Prevention of Coronary Restenosis
The Evolving Evidence Base for Radiation Therapy

Richard E. Kuntz, MD, MSc; Donald S. Baim, MD

Restenosis, the time-limited renarrowing of the lumen of a coronary artery, affects 20% to 40% of patients in the months after an initially successful intervention. As such, it represents the extreme form of the healing response that produces a normally distributed amount of late loss in lumen diameter at all interventional sites. To some extent, the percentage of patients who develop renarrowing can be reduced by acutely achieving the largest possible lumen diameter (by stenting) via the “bigger is better” principle. Stenting can also prevent any late loss caused by vascular contraction, although it does not reduce (and, in fact, increases) the amount of late loss due to excessive intimal hyperplasia. To lower the restenosis rate further and to provide durable treatment for in-stent restenosis when it occurs, potent treatments to blunt this late loss are thus required.

See p 2165

Although a number of pharmacological approaches have been tried to limit late loss, only a few have shown even preliminary efficacy. However, radiation therapy seems to provide an interesting, nonpharmacological approach to controlling this excessive response to injury response that is analogous to its role in limiting the growth of many rapidly proliferating neoplasms and non-neoplastic conditions of excessive proliferation (eg, exophthalmos of Grave’s disease or keloid scar formation).

There are some concerns with this hypothesis. First, the number of proliferating cells in an active restenosis lesion is generally small, and such cells are virtually absent in a de novo lesion that might undergo prophylactic radiation at the time of original intervention. Because the main effect of vascular radiotherapy is breaking single- and double-stranded DNA and, thereby, killing actively dividing cells in the media and intima, the paucity of such actively dividing cells in the target tissue is of concern. Hopefully, radiation can also injure the dormant cells located in the media and adventitia that will be called on to migrate, proliferate, and synthesize matrix after the coronary intervention in a manner similar to the radiotherapy inhibition of the infiltration by inflammatory cells and fibroblasts after initial keloid excision. Otherwise, the radiation of de novo lesions may have to wait until active cell division has begun.

Other theoretical problems include dosing, paradoxical stimulation, late failure, as well as dosimetry and other practical issues. The minimum radiation dose that will prevent excessive hyperplasia in aggressive proliferators who would have restenosed, without interfering with the healing required to repair dissections and to cover the surface of stents in the majority of patients who would not have restenosed, has yet to be determined. Paradoxical stimulation is the potential for subtherapeutic (sublethal) doses to injure some cellular populations and cause paradoxical excessive tissue proliferation. Late failure, the potential for late aneurysm formation or very late term (>5 years) coronary renarrowing like that seen after higher-dose (~50 Gy) treatments for Hodgkin’s disease, is also a concern. Dosimetry issues relate to lack of centering the source within the vessel (which may lead to a extreme differences in dose to the near and far vessel walls) and the penetration distances of β- and γ-radiation (which may lead to the shielding of deeper tissue from β rays or the irradiation of deeper, perivascular tissue by γ rays). Finally, practical issues are related to the need to accurately treat long segments and bifurcation lesions or to retreat segments when new disease arises, as well as the need to have a radiation oncologist administer the brachytherapy treatment. Despite these obstacles, both γ and β radiotherapy have demonstrated efficacy in porcine models. This efficacy is now being confirmed in early human studies.

The early clinical trials have demonstrated that many of these theoretical problems are clinical realities. (1) A greater demonstrated benefit of radiation therapy exists in patients with aggressive in-stent proliferation compared with de novo lesions, possibly suggesting the importance of matching the timing of therapy to the presence of actively dividing cells. (2) Unusually late (months, rather than days) stent thrombosis occurs in patients who undergo radiation therapy, suggesting that radiation has the potential to inhibit even the minimum healing response required to cover the stent struts. (3) The effects of treatment are inconsistent among the β-brachytherapy and β-radioactive stent trials (with the occurrence of “candy wrapper” restenosis at the ends of the treatment zone), which suggests a stimulatory effect of subtherapeutic radiation doses or the failure to deliver the prescribed radiation dose to an appropriate target depth in the iatrogenically-injured target vessel segment (so-called geographical miss).

