.2 to 12.4] versus 23.5±5.82 [range 12.3 to 41.7] Gy) between the 2 studies. In fact, lumen
volume increase/maintenance was primarily achieved by positive vessel remodeling in other studies, which may not affect lumen dimensions of stented lesions for ISR treatment. Furthermore, there may be a minimum dose threshold at which the dose-dependent intimal response weakens or disappears. This speculation may be supported in part by the results of the γ-radiation trial (192Ir) that indicated that minimum dose exposure of 8 Gy to the adventitial border produced a profound treatment effect with very little late loss and a very low loss index.20

Study Limitations
This investigation has several potential limitations. First, the study population was relatively small (n = 30). Second, some bias should be considered in the case selection, because follow-up IVUS examinations may not have been performed in some emergent or tightly stenotic cases. Third, the obtained dose was based on the assumption that both the IVUS and delivery catheters were lying in the same position within the target coronary segment. However, these 2 catheters may not have occupied the same position because of variations in size and stiffness between the 2 catheters and variable axial and longitudinal movements during the cardiac cycle and during radiation. Fourth, the influence of radiation attenuation caused by the stent21 or different tissue characteristics (soft or hard plaque; calcification) has not been taken into consideration for dosimetry calculation. Fifth, despite careful attention to the adjustment of injured/radiated zone segmentation, some errors might occur during the conversion of angiographic geographical information into the IVUS data set, especially in cases with inconsistent obliquity of angiographic vessel appearance. Sixth, differentiation of in-stent tissue components is difficult because of the finite resolution of IVUS. Therefore, “intimal hyperplasia” used in the present analysis may potentially include true intima and some thrombus/fibrin complex. Finally, some lesions or portions might receive unnecessarily superfluous doses. A reduction of the prescribed dose might reduce the incidence of these excessive dose segments; however, it might also create a chance for insufficient dose portions owing to the inhomogeneous vascular structure throughout the lesions with the use of the isodose delivery system.

Conclusions
The current dose-prescription protocol of 90Sr/Y radiation to native ISR lesions may provide substantial inhibition of neointimal reproliferation regardless of the actual delivered dose intensity. Meanwhile, some ISR lesions may be less sensitive to doses of radiation that are effective in other ISR lesions, which may account in part for recurrent restenosis that remains despite adjunctive radiation therapy. Additional clinical investigations for more precise identification of lesion characteristics and response to radiation dosage will enable the interventionalist to further optimize care for the patient with coronary artery disease.

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