Clinical Cardiology: New Frontiers

New Frontiers in Interventional Cardiology
Intravascular Radiation to Prevent Restenosis

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Any antirestenosis therapy under consideration must contend with the two basic mechanisms of vessel renarrowing following coronary intervention. The first renarrowing mechanism is vascular contraction, which can be mechanically blocked with a typical balloon expandable stent. The second renarrowing mechanism, neointimal proliferation, is a complex cellular reaction to the injury caused by the actions of mechanical devices such as balloons, stents, and atherectomy catheters. The search for an effective antiproliferative agent has been long and frustrating. Over 100 drugs and devices have been tested resulting in preclinical or clinical failures. This legacy of previous failures has made the recent successes of radiotherapy particularly gratifying.

The treatment of restenosis with vascular radiation appears to work through inhibition of smooth muscle cell proliferation. The energy emitted from an active isotope is believed to block mitosis by causing a double-stranded break in the cell’s DNA (Figure 1). Thus, by performing surgery on the vascular smooth muscle cell’s DNA, radiation prevents the proliferative ingrowth of tissue that often reblocks the vessel lumen after a successful angioplasty. The United States Food and Drug Administration’s recent premarket approval of two radiation devices has now propelled this first effective antiproliferative treatment into the mainstream of patient care. This report provides an overview of the basic laboratory and clinical data supporting the effectiveness of brachytherapy as well as some of the challenges and controversies surrounding its integration into clinical practice.

Intravascular Radiotherapy Devices
A fundamental component of any radiation delivery system is the radioisotope itself. Each isotope has important physical characteristics such as energy and half-life. Perhaps the most important differentiating characteristics of a particular radiation source is its characterization as either a γ- or β-energy source. Because both γ and β sources have been shown to be effective in the prevention of restenosis, the differences between them have been spotlighted, and the respective arguments have fueled one of the current hot debates in the vascular radiotherapy field. Regardless of whether the radiation source is photons (γ) or electrons (β), radiation probably inhibits the cellular proliferative response to injury after angioplasty by preventing cell division.

The technique of brachytherapy involves bringing the radioisotope in close proximity of the target, reducing the source to target distance (brachy: Greek from brachys, short). This minimizes undesired tissue exposure compared with treatment with external beam radiation. Brachytherapy has been routinely used by radiation therapists for several decades. Although many traditional radiotherapy concepts have been adapted for vascular use, a wide array of new technologies specifically invented for coronary artery treatment are currently under development. These new devices encompass line sources, liquid sources, gas and membrane sources, as well as stent-based delivery systems.

Catheter-Based Line Sources
Line sources are commonly used to deliver radiation to a variety of benign and malignant disorders. Radioactive sources, such as 192Ir, 32P, 90Sr, and 90Sr/Y, can be encapsulated and manufactured in 0.014- to 0.040-inch diameters that can pass easily through intracoronary catheters. Typically, after dilatation, atherectomy, and/or stenting of the target lesion, a 3 to 5 Fr catheter containing a closed-end source delivery lumen is advanced over a guidewire and positioned across the target lesion. A wire (usually composed of nylon, nitinol, or a polymer) containing radioactive sources at its distal tip is then loaded into the source lumen of the catheter and advanced distally until the radioactive sources span the target lesion. This process, called afterloading, can either be accomplished manually by the radiation oncologist advancing the source wire by hand, or automatically by a motor-driven unit. Remote automatic afterloaders can be programmed to advance and then withdraw the source wire at specific time intervals without the need for physician handling, thus reducing exposure to personnel. One variation of the line source concept is a hydraulic delivery system, where encapsulated sources are injected into a blind-end catheter by a syringe or automated pumping system.

Radiation delivery via a line source with a simple catheter can result in a source placed eccentrically within the vessel lumen. Assuming the target for radiotherapy is the adventitial...
border, a noncentered source will deliver a higher radiation dose to the adventitia closest to the catheter and a lower radiation dose to the adventitia furthest from the catheter. Alternatively, catheter centering systems, using either a segmented balloon or a helical balloon that allows perfusion during inflation have been developed to reduce dose heterogeneity by maintaining the source in the center of the lumen.

Radioactive Balloon Membranes

One method of centering a radioactive source is to create a radioactive balloon membrane. A polymer embedded with \(^{32}\)P can be sandwiched between two layers of balloon material. During balloon inflation, the radioactive membrane is brought close to the vessel wall. This hot membrane provides a relatively homogeneous radiation dose to the luminal surface. The risk of radiation leakage from this balloon material is minimal. Importantly, environmental radiation exposure from \(\beta\)-radioactive balloon materials and membranes can be minimized by using a simple Lucite shield. These devices, therefore, are particularly user friendly and can be easily adapted to the catheterization laboratory.

