Late Vascular Response to Repeat Stenting for In-Stent Restenosis With and Without Radiation
An Intravascular Ultrasound Volumetric Analysis

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Background—Re-stenting of in-stent restenosis (ISR) improves acute angiographic results.

Methods and Results—Volumetric intravascular ultrasound analysis was performed in 70 ISR lesions that received either placebo (n=36) or 192Ir radiation (n=34). ISR lesions treated by re-stenting were divided into 3 groups: old stent not re-stented (A), old/new stent overlap (B), and new stent only (C). ISR lesions treated without re-stenting were categorized as D. In placebo patients, postintervention lumen volume index (LVI) was significantly greater in re-stented segments B and C than in non–re-stented segment A (P<0.05). At follow-up, however, LVI was similar in all 4 segments secondary to the increased intimal hyperplasia (IH) reaccumulation within the re-stented segments. In patients treated with 192Ir radiation, LVI was maintained from baseline to follow-up only in non–re-stented segments A and D. Conversely, there was a significant decrease in LVI in re-stented segments B and C (P<0.05). Qualitatively, 79% of patients in the irradiated group had stent struts with undetectable neointimal versus only 27% in the placebo group (P<0.001). Coefficient of variation of IH reaccumulation was greater in re-stented segments of 192Ir patients (B 57.3% and C 58.9%) than in re-stented segments in placebo patients (B 27.3% and C 26.8%) and non–re-stented segments in irradiated patients.

Conclusions—Additional lumen gain from re-stenting ISR lesions is counteracted by exaggerated neointimal proliferation in placebo patients. Maximum effectiveness and safety of radiation can be achieved for ISR lesions when treated without re-stenting. Thus, regardless of supplementary intravascular brachytherapy, repeat stenting strategies provided little long-term advantage. (Circulation. 2002;105:2465-2468.)

Key Words: restenosis ▪ radioisotopes ▪ stents ▪ coronary disease

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regardless of the mechanical technique and the number of attempts, recurrent rates after treatment of in-stent restenosis (ISR) remain high.1,2 Conversely, recent studies of adjunctive intravascular brachytherapy (IVBT) have shown a striking improvement in long-term outcomes.3-5 In the early IVBT trials, late stent thrombosis occurred in 5% to 10% of patients and was associated with fresh stent deployment and early discontinuation of antiplatelet therapy.6,7 As a result, guidelines for IVBT include the recommendation to avoid re-stenting. Interventionists, however, view re-stenting of ISR lesions as a relatively easy technique to obtain good acute lumen dimensions. Thus, “to re-stent or not to re-stent” these lesions is an ongoing debate. The aims of the current study are to evaluate vascular responses after re-stenting of ISR lesions and to investigate the impact of gamma radiation on these responses.

Methods

Study Population and Protocol
The study population consisted of patients from WRIST (Washington Radiation for In-stent Restenosis Trial),6 a single center, prospective, double-blinded, randomized, placebo-controlled trial that evaluated the safety and effectiveness of IVBT gamma radiation in patients with ISR. ISR lesions in native coronary arteries were selected for the current analysis. In WRIST, additional stents were used, as needed, to optimize final angiographic results or to cover unstented portions of the lesion (including edge dissection). All patients received ticlopidine 500 mg/d for 1 month, regardless of additional stent use. Inclusion/exclusion criteria, intervention procedure, 192Ir-source selection, and prescribed dose have been published.5

Intravascular Ultrasound Imaging and Analysis
Intravascular ultrasound (IVUS) was performed after radiation and at a 6-month follow-up. Images were acquired using commercially

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available imaging systems with 30 or 40 MHz mechanical transducers (CVIS/Boston Scientific Corporation) with automated transducer pullback (0.5 mm/sec) after administration of intracoronary nitroglycerin (150 to 200 μg).

All IVUS images were interpreted at an independent core laboratory blinded to the treatment protocols (Stanford Cardiovascular Core Analysis Laboratory). Quantitative analysis was performed with validated, commercially available planimetry software (TapeMeasure, IndecSystems, Inc). Cross-sectional measurements of lumen and stent area were performed manually every 1 mm throughout the ISR lesion.

Four segment types were identified. ISR lesions treated with repeat stenting were divided into old stent not re-stented (A), old stent/new stent overlap (B), and new stent only (C). ISR lesions treated without repeat stenting were categorized as segment D. Any segment <3 mm in length was excluded from analysis. For the 192Ir-radiation group, only fully irradiated segments confirmed by the independent angiographic core laboratory (Cardiovascular Research Foundation, New York) were included.

