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Review

Prevention of Coronary Restenosis with Radiation Therapy: A Review

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Summary: The problem of restenosis after percutaneous transluminal coronary angioplasty remains the major limiting factor of the procedure. Over the last 10 years, investigators have been studying the use of radiation therapy for preventing restenosis after angioplasty or stent placement. Since radiotherapy has been proven in other cases to be effective in disrupting the cell cycle regulatory proteins and thereby slowing or stopping growth, it was decided to apply the same principle to neointimal hyperplasia. To review the data that have emerged regarding vascular radiation with an emphasis on irradiated stents, 65 articles were reviewed and both preclinical and clinical experiments were included. Overall, studies with gamma and beta radiation show promising results. Endovascular gamma radiation has been shown effective in randomized trials, even at 3-year follow-up. Beta radiation is preferred because of greater safety and localization, and because it has also shown encouraging results in initial clinical trials, as well as in larger randomized studies. Consequently, the Federal Drug Administration has approved the use of both. In both types of endovascular brachytherapy, it seems the greater the dose, the better the initial response. Safety concerns include an increased incidence of late thrombosis and greater restenosis at margins. With irradiated stents, however, the situation is not as clear. At times, animal models have presented confusing results. These have ranged from significant suppression of hyperplasia to outright adverse effects of radiation on the vessel wall. While some clinical trials have been encouraging, others have not. Follow-up of up to 1 year has been disappointing so far. Many issues, such as the "candy wrapper" effect and rebound hyperplasia, must be dealt with before this becomes a viable form of therapy. It has become clear that radiation therapy in this setting, while having potentially great benefits, can cause deleterious effects as well. However, the mixed bag of positive and negative results seen so far, and the attractiveness of stents or percutaneous transluminal coronary angioplasty being "restenosis-proofed," eventually is cause for cautious optimism.

Key words: brachytherapy, stent, radiation, angioplasty, endovascular radiation, irradiated stent, neointimal hyperplasia

Introduction

The problem of restenosis after percutaneous transluminal coronary angioplasty (PTCA) remains the major limiting factor of the procedure. This problem has plagued interventional cardiologists for the past two decades and requires additional treatment, including repeat angioplasty or bypass surgery in about 25% of patients.[1] Restenosis rates of as high as 60%[2,3] at 6 months post angioplasty have been commonly reported. Even with stent placement, restenosis occurs up to 30% of the time.[4] A variety of pharmacologic agents to combat this problem have been tried unsuccessfully in various clinical trials. Over the last 10 years, investigators have been studying the use of radiation therapy in preventing restenosis after angioplasty or stent placement. One advantage of radiation over more specific drugs is that its response is nonspecific and it stops proliferation in cells even if there are multiple stimuli to proliferation.[5] Initial experiments with animal models suggested that radiation to the vessel wall, by placing irradiated stents to stenotic lesions or exposing the vessel to radiation via catheters, seeds, liquids, and so forth, after angioplasty, all reduced restenosis rates significantly. These studies have stimulated intense interest and have led to currently ongoing clinical trials with various forms of vessel irradiation. The following is a review of the data that have emerged regarding coronary artery radiation with an emphasis on irradiated stents. Both preclinical and clinical experiments have been included.

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Background

Percutaneous transluminal coronary angioplasty entails advancing a catheter balloon system to the point of occlusion in a coronary artery and then inflating the balloon to dilate the artery, thereby enlarging the lumen. In many cases (> 50% at present),[6] a stent is applied to the same area to give more stability to the dilated segment (the indications for stent placement are multiple, ever changing and increasing). This procedure causes injury to the vessel wall and reacts with inflammation, elastic recoil, neointimal hyperplasia, and late arterial remodeling.[7] The process of neointimal hyperplasia is key to the irradiation theory. After injury, a wound-healing phase begins, which includes smooth muscle cells and fibroblasts migrating from the media to the intima in response to various stimuli and mediators. A course similar to scar formation is initiated, and smooth muscle cells begin to proliferate toward the center, eventually causing restenosis. It has been recognized that this process is similar to other proliferative disorders secondary to injury, such as pterygium, keloid, and heterotopic ossification following total hip arthroplasty. Since radiotherapy has been proven in other cases to be effective in disrupting the cell cycle regulatory proteins and thereby slowing or stopping growth, it was decided to apply the same principle to neointimal hyperplasia. This particular vascular response to PTCA or stents is seen as "scar or tumor" formation. A porcine animal model as well as rabbit and, more recently, canine models, have been developed and studied extensively.[8–10] In these models, a coronary vessel is overstretched to provide balloon injury and various interventions, including stents and radiation, are applied. After varying periods of time, the vessels are examined to assess response to different therapies. Therapies that have been used include external radiation, endovascular radiation with temporary implants through catheter-based techniques, and radioactive stents with a variety of radioactive isotopes. External radiation has had results that, in some studies (Schwartz *et al.*), have shown it to be worse than stenting alone and, in others, even to cause myocardial necrosis.[11] Better results have been obtained with the latter two methods.

Catheter-Based Radiation

Two types of radiation have been studied extensively in regard to this approach: gamma and beta.