Radioactive Stents

Permanent implantation of a radioactive stent would have significant practical advantages over other radiation delivery systems. Currently, the majority of patients undergoing percutaneous coronary interventions receive coronary stents. Coupling the radiation delivery to the stent itself makes radiation delivery more efficient, obviating the need for a separate radiation delivery step. Several radioactive stent systems have been developed including ion-implantation of phosphorous-32 (\(^{32}\)P)\(^{11,12}\) and activation of a stainless steel stent in a cyclotron producing a spectrum of radioisotopes.\(^{12}\) Most clinical investigation has been undertaken with the \(^{32}\)P \(\beta\)-emitting stent. Stents ion-implanted with \(^{32}\)P containing a specific activity ranging from 0.5 to 20 microcuries have a 14.3-day half-life, thereby effectively exposing the vessel to \(\beta\)-radiation for about 45 days (approximately 3 half-lives). These stents are of extremely low activity and can be handled with the aid of a 1-cm thick acrylic shield. Unfortunately, initial clinical trials using the \(^{32}\)P stent demonstrated restenosis rates of approximately 50%, largely due to intimal proliferation at the stent edges.\(^{13,14}\) These clinical failures have inspired recent investigation of \(^{103}\)Pd (a \(\gamma\)-emitting isotope) and \(^{192}\)Au emitting stents.

Radiotherapy in Animal Models of Restenosis

Wiedermann et al\(^{15}\) and Waksman et al\(^{16}\) were the first to demonstrate significant reduction in intimal proliferation using radiotherapy in the swine model of restenosis. Wiedermann et al used a swine balloon overstretch injury model of coronary injury to test iridium-192 (\(^{192}\)Ir, a \(\gamma\)-emitter), delivering 2,000 cGy over a 30 to 45 minute dwell time. Morphometric analysis at 30 days demonstrated a maximal neointimal area of 0.84±0.60 mm\(^2\) in control animals compared with only 0.24±0.13 mm\(^2\) in treated animals (\(P<0.001\)). At 6-month follow-up, these differences were 1.59±0.78 versus 0.46±0.35 mm\(^2\) (\(P<0.001\)).\(^{17}\)

Later, Waksman et al\(^{16}\) provided insight into the target of vascular radiotherapy and its mechanism of action. Balloon injury was performed on swine coronary arteries, followed immediately by either strontium-90/yttrium-90 (\(^{90}\)Sr/Y) or \(^{192}\)Ir sources designed to deliver 1400 or 2800 cGy at a depth of 2 mm from the source. Animals were euthanized at 3, 7, or 14 days. Bromodeoxyuridine was administered 24 hours before euthanasia to label proliferating cells. On day 3, cellular proliferation was significantly reduced in both the adventitia and the media of treated vessels compared with controls. At 2 weeks postinjury, there were fewer \(\alpha\)-actin–positive myofibroblasts in the adventitia of treated compared with controlled animals, and morphometric analysis indicated the vessel perimeter of treated vessels was significantly larger than controls. Apoptosis was estimated by terminal deoxynucleotidyl transferase dUTP-biotin nick-end labeling (TUNEL) at 3 and 7 days after injury. No differences in TUNEL-labeled cells were found between treated and control vessels. These studies suggest that intracoronary radiation primarily inhibits cellular proliferation in both the media and adventitia and suggests a mechanism other than apoptosis. They also suggest a favorable effect on late remodeling probably by preventing adventitial fibrosis at the injury site.

Numerous other investigators have demonstrated the efficacy of both \(\gamma\)- and \(\beta\)-radiation in various animal models of restenosis. Others have successfully inhibited neointimal proliferation using \(\beta\)-emitting radioactive stents.\(^{11,12}\) Importantly, these animal models demonstrated efficacy without evidence of necrosis, significant fibrosis, or aneurysm formation.