For each of the 4 segment types, Simpson’s method was used to calculate stent, lumen, and intimal hyperplasia (IH; stent−lumen) volumes. Volumes were then divided by length to create an index (ie, stent, lumen, and IH volume index); results are reported as mm³. The axial variability in IH reaccumulation was assessed by calculating the coefficient of variation of the increase in IH for each segment by dividing mean IH×100 by the standard deviation of IH. Qualitative analysis was used to assess “undetectable neointima,” defined as the lack of neointimal coverage (at follow-up) of newly placed stents (segments B and C) by visual assessment.

### Summary of Volumetric IVUS Results

<table>
<thead>
<tr>
<th>Segment</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, n</td>
<td>11</td>
<td>13</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>ISR Length, mm</td>
<td>18.2±9.1</td>
<td>14.2±9.2</td>
<td>12.8±7.0</td>
<td>23.6±10.0</td>
</tr>
<tr>
<td>Postintervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen volume index, mm³</td>
<td>5.8±1.6</td>
<td>7.2±0.7</td>
<td>7.7±2.2</td>
<td>6.6±2.8</td>
</tr>
<tr>
<td>Stent volume index, mm³</td>
<td>8.7±2.6</td>
<td>7.2±0.7</td>
<td>7.7±2.6</td>
<td>9.3±3.7</td>
</tr>
<tr>
<td>IH volume index, mm³</td>
<td>2.9±1.2</td>
<td>0</td>
<td>0</td>
<td>2.7±1.2</td>
</tr>
<tr>
<td>CV of IH area, %</td>
<td>31.5±12.8</td>
<td>NA</td>
<td>NA</td>
<td>32.4±13.5</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen volume index, mm³</td>
<td>4.8±2.1</td>
<td>4.7±2.0</td>
<td>4.5±2.7</td>
<td>5.0±2.8</td>
</tr>
<tr>
<td>Stent volume index, mm³</td>
<td>9.0±2.3</td>
<td>7.8±4.7</td>
<td>7.6±1.5</td>
<td>9.4±3.7</td>
</tr>
<tr>
<td>IH volume index, mm³</td>
<td>4.2±2.3</td>
<td>3.2±1.7</td>
<td>3.1±1.6</td>
<td>4.4±2.4</td>
</tr>
<tr>
<td>CV of IH area, %</td>
<td>29.4±12.3</td>
<td>27.3±18.2</td>
<td>26.8±15.2</td>
<td>30.6±13.0</td>
</tr>
<tr>
<td>192Ir, n</td>
<td>13</td>
<td>11</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>ISR length, mm</td>
<td>15.3±7.5</td>
<td>14.7±8.8</td>
<td>12.3±5.4</td>
<td>20.6±6.8</td>
</tr>
<tr>
<td>Postintervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen volume index, mm³</td>
<td>6.4±2.1</td>
<td>7.1±2.2</td>
<td>7.2±2.3</td>
<td>6.0±2.0</td>
</tr>
<tr>
<td>Stent volume index, mm³</td>
<td>9.5±2.4</td>
<td>7.1±2.2</td>
<td>7.2±2.3</td>
<td>8.8±2.5</td>
</tr>
<tr>
<td>IH volume index, mm³</td>
<td>3.1±1.0</td>
<td>0</td>
<td>0</td>
<td>2.8±1.0</td>
</tr>
<tr>
<td>CV of IH area, %</td>
<td>28.2±10.4</td>
<td>NA</td>
<td>NA</td>
<td>36.3±11.3</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen volume index, mm³</td>
<td>6.7±2.4</td>
<td>6.1±1.8</td>
<td>5.6±2.4</td>
<td>5.4±2.5</td>
</tr>
<tr>
<td>Stent volume index, mm³</td>
<td>9.5±2.7</td>
<td>7.5±2.2</td>
<td>7.1±2.3</td>
<td>8.7±2.4</td>
</tr>
<tr>
<td>IH volume index, mm³</td>
<td>2.8±1.3</td>
<td>1.4±0.8</td>
<td>1.5±1.3</td>
<td>3.3±1.4</td>
</tr>
<tr>
<td>CV of IH area, %</td>
<td>30.0±12.1</td>
<td>57.3±58.7</td>
<td>58.9±67.5</td>
<td>42.4±12.6</td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean±1 SD and categorical data are expressed as frequency. CV indicates coefficient of variation.

### Statistical Analysis
Continuous data are presented as mean ± ISD, and categorical data are presented as frequencies. Continuous variables were compared using ANOVA and paired or unpaired Student’s t tests. Categorical variables were compared using χ² statistics and Fisher’s exact test. P<0.05 was considered significant.