Gamma Irradiation

Multiple animal (porcine) experimental models, using ^{192}Ir delivered to the vessel wall via catheter, have demonstrated positive results. Mazur *et al.*[12] showed that ^{192}Ir suppressed intimal thickening at 4 weeks post PTCA when using 10 to 25 Gy at 1.5 mm. Wiedermann *et al.*[13, 14] also found similar suppression of neointimal hyperplasia at 4 weeks and later at 6 months with 20 Gy at 1.5 mm given after angioplasty. The first significant clinical trial took place in 1994 with a study in Venezuela by Condado *et al.*,[15] using 20–25 Gy at 1.5 mm with ^{192}Ir wire. Results showed a restenosis rate of 28% and late loss index of 0.19 at 6 months, both better than after angioplasty alone, which has historically shown rates of 30–60% restenosis and a 0.40–0.50 late loss index. Although there has been some aneurysm formation in select patients, the patients have remained stable over at least the last 3 years.

In 1998, Teirstein *et al.*[16] published the follow-up results of the landmark Scripps Coronary Radiation to Inhibit Proliferation Post Stenting (SCRIPPS) trial on catheter-based radiotherapy to inhibit restenosis after coronary stenting, a double-blind randomized trial. This demonstrated a reduction in target lesion revascularization in vessels irradiated with ^{192}Ir with a dose of 8 to ≤ 30 Gy. Target lesion revascularization at 6 months was 44.8% in the placebo group and 11.5% in those treated. After 2 years, target lesion revascularization remained 44.8% in the placebo group and 15.4% in those treated with radiation. The angiographic restenosis rate in treated subjects showed a 69% reduction and the late loss index showed 80% reduction, both at 6 months. Significantly, at 2-year follow-up, the composite endpoint of death, myocardial infarction, or target-lesion revascularization was significantly lower in the group that received radio therapy (51.7% for placebo vs. 23.1%, $p = 0.03$).[17] Three-year follow-up has shown continued suppression of neointimal proliferation.[18] The first placebo-controlled multicenter trial of intracoronary radiation for in-stent restenosis, the Gamma I Trial, has also shown positive results. Gamma I enrolled 252 patients versus 50 in the SCRIPPS trial. Here, Leon *et al.*[19] used ^{192}Ir with a mean dose of 1351 cGy. In 6 months, in-stent restenosis was reduced by 58% (52% for placebo vs. 21.6% for radiation), and there was a 43% reduction of in-lesion restenosis (56.4 vs. 32.4%). Waksman *et al.*[20] have also reported encouraging results with ^{192}Ir at 15 Gy in the Washington Radiation Forum for In-Stent Restenosis (WRIST) trial. In this study, target lesion revascularization was reduced 79% (67.7% for placebo vs. 26.2% for radiation) and restenosis by 67% (48 vs. 16%), both at 6 months. Saphenous Vein Graft (SVG) WRIST showed reduction in restenosis in irradiated vein grafts as well.

It is important to note that there have been no significant side effects reported in the SCRIPPS study. While there were four deaths reported, two were in the placebo group. However, the WRIST study has shown prolapse into the lumen through intravascular ultrasound. Although all these trials have used ^{192}Ir, the SCRIPPS, WRIST, and Gamma I trials have all used irradiated seeds, whereas the Angiorad Radiation Technology for In-Stent Restenosis Trial in Coronaries (ARTISTIC) trial and that of Condado *et al.*[15] used irradiated wire. In ARTISTIC, restenosis rates were 19.0% in-stent and 23.8% in lesion, indicating that intracoronary gamma radiation with source-wire is effective in preventing in-stent restenosis.[21]

Beta Irradiation

The advantages of using a beta-emitting radioisotope are the following. First, it is more easily integrated into catheterization laboratory procedures. In addition, penetration of the isotope is weaker, so no special protective clothing or devices not already available in the catheterization lab are required.

Beta radiation does not extend to great distances, so there is less potential for radiation reaching areas where it is not wanted. For example, ^{192}Ir, a gamma emitter, for 2 min at 10 Gy, is about 10,000 msv whereas 10 Gy of ^{90}Sr, a beta-particle emitter, is only 5 msv. These properties indicate that beta radiation may be more suited for localized irradiation. However, these advantages can also be disadvantages. It can be more difficult to achieve delivery of the required dose to deeper layers of the arteries (media/adventitia) with the beta emitters. On a more mundane front, they will be more difficult to find if lost in the catheterization lab or during procedure. Various isotopes have been experimented with, including ^{90}Y, ^{90}SR/Y, and ^{188}Re.

