Review Article

Irradiation and Postangioplasty Restenosis

A recent overview

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SUMMARY

One of the most intriguing developments in recent years towards prevention of restenosis after angioplasty is the use of ionizing radiation. The background for the use of radiation treatment for this application is sound, since radiation is used not only to treat malignant cancerous growths but also is used for treatment of benign hyperplastic disorders such as post-surgical keloid formation and recurrence of pterygium after surgical removal. Restenosis can be considered a form of overexuberant wound healing triggered by angioplasty. Ionizing radiation inhibits serum-stimulated proliferation of many cell types including fibroblasts and smooth muscle cells *in vitro* and also suppresses the synthesis of collagen by cultured fibroblasts. Liermann who showed inhibition of post-stent restenosis first used ionizing radiation for restenosis prevention clinically in iliac and iliofemoral arteries. Subsequently, extensive animal studies in various restenosis models have shown a profound inhibitory effect of catheter-based radiation (endovascular brachytherapy) on neointima formation and overall vessel shrinkage (negative remodeling). Based on these results clinical trials have been initiated with several types of devices and isotopes. Among these are ^{192}Ir, ^{32}P, ^{90}Y, ^{90}Sr / Y and ^{188}Re. Additionally, radioactive stents have been developed; devices for clinical use are made radioactive at the μCi level by surface implantation of 32P ions. Results from early clinical trials are encouraging and brachytherapy appears safe for clinical use and at an appropriate dose, may be highly effective for restenosis prevention. (Jpn Heart J 2000; 41: 541-570)

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IN 1977, Andreas R. Gruentzig, heralding a new era and launching the field of interventional cardiology[1)] performed the first coronary balloon angioplasty. After more than 20 years, percutaneous transluminal coronary angioplasty (PTCA) is now widely accepted as an effective therapy for selected patients with symptomatic coronary artery disease. However, the over-compensatory wound healing response to angioplasty causing restenosis significantly limits the long-

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term success and cost effectiveness of coronary angioplasty. Restenosis is common after PTCA occurring in at least 30% of patients within the first six months.[2,3] Stents have reduced the clinical incidence of angiographic restenosis; however, the restenosis rate in stented vessels remains about 20%.[4,5] Moreover, the restenosis rates are likely to be higher in less ideal lesions including those in small vessels, ostial lesions, complex long and bifurcating lesions, vein grafts, and diffuse in-stent restenosis.

Several strategies have been studied to modify the postangioplasty restenosis process including pharmacological agents, new mechanical devices and gene therapy. However, the restenosis problem has not been solved and remains the Achilles heel of PTCA. It is the most vexing problem facing the field of coronary interventions.

The search for newer prevention modalities has recently focused on the area of ionizing radiation, which has been utilized for decades by oncologists to control cellular proliferation in both malignancy and benign proliferative conditions. Restenosis, the response to injury of the vessel wall could itself be considered at least in part a proliferative problem and thus is potentially suitable for prevention by radiation. Therefore, there is a firm rationale for the idea of locally delivering ionizing radiation energy to the sites of coronary angioplasty and stenting to prevent restenosis.

The use of radiation for reducing restenosis after angioplasty is derived from the concept that restenosis is a proliferative wound healing process, and proliferating cells are sensitive to low dose radiation. Since the discovery of X-rays by Roentgen in 1895 and of radium by Madame Curie in 1898, ionizing radiation is well known as a potent antiproliferative agent for both malignant and benign disorders and the use of radiation to modify the wound healing response has also been well-documented.[6,7] Low dose external radiation is currently used for a number of different problems including the prevention of keloid formation after surgery and recurrence of pterygium after surgical removal.[8-11]

Restenosis may be considered as a type of exuberant wound healing. The formation of new intraluminal tissue and the subsequent overall vessel constriction are similar to scar formation and contraction that occurs during the healing process after injury. Histopathological evidence as revealed by autopsy studies shows the responses of human coronary arteries to angioplasty are a form of vessel wall stretch and dissection injury with subsequent scarring in the form of a proliferative neointima rich in extracellular matrix, similar to scars in other tissues.[12-16]

This safe and effective use of radiation therapy for benign proliferative conditions has led a number of investigators to test whether local irra-

diation might affect restenosis. This review is focused on the potential clinical application of endovascular brachytherapy for restenosis prevention. A brief description of the process of restenosis is outlined below and the data that supports endovascular brachytherapy is subsequently reviewed.

