Advances in Interventional Cardiology II: A Case Study

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Table of Contents

Introduction ........................................ 2
Case Patient 1 ................................. 2
Radiation Physics and Biology ............. 4
Conclusion ........................................ 8
Summary Points ............................... 8
References ..................................... 9

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I. INTRODUCTION

Since its inception, the success of percutaneous transluminal coronary angioplasty (PTCA) has been limited by the problem of restenosis of the treatment site. Restenosis is now understood to be a multifactorial process. First, there is elastic recoil of the overstretched vessel wall, which occurs nearly immediately after balloon deflation. Second, neointima formation occurs for up to several months, with increased proliferation and migration of multiple cell types as well as increased matrix production. Third, in a process akin to wound healing, vascular remodeling occurs, which decreases the size of the vessel area. Each of these effects contributes to a decrease in the size of the lumen.

Multiple pharmacologic approaches to prevent restenosis have been attempted. Although many showed promising results in animal trials, none have proven successful in large-scale clinical trials. The use of intracoronary stents has reduced the occurrence of clinically significant restenosis in a limited number of lesion types by preventing elastic recoil and negative vascular remodeling. By stimulating inflammation, however, these stents may actually increase neointimal formation, resulting in a new lesion type, in-stent restenosis. Most recently, the use of intravascular radiation as a means of preventing restenosis has gained considerable attention. Researchers realized ionizing radiation’s ability to inhibit or kill rapidly dividing cells (hence its effectiveness in treating cancer and benign hypertrophic conditions) might directly alter the major processes of restenosis (e.g., neointima formation and negative remodeling).

This is the second part of a 2-part review on interventional cardiology. The first part emphasized diagnosis and treatment of multivessel coronary artery disease as well as coronary thrombosis (Hospital Physician Cardiology Board Review Manual, Volume 6, Part 5). Two case patients were presented to highlight features of the management of these conditions. The second part presents one case patient and discusses intravascular radiation for the prevention of restenosis after angioplasty. A complete review of interventional cardiology is well beyond the scope of this article; however, major advances in the field are described as are trials supporting the use of current interventions.

II. CASE PATIENT 1

PRESENTATION

Patient 1 is a 67-year-old man who underwent angioplasty to his mid-left anterior descending artery (LAD) (lateral branch of a double-barrel LAD) for treatment
of exertional angina. He had an excellent result with balloon dilation alone, resulting in a residual stenosis of less than 10% as shown by angiography. His postprocedural course was unremarkable; he did well and had no symptoms for 3 months.

Subsequently, he had a gradual return of his exertional angina. Repeat cardiac catheterization revealed normal left ventricular function, mild disease in the right coronary artery (RCA) and circumflex systems, and a recurrence of the lesion in his mid-LAD. He again underwent PTCA, and this time an intracoronary stent was placed with excellent results. He was treated for 1 month with a thienopyridine; he then received long-term treatment with aspirin and aggressive lipid-lowering agents. He did well for approximately 4 months before again developing exertional angina. Repeated angiography reveals diffuse in-stent restenosis of his mid-LAD (Figure 1).

- What are the most appropriate treatment options for patient 1’s coronary artery disease?
  A) Repeat angioplasty in the stented segment, with adjunctive endovascular brachytherapy
  B) Balloon angioplasty of the stented segment with a slightly oversized balloon
  C) Referral to a cardiothoracic surgeon for coronary artery bypass graft surgery (CABG)
  D) Debulting of the in-stent stenosis with rotational atherectomy followed by balloon angioplasty

Discussion

The correct answers are B, C, and D. Assuming that the initial stent was properly deployed, these choices are all currently considered standard therapy. They all, however, have considerable limitations. Balloon angioplasty alone for in-stent stenoses has been associated with restenosis rates of more than 50%. Initial evaluations of rotational atherectomy showed continued high restenosis rates with no difference in target vessel revascularizations when compared with balloon angioplasty alone. Other ablative devices such as excimer laser have also been compared with both balloon angioplasty and rotational atherectomy, but again no significant difference was found in the need for revascularization at long-term follow-up. Finally, surgery has its own limitations as previously discussed in the first part of this review (Hospital Physician Cardiology Board Review Manual, Volume 6, Part 5, “Advances in Interventional Cardiology I: Case Studies”).