In 1996, Verin *et al.*[22] released results of a pilot study to evaluate the clinical feasibility and safety profile of delivering 18 Gy of radioactive ^{90}Y to the vessel wall via a purely metallic source. Results at 6 months showed a restenosis rate of 40% and a late loss index of 0.50. These results were disappointing, but they did show that this approach was feasible and that no side effects attributable to the radiation were present at 6 months. It is thought that the poor results were due to inadequate dosage. The study also demonstrated the use of a segmented balloon-centering device to deliver the radiation. In animal models, the plaque, which is targeted, is generally singular and uniform. In clinical models, there are multiple "bumps" in the arterial wall because of extensive disruption of the media and adventitia. This requires a delivery system that can achieve an even distribution of radiation and this is what the segmented balloon attempted to do. The search for an adequate system has resulted in multiple types of coils, wires, and seeds. Robinson *et al.*[23] have shown that a liquid-filled balloon catheter system results in delivery of homogeneous amounts of radiation to the target area (in pig coronary arteries). For a significant response, however, higher doses of the ^{186}Re liquids (20–30 Gy) than those in more conventional systems were required.

Verin *et al.* have since published additional studies that have had more success with Y^{90}. One dealt with 130 patients undergoing PTCA without stenting, who received 9, 12, 15, or 18 Gy of radiation. Upon follow-up, both restenosis at 6 months and repeat revascularization were less frequent in the higher-dose groups. There was also a dose-dependent enlargement of the vessel lumen, most commonly in those receiving 18 Gy.

The Beta Energy Restenosis Trial (BERT),[24] results of which were published in 1998, employed ^{90}Sr/Y seeds using 12, 14, and 16 Gy at 2 mm after angioplasty. At follow-up, this study showed a late loss index of 4% and a restenosis rate of 15%. In addition, the use of a beta emitter was shown to reduce radiation exposure to the operator and also resulted in less treatment time required compared with ^{192}Ir. The experiment was extended to more patients in Montreal and Rotterdam with similar results. In Montreal, results published showed a late loss index of -0.09 ± 0.46 with restenosis of about 10%. In addition to the fact that these studies demonstrated a positive response to beta radiation post angioplasty, they are also significant for comparison with gamma radiation. Both the percentage of restenosis and the late loss index are less with beta radiation. The higher the dosage given, the better the results (12 Gy showed a late loss of 0.16 vs. -0.10 with 16 Gy). Also, with the exception of the study of Condado *et al.*,[15] gamma radiation studies have been concerned with in-stent restenosis. The BERT study consisted of patients post angioplasty. This is significant because restenosis after stent placement is recognized as being almost entirely secondary to neointimal and tissue hyperplasia, while restenosis after angioplasty alone is due to neointimal hyperplasia and vascular remodeling. The Montreal and Rotterdam cohorts were followed by intravascular ultrasound in addition to angiography (the original BERT study group follow-up was with angiography only). Intravascular ultrasound (IVUS) in this case, as reported by Meerkin *et al.*,[25] in addition to providing information on minimal lumen diameter (MLD), was also able to show an absence of decrease in the external elastic membrane (EEM) area, a measurement not available with angiography alone. The IVUS results, theoretically, indicated not only decreased neointimal hyperplasia, but also suggested decreased late remodeling.

Additional clinical trials are now pending, open, or resulted. These include the BETA-CATH[7] System (Novoste Corp., Atlanta, Ga.) trial, which is a large triple-masked study that includes provisional stenting, and the Stent versus Angioplasty Restenosis Trial (START), which is testing beta radiation in stent restenosis. Factors that must be kept in mind with vascular radiation are type of isotope, dose, delivery and centering systems, timing of dosage, and vascular reperfusion during procedure. Various isotopes are being tried, since one of the reasons for the testing of beta radiation is that ^{192}Ir was felt to be a greater health hazard. The delivery and centering systems, as mentioned before, are difficult to develop because of the irregular and multiple "centers" of plaques in humans. The BERT, BETA-CATH, and START trials have used radioactive ^{90}Sr/Y seeds. In the case of BERT, these were 2.5 mm long and 0.61 mm in diameter. A total of 12 seeds were used to cover a length of 30 mm, which were delivered via catheter.

The BETA-CATH trial[26] was the first and largest prospective, randomized, blinded, placebo-controlled multicenter study that evaluated the use of vascular brachytherapy in de novo lesions with PTCA alone or combined with stent placement. In this trial, the primary clinical endpoint of target vessel failure (TVF) was not shown to be significantly lower in the radiation arms than in the placebo arms. This was the case despite the fact that in the PTCA branch there was a 37.6% reduction in in-lesion restenosis rate and a 34.6% reduction in TVF/major adverse coronary events (MACE) rate. The investigators explain this by the restenosis in the combined stent branches where, despite a 28.9% reduction in the in-lesion segment restenosis rate, there was a 30% increase in the actual analysis segment (radiation + injury + 5 mm at each end). The authors suggest that "geographic miss" may have contributed to the negative results of ^{90}Sr. There was also a higher than expected rate of late thrombosis when radiation was used with stent implantation.

The Proliferation Reduction with Vascular Energy Trial (PREVENT)[27] used a ^{32}P wire source within a helical centering balloon. Angiography at 6 months showed a target site late

loss index of 11% in radiotherapy-treated patients versus 55% in controls, restenosis rates of 8 versus 39% at the target site, and target lesion revascularization in 6% of radiotherapy-treated versus 24% of control patients. The BETA WRIST trial at Washington Hospital is following in-stent restenosis with a ^{90}Y coil with 18 Gy (similar to the Verin trial). The BETA WRIST trial has shown a 22% restenosis rate at 6 months follow-up.[28] The Columbia University Restenosis Elimination Safety Trial (CURE) (which has shown clinical restenosis with need for target vessel revascularization at a rate of 17% at 6 months[29]) is exploring the feasibility of using balloons filled with radioactive ^{188}Re fluid. A study by Hoher *et al.*[30] has shown that irradiation with an ^{188}Re-filled balloon is technically feasible. At 6 months follow-up, the late loss index was 0.57 and target lesion restenosis rate was 12%. As previously mentioned, this is thought to deliver a more homogeneous dose to the required area.