In light of these considerations, our understanding of coronary radiation therapy and its effect on vascular renar-
narrowing is far more limited than our now relatively mature understanding of the vascular renarrowing process after conventional therapy (nonradiation) with coronary devices, and each subsequent trial adds importantly to our understanding of, and comfort with, radiation therapy. The γ-Washington Radiation for In-Stent restenosis Trial (WRIST) reported in this issue of Circulation is one such trial, and it provides strong evidence supporting the use of γ-radiation in the treatment of in-stent coronary restenosis. This cohort of patients is ideal for study because they have a high (50% to 80%) restenosis rate when treated with other modalities, they are in the midst of a proliferative process (greater radiation sensitivity), and excessive proliferation is the only mechanism for in-stent restenosis.

**Current Evidence for In-Stent Radiation Efficacy**

The 130-patient γ-WRIST by Waksman et al is 1 of 3 small-to-moderate sized (but each markedly positive) randomized trials that have demonstrated the efficacy of 192Ir γ-radiation in the prevention of restenosis in patients with in-stent restenosis. The other 2 trials were the 55-patient Scripps Coronary Radiation to Inhibit Proliferation Post Stenting (SCRIPPS) trial and the 252-patient, multicenter GAMMA-I trial. The γ-WRIST trial had an efficacy similar to that of the SCRIPPS trial against binary angiographic restenosis (treatment effect, 67% and 69%, respectively), which was larger than the 41% treatment effect reported in the larger multicenter GAMMA-I trial. Although it is typical for the best results to be seen in smaller, pioneering, single-center studies, with a lower efficacy seen in subsequent larger multicenter trials, we need to be observant for slight differences in treatment technique (particularly dosing) that may also explain the observed differential efficacy.

**Evidence for Radiation Efficacy Outside In-Stent Restenosis**

Trials to demonstrate the usefulness of radiation therapy for non-in-stent coronary obstructions must be larger and more complex than the simple in-stent restenosis trials. The reasons include (1) the more complex mechanisms of initial narrowing (variable proportions of chronic plaque build-up and vascular contraction as well as the variable contributions of radiotherapy on neointimal proliferation versus vessel wall remodeling) and (2) the larger sample sized needed due to the low expected control-arm clinical restenosis rate compared with that seen in a study of in-stent restenosis. To illustrate this point, the BETA-CATH trial, a multicenter pivotal trial of adjunctive 90Sr/90Y β-therapy for non-stented obstructions that is currently in the follow-up phase, has randomized 1455 patients to measure the radiation efficacy for both stent and non-stent coronary interventions. Given these limitations, it is not surprising that currently, no pivotal data demonstrate any efficacy for γ- or β-radiation therapy in non-stented coronary obstructions. However, many promising small, single-arm studies have reported low restenosis rates and low loss indexes under these conditions for both β- and γ-brachytherapy, as well as with β-radioactive stents. More interesting are the intravascular ultrasound findings suggesting favorable (expansion) vascular remodeling with β-brachytherapy, although such small, single-arm studies require further confirmatory imaging from randomized datasets.

**β Versus γ Radiation**

Currently, randomized evidence for a beneficial effect of radiotherapy on the prevention of restenosis in patients with in-stent restenosis is limited to the γ-source 192Ir, although Waksman et al have reported a promising recent single-arm study that uses β-radiation (125I wire). β-radiation therapy may prove to be equally efficacious as that with γ-radiation, and it has several practical advantages, including fewer changes in policy and catheterization laboratory equipment and the reduced potential for radiation exposure to patients and staff. However, β-radiation also has potential shortcomings, including its relative lack of adventitial penetrance. At least one small, uncontrolled β-radiation pilot study using 90Y showed no effect of radiation in the prevention of restenosis with a calculated 2-mm deep tissue dose <3 Gy, despite a prescribed dose of 18 Gy at the lumen surface. Potential solutions for improving uniform β-penetration include the use of higher energy β sources (such as 90Sr) and radioactive liquid-filled balloons to place the source closer to the vessel wall. Until comparable trials are available, it would be premature to conclude decisively that the current evidence base supports the efficacy of sources other than 192Ir or of radiation therapy for non-stented coronary obstructions or stented de novo lesions.