TREATMENT

Patient 1 is treated with balloon angioplasty and β-irradiation; he has good results by angiography and no recurrence of symptoms after 1 year (Figure 2).
Treatment using intravascular radiation is discussed in greater detail in the following section.

III. RADIATION PHYSICS AND BIOLOGY

GENERAL PRINCIPLES

Ionizing radiation is radiation of sufficient energy to induce atom ionization or to break chemical bonds. It is classically divided into electromagnetic (e.g., x-rays and γ-rays) and particulate (e.g., α particles, β particles, protons, neutrons). Radiation sources contain radioisotopes that are characterized by various parameters including activity, half-life, and type of radiation emitted (Table 1). Most studies on intravascular radiation therapy have used sources that emit either β or γ radiation or both. All of the β and γ sources have defined dosing characteristics, with β-emitters generally having higher energy and γ-emitters having greater penetration. Radioisotopes may be naturally occurring or be manufactured by fission or particle bombardment (Table 2).

The effects of radiation on living tissue vary with the dose delivered and the susceptibility of the tissue to damage. Highly differentiated, nonproliferating cells can tolerate much higher doses of radiation than can rapidly dividing cells. For intracoronary radiation therapy, this difference allows the uninjured and thus relatively quiescent cells of the vasculature to remain essentially unafected by radiation and allows for selective action against the hyperproliferative cells involved in restenosis. At the doses used for intravascular radiation therapy, the principle response in the vasculature is loss of cell replication and eventual cell death from chromosomal damage, with some additional evidence for induction of apoptosis.

ANIMAL STUDIES

Various animal models have been developed to evaluate intravascular radiation for the prevention of restenosis. In general, these studies use an arterial overstretch injury model with or without the use of stents followed by intravascular radiation therapy delivered by numerous different means. Repeated angiography and histomorphometric analysis at various time-points are used to evaluate the efficacy of therapy.

Using a pig coronary balloon overstretch model, Wiedermann and colleagues were the first to demonstrate the effectiveness of intravascular radiation therapy. They used a low-activity gamma source (192Ir) delivered manually in a noncentered catheter and administered a 20-Gy dose at a radial depth of 1.5 mm immediately before balloon injury. This treatment resulted in a greater than 70% reduction in neointima formation at 30 days compared with control. In a follow-up study, the same group demonstrated a persistence of this treatment benefit after 6 months. Waksman and colleagues confirmed these results in a similar model and demonstrated a dose-response relationship, with their highest radiation dose (14 Gy) having the greatest effect. Interestingly, this group was also able to show that delivery of the radiation dose 2 days after injury was more effective than dosing at the time of injury. This effect is not unexpected because at 2 days after injury, more cells are actively dividing and thus more susceptible to radiation therapy. Additional work has shown similar reductions in neointima formation for γ radiation in stented arteries.

Similar beneficial effects were demonstrated for β-irradiation by Waksman and colleagues who delivered a broad range of doses (7 to 56 Gy at 2 mm from the source) via a noncentered 5F catheter with a hydraulically actuated 99Sr/Y source train. As with their γ-irradiation work, these investigators were able to demonstrate a significant reduction in neointima formation in a dose-dependent fashion and, for the first
time, a prevention of the vessel constriction that, as previously discussed, is an additional component of restenosis. Additionally, β-irradiation has been shown to inhibit neointima formation in stented coronary arteries.  

**HUMAN STUDIES**

The positive results observed in animal studies have led to multiple clinical trials of intracoronary radiation therapy using both γ and β sources.