It has been suggested that the radiotherapy be given at least 48 h after injury to potentiate the effects of the treatment. This was demonstrated by Waksman *et al.*[31–33] and shows the importance of timing in vascular response to injury and radiation. The catheter-based delivery systems of vascular radiation also have the problem of transient ischemia during radiation delivery in systems that require an inflated balloon. In the Verin trial, the dosage was delivered over 400 s but ischemia did develop in 27% of patients. Radiation therapy, as a whole, has been shown to be most effective in well-oxygenated cells, and the search for a centering device that allows adequate perfusion during procedure continues. Finally, the appropriate dosage to be applied is still not clear. Although most trials have indicated that the higher the radiation doses in endovascular radiotherapy, the better the response, the issue is still far from decided. Smooth muscle cells and fibroblasts that move to the intima originate and also proliferate in the media and adventitia.[34] The response to injury is regulated to a large part in these layers of the vessel wall. In a calcified, diseased coronary artery, the thickness can exceed 2 mm.

Overall, both gamma and beta endovascular brachytherapy show promise, and clinical trials with both have had positive results (Table I). The FDA has approved both gamma and beta intracoronary radiation for use after initial mechanical treatment of in-stent restenosis;[35] however, two safety concerns have arisen. Some trials have shown greater restenosis at the stent margins.[36] Also, as mentioned above, a higher incidence of late thrombotic events and myocardial infarctions has been seen. The issue of restenosis at the margins, or the "edge effect," is dealt with further in the section concerning stents. As noted in the Gamma-One trial,[37] late thrombosis occurred with irradiation only if oral antiplatelet therapy with ticlopidine or clopidogrel had not been given or had been discontinued. Further, it occurred only in those patients in whom a new stent had been placed at the time of radiation treatment. Similar findings were seen in BETA-CATH. With this in mind, the FDA suggests that antiplatelet therapy (aspirin plus clopidogrel) be given for at least 6 months after brachytherapy. Although the FDA also suggested avoidance of placement of new stents when brachytherapy is used, if one is implanted, antiplatelet therapy should continue for a minimum of 1 year.

Stents

After an occlusion is opened by angioplasty, the following factors affect restenosis: thrombosis, elastic recoil of the artery,

TABLE I Selected clinical trials of gamma and beta radiation delivered via catheter

	Radiation source	Dose	Resultant restenosis rate	Late loss index	Type
Gamma trials					
Condado[15]	^{192}Ir wire	20–25 Gy	28%[a]	19%[a]	Post PTCA
SCRIPPS[b]	^{192}Ir seeds	8 – ≤ 30 Gy	16%[a] (53.6% in controls)	12%[a]	In-stent resenosis
GAMMA I[b]	^{192}Ir seeds	8 – ≤ 30 Gy	21.6%[a] (52% in controls)	< than controls	In-stent resenosis
WRIST[b]	^{192}Ir seeds	15 Gy	16%[a] (48% in controls)	< than controls	In-stent restenosis
Beta trials					
Verin[22]	^{90}Y coil	18 Gy	40%[a]	50%[a]	Post PTCA
BERT[b]	^{90}Sr/Y	12, 14, 16 Gy	15%	4%	Post PTCA
Hoher[30]	^{188}Re balloon	15 Gy	12%[a] at target lesion (46%[a] total restenosis)	57%[a]	Post PTCA/stent
PREVENT[b]	^{32}P wire	16, 20, 24 Gy	8%[a]	11[a]	Post PTCA

[a] At 6 months.

[b] Full title of trial is mentioned in the text.

Abbreviation: PTCA = percutaneous transluminal coronary angioplasty.