MECHANISMS OF RESTENOSIS

After balloon angioplasty: Many different mechanisms have been proposed to explain the sequence of events leading to restenosis after angioplasty within the first six months. One of the main causes of restenosis is excessive intimal proliferation of smooth muscle cells as part of the natural healing process in response to vascular injury. It is clear from histologic studies that nearly any injury to the vessel wall will invoke neointimal hyperplasia as a nonspecific tissue reaction, which in the case of angioplasty ultimately leads to restenosis when it is excessive. The well known mechanisms contributing to restenosis include 1) elastic recoil, 2) variable amounts of mural thrombosis with thrombus organization, 3) smooth muscle cell migration, proliferation, and synthesis of extracellular matrix, and 4) late vessel cross-sectional constriction or shrinkage (so-called negative remodeling).[17-19)]

Elastic recoil, which is an early phase mechanical collapse after balloon expansion of vessel wall, does not seem to progress much beyond the first few minutes after balloon deflation. Observations made the day following balloon angioplasty show little further decrease in lumen size. Elastic recoil may contribute to restenosis or acute vessel closure as the result of rheological problems.

The second component of restenosis is the complex interaction among many hemostatic factors triggered immediately after vascular injury. This process has been implicated as a major early mechanism underlying restenosis. The platelet response to vascular injury begins immediately by exposure of blood to subendothelial structures. Platelet and fibrin-rich mural thrombi formed at the site of vessel wall damage induce activation of both coagulation and fibrinolytic systems. Following mural thrombus formation, numerous growth factors and cytokines secreted at the injury site activate a complex cascade of cellular reactions[20,22)]

Recent animal and clinical data suggest that GPIIb / IIIa antagonists may modify the restenosis process by controlling platelet activation and thrombus formation, and therefore local release of mitogens which induce neointimal proliferation. Additionally, abciximab, a chimeric monoclonal

antibody to GPIIb / IIIa, can bind to and block other integrins with known roles in smooth muscle cell, fibroblast and endothelial cell migration and proliferation.[23,24)]

The third component of restenosis is neointima formation, new intimal tissue growth that is an inevitable continuation of the repair process. This process begins within a few days after vessel injury and continues for weeks to months until equilibrium between the vessel wall and lumen is achieved. Its primary components are: 1) the migration of activated medial or adventitial, and existing intimal SMCs into the adluminal space; 2) the replication of these cells via the cell-division cycle; and 3) the synthesis and deposition of extracellular matrix elements including collagen and proteoglycans. When neointima formation is excessive, severe luminal renarrowing can occur.[25-27)]

The fourth mechanism of restenosis that has been more recently elucidated is analogous to wound contracture which occurs in other tissues such as the skin. This process may be related to contraction of the periadventitial fibroblastic scar. Several experimental studies have suggested that restenosis in animal models results not only from neointima formation but also from elastic recoil and remodeling. Recent investigations have demonstrated the involvement of the adventitia in the vascular repair process after medial injuries in a porcine overstretch injury restenosis model. Scott, *et al.* as well as Robinson and Schieffer[28-30)] suggested that the transient appearance of alpha-actin in adventitial cells for several weeks after coronary arterial injury may participate in constriction or shrinkage of the injured vessel and thereby also contribute to late lumen loss after angioplasty. Shi, *et al.*[31)] also showed that the hypercellularity of the adventitial layer, proliferation of fibroblasts, and modulation of their phenotype to myofibroblasts and increased collagen deposition are temporally associated with the development of a thickened adventitia, and suggested this may cause vascular remodeling. These data imply that the adventitial myofibroblasts and associated collagen fibers contribute significantly to coronary renarrowing by a form of scar contraction analogous to the transient expression of alpha-actin in fibroblasts during skin wound healing, which is responsible for contraction in that setting. Whether this process occurs in clinical angioplasty of atherosclerotic vessels remains to be determined.