### Results

#### Overall Results
Complete serial (post-irradiation and follow-up) IVUS studies were available in 70/100 native artery ISR lesions (34 192Ir-irradiated; 36 placebo). New stents were implanted into 14/34 192Ir-irradiated and into 15/36 placebo lesions. There was no statistical difference between these 2 groups in baseline clinical, lesion, and procedural characteristics compared with the overall cohort.

The Table summarizes baseline and follow-up IVUS results. In both 192Ir and placebo groups, ISR lesions treated without repeat stenting (segment D) were significantly longer than re-stented segments (B or C) in both irradiated and placebo lesions (P<0.05 for both).

#### Normal Vascular Responses to Re-Stenting ISR in the Placebo Group
The left panel of Figure 1 shows the results for the placebo patients. Post-intervention lumen volume index was signifi-
cantly larger in re-stented segments B and C than in non-re-stented segment A ($P<0.05$). At follow-up, however, lumen volume index was similar in all 4 segments ($P=\text{NS}$) because of the increased amount of neointimal hyperplasia in segments B and C ($P<0.05$). These results suggest that re-stenting ISR lesions obtains larger acute lumen dimensions but is associated with increased intimal proliferation, which results in similar absolute lumen volumes at follow-up.

**Impact of Gamma Radiation on Late Vascular Responses**

The right panel of Figure 1 shows the results of the irradiated patients. In patients treated with $^{192}$Ir, lumen dimensions were maintained from postintervention to follow-up only in non-re-stented segments A and D. Conversely, there was a significant decrease in lumen dimensions in re-stented segments B and C ($P<0.05$). These observations suggest that the maximum effectiveness of $^{192}$Ir radiation in treating ISR lesions is limited to non-re-stented segments.

**Comparison of Placebo and Patients Exposed to Gamma Radiation**

Qualitative analysis showed that 79% (11/14) of patients in the irradiated group who received newly placed stents had struts with undetectable neointima at follow-up versus only 27% (4/15) in the placebo group ($P<0.001$).

We assessed the axial variability in IH reaccumulation in both the irradiated and placebo patients by calculating the mean coefficient of variance of the increase in IH. The coefficient of variation of IH was greater in the re-stented segments of the $^{192}$Ir patients (B = 57.3% and C = 58.9%) than in the re-stented segments in the placebo patients (B = 27.3% and C 26.8%) and the non-re-stented segments in the irradiated patients (Table). Along with the reduction of overall IH, radiation caused greater point-to-point heterogeneity in IH thickness, accounting for poorly covered struts when new stents are implanted. Figure 2 shows representative cases demonstrating the axial variability of IH in the re-stented segment of the 2 groups.
Discusison

ISR: “To Re-Stent or Not to Re-Stent?”
This IVUS investigation has several important messages for ISR treatment strategies. Additional stent deployment that creates a “stent sandwich” is a relatively simple technique with angiographically better acute results. The acute benefit of re-stenting (ie, larger lumen dimensions), however, is offset by exaggerated intimal proliferation. This results in equivalent lumen dimensions at follow-up in re-stented and non-re-stented segments, whether or not patients were treated with vascular brachytherapy at the time of re-stenting.

ISR lesions result from an exaggerated biological response to stent metal. Re-stenting seems to evoke a similar exaggerated intimal response. In addition, re-stenting may increase creatine kinase-MB release. Therefore, in the current era, the main benefit of additional bare metal stent implantation may be the prevention of acute occlusion due to a dissection flap.

Stenting ISR With Adjunctive Radiation
After re-stenting, some amount of neointimal proliferation is necessary to cover the newly placed stent struts, whereas maximum inhibition of additional neointimal proliferation is welcomed in the previously placed and endothelialized old stent. Adjunct vascular brachytherapy seems to suppress additional neointimal proliferation in the old stent, but at the expense of preventing endothelialization of the new stent. In the current analysis, 80% of the new stents might have areas of limited endothelialization. This may help to explain the increased late thrombosis rate in re-stented lesions. Thus, there are 2 reasons that re-stenting should be avoided. The acute-lumen-gain benefit of re-stenting is not sustained and areas of the newly placed stents may not be covered with neointima.

Limitations
There are several limitations to the current study, including lack of randomization of the repeat stenting strategy, different lengths of segments A, B, C, and D, and small numbers of lesions in the various groups. In addition, because of the finite resolution of IVUS, endothelialization and very thin neointima layer on the struts could not be differentiated by qualitative analysis.

Conclusions
Additional lumen gain from re-stenting ISR lesions is counteracted by exaggerated neointimal proliferation. Regardless of supplementary intravascular brachytherapy, re-stenting strategies provide little advantage to improve long-term outcomes.

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References
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