**Gamma Radiation**

The first clinical trial in coronary arteries, conducted by Condado and colleagues, was an unblinded trial in 22 arteries of 21 patients using a 30-mm 192Ir source delivered manually via a noncentered 4F monorail system with a calculated dose of 20 to 25 Gy at 1.5 mm from the source. PTCA was successful in 19 of 22 patients, and all patients received radiation without difficulty. Initial follow-up (mean, 8 months) demonstrated a restenosis rate of only 28%. Of note, 2 patients had subacute thrombosis, 1 patient had pseudoaneurysm formation, and 3 additional patients had vessel dilation or irregularities. At 3-year follow-up, the restenosis rate had declined to 23.8% (because of regression of stenosis in one lesion), but 3 additional pseudoaneurysms were noted. This study demonstrated the feasibility of clinical intracoronary therapy but raised concerns about possible safety. Recalculation of the actual delivered radiation doses revealed that in the arteries that developed pseudoaneurysms, the actual dose was considerably higher than predicted (in one case, as high as 92 Gy). This dose could also have accounted for the increased subacute closure rate because high-dose radiation is known to result in delayed endothelialization and retained thrombus.

The first randomized, placebo-controlled trial of intracoronary radiation therapy (the SCRIPPS [Scripps Coronary Radiation to Inhibit Proliferation Post Stenting] trial) also used an 192Ir source. This trial enrolled 55 patients with in-stent restenosis or restenotic lesions in which a stent was to be implanted in either native vessels or saphenous vein bypass grafts. After optimal intervention, patients underwent intravascular ultrasound to determine proper dosing, with a goal of no less than 8 Gy delivered to the medial target nearest the source and no more than 30 Gy delivered to the medial target farthest from the source. At 6-month follow-up, the angiographic restenosis rate was 17% in the treated group compared with 54% in controls (P = 0.01). The composite clinical endpoint (death, myocardial infarction, stent thrombosis, target vessel revascularization at 12 months) was reached in 15% of the treated group and 48% of controls (P = 0.01). In contrast to Condado’s series, no patients had aneurysm formation, which was likely because of more careful dosing. At 2-year follow-up, this clinical benefit was preserved, with target revascularization occurring in 15.4% of treated versus 44.8% of controls (P = 0.01). Three-year follow-up data are now available showing statistically significant reductions in target vessel revascularization and restenosis in the irradiated group, with no new adverse events noted.

Two additional clinical studies using intracoronary γ-radiation have been completed. WRIST (Washington Radiation for In-stent Restenosis Trial) randomly assigned 130 patients with in-stent restenosis (both native vessel and saphenous vein grafts) to receive placebo or 15 Gy of noncentered radiation at 2 mm from a 192Ir source. After 6 months, restenosis was 19% in the treated group compared with 58% in the placebo group, whereas major adverse cardiac events occurred in 29% of the irradiated group and 68% of the placebo group (P < 0.001). In the Gamma-I study, 252 patients with native vessel in-stent restenosis were randomly assigned to receive either 8 to 30 Gy of radiation (to the level of the adventitia) or placebo via 6-, 10-, or 14-seed source trains. Overall in-stent restenosis rates after 6 months were 21.6% versus 52% (treatment versus placebo, P < 0.001), whereas in-lesion rates were 32.4% versus 56.4%, respectively (P = 0.001).

**Beta Radiation**

The first clinical trial of intracoronary β-radiation was a nonrandomized pilot study conducted by Verin and colleagues of 15 patients with de novo or restenotic
native artery lesions. Using an $^{90}$Y source with a segmented centering balloon, 18 Gy of radiation was delivered at the luminal surface, with an average dwell time of 6.5 minutes. After 6 months, angiographic restenosis occurred in 40% of subjects, with target lesion revascularization occurring in 27%. There was no evidence of aneurysm formation or retained thrombus. This pilot study showed the feasibility and short-term safety of this dosing method. Its lack of efficacy may be attributed to inadequate dosing, since the 18-Gy dose at the luminal surface yielded only approximately 8 Gy at 1 mm and less than 4 Gy at 2 mm into the vessel wall.