In-stent restenosis: In recent years, coronary stenting has made a dramatic impact in reducing the incidence of acute vessel closure. Restenosis is also decreased in 'ideal' lesions and non-diabetic patients, mostly by achieving a bigger post-procedural lumen diameter and preventing early elastic recoil and late arterial remodeling.[4,5,32-34)] Antiplatelet therapy with aspirin and

ticlopidine or clopidogrel decreases the complications of subacute stent thrombosis and access site bleeding induced by warfarin, so coronary stenting is now being used in an ever-increasing variety of clinical settings and complex lesions. However, despite their proven benefits, coronary stents continue to have several limitations. Stents induce a more severe vascular reaction as evidenced by histomorphometry in animal studies and by IVUS in angioplasty patients[35,36] resulting in the difficult to treat entity of in-stent restenosis. The increased late lumen loss with stenting compared to angioplasty is due to both mural thrombus and neointima formation. Chronic low-level cell proliferation and foreign body response may also play important roles in in-stent restenosis.[37-39] Thus, the main cause of in-stent restenosis seems to be proliferative neointima with smooth muscle cells (SMCs), and macrophages, and abundant extracellular matrix. This may be a suitable target for prevention by endovascular radiation.[40-42]

CHOICE OF RADIATION SOURCE

There are various techniques for application of ionizing radiation to coronary arteries (Table I). The platforms to deliver radiation are: 1) external by linear accelerator; and 2) a catheter-based endovascular approach using gamma or beta-emitting isotopes as source wires, radioactive seeds, radioactive gas and liquid-filled balloons, or radioactive stents.

External radiation can eliminate the requirements for an intracoronary radiation catheter and prolonged procedure, and it has been shown effective in some animal preparations.[43-46] However, at present no systems are available to precisely target the desired treatment volume, i.e., the coronary artery in motion.

On the other hand, at present the readily available alternative is catheter-based endovascular brachytherapy. A large number of studies have demonstrated remarkable suppression of neointima formation using radia-

Table I. Isotopes and Delivery Systems Used in Endovascular Brachytherapy

Isotope	Emission	Max energy	Half-life	Radiation delivery system
^{192}Ir	γ, β	0.37 MeV	73.8 days	Seeds in nylon ribbon. Fixed wire via balloon
^{90}Sr / ^{90}Y	β	2.3 MeV	29.2 yrs	Multiple seeds hydraulically
^{90}Y	β	2.3 MeV	64.1 hrs	Fixed wire via balloon by afterloader
^{32}P	β	1.71 MeV	14.3 days	Fixed wire via balloon by afterloader
^{188}Re	β, γ	2.12 MeV	17 hrs	Liquid filled balloon
^{186}Re	β	1.08 MeV	90 hrs	Liquid filled balloon
^{133}Xe	β, γ, X-ray	360, 81, 32 keV	5.3 days	Gas filled balloon
^{99m}Tc	β, X-ray	0.14MeV	6hr	Direct injection

tion delivered in this fashion. Furthermore, catheter-based rather than stent-based techniques have the potential advantage that they do not require a permanent implant and can be applied in a wider spectrum of situations.

Some of the early experimental studies used an endovascular gamma radiation catheter-based delivery system which consisted of a commercially based high dose rate after-loader source and an ^{192}Ir ribbon. Gamma irradiation by hand-held sources can be impractical, since treatment time is relatively long with associated potential problems of prolonged myocardial ischemia and cath lab occupation. Use of a high dose rate afterloader with high-activity gamma emitters requires expensive modification of room shielding to protect the catheterization laboratory personnel since it is deeply penetrating, and not effectively shielded by standard lead aprons. Long distances or very thick lead shields and short exposure times are the only effective protective measures for high dose rate gamma radiation.

In contrast, beta irradiation may be a more practical solution for the application of endovascular irradiation since it has a limited tissue penetration, delivering a significantly smaller dose beyond the target area and requires only a short treatment time.[47,48] Strontium-90 / yttrium-90 (^{90}Sr / Y), ^{32}P, and ^{90}Y are pure beta-emitter isotopes with favorable radiation characteristics that can deliver a prescribed dose to an appropriate depth in coronary artery tissue with a short treatment time. Thus exposure to the catheterizing personnel is minimal and it can easily be incorporated within the current catheter laboratory environment.

More recently, several groups have investigated the use of beta-emitting ^{186}Re or ^{188}Re liquid-filled balloon catheter.[49-51] This system gives the advantage of a very homogeneous dose distribution and implementation for a standard PTCA catheter and simple shielding system. However, the potential hazard of leakage, though small, is a concern.