proliferation of cells (from the intima, media, or adventitia), late remodeling, and inflammation. With the beginning of stenting in 1986, it became possible to control two major factors in restenosis. A stent is essentially a latticework of metal that, after placement to a dilated segment of artery, expands peripherally to an acceptable diameter. It can either continue to expand until a programmed diameter is met or it can expand until the radial forces are overcome by vascular tissue tone. Either way, the issue of early elastic recoil is resolved, as the stent does not allow the vascular wall to exert its elastic forces. The fact that the stent is in the vessel, maintaining a predesigned shape, reduces the possibility of remodeling as well. As mentioned before, it has been seen in many studies that in vessels that have received only angioplasty, vascular remodeling, more than neointimal hyperplasia, is probably the most significant factor causing restenosis. Stents also allow for more safety, as an aggressive approach regarding how much to dilate is taken by many interventionalists. Many believe that obtaining a better result is directly proportional to obtaining a larger luminal diameter after angioplasty. The resulting response to dilation and injury is greater than in procedures in which lesser gain is acquired. In these situations, stents, with their ability to stabilize the treated area, are obviously better than angioplasty alone. With regard to thrombosis, various clinical trials, the Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment (CAPTURE) trial, the Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) trial, and the Randomized Efficacy Study of Tirobifan for Outcomes and Restenosis (RESTORE) have shown the platelet thrombus to be the principal cause of subacute stent thrombosis.[38, 39] The use of powerful antiplatelet inhibitors, such as ticlodipine and glycoprotein IIb/IIIa receptor antibody, in addition to aspirin alone has markedly reduced the rate of stent thrombosis. In procedures in which aspirin, dipyrimidole, heparin, and coumadin were used, the rate of thrombosis remained at 4–5%. After using stronger platelet inhibition, such as mentioned above, the rate dropped to less than 1% in some cases. New drugs to suppress platelet function even more effectively are still being developed. In addition, stents that are coated with IIb/IIIa blocking agents are being tested. The Belgian Netherlands STENT (BENESTENT) II[40] randomized trial demonstrated the effectiveness of heparin-coated stents. Subacute thrombosis in this trial was < 0.2%. With the above in mind, it can be safely said that while thrombosis remains a problem, significant improvement in the rates of subacute thrombosis post-stent placement have been made.

The rate of restenosis after angioplasty alone is between 30 and 60%, as mentioned above; with stent placement, this rate can be reduced to 20 to 30%—still a very high rate of restenosis that requires repeat procedures in about 6 months. The effects of a stent on elastic recoil and vascular remodeling along with the greater platelet inhibition now available means that up to 30%, or half of restenosis after angioplasty, and virtually all after stent placement can be attributed to neointimal hyperplasia. In the context of an irradiated stent, the fact that the stent is a meshwork or lattice of metal allows for the "electron fence" theory with regard to smooth muscle cell migration and proliferation. Smooth muscle cells and fibroblasts migrate from the adventitia and media to the intima. As cells reach the level of the metal in a stented artery, they are exposed to the radiation emitted by an irradiated stent. At this point, cell growth toward the lumen should stop and should not exceed the barrier set by the stent.

Irradiated stents theoretically have advantages over endovascular radiation other than just the prevention of elastic recoil and late remodeling. An irradiated stent is physically placed against the vessel wall and would be much more effective in delivering a dose—and a more homogeneous dose—of the required radiation to the vessel wall. It is believed that restenosis is a process that occurs between Weeks 1 and 8 after angioplasty or stent placement. An isotope that can radiate the vessel wall for the first 2 months or less and then decay would be an excellent choice. ^{32}P, for example, is a radiation source that has a half life of about 2 weeks, whereas exposure time is limited to a certain number of minutes with endovascular radiation.

In 1993, at Heidelberg University, Hehrlein *et al.*[42] implanted radioactive stents in nondiseased rabbit iliac arteries. This was the first report of radioactive stent usage. The procedure used in this initial study resulted in the production of both beta and gamma radiation from the stents. The stents used had various activities with 3.9, 17.5, and 35 mCi. In these models, a reduction in smooth muscle cell counts at 4 weeks demonstrated the ability of radiation to inhibit neointimal hyperplasia; however, only the 17.5 and 35 mCi stents showed these results. In addition, while the rate was slowed, reendothelialization was otherwise unaffected. In addition, the method used to create the radioisotopes was to place a stainless steel stent in a nuclear reactor. In addition to creating both gamma and beta radiation sources, radiation was emitted by multiple isotopes including cobalt, magnesium, and iron.

In light of these encouraging findings, investigators began to look for more precise and safer forms of radiation delivery. The advantages of beta over gamma radiation have been discussed earlier. In addition, with fluoroscopy during angioplasty, the patient receives 10,000 times the radiation dose delivered by an irradiated stent. The radioisotope ^{32}P was found to have many attractive properties with the above in mind. First, ^{32}P is exclusively a beta-particle emitter. It has a short half life (14 days), and its activity reduces to insignificant levels by 6 months, providing a source of radiation only in the time frame most important to suppress restenosis. ^{32}P is cheap and easily available. Its maximum range of dose delivery is in 6 mm, and 95% of the dose is delivered within 4 mm of the edge of the stent. Laird *et al.*[41] were among the first to describe ^{32}P implants on a radioactive coil stent. Their study investigated whether low-dose radiation from a beta particle-emitting stent would inhibit neointimal hyperplasia in a porcine model. A stent with an activity of 0.14 mCi was used, and seven animals with beta-irradiated stents were matched against seven controls. At Day 28, angiography and histomorphologic examination were carried out on the iliac arteries used. Results showed a significant reduction in neointimal area (1.72 mm in

treated stents vs. 2.81 mm in controls), reduced neointimal thickness (0.10 vs. 0.26 mm), and decrease in percent area stenosis (24.6 vs. 36%). This low-dose irradiation, however, did not inhibit endothelialization. Unfortunately, the process by which the stents were made radioactive (nonradioactive ^{32}P was first implanted on the stent and then the entire stent was exposed to radiation) resulted in the formation of isotopes other than only ^{32}P.