Clinical Trial Results

Several small randomized trials and registries provided early encouraging data that fueled enthusiasm for vascular radiation therapy (Figure 2).\(^{6,8–10,19–23}\) Recently, the results of 3 large, multicenter, double-blind, randomized trials have clearly demonstrated the efficacy of vascular radiation, paving the way for widespread acceptance. The GAMMA I trial\(^{24}\) randomized 252 patients with native coronary in-stent restenosis up to 45 mm in length to \(^{192}\)Ir, a \(\gamma\)-emitter, versus placebo. The need for repeat revascularization of the target vessel at 9 months was reduced from 46% in placebo to 31%
in treated patients ($P<0.01$). The START trial randomized 472 patients with native, in-stent restenosis treatable with a 20 mm balloon to either $^{89}$Sr/$^{90}$Y, a $\beta$-emitter, or placebo. The target vessel revascularization rate at 9-month follow-up was reduced from 24% in placebo patients to 16% in treated patients ($P=0.026$). The INHIBIT trial randomized 332 patients with in-stent restenosis up to 40 mm in length to $^{32}$P, a $\beta$-emitter, versus placebo. At 9 months, the need for target vessel revascularization was reduced from 31% in placebo patients to 20% in treated patients ($P=0.033$). The concordant results of these 3 pivotal multicenter trials using 3 different sources cemented the notion that intracoronary brachytherapy is the first proven effective antiproliferative strategy.

Longer-term follow-up is now accumulating. In the GAMMA I trial, after two-year follow-up, the freedom from death, myocardial infarction, or target lesion revascularization in $^{192}$Ir patients was increased from 48% in placebo patients to 59% in treated patients ($P<0.017$). In 1995, the SCRIPPS trial randomized 55 patients with restenosis to $^{192}$Ir versus placebo. At three-year angiographic follow-up, despite its small sample size, significant differences in restenosis rates persisted (66% versus 33%, $P=0.05$) (Figure 3). However, despite these encouraging longer term results, in the SCRIPPS trial, late angiography demonstrated a small reduction in lumen diameter between 6 months and 3 years in treated but not in placebo patients. The observations from this small series raise the possibility that in some patients, radiation may only delay and not eliminate restenosis.

Radiotherapy has also been tested for the treatment of peripheral vascular disease. Following reports from several small registries, a randomized study of 113 patients compared $\gamma$-radiotherapy to placebo after balloon angioplasty of long segment and/or occluded superficial femoral artery. Treatment with radiation increased cumulative patency at 12 months from 35.3% in placebo to 63.6% in treated patients ($P<0.005$). Thus, radiation appears to be an effective antirestenosis strategy for patients undergoing peripheral as well as coronary intervention.

**Radiation Failures**

The striking success of Brachytherapy in inhibiting the proliferative process and breaking the cycle of repeat restenosis in most patients, makes its failure to benefit some patients especially frustrating and worthy of investigation. Two failure modes have received considerable attention: late thrombosis and edge restenosis.

**Late Thrombosis**

Similar to challenges encountered in the early 1990s during the first attempts at stent implantation, the initial enthusiasm for coronary vascular radiotherapy was dampened by reports of target lesion thrombosis, particularly thrombosis occurring late (>30 days) after treatment. In early trials, late thrombosis after brachytherapy was universally encountered, with an incidence of 3% to 10% independent of isotope and delivery system tested. The thrombotic episode usually manifested as a sudden target vessel occlusion, occurring 1 to 9 months after radiation treatment, resulting in acute myocardial infarction. The emergence of this complication seriously jeopardized radiation as a viable treatment modality for coronary disease. Although restenosis is an unwanted, inconvenient, and expensive problem, its reduction cannot be gained at the expense of an increased risk of transmural myocardial infarction.

Careful study, however, yielded two helpful clues that led to a dramatic reduction in radiation associated late thrombosis. First, the overwhelming majority of patients sustaining a late thrombosis had a new stent freshly implanted (to treat recoil or dissection) at the time of the radiation procedure (Figure 4). Second, almost all patients sustaining late thrombosis had discontinued ADP inhibitor antiplatelet therapy (thienopyridines) one or more months before the throm-
hypothesis thus emerged: radiotherapy effectively blocks unwanted neointimal hyperplasia but also prevents the ingrowth of desirable cellular and extracellular elements needed to passivate stainless steel stent struts. Without neointimal protection, platelets and thrombus accumulate on the bare metal stent, leading to thrombotic vessel closure. Aspirin and the thienopyridines (clopidogrel and ticlopidine) appear to protect against platelet accumulation on bare stent struts.