Another novel concept of delivering radiation to the vessel wall via the endovascular route is the use of 'soft X-rays' or Grenz rays. These X-rays are of a longer wavelength and thus less penetrating than those conventionally used in radiotherapy settings. The use of soft X-rays from an endovascular miniature X-ray generator would have potential advantages over beta or gamma-isotopes. These would include the lack of requirement for isotope storage and disposal, no risk of isotope loss either in the patient or with external spillage, and also the lack of need for oversight by nuclear regulatory authorities.

Isotope selection should take into account variables such as physical and chemical form penetration, half-life and incident exposure. The major

disadvantage of beta emitters is the rapid fall-off of dose in a radial distribution, which decreases the achievable dose and prolongs treatment time in larger arteries. Furthermore, in stented arteries absorption and scattering of beta particles by stent struts will cause some perturbation in the uniformity and magnitude of the radiation dose. Amols, *et al.* reported that average dose reduction varied from 4% to 14% in the presence of various stents and the observed dose perturbations decreased rapidly with increasing distance for the stent, which may mitigate the clinical impact of these findings.[52)]

Dose uniformity within the arterial wall may be important. For endovascular radiotherapy it depends critically on centering the source within the lumen and the cylindrical symmetry of the arterial wall. In these situations, some investigators have advocated centering the delivery catheter within the lumen. Small arteries (< 3.0 mm) may not require centering when delivery catheters of 4-5Fr occupy most of the vessel lumen. However in larger arteries, the lack of centering may be associated with overdosing one side of the vessel wall and underdosing the contralateral side. Specific catheter designs with segmented or helical balloons have been developed which provide centering apposition and allow distal blood flow.[53,54)] However, even if the source is perfectly centered in the lumen, dose asymmetry will result if the artery is deformed and plaque are located eccentrically, or the radiation is performed on an angulated section of artery. The most important issue regarding centering may not be putting the isotope in the center of the lumen but in the center of the vessel.

The next option for local endovascular radiation therapy is the use of radioactive stents which contain activity in the μCi range. Two basic methods are used to prepare such a device: one is neutron bombardment of the stent to render the entire stent radioactive, and the other is the impregnation of radioactive particles into the surface of the stent metal. The dosimetry of a radioactive stent is complicated and depends on stent geometry, which varies across stent designs. The 15 mm long Palmatz-Schatz stent and BX^{TM} stent have been used and the activity of beta-emitting stents used in the clinical trials ranged from 0.5-20 μCi.[116-118)] Several possible disadvantages of radioactive stents should be considered, including; 1) potential leaching of the radioactive material from the stent surface (although an insignificant problem); 2) possible thrombosis on the stent wire due to delayed re-endothelialization of the stent struts; 3) continued delivery of radiation by a permanently implanted stent, beyond the period of time required to inhibit restenosis; 4) possible heterogeneity of dose use to the irregular shape of the metal prosthesis; and 5) inaccessibility

of lesions to stent placement such as in small vessels, tortuous calcified arteries, bifurcation lesions, and so on. Taking these several disadvantages into consideration, the concept of radioactive stenting remains an interesting possibility. However, a recently identified potential problem, the 'candy-wrapper phenomenon', as a demonstrable feature of an 'edge effect' with apparent exacerbation of stenosis just below the stent edges may require mitigation.

RADIOBIOLOGY OF THE ARTERIAL WALL

Many radiobiological responses of the vessel wall have been known for decades. A well-established mechanism of radiation injury in many cells results from the formation of reactive oxygen species (oxygen radicals) which damage molecular components (especially nucleic acids) of the cells. In the oncological field the application of external beam radiation is frequently used in conjunction with hyperboric oxygen to induce a high tissue oxygen concentration, since oxygen appears to sensitize the tissue to ionizing radiation, potentially by increasing the development of O_2 free radicals.