Hehrlein *et al.*,[42] following up on their earlier work, managed to produce a much more specific isotope emitter by first subjecting reduced amorphous ^{31}P to neutron radiation, forming ^{32}P, and then implanting it onto a stent. Again rabbit iliac arteries were used. Activity levels of 4 and 13 mCi with conventional stents were used in control animals. At 4 and 12 weeks, histomorphometry showed significant neointimal suppression only with 13 mCi compared with controls. This further supported the initial findings indicating a dose–response relationship. Maximal response was shown at 13 months. Again, while endothelialization was less dense than in controls, by 4 weeks there was significant recurrence.

Carter and Fischell[43] undertook a porcine study with a broader range in radiation dosage. The stents used (known as the Fischell Iso-stent) were modified Palmaz-Schatz type with ion implantation of ^{32}P, as described earlier. Stents with activities ranging from 0.15–23.0 mCi were placed in 39 pigs along with control stents. The results were divided into those of low activity stents (0.15–0.5 mCi), 1.0 mCi, and high activity (3.0–23 mCi). At 28 days, the neointimal area in the 0.15–0.5 mCi group was reduced to 1.63 mm in the treated group vs. 2.40 mm in controls; percent area stenosis in this group was 26% versus 37%. In the high-activity group (3.0–23.0 mCi), the neointimal area was reduced to 1.73 mm and percent area stenosis to 26%. Medial cellularity decreased as well, but less than it did in the neointima (40 vs. 60%), an expected response, as the radiated isotope is closer to the neointima. Cellularity also showed greater reduction with higher dosimetry; however, while encouraging results were seen with these two subsets, the group treated with 1.0 mCi showed a much poorer response. Neointimal area measured 4.67 mm, almost double the control value, and the percent area stenosis was as high as 64%. This unexpected outcome may have been due to the fact that, at this dose, delayed endothelialization set about a sequence of events that led to smooth muscle proliferation. The delayed endothelialization in this group may be much more severe than at lower doses, but when it does occur, it needs higher doses such as those in the 3.0–23.0 mCi groups to prevent it from leading to neointimal hyperplasia and matrix protein-rich cells. Another reason postulated for the outcome is that there may be a "stochastic" effect on extracellular matrix protein; there may also be different responses by different species to similar doses of radiation. A much simpler cause could be that there was more injury in this subset due to the procedure. In any case, there is evidence that a U-shaped curve in regard to the dose–response relationship may exist.[43]

In addition to the above, a 6-month follow-up of the higher-dose group (3.0–23 mCi) has actually shown an increase in neointimal area.[44] These findings were elucidated by follow-up angiography and histomorphometry. Stent thrombosis occurred in 7.7% of the irradiated study group but did not occur at all in controls. There was a dose-dependent increase in late lumen loss ($r = 0.72$). Mean neointimal area was 3.56 for the radiated group. Percent in-stent stenosis was $r = 0.64$. Both of these values were higher than those in controls. The neointimal proliferation consisted of smooth muscle cells, calcification, cholesterol, and foam cells, leading to formation of the so-called "atheromatous" neointima. The effects on the neointima were dose dependent, with greater hyperplasia/atherosclerosis with higher doses.

It also must be remembered that species-specific endothelial regeneration and fibrinolytic activity exist and must be taken into account with various dosimetry responses. Taylor *et al.* experimented with a canine model studying the effects of ^{32}P-emitting stents in normal canine coronary arteries. One of the most attractive reasons for this study was the fact that, compared with the porcine model, the canine model has increased intrinsic fibrinolytic capacity and should therefore have a lesser tendency for thrombus formation. It was believed that this would provide results that would be more similar to the human vascular reaction to irradiated stent placement. Stents with activities of 3.5–14.4 mCi were used. The results showed outright adverse vascular effects at 15 weeks. A 25% increase in luminal stenosis (32.7% in controls vs. 44.6% in irradiated stents) and an increase in neointimal thickness (0.28 vs. 0.35 mm) were seen. There was also delayed neointimal healing that worsened with higher doses.

Obviously, the animal models have shown significant variations with regard to dosimetry and eventual response. Trials with radioactive stents in porcine, rabbit, and canine models give different results. This has generated debate regarding the response of the vessel to the initial injury, its response to radiation, and the response of the wall to various doses of radiation. It may be that lack of neointimal healing results in a platelet/fibrin-rich neointima. In addition, radiation may actually increase exposure time to various growth factors (e.g., TGF-B). To complicate matters further, it is not yet certain which animal model's reaction would be most similar to the human vascular response.

