Disappearance of Intima Over the Stent and Ulcer Formation After Intracoronary Radiation for In-Stent Restenosis
—— Angioscopic Findings in Human Coronary Arteries ——

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Little is known about the alterations of the vascular surface after radiation therapy for in-stent restenosis in humans, even though animal experiments suggest that delayed healing of the neo-intima is a cause of late thrombosis. Coronary angioscopy, together with coronary angiography, was performed at 3 months follow-up of 7 patients with in-stent restenosis who underwent $\beta$-radiation therapy. Minimal lesion diameter (MLD) of the lesion increased from $1.00\pm0.30\text{mm}$ (immediately before) to $2.44\pm0.39\text{mm}$ (immediately after) and the MLD was well maintained 3 months later ($2.34\pm0.62\text{mm}$) without any cases of restenosis. In 5 patients, the intima was so thin that some stent struts could be seen through it on angioscopy and in 2 of those, the intima over the stent had disappeared and 1 patient showed ulceration of the vascular wall beneath the stent. After intracoronary radiation therapy, the intima can become so thin that some stent struts are exposed to the lumen, which may be related to the occurrence of late thrombosis. Accordingly, patients who are treated with intracoronary radiation therapy may need long-term antiplatelet therapy. (Circ J 2003; 67: 366–368)

Key Words: Coronary angioscopy; In stent restenosis; Intracoronary radiation therapy; Neointima; Late thrombosis

Beta-radiation therapy has the beneficial effect of preventing restenosis after angioplasty;\textsuperscript{1–4} however, late thrombosis is a major problem of this therapy and it is speculated that the cause is delayed re-endothelialization. Although the surface of the vascular wall is considered to be damaged after radiation therapy, little is known about the effects on the intima of the human coronary artery, so we used coronary angioscopy to investigate the chronic changes of the vascular luminal surface after radiation therapy.

Methods

We performed coronary angioscopy, together with standard coronary angiography, at 3 months follow-up of 7 patients (age: $68\pm5$; male/female: 4/3) with in-stent restenosis who underwent radiation therapy (Table 1). The target vessels of radiation were the left anterior descending artery in 2 patients, and the right coronary artery in 5 patients.

All patients were to continue taking 100 mg of aspirin and 200 mg of ticlopidine daily, starting from the initial intervention until 9 months after brachytherapy. The study design was approved by the Ethics Committee of Kansai Rosai Hospital and all patients gave informed written consent for both intracoronary radiation and study participation.

Radiation Delivery System

The intravascular radiation system (Galileo system: Guidant, Santa Clara, CA, USA) has 3 components\textsuperscript{5} The source wire is a 0.018-inch flexible Nitinol wire, with the active $^{32}\text{P}$ source encapsulated in the distal 20 mm of the wire. The centering balloon catheter is a double-lumen catheter with a short monorail distal tip for rapid exchange method of delivery and a spiral balloon, with nominal diameters of 2.5, 3.0 or 3.5 mm, which centers the source within the lumen while allowing side branch and distal perfusion. The source delivery unit provides safe storage of the active wire and automated delivery and retrieval.

Radiation Procedure

After completing the angioplasty procedure using a femoral approach with an 8Fr guiding catheter, the centering catheter was advanced to the lesion site and the markers were optimally positioned to straddle the target lesion segment dilated with the balloon catheter. We did not use debulking devices nor did we implant additional new stents as pretreatment of brachytherapy. The centering balloon was inflated with normal saline, and contrast was injected through the guiding catheter to assess flow to the side branches and the distal artery. An inactive wire was advanced into the centering catheter, its position was optimized, and it was withdrawn. Then the active wire was advanced to the same location, which was verified angiographically. In the Galileo system, the source delivery unit automatically identifies the diameter of the centering catheter.
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Circulation Journal Vol.67, April 2003

When the reference vessel diameter is programmed into the computer, it calculates the dwelling time for the active wire required to deliver 20 Gy to a depth of 1 mm into the vessel wall. Radiation was applied in a 2-stage process for a catheter of 32 mm length and in 3 stages for a catheter of 52 mm length, as the length of active wire was 20 mm. Final coronary angiography was performed at the same angle as the control angiogram to analyze the minimal lesion diameter (MLD).

Dosimetry

The radiation prescription was based on the average of the lumen diameters of the proximal and distal reference segments, as measured by intravascular ultrasound. This value was entered into the source delivery unit, which used source activity to calculate the dwelling time needed to deliver the specified dose.

Follow-up Coronary Angiography and Angioscopy

Follow up angiography was performed 3.4±0.5 months after the radiation therapy. After a coronary angiogram with the same angle as the control was taken, angioscopy was performed with Vecmover (Clinical Supply Co, Gifu, Japan) or Fiber Imaging System FT-201 (Intertech Medical Co, Osaka, Japan).

Results

The MLD was 1.00±0.30 mm and the lesion length 25.7±12.4 mm before angioplasty. A centering balloon of 32 mm in length was used in 2 patients and that of 52 mm in 5 patients. In all patients, balloon angioplasty and radiation were successfully completed without any complications. The MLD was 2.44±0.39 mm on the final angiogram.

