Late Total Occlusion After Intracoronary Brachytherapy for Patients With In-Stent Restenosis

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OBJECTIVES
The study sought to determine the incidence and predictors of late total occlusion (LTO, >30 days) in-patients with in-stent restenosis who were treated with intracoronary radiation.

BACKGROUND
Intracoronary radiation both with beta and gamma emitters has been shown to reduce recurrent in-stent restenosis.

METHODS
We reviewed the records of 473 patients who presented with in-stent restenosis and who were enrolled in various radiation protocols, whether randomized to placebo versus radiation or entered into registries. There were 165 placebo and 308 radiated patients, including both gamma and beta emitters. Maximum dose to the vessel wall was 30 to 55 Gy. Following radiation, all patients received antiplatelet therapy with aspirin and either ticlopidine or clopidogrel for one month. All patients completed at least six months of angiographic follow-up.

RESULTS
The LTO was documented in 28 patients (9.1%) from the irradiated group versus 2 placebo patients (1.2%), p < 0.0001. The LTO rates were similar across studies and emitters. In the irradiated group, LTO presented as acute myocardial infarction in 12 patients (43%), unstable angina in 14 (50%), and asymptotic in 2 (7%). Mean time to LTO was 5.4 ± 3.2 months in the irradiated group versus 4.5 ± 2.1 in placebo patients (p = NS). The overall rate of restenting for the entire study group at the time of radiation was 48.6%. Importantly, new stents were placed in 82% of the irradiated and in 100% of the placebo patients who presented with LTO. Multivariate analysis determined that new stenting was the main predictor of LTO.

CONCLUSIONS
Intracoronary radiation for patients with in-stent restenosis is associated with a high rate of LTO. Restenting may contribute late thrombosis. Prolonged antiplatelet therapy (up to six months) should be considered for these patients. (J Am Coll Cardiol 2000;36:65–8) © 2000 by the American College of Cardiology

Vascular brachytherapy is effective in preventing restenosis. Preclinical studies utilizing both beta and gamma emitters have shown a reduction of smooth muscle proliferation, prevention of late contraction, and a delayed healing response following vascular injury (1–4).

An important clinical application of vascular brachytherapy is as adjunct therapy for the treatment of in-stent restenosis. Several studies, including three randomized trials, have shown a reduction in recurrent in-stent restenosis of 50% to 70% compared to conventional therapy (5–9). However, radiation has been reported to induce thrombosis. Previous studies on the vascular effects of external beam radiation have suggested that increased thrombosis is a complication of delayed healing (10,11).

Thrombotic occlusion following balloon angioplasty usually occurs either immediately or within 24 hours following intervention. Stents are more often associated with subacute thrombosis (within 30 days of implantation), which is well controlled using antiplatelet therapy for 15 days (12–15). Among the complications associated with vascular brachytherapy is a new phenomenon of late coronary thrombosis (>30 days) (16,17).

The purpose of the current study was to determine the rate of late total occlusion (LTO) following brachytherapy for in-stent restenosis as well as its clinical presentation and predictors.

METHODS
From February 1997 to December 1998, a total of 473 patients with in-stent restenosis at the Washington Hospital Center were enrolled into six randomized vascular brachytherapy trials—WRIST (Washington Radiation for In-Stent restenosis Trial), LONG WRIST (long in-stent restenosis lesions 36 to 80 mm), SVG WRIST (in-stent restenosis in vein grafts), GAMMA-1, ARTISTIC (Angioid Radiation Therapy for In-Stent restenosis Trial in Coronaries), PREVENT (Proliferation Reduction with Vascular Energy Trial)—and into two registries, BETA WRIST (beta radiation for in-stent restenosis) and LONG WRIST HIGH DOSE (long lesions 36 to 80 mm using 15 Gy at 2.4 mm at the perspiration point). All clinical trials were approved by the Food and Drug Administration and...
by the Institutional Review Board and the radiation safety committee at the Washington Hospital Center. All patients signed consent forms before enrollment and completed at least six months of clinical and angiographic follow-up.