Clinical Trials

Fortunately, as studies in animal models continue, clinical trials are also underway with a few results reported. In 1996, the feasibility phase of the Isostents for Restenosis Intervention Study (IRIS)[45] was started. In this study, Palmaz-Schatz stents had ^{32}P embedded under the stent surface. These stents were used on 32 patients (22 with de novo lesions and 10 with restenosis). The initial stents used were designed to impart a radioactivity of 0.5–1.0 mCi, with an average stent activity of 0.71 when implanted. After implantation, the patients were treated with both aspirin and ticlodipine. After 1 month, there were no cases of target vessel revascularization, non-Q-wave myocardial infarction (MI), MI, emergency coronary artery bypass graft (CABG), stent thrombosis, neutropenia, or death. With these encouraging results, it was decided to expand the

original study (IRIS IA) to a clinical trial using similar coronary stents, but with a higher radiation level. These stents in the IRIS IB trial used the same ^{32}P but tested radiation levels of between 0.75 and 1.50 mCi with a mean of 1.06 mCi at implantation. Twenty-seven stents were placed with 22 in de novo lesions and 3 in restenotic lesions. The IRIS IA trial took place at three centers while the IRIS IB added an additional five centers to its study. The IB results of follow-up at 1 month also showed no resultant MI, vessel closure, death, or other adverse complications. The 30-day follow-up for both of the above trials was convincing and showed promise.

However, 6-month follow-up has, so far, shown unexpected results. The restenosis rate in the group with lower activity levels was 31%. This is as good as or slightly worse than the rate achieved by nonirradiated stenting. The late loss was less for restenosis compared with de novo lesions. In Heidelberg, studies have shown target vessel revascularization of 36% with stents emitting 1.5–3.0 mCi. Dose escalation trials using stents with activities of ≥ 3 mCi are in progress.[46]

Results published by Albiero *et al.*[47] at 6-month follow-up in The Milan Dose-Response Study complicate matters further. In all, 122 stents ranging in activity from 0.75 to 12.0 mCi were used in 82 patients. This was a single-center, nonrandomized, dose–response study. Palmaz-Schatz stents were used in the 0.75–3.0 mCi group; BX stents were used for the 3.0–6.0 mCi and 6.0–12.0 mCi groups. More than 90% of the lesions treated were de novo. The patients were followed up with both angiography and IVUS. Pure intrastent restenosis decreased from 16% in the 0.75–3.0 mCi group to 3% in the 3.0–6.0 mCi and 0% in the 6.0–12.0 mCi groups (Fig. 1). These values are all lower than restenosis seen with stenting alone. There are, however, interesting results with regard to intralesional restenosis (Fig. 2). Restenosis rates of 52% in the lower, 41% in the higher, and 50% in the highest groups were seen. Late-loss index ranged from 0.71–0.57. The explanation for these results is believed to be the following. According to the electron fence theory, there should be no neointimal hyperplasia in areas covered by the irradiated stent; however, a stent does not cover the entire length of a lesion. Those areas of the lesion not covered by the stent, or those that are adjacent to articulating areas, will demonstrate neointimal hyperplasia. These areas are usually at the proximal or distal edges of the lesion, resulting in the "candy wrapper" effect on follow-up angiography. This is not seen with conventional stenting because the hyperplasia occurs in the stented area as well as at the edges and therefore presents a smooth outline on angiogram. Similar "edge effects" have been seen in other studies as well. Factors that may be responsible for these effects are low-dose radiation, which is present just beyond the stent edge and may actually stimulate noninjured tissue to proliferate; injury to the irradiated segment during an aggressive procedure; or a combination of the two. Follow-up studies by Albiero *et al.*,[48] however, have shown that with higher radiation dosage (12–21 mCi), and a nonaggressive stent implantation strategy, the problem of edge restenosis persists at 6 months. At these higher dosages, the problem was attributed to negative remodeling, whereas tissue growth was the mechanism in the lower dosage studies. Possible solutions to this problem include a mixture of radioactive stent- and catheter-mediated delivery of radiation, hot-ended stents, cold-ended stents, self-expanding nitinol irradiated stents, or a square-shouldered balloon.[49]

A similar edge effect has been noticed after catheter-based beta radiation. For example, Hoher *et al.*[30] noticed a target lesion restenosis of 12% but a total restenosis rate of 46%.

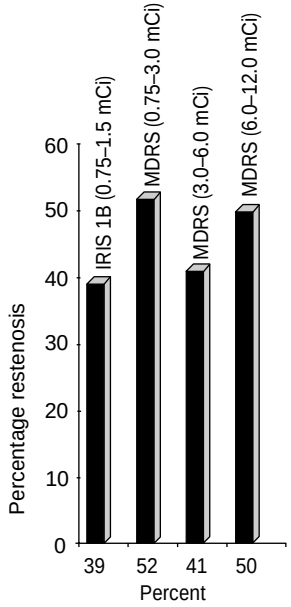

FIG. 1 Comparison of intralesional restenosis in clinical trials. MDRS = Milan Dose Response Study.

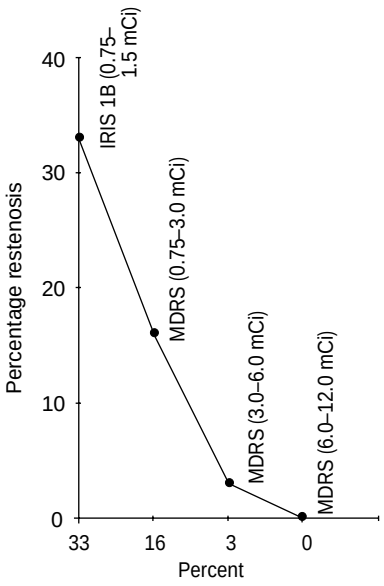

FIG. 2 Comparison of in-stent restenosis in clinical trials. Abbreviation as in Figure 1.