A second feasibility trial using $\beta$-irradiation was the Beta Energy Restenosis Trial (BERT).\(^3\) Patients with single, de novo, native vessel lesions received doses of 12, 14 or 16 Gy at 2 mm from a $^{90}$Sr/$^{90}$Y source-train delivered by a noncentered, hydraulically actuated monorail catheter system in this nonrandomized study. Six-month angiographic follow-up demonstrated a restenosis rate of 15%.

A third catheter system, which uses the $\beta$-emitter $^{90}$Y, was evaluated in the Beta-WRIST study of patients with in-stent restenosis.\(^3\) Fifty patients with in-stent restenosis treated with various interventional techniques were additionally treated with $\beta$-radiation from a balloon-centered, 29-mm long source wire to a dose of approximately 21 Gy at 1.0 mm from the balloon surface. The placebo group from the WRIST trial was used as a control. The 6-month angiographic restenosis rate was 34% in the treated group compared with 71% in the historic control ($P = 0.001$). Additionally, target lesion revascularization (28% versus 66%), target vessel revascularization (34% versus 72%), and major adverse cardiac events (34% versus 76%) were all significantly reduced ($P = 0.001$) in the treatment group versus controls, respectively.

PREVENT (Proliferation REduction with Vascular ENergy Trial) enrolled 105 patients with de novo (70%) or restenotic lesions (30%) who underwent PTCA with or without placement of a stent.\(^3\) Patients were randomly assigned to receive 0, 16, 20, or 24 Gy of $\beta$-radiation delivered at 1 mm into the arterial wall by a $^{32}$P-nitinol, balloon-centered source wire. The 6-month restenosis rate of the angiographic target site was 8% in the treatment group and 39% in controls ($P = 0.0012$). The 12-month clinical follow-up showed a target lesion revascularization rate of 6% in the treatment group compared with 24% in controls ($P < 0.05$), with no significant difference in major adverse cardiac events between groups. No differences were noted among the 3 dose groups.

START (STents And Radiation Trial)\(^4\) enrolled 476 patients with in-stent restenosis less than 20 mm in length and randomly assigned them to receive either placebo or $\beta$-radiation from the same system used in the BERT study. The prescribed dose was 16 to 20 Gy at 2 mm from the center of the source, depending on vessel size. Using angiography, the 8-month segment restenosis rate was 28.8% in the treatment group compared with 45.2% in controls ($P = 0.001$). Target vessel revascularization was reduced from 24.1% in the placebo group to 16.0% in the treatment group ($P = 0.008$). Additionally, major adverse cardiac events occurred in 25.9% of controls and 18.0% of the radiation group ($P = 0.039$).

### Radioactive Stents

An additional method for delivering intravascular radiation is to deploy a metallic stent that has been made radioactive. Because stents are permanently deployed within the artery, the radioactive source must have a relatively low activity and short half-life to ensure that the total dose of radiation delivered is within a therapeutic range. Carter and colleagues\(^4\) implanted $^{32}$P-containing...
stents with a broad range of activities in a pig coronary injury model. Stents from the low-activity (0.15–0.5 µCi) and high-activity (3.0–23.0 µCi) groups demonstrated a significant reduction in neointima formation when compared with nonradioactive control stents at 30 days (P ≤ 0.01). The stents from the intermediate-activity (1.0 µCi) group had markedly increased neointima formation when compared with controls (P ≤ 0.01); this result may have been related to delayed endothelialization. A 6-month follow-up showed a loss of benefit in the low-activity group suggesting its initial effect may have been only to delay neointima formation rather than to prevent it.43

As with catheter-based delivery systems, the evaluation of radioactive stents has quickly moved into clinical trials. IRIS (Isostent for Restenosis Intervention Study) was a 2-part, nonrandomized trial using 32P-embedded Palmaz-Schatz stents for de novo or restenosed lesions in native vessels. Part 1 (n = 32) of this trial evaluated stents with low activity (0.5–1 µCi) and found no significant adverse events at the 30-day endpoint but did demonstrate a 31% restenosis rate at 6 months;44 7 of the restenosed vessels were less than 2.5 mm in size. In part 2 of the trial, stents with slightly higher activity (0.7–1.5 µCi) were implanted in an additional 25 patients with a similar 39% segment restenosis rate at 6 months.45

Four additional radiation doses have been evaluated in similar studies by Albiero and colleagues.46 In the first study, 2 types of radioactive stents were used: a Palmaz-Schatz with an activity of 0.75 to 3.0 µCi (group 1) along with a BX stent with activities of 3.0 to 6.0 µCi (group 2) and 6.0 to 12.0 µCi (group 3).46 Initial lesion characteristics were similar in the 3 groups except that lesions were slightly longer in group 3. At 6-month follow-up, there were no deaths and only one myocardial infarction (from subacute closure of the stent 3 months after implantation). Quantitative angiography revealed an apparent dose-related reduction in neointimal hyperplasia with pure intrastent restenosis rates of 16% in group 1, 3% in group 2, and 0% in group 3. Intralesion restenosis, however, was 52% in group 1, 41% in group 2, and 50% in group 3 (P = not significant [NS]) with corresponding target vessel revascularization rates of 52%, 43%, and 52% (P = NS), respectively. In a subsequent study, a fourth group of patients received a radioactive BX stent with an activity of 12.0 to 21.0 µCi.47 At 6-month follow-up, a similar safety profile was seen as was a very low intrastent restenosis rate (4%) but intralesion restenosis remained high at 30%. Table 3 compares the results in all 4 groups. The discrepancies between intrastent and intralesion restenosis rates are the result of increased neointima formation at the ends of the stents, the so-called “candy wrapper” or edge effect which is discussed in the next section.

The high lesion restenosis rates as well as questions about manufacturing and shelf-life of the radioactive

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**Table 3. Angiographic Data for 32P Radioactive β-Emitting Stents Implanted for Treatment of De Novo, Native Vessel Coronary Disease**

<table>
<thead>
<tr>
<th>Activity of Radioactive Stent, µCi</th>
<th>0.75–3.0*</th>
<th>3.0–6.0*</th>
<th>6.0–12.0*</th>
<th>12–21†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>23</td>
<td>29</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Vessel reference diameter, mm</td>
<td>2.91 ± 0.55</td>
<td>3.00 ± 0.36</td>
<td>3.08 ± 0.44</td>
<td>3.13 ± 0.45</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>12.7 ± 8.4</td>
<td>13.8 ± 6.1</td>
<td>17.6 ± 7.5</td>
<td>10.9 ± 4.6</td>
</tr>
<tr>
<td>Preprocedure MLD,‡ mm</td>
<td>0.92 ± 0.39</td>
<td>0.77 ± 0.38</td>
<td>0.74 ± 0.47</td>
<td>0.96 ± 0.54</td>
</tr>
<tr>
<td>Postprocedure MLD,‡ mm</td>
<td>3.07 ± 0.48</td>
<td>3.11 ± 0.37</td>
<td>2.87 ± 0.49</td>
<td>3.01 ± 0.47</td>
</tr>
<tr>
<td>Follow-up MLD,‡ mm</td>
<td>1.60 ± 1.08</td>
<td>1.90 ± 0.90</td>
<td>1.74 ± 1.15</td>
<td>2.08 ± 0.81</td>
</tr>
<tr>
<td>Intrastent restenosis, %</td>
<td>16</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Intralesion restenosis, %</td>
<td>52</td>
<td>41</td>
<td>50</td>
<td>30</td>
</tr>
</tbody>
</table>

MLD = minimal luminal diameter.


‡Data were obtained at baseline (preprocedure), immediately after the procedure (postprocedure), and 6 months later (follow-up).
stents have dramatically slowed further research on radioactive stents and shifted even more effort toward catheter-based delivery methods.

UNRESOLVED ISSUES

The weight of this evidence has led the U.S. Food and Drug Administration to issue preliminary approval recommendations for intracoronary brachytherapy for the treatment of in-stent restenosis using both $\gamma$ and $\beta$-source products. Multiple problems need to be addressed, however, before final approval is granted (see following 2 sections). In addition, questions about long-term safety and efficacy, the relative benefit of using $\gamma$ versus $\beta$-sources, cost-effectiveness, as well as operator training and regulation have yet to be answered.

Edge Effect

The first problem is the edge effect phenomenon, in which increased restenosis occurs in the vessel segments immediately adjacent to the target lesion. This phenomenon was first seen in trials of radioactive stents but has also been identified in both $\gamma$ and $\beta$-source trials; this increased restenosis significantly increases the need for target vessel revascularization. The effect appears to result from balloon injury to the vessel segments adjacent to the target lesion with the subsequent application of inhomogeneous and perhaps stimulatory doses of radiation.

In PREVENT, if restenosis is evaluated by including adjacent segments, the 6-month rate increases to 22% in the treatment group, although this still remains significantly reduced from the control group at 50% ($P = 0.018$). Additionally, although target lesion revascularization was significantly reduced by treatment, target vessel revascularization (a clinical measure of the significance of the edge effect) was nonsignificant by 12 months. In START, the restenosis rates reported for the analysis segment included the vessel 5 mm proximal and distal to the target lesion. However, if only the target lesion is analyzed, the restenosis rate was halved to 14% in the irradiated group. To overcome the edge effect phenomenon, recent trials have sought to incorporate wide margins for radiation treatment to clearly treat all segments that undergo balloon dilation. Whether these wide margins are effective is yet to be determined.

Late Thrombosis

The second major problem is the occurrence of late thrombosis of the irradiated vessel. As with the edge effect, this problem was originally thought to be anecdotal. However, late thrombosis is now believed to occur in anywhere from 6% to 14% of patients treated with either $\gamma$ or $\beta$-radiation and occurs well beyond the usual 14-day window associated with conventional stent placement. The predominate theory is that radiation damage leads to delayed re-endothelialization of the vessel, resulting in a prolonged prothrombotic state. This late thrombosis is of greatest concern when a new stent is placed in the irradiated segment. It is not clear whether extended treatment with thienopyridines can prevent this problem. However, data from START showed that switching to a 60-day course of a thienopyridine markedly reduced thrombosis rates.

IV. CONCLUSION

Interventional cardiology remains an actively expanding and changing field. Although the fundamental design of the simple balloon dilation catheter has changed little since Gruentzig's initial work, vast improvements in materials and construction have altered its use considerably. At the same time, significant advances have occurred in our understanding of the pathophysiology of atherosclerosis and its responses to treatment that have allowed for further refinement of PTCA use. These advances and the development of numerous adjunctive therapies (mechanical and pharmacologic) have increased the number of patients who are now candidates for endovascular treatment. Currently, it is not clear whether ongoing research will resolve continuing problems with restenosis and treatment of diffuse disease in selected patient populations.

V. SUMMARY POINTS

- Restenosis remains the main problem limiting the long-term success of PTCA.
- Restenosis is a multifactorial process involving vessel-wall remodeling and neointimal proliferation.
- Intracoronary stents have essentially eliminated mechanical remodeling but have led to the more difficult problem of in-stent restenosis, which is a purely proliferative process.
- Ionizing radiation is highly effective in preventing neoproliferative processes. The intracoronary application of ionizing radiation as an adjunctive therapy to prevent restenosis after PTCA with and without stents appears very promising. However, questions remain with regard to proper lesion treatment, long-term safety, and efficacy.
REFERENCES