The description of trials, the isotope, and the dose are displayed in Table 1. The protocols had similar inclusion criteria including in-stent restenosis with a diameter stenosis (DS) >50%, in vessels 2.5 to 5.0 mm in diameter, a lesion length up to <80 mm, and successful primary intervention by balloon, ablation (laser or rotational atherectomy), restenting, or the combination with a <30% residual DS without complications. The main exclusion criteria were patients with acute myocardial infarction (MI) <72 hours previously, a left ventricular ejection fraction <20%, prior irradiation treatment to the chest, evidence of thrombus by angiogram, and multiple lesions in the same vessels.

Typically, focal lesions (<10 mm in length) were approached with balloon dilation, and diffuse lesions (≥10 mm in length) underwent ablation using excimer laser angioplasty or rotational atherectomy. Restenting was performed in 41% of patients when necessary to optimize the primary angiographic results, to cover the entire lesion length (especially when the in-stent restenosis process extended beyond the length of the stent) or to treat edge dissections. In preparation for the radiation treatment the activated clotting time (ACT) was monitored and adjusted.

Restenting was performed per protocol and left in place for a sufficient time to deliver the assigned dose. Cinefluoroscopy was used to verify catheter and source position.

Following radiation procedure, a final angiogram was performed and further balloon dilation or stent implantation was performed if the angiographic result had deteriorated significantly (>30% DS). The femoral sheaths were removed at the day of the procedure and patients received routine afterangioplasty care including ticlopidine 250 mg twice daily or clopidogrel 75 mg daily for one month and aspirin 325 mg daily. Gamma-1 patients who underwent restenting were instructed to continued ticlopidine for two months.

All patients completed clinical and angiographic follow-up at six months after enrollment. Quantitative coronary angiographic (QCA) analysis was performed using automated edge-detection algorithm. Selected end-diastolic cineframes were optically magnified (2.4:1) and digitized using a cine-video converter. Using the contrast filled catheter as the calibration standard, minimal lumen diameter (MLD), reference diameter, and percent diameter stenosis (DS) pre- and postintervention were measured. For the purpose of the current analysis, subacute thrombosis was defined as angiographically documented total occlusion ≤30 days; and LTO was defined as angiographically documented total occlusion >30 days’ postintervention. The LTO was applied for patients who had patent artery at six months’ follow-up and presented with total occlusion of the same site at a later time.

The time to LTO and the relevant clinical event associated with LTO were recorded and adjudicated. Several approaches were used to treat the LTOs including thrombolytics (5 patients), thrombectomy (Angiojet, Possis Medical, Minneapolis, Minnesota), PTCA (percutaneous transluminal coronary angioplasty) (14 patients), coronary artery bypass surgery (7 patients), and conservative medical therapy (7 patients); these treatment choices were not mutually exclusive.

**Statistical analysis.** Data were recorded prospectively and forwarded to the data-coordinating center. The results are expressed as mean ± 1 SD. Continuous variables were compared using unpaired, two-tailed Student t test. Categorical values were compared using chi-square or the Fisher exact test. P values <0.05 were considered statistically significant. Multivariate logistic regression analysis to determine the predictors of late thrombosis included demographic, morphological and

<table>
<thead>
<tr>
<th>Study</th>
<th>Emitter</th>
<th>Dose (Gy)</th>
<th>Late Total Occlusion Rate</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td>Treated</td>
</tr>
<tr>
<td>WRIST</td>
<td>Ir-192</td>
<td>15 at 2 mm</td>
<td>10/104 (9.6%)</td>
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<tr>
<td>GAMMA-1</td>
<td>Ir-192</td>
<td>8–30 by IVUS</td>
<td>3/20 (15%)</td>
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<tr>
<td>ARTISTIC</td>
<td>Ir-192</td>
<td>15 at 2 mm</td>
<td>2/24 (8.3%)</td>
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<tr>
<td>SVG WRIST</td>
<td>Ir-192</td>
<td>15 at 2 mm</td>
<td>1/27 (3.7%)</td>
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<tr>
<td>LONG WRIST</td>
<td>Ir-192</td>
<td>15 at 2 mm</td>
<td>4/45 (8.8%)</td>
</tr>
<tr>
<td>High-dose WRIST</td>
<td>Ir-192</td>
<td>15 at 2.4 mm</td>
<td>2/29 (6.9%)</td>
</tr>
<tr>
<td>BETA WRIST</td>
<td>Y-90</td>
<td>20.6 at 1 mm</td>
<td>4/49 (8.1%)</td>
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<tr>
<td>PREVENT</td>
<td>P-32</td>
<td>20–24 at 1 mm</td>
<td>2/10 (20.0%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>All</td>
<td>Any</td>
<td>28/308 (9.1%)</td>
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*Registries in which all patients received radiation.

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**Abbreviations and Acronyms**

- ACT = activated clotting time
- DS = diameter stenosis
- LTO = late total occlusion
- MI = myocardial infarction
- MLD = minimal lumen diameter
- PTCA = percutaneous transluminal coronary angioplasty
- QCA = quantitative coronary angiographic
- WRIST = Washington Radiation for In-Stent restenosis Trial
Of the 473 patients entered into the various trials, 308 patients were treated with active radiation and 165 were treated with placebo.

RESULTS

Predictors stay in the model. We used a level of 0.05 as a cut-off point to let the backward selection method was used to find predictors of the outcome. Clinical, Procedural, and Angiographic Findings in 28 Patients Who Received Brachytherapy for In-stent Restenosis and Who Presented With Late Total Occlusion

<table>
<thead>
<tr>
<th>Demographics</th>
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<tr>
<td>Age (yrs)</td>
<td>58.0 ± 11.4</td>
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<tr>
<td>Gender (male)</td>
<td>67.8</td>
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<tr>
<td>Number of in-stent restenosis episodes</td>
<td>2.3 ± 1.5</td>
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<tr>
<td>Angiographic findings preintervention</td>
<td>Reference (mm) 2.44 ± 0.34, Minimal luminal diameter (mm) 0.76 ± 0.37, Diameter stenosis (%) 76 ± 15</td>
</tr>
<tr>
<td>Device used to treat in-stent restenosis</td>
<td>Balloon 8 (28.6%), Rotational atherectomy 12 (42.8%), Excimer laser angioplasty 8 (28.6%), Restenting 23 (82.1%)</td>
</tr>
<tr>
<td>Angiographic findings postintervention</td>
<td>Minimal luminal diameter (mm) 2.05 ± 0.42, Diameter stenosis (%) 26 ± 9</td>
</tr>
<tr>
<td>Clinical presentation of late total occlusion</td>
<td>Time to late total occlusion (months) 5.4 ± 3.2, Acute MI 12 (42.8%), Recent onset unstable angina 14 (50.0%), Asymptomatic 2 (7.2%)</td>
</tr>
</tbody>
</table>

*Not mutually exclusive.

Clinical variables. Logistic regression is widely used to fit models for binary or ordinal, multivariate variables. We entered all clinically relevant variables in the model, and then backward selection method was used to find predictors of the outcome. We used a level of 0.05 as a cut-off point to let the predictors stay in the model.

RESULTS

Of the 473 patients entered into the various trials, 308 patients were treated with active radiation and 165 were treated with placebo. Subacute thrombosis occurred in three (0.9%) patients treated with radiation and in none of the placebo-treated patients. Late total occlusion occurred in 28 patients treated with radiation (9.1%), but in only 2 placebo patients (1.2%, p < 0.0001). Late late total occlusion occurred in two patients (0.6%) treated with radiation and none of the placebo patients. The rate of LTO did not vary significantly across protocols, emitters, and dosage. The clinical, angiographic, and procedural details of the 28 patients who received radiation to treat in-stent restenosis and who presented with LTOs are shown in Table 2. The mean time to LTO was 5.5 ± 3.1 months, with the majority of the 24 patients presenting between two and seven months. Late LTO occurred in two patients at 12 and 18 months despite absence of pathology on a six-month angiographic follow-up. The LTO was associated with acute MI in 12 (43%) of the patients and unstable angina in 14 (50%) patients; only 2 (7%) LTO patients were asymptomatic; in these patients total occlusions were found at routine six-month follow-up. The LTO from the irradiated group was treated: medically, 9 patients; repeat angioplasty, 14 patients; bypass surgery, 5 patients. There were three deaths among the patients who presented with LTO, one death from the medically treated group, one postbypass surgery, and one following angioplasty. The two patients with total occlusion from the placebo group were crossed over to radiation therapy and presented with patent artery at six months.

Restenting as part of the treatment of in-stent restenosis was performed in 230 of 473 (48.6%) patients. Importantly, 22 of the 28 irradiated patients (79%) who subsequently presented with LTO had a new stent placed during the treatment of in-stent restenosis. The LTO rate among patients who received stents and radiation was 14.6%. The rate of LTO in the patients who were treated with radiation, but no new stenting, was 6 of 157 (3.8%).