However, a study by Kozuma *et al.*[50] suggests that low-dose radiation may not be responsible for this phenomenon, and that nonmeasurable device injury may instead be the culprit. In this study, a similar increase in plaque volume was seen in all segments compared. These included noninjured edges of the irradiated group (19.6% increase), noninjured edges of the placebo group (21.5% increase), and the irradiated segment itself (21.0% increase). In the WRIST trial of patients with in-stent restenosis, edge stenosis was found in 10% of patients with radiation versus 4.7% with placebo. It was believed that geographical miss was the cause—that, in this situation, the radiation did not cover the entire segment of artery injured during PTCA.

Recently, a report by Kay *et al.*[51] has shown a late progression of in-stent neointimal hyperplasia between 6 months and 1 year post implant that has caused concern. Of those patients who were event free at 6 months post implant, 19% required reintervention by 1 year. The event-free rate at 1 year in the patient group was 53% (worse than with conventional stenting). The authors of the report believe that the irradiated stent inhibits neointimal hyperplasia within the first 6 months (as reported by Albiero) and especially in the initial 3 months. After this, however, it is felt that a "rebound" phenomenon occurs, causing cellular proliferation between 6 months and 1 year. In nonradiated stents, this same time period shows very few changes in lumen diameter. Also, stenosis progression from the edges was not seen, which indicates that the candy wrapper effect is a short-term response. Overall, the report suggests that "irradiated stents delay but do not prevent neointimal hyperplasia," which is a setback in terms of irradiated stent efficacy.

New Developments

There are a few new experimental developments in stents. Li *et al.* experimented with a position-emitting ^{48}V nitinol stent. This particular type of stent emits both gamma and beta radiation. The beta component can be useful for providing the means by which a localized area of tissue is irradiated. On the other hand, the gamma emissions will provide a safety net, as gamma radiation is more easily picked up if the stent is lost during the procedure. There are no human trials yet with this type of stent. Alt *et al.*[52] have been experimenting with stents coated with gold. ^{198}Au was created by placing these stents in a nuclear reactor. Various dose activities have been produced (0–20 Gy). These were implanted in mini-pigs, and no acute complications were initially reported. At 4 weeks' follow-up, IVUS showed a greater reduction in neointimal growth than in controls, as well as better response with higher doses. A report by Schulz and Alt *et al.*,[52, 53] however, has shown ^{198}Au to induce neointimal proliferation rather than inhibit it (this dealt with activity levels of 10.4–55.4 mCi). Changes in the actual stent design are being studied as well. The standard stent used today is the Palmaz-Schatz stent. This stent has a central articulating area made up of a separate 1 mm piece connecting two larger metal hemistents. This design was intended to afford greater flexibility. A drawback is that, when irradiated, this design cannot distribute an even dose of radiation to the tissue throughout the stent length. Because of irregular dosimetry at the articulating areas, the response of neointimal hyperplasia is much greater in areas with less radiation. The BX stent, mentioned in the Milan Dose-Response Study, is a new generation of stent designed to be confluent, but, because of its unique design, is also flexible. This will allow more equal distribution and therefore more even suppression of hyperplasia. Other new radiation delivery systems that are proposed include gamma stents and the previously mentioned stents to help combat the candy wrapper effect.

Conclusion

Radiation therapy has the potential to be a very useful tool against restenosis after PTCA and/or stenting. Studies with gamma and beta radiation show promising results. Endovascular gamma radiation has been shown to be effective in randomized trials, even at 3-year follow-up. Beta radiation is preferred because of greater safety and localization, and it has also shown encouraging results in initial clinical trials, as well as in larger randomized studies; consequently, the FDA has approved the use of both. In both types of endovascular brachytherapy, it seems that the greater the dose, the better the initial response. Safety concerns include an increased incidence of late thrombosis and greater restenosis at margins. With irradiated stents, however, the situation is not as clear. Animal models have presented confusing results at times. There is a great deal of variation in neointimal response to radiation between different species, ranging from significant suppression of hyperplasia to outright adverse effects of radiation on the vessel wall. While some clinical trials have been encouraging, others have not. Follow-up of up to 1 year has been disappointing so far. Many issues, such as the candy wrapper effect and rebound hyperplasia, must be dealt with before this becomes a viable form of therapy. The questions of dosimetry are complex and require more study. In addition, delivery of radiation is not just a question of catheter versus stent. There are many different forms of delivery, each of which still needs to be adequately studied. In fact, there is still not even consensus on which ion should be used. On a more long-term note, more time is needed for further follow-up studies. Overall, there is a great amount of work to be done, and clinical studies concerning this form of neointimal hyperplasia prevention are still in an early phase. It has become clear that radiation therapy in this setting, while having potentially great benefits, can have deleterious effects as well. However, the mixed bag of positive and negative results seen so far and the attractiveness of stents or PTCA eventually being "restenosis-proofed" is cause for cautious optimism.

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