Two strategies to prevent late thrombosis were tested. First, the implantation of new stents during or immediately after treatment with brachytherapy was strongly discouraged. A small or even moderate amount of recoil was tolerated and stents were implanted only for the treatment of significant dissection. Interestingly, when data from the SCRIPPS, WRIST, and GAMMA I trial were pooled, patients receiving /H9253-radiation without new stents not only demonstrated a significant reduction in late thrombosis, but also enjoyed a higher reduction in the primary endpoints of restenosis (Figure 5). Second, antiplatelet therapy with aspirin and a thienopyridine was extended for 6 to 12 months after the radiation therapy procedure. This strategy has now been tested with apparent success in several large series. In the START trial, the late thrombosis rate was 0.5. In the WRIST PLUS/35 and INHIBIT/26 trials, thrombosis rates were under 3%. In the ongoing SCRIPPS III trial, the late thrombosis rate is 0%. Perhaps most convincingly, an early review of the Beta-Cath trial by the data safety monitoring board (DSMB) discovered that patients treated with new stents plus radiation had a 6.8% rate of late stent thrombosis. In response, the DSMB extended this trial to include additional patients treated with new stents who also receive a minimum of three months of aspirin and a thienopyridine. In this added subgroup, the late thrombosis rate fell to baseline (1.3% in both treated and placebo arms) providing substantial evidence that the late thrombosis problem can be resolved by extended antiplatelet therapy. Current recommendations for patients undergoing vascular brachytherapy are to prescribe aspirin and a thienopyridine (clopidogrel or ticlopidine) for 6 months if no new stent was implanted during the radiation treatment and 12 months if a new stent was implanted. However, follow-up of patients enrolled in clinical trials is continuing and if late thrombosis should reemerge as a significant problem after discontinuation of antiplatelet therapy a longer duration of thienopyridine therapy (perhaps indefinite) may be recommended.

**Edge Failure**

When restenosis occurs after brachytherapy, the renarrowing is found at the treatment edges in one-third to one-half of patients. Edge failure is especially prominent in vessels treated with radioactive stents (Figure 6)./13,14 Many theories regarding the mechanism of edge failure have been proposed. One explanation is that failure at the treatment edges is due to a drop-off of radiation dose as one moves longitudinally away from the radiation source, causing stimulation of neointimal proliferation. In animal models of restenosis, a subtherapeutic dose of radiation has been shown to stimulate neointimal proliferation.37

Other theories for failure at the treatment edges focus on the concept of “geographical miss.” In several studies using catheter-based radiation, careful, quantitative coronary angiographic measurements have documented a surprisingly high incidence of inadequate coverage of the treated region by the radioactive source. This phenomenon, termed geographic miss, occurs when the treating physician essentially misses...
the target (Figure 7). With increasing experience, we have learned there are numerous ways for the physician to be misled. Perhaps the most important cause of geographic miss typically overlooked by the treating physician is the result of dose variations along the length of the radiation source (Figure 8). When radiation is emitted from a line source, the dose emitted at any one point along the axial length of the source is an aggregate of the radiation emitted by that one point in addition to the points on either side of it. This summation effect of radiation is reduced at the edges, where there can only be contribution from the points to the inside of the source’s edge. This results in a significant drop-off in dose (in some devices as much as 50%) over the few millimeters adjacent to the source edge. Unless the treating physician extends the radioactive source longitudinally by several millimeters to take this drop-off into consideration, the edges of the target (injured during the angioplasty procedure) will receive a lower, and perhaps ineffective, dose. When combined with local balloon or stent injury, the combination of suboptimal radiation dosage and vascular injury may lead to excessive proliferation.

Although the causes of edge failure are still unclear, one therapeutic imperative for the treating physician is to avoid geographic miss by providing a very wide margin (ie, 4 to 10 mm) of radiation source on either side of the injured vessel region. This may not eliminate edge failure but will probably considerably reduce its occurrence.

The overwhelming preponderance of evidence supporting vascular radiotherapy’s efficacy and safety involves its use for the treatment of in-stent restenosis. In particular, this new therapy is often prescribed for patients who have had more than one episode of in-stent restenosis. Patients with in-stent restenosis are at a higher risk for subsequent restenosis compared with their risk following their initial intervention. Repeat angioplasty of patients with longer in-stent restenosis (>10 mm lesion length) is associated with a >50% subsequent failure rate. Diabetic patients with in-stent restenosis have an even higher (>75%) failure rate after repeat angioplasty. Thus, the patient with multiple restenoses, the diabetic, or the nondiabetic with a >10 mm restenotic lesion length are prime candidates for radiation treatment. The results of the SVG Wrist (Waksman R, Late Breaking Trials, ACC, unpublished data, 2001) may extend this indication to patients with in-stent restenosis within a saphenous vein bypass graft; a subgroup also at high risk for repeat interventions following angioplasty.