Table 1 Patients Characteristics and Angioscopic Findings

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (year)</th>
<th>Gender</th>
<th>Lesion location</th>
<th>Stent Type</th>
<th>Stent Diameter (mm)</th>
<th>Stent Length (mm)</th>
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<td>2</td>
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<td>F</td>
<td>RCA</td>
<td>S670</td>
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<td>Radius</td>
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</tr>
<tr>
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<td>RCA</td>
<td>Radius</td>
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<tr>
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<tr>
<td>7</td>
<td>68</td>
<td>M</td>
<td>LAD</td>
<td>BX velocity</td>
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Table 2 Angioscopic Findings of All Patients

<table>
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<tr>
<th>Patient no.</th>
<th>Yellow plaque</th>
<th>Intima at radiation site</th>
<th>Thrombus</th>
<th>Ulcer</th>
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</tr>
<tr>
<td>7</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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</table>

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

Fig 1. Representative coronary angioscopic findings at 3 months follow-up in 2 patients who underwent radiation therapy for in-stent restenosis. (Upper panel) Patient no. 2. The intima over 3 struts in the proximal segment of the stent has disappeared and there is ulceration of the vascular wall under the struts (Left and Middle), although the intima in the distal radiated segment of the stent is almost normal (Right). (Lower) Patient no. 3. The proximal half of the stent strut is reflecting the light of the angioscope, which shows that the intima over the stent has completely disappeared (Left). A stent strut beneath the thin intima and a small thrombus on the yellow plaque can be seen (Middle). The intima over the stent is so thin that the stent strut is easily seen underneath (Right).

Fig 2. Angioscopic findings of patients nos 1, 4, 5, 6 and 7 (from Left to Right) at 3 months follow-up. Patients no. 1 and 7 have normal intima and the others have thin transparent intima over the stent.
Follow-up angiography after 3 months showed that the MLD (2.34±0.62mm) had been well maintained. No one showed restenosis or subacute thrombosis and none underwent target lesion revascularization.

The angioscopic examination (Table 2) showed that the intima over the stent disappeared in 2 patients and ulceration of the vascular wall was observed in 1 patient (Fig 1). Two patients had normal intima and the others had transparent intima over the stent (Fig 2).

Discussion

Angioscopic examination was performed at 3 months follow-up to evaluate the early changes of the intima after radiation of a coronary artery segment for in-stent restenosis. Bare stent struts not covered with intima were observed in 2 patients, and 1 patient showed ulcer formation under the stent.

Mega trials (PREVENT1 and INHIBIT4) showed the effectiveness of radiation therapy in preventing restenosis after angioplasty, and there are several reports of marked inhibition of neointimal hyperplasia in animal models.5,6 We observed the lack of intima over the stent, so radiation may not only inhibit further proliferation of the neointima, but may also debulk the intima that had increased after the initial stent implantation. Although detachment of the neointima might occur with balloon angioplasty alone before the radiation therapy, we previously demonstrated that the neointima increased and covered the stent at least 1 month after standard implantation of a stent without subsequent radiation. Shiran et al reported that intravascular ultrasound revealed tissue neointimal formation over the stent shortly after catheter-based treatment of in-stent restenosis.8 Therefore, transparent, thin intima and lack of intima over the stent at 3 months after radiation suggest the decrease in the thickness of the intima over the stent occurred after the brachytherapy, although we lack angioscopic images from immediately after brachytherapy. It is conceivable that the intimal cells over the stent may become apoptotic or necrotic, and subsequently disappear after radiation.

Thrombosis is a major problem with radiation therapy10,11 and based on the results from animal experiments it is generally recommended that the patients who undergo radiation therapy should take antiplatelet medicine for a long time to prevent late thrombosis or total occlusion. Vodovotz et al reported that the healing response in irradiated porcine arteries was delayed and that this delay may promote thrombus formation associated with impaired reendothelialization.9 Furthermore, radiation impaired the endothelium through reduction of nitric oxide production, which can potentially result in thrombosis.11–13 In the present patients, who had both aspirin and ticlopidine, none had evidence of clinically significant thrombus formation. Sufficient antiplatelet therapy will prevent late thrombosis, because there was only one patient in the present study with a small thrombus in the radiated segment. Waksman et al reported that late total occlusion occurred in 28 patients treated with radiation (9.1%) after brachytherapy for 308 patients with in-stent restenosis.14 In that study, patients received ticlopidine 250mg twice daily or clopidogrel 75mg daily for only 1 month and aspirin 325mg daily. A recent trial showed a lower rate of late thrombosis with long-term antiplatelet therapy.15

Study Limitations

The incidence of ulceration of the vessel wall may have been higher because angioscopy can not observe the whole vessel wall. A longer term follow-up study is needed to delineate the fate of the ulceration and the bare stent struts.

Conclusion

We detected a lack of intima formation over the stent after radiation therapy for in-stent restenosis. Angioscopy was useful in characterizing the surface of the arterial wall.

References