**Dosing**

Formal, definitive, randomized, dose-finding studies have not been performed for either γ- or β-radiation in the treatment of human intracoronary lesions. The prescribed doses, which are determined largely on the basis of porcine studies, have generally involved a prescription of a mean dose of 12 to 18 Gy at a depth of 2 mm. Because of geometrical factors, actual delivered doses may be significantly higher or lower in different parts of the vessel. A retrospective analysis of calculated delivered doses, however, suggests a dose-response relationship for 192Ir. Because of a lack of centering, most γ-radiation trials have prescribed at least 8 Gy to the far wall, with no more than 30 Gy to the near wall. Finally, the importance of finding the optimal dose is underscored by the suggestion that doses <10 Gy may be stimulatory, as was found in one porcine study but not in a second. These low doses may also affect vascular contraction adversely, which is important because current systems administer such sublethal dosing to deeper vascular structures and just beyond the end of the indwelling source in every intracoronary radiation treatment. If such areas were exposed to the mechanical trauma of an intervention, such as a balloon injury beyond the edge of the radiation source, this might explain the intense candy wrapper effect seen at the ends of some radioactive stents.

**Late Stent Thrombosis**

The problem of late stent thrombosis was first raised in the public forum when the data and safety monitoring board for
the multicenter BETA-CATH trial recognized an unusually high (~6%) rate of late acute thromboses in patients with de novo lesions who were randomized to stenting but not in those randomized to balloon angioplasty. Both the magnitude of the thrombosis rate (~6%) and the timing (30 to 90 days) of the thrombosis were unusual compared with other stent experiences. Presumably, the same mechanism of action intended to reduce restenosis (namely, the inhibition of neointimal formation) might also have affected the neointimal and endothelial regrowth required to cover the stent struts by 2 weeks after non-radiation stenting. In November 1998, the Food and Drug Administration was notified, and a 400-patient randomized stent branch with extended (>3 months, compared with 4 weeks in the initial stent branch) antiplatelet (ticlopidine or clopidogrel) therapy was added to the BETA-CATH Trial. Only after this attention to the problem did the occurrence of late stent thrombosis with other γ and β systems come to light. Interestingly, no reports of late thrombosis were seen in the IsoStent radiation stent registries, suggesting a potential mitigating effect of dose fractionation over a longer time compared with the near-instantaneous delivery in the brachytherapy trials. The γ-WRIST Trial has a 7% late stent thrombosis rate, which was a major contributor to the combined end point of late major adverse cardiac events. A pooled analysis of the SCRIPPS, GAMMA-I, and γ-WRIST studies suggests that patients treated with γ-brachytherapy for in-stent restenosis are at a much higher risk of late thrombosis when a new stent is deployed when compared with a non-stent treatment. Because none of these trials required extended (>2 months) antiplatelet therapy, it is not currently known whether extended antiplatelet therapy will mitigate the late stent thrombosis problem after radiation.

Do We Need a New Restenosis Model for Radiation Therapy

The prevalent model for restenosis looks at the size of the coronary lumen at 6 months; after this point, the model assumes that lumen size remains stable. The past 5 years of experience with radiation therapy have demonstrated that we must expand our views of restenosis, or at least look well beyond the 6-month time described by Nobuyoshi et al and Serruys et al for balloon angioplasty, which was confirmed for stents. Recent 3-year angiographic follow-up data from the SCRIPPS trial demonstrate that the renarrowing process continues well beyond the traditional 6-month boundary; thus, longer follow-up is appropriate. Also, a simple analysis of the luminogram within the stented segment will not suffice. Different mechanisms of postradiation restenosis may operate in the original lesion segment, the stented segment, the ballooned segment, and the actual irradiated segment, and they may also relate to the changing doses via source-specific axial fall-off. Only a combination of intravascular ultrasound and careful angiography, which documents balloon, stent, and radiation source positioning, can fully describe the contributions of contraction (or negative remodeling), expansion (or favorable remodeling), and geographical miss to the restenosis process.

Coronary Radiation Therapy Today

Coronary radiation therapy is still far from being a panacea, but it continues to gather momentum as the first potent therapy for in-stent restenosis. Only when the problem of late stent thrombosis is controlled, the precise anatomical prescription and optimum dose are fully determined, and the relative places of the radiation types (γ versus β) and sources are established will we be able to put this potent new therapy in its correct clinical perspective. However, given the high risk of recurrent restenosis in patients who present with in-stent restenosis, the absence of other effective interventional treatments, the simple pathophysiological model of pure proliferation that is ideal for radiation, and the unprecedented efficacy demonstrated for γ-radiation in 3 randomized trials, intracoronary brachytherapy does seem to be a breakthrough treatment for patients with in-stent restenosis.

References


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