More controversial is the use of vascular radiation for the patient with a de novo lesion; particularly, when radiotherapy is viewed as an alternative to stent implantation. Radiation’s effects on inhibition of smooth muscle cell proliferation and its promotion of favorable remodeling have led some to advocate radiation’s use as a primary antirestenosis strategy that avoids implantation of a permanent prosthetic device. This concept has been fueled, in part, by the results of the GENEVA randomized dose-finding study, which compared 4 incremental doses of β-radiation using 90Y in patients with de novo disease. In nonstented patients, the angiographic restenosis rate was only 3.9% in patients receiving 18 Gy (the highest dose tested) compared with 28.1% in the low dose (9 Gy) group. However, the recently reported large, 1455 patient, double-blind, randomized trial comparing β-radiation using 90Sr/90Y to placebo in patients with short, uncomplicated de novo lesions casts serious doubts on the use of radiation for this indication, particularly in patients receiving stents. At eight month follow-up, the need for target vessel revascularization in patients undergoing balloon angioplasty without stents was 17% in placebo compared with 12.3% in treated patients (P=0.12), but stented patients treated with...
radiation had worse outcomes compared with placebo patients (14.7% versus 22.6%, \( P = 0.001 \)). Some radiation failures were clearly due to geographic miss. However, modern stents are extremely effective and provide reliable treatment for short de novo lesions. It is hard, therefore, to envision radiation replacing stents for this indication. Possibly, patients with diabetes mellitus, diffuse coronary disease, small vessel diameters, and branch stenoses may be attractive candidates for radiation therapy rather than stent implantation if this therapy is proven effective.

**Long-Term Adverse Effects**

Whereas early safety and efficacy has been demonstrated in numerous animal studies and several human trials, the long-term efficacy and, most importantly, safety of this technique has been questioned. The possibility of late untoward consequences such as aneurysm formation, perforation, or accelerated vascular disease are significant concerns. In addition, it is not known if the beneficial effects of radiation therapy will be durable, or if radiation will only delay and not permanently reduce restenosis. With the prospect of an increasing number of patients being exposed to intravascular radiation, it is essential to obtain long-term clinical follow-up.

Presently, long-term follow-up of patients enrolled in clinical trials using vascular radiotherapy is very limited. Five-year angiographic follow-up after intracoronary \( \gamma \)-radiation was reported by Condado et al. The restenosis rate was low at 28%, but this study lacked a control group for comparison. Several coronary aneurysms, and one definite pseudoaneurysm, reported in the series from Condado et al, developed possibly because the vessels were potentially exposed to very high radiation doses (up to 92 Gy at 2 mm from the source) compared with the lower 12 to 20 Gy at 2 mm from the source used in most other clinical experiences. In other reports, long-term follow-up has documented high patency rates in femoropopliteal arteries undergoing angioplasty plus intravascular \( \gamma \)-radiation. The SCRIPPS trial obtained angiographic follow-up in 19 patients treated with \( \gamma \)-radiation at 3 years. There were no perforations, aneurysms, pseudoaneurysms, or other special safety concerns.

**Conclusions**

Vascular radiotherapy is the first proven, clinically effective antirestenosis therapy. Despite its established efficacy, there is much room for improvement. The optimum dose and isotope has not yet been established for any of the radiotherapy devices in clinical use. Dose finding studies and randomized comparisons between devices will be required to optimize safety and effectiveness. Although the role of antiplatelet therapy in minimizing late thrombotic events has been established, the optimum duration of therapy must be clearly defined. The possibility of radiation as a primary therapy with and without stents to treat some de novo disease must be further explored. Finally, continued long-term follow-up is required to accurately define the long term consequences of this new therapy.

While vascular radiotherapy is rapidly evolving, other competitive antiproliferative technologies have emerged. Most exciting is the impending onslaught of clinical trials testing antiproliferative, drug eluting stents. A recent report documented the 8-month angiographic and intravascular ultrasound outcome following implantation of a Rapamycin-coated stent in a 15 patient registry. No significant late loss was observed within the stent or at the stent margins in any treated patients. Despite the small size of this early, nonrandomized registry, the absence of significant neointimal formation within or around any of the stents is compelling. Indeed, an end to restenosis now seems possible. Of course, problems with drug coated stents are likely to emerge, and we should contain our enthusiasm until multicenter, randomized trials are completed. We try to remain skeptical, but for those of us whose careers have grown along with angioplasty, the prospect of a world without restenosis is a fantasy come true. The implications for the future of percutaneous revascularization are profound. Very possibly, radiotherapy has ushered in a new era in percutaneous revascularization where effective mechanical devices are coupled with equally effective antiproliferative and antithrombotic agents to dramatically improve long-term outcomes for patients with coronary artery disease.

**References**


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