Multivariate logistic regression analysis was performed for the patients in the various WRIST studies. We specifically entered the following variables into the model: gender, diabetes, lesion length, reference vessel diameter, lesion length, final lumen diameter, beta radiation gamma radiation, and additional stenting. New stenting (odds ratio [OR] = 2.55, 95% confidence interval [CI] = 1.0–5.1, p = 0.04), and long lesions (OR = 1.15, CI = 1.0–1.2, p = 0.04) were found to be the predictors for late thrombosis.

DISCUSSION

In the current study we report a high rate of LTOs in patients undergoing radiation therapy to prevent recurrent in-stent restenosis. Although some of these LTOs may be the result of excessive tissue proliferation and exaggerated in-stent restenosis, the clinical and angiographic features suggest that the main etiology for LTO for this cohort is thrombus formation. Late thrombosis following coronary intervention and vascular brachytherapy is a new phenomenon. Because late thrombosis is rarely seen following conventional intervention, the cases of late thrombosis in the current study should be attributed to the use of radiation therapy.

Mechanisms. We have previously reported a correlation between the radiation dose and the thrombosis rate in the porcine model (18). Our findings suggested that healing response in irradiated arteries is delayed and that this delay may promote thrombus formation—especially in stented arteries with impaired re-endothelialization. In the current study, LTO was manifest as late closure and was found irrespective to the type of the radiation (beta versus gamma) or the prescribed dose to the vessel wall or the adventitia. Salame et al. (19) observed platelet recruitment at the irradiated injured site in porcine coronaries at 28 days. Previous studies on the vascular effects of external beam radiation have suggested that increased thrombosis is an adverse late healing effect (10,11). Furthermore, thrombi present in irradiated arteries tend to be acellular, with an absence of macrophages and lymphocytes thought to be involved in the repair mechanism. Decreased numbers or impaired function of macrophages may prolong the residence of the thrombus and its components (platelets and fibrin) at the injured segment and may delay its organization. Our animal
studies showed that thrombosis is related more to the total dose at the adventitia rather than to the luminal surface (18). Recent studies examining human carotid arteries that were exposed to external radiation have demonstrated impaired endothelium with reduction of nitric oxide production, which can potentially result in thrombosis (20).

**Predictors of late thrombosis.** In the current study, late thrombosis occurred mainly in patients who underwent new stent implantation at the time of brachytherapy. Conversely, the late thrombosis rate in patients who did not receive a new stent at the time of irradiation was similar to the nonirradiated group. Restenting an in-stent restenosis lesion has been advocated as one approach to this clinical problem. While it achieves the largest acute lumen dimensions, the long-term recurrence rate may be similar to other nonbrachytherapy techniques.

There are a number of potential explanations for late thrombosis in the setting of new stent implantation. First, small dissections can occur at the stent edges of newly implanted stents. Radiation may delay the healing of these edge dissections, which may remain thrombogenic. In a recent study using beta radiation, it was found that 7 of 16 (45%) dissections in unstented arteries remained unhealed at six-month follow-up (21). Second, incomplete, delayed, or impaired re-endothelialization may contribute to the initiation of a thrombus. Although the majority (26/28) of late thromboses occurred between two and seven months following irradiation, two patients had documented patency at six months and presented with “late late total occlusion” at 12, and 18 months. The “late LTOs” may be related to regression or erosion of tissue outside the stent. This may leave the stent unopposed to the vessel wall and serve as a nidus for thrombosis.

**Conclusions.** Our study clearly demonstrates a new complication of intracoronary radiation for patients with in-stent restenosis—late total occlusion. This phenomenon is more pronounced after restenting, but not after radiation and no new stenting.

These findings suggest that patients treated with stenting and radiation should be placed on prolonged antplatelet therapy; we suggest a duration of at least six months. However, it is possible that prolonged antplatelet therapy will only delay late thrombosis. If this occurs, increasing the rate of “late LTO,” antplatelet therapy will be required for longer than six months or other agents that may enhance the healing response and the re-endothelialization of new stents placed in irradiated arteries. Further, restenting should be avoided unless absolutely necessary, and the use of heparin-coated stents may be beneficial.

**REFERENCES**