One effect of low-dose radiation on cell potentiation of apoptosis is due to irreparable changes in the DNA structure and loss of the ability to replicate, rather than loss of cell integrity or necrosis.[55-61] At higher doses, direct cell killing occurs from extensive ionization damage. Low-dose ionizing radiation has been shown to inhibit thymidine uptake and collagen synthesis by cultured fibroblasts. Thus, radiation may effectively inhibit neointima formation by killing more rapidly dividing, synthetic smooth muscle cells.[7]

Regarding vasomotor function, one early study evaluated the effects of high-dose intracoronary irradiation, 20 Gy, using the gamma emitter ^{192}Ir, on intimal hyperplasia and vasomotor function. Intracoronary irradiation acutely impaired both endothelium-dependent and independent vasomotor function. There was a paradoxical recovery of the normal endothelial response to acetylcholine, but persistent impairment of NTG-mediated vasodilatation at 32-day follow-up. Histology revealed focal medial fibrosis, but without significant intimal proliferation or luminal compromise.[62]

The biologic effects of radiation on the vessel wall demonstrated within a range of doses from 14 to 20 Gy and using different isotopes are quite similar. Primarily, neointimal proliferation as a consequence of injury is greatly inhibited or eliminated. In these and the radioactive stent

preparations mural thrombi and perivascular intramural hemorrhages are not absorbed and organized, but persist at even the 4-week time point. This phenomenon suggests that radiation delays the healing process resulting in the formation of an "immature" neointima,[63] due to suppression or delay of the complex wound healing process occurring after vascular injury.

Pathological data on radiation injury suggests that endothelial cells are the most radiosensitive cellular element of the mesenchyma. It is clear that the radiation produces not only endothelial cell death at high doses but also sublethal effects with low doses. At a higher dose of > 21 Gy, reendothelialization is not completed even at 4 weeks.[64] Furthermore, Gillete and co-workers found that aortic thrombosis, aneurysm formation and hemorrhage were associated with use of high-dose, large-volume intraoperative gamma-irradiation of the thorax in an animal study.[65]

Waksman, *et al.* using an extended dose range of 28 and 56 Gy to explore the limits of safety of endoluminal irradiation using beta-irradiation in the juvenile pig angioplasty model, demonstrated that neointima consisted almost solely of fibrin / platelet mural thrombus without evidence of thrombus organization or mesenchymal cell ingrowth. Nevertheless, there were no thrombotic occlusions or premature deaths in these dose groups. Scanning electron microscopy of 14 Gy irradiated coronary arteries 2 weeks after balloon injury showed recovery of the luminal surface with a confluent layer of cells with endothelial-like morphology.[66]

On the other hand, radioactive stents might have potential increased risk of thrombosis due to a delayed re-endothelialization process. The neointima covering stents is characterized by a reduced number of smooth muscle cells and endothelial cells. The endothelialization of stents is an important healing response of the arteries reducing the risk of thrombotic stent occlusions.

Several presentations have been made showing that there is substantial fibrin thrombosis deposition following catheter based treatments leading to vessel thrombosis in animal models. However, stent thrombosis is not always seen in animal models of catheter based brachytherapy. Fischell and co-workers[67] postulated delayed endothelialization predisposing the thrombus formation. Hehrlein and co-workers have shown that the re-endothelialization after low-dose radioactive stent implantation was delayed, with the rate of stent endothelialization being dose-dependent. Nevertheless, endothelialization was completed at 4 weeks and no difference in thrombotic events between the radioactive and conventional stents was seen.[68] Laird, *et al.* have demonstrated that sublethal doses of beta-

particle irradiation may also inhibit SMC migration and, additionally, endothelialization was seen after 28 days of radioactive stenting.[69]

PRECLINICAL STUDIES USING ANIMAL MODELS

Because of the similarities of restenosis to wound healing, and the known capacity for low-dose radiation to prevent hyperplastic scarring, there appears to be a firm rationale for the idea of delivering ionizing radiation to the sites of coronary angioplasty and stenting to prevent restenosis. A number of approaches for testing this hypothesis have been applied in preclinical models of vascular lesion formation. Several factors have been suggested to influence the effect of radiation in the vessel wall, such as the radiation source, the method of radiation application, the dose distribution, the timing of application of radiation during the interventional procedure, and tissue hypoxia. To evaluate the proper method to apply this new modality of treatment, several investigators have used both externally delivered X ray-irradiation as well as various catheter-based and radioactive stent endovascular approaches with various isotopes in experimental studies primarily using pigs and rabbits.[6,7,70,71]

STUDIES OF EXTERNAL BEAM IRRADIATION

The concept of external beam irradiation is an attractive possibility. If it would work, the requirements for an intracoronary radiation catheter and prolonged angioplasty procedures would be eliminated. Results using the external approach have been mixed.[46,72-75] One previous study using external beam radiation demonstrated no beneficial effect on restenosis. In one of the first studies to apply external beam radiation, Schwartz and colleagues found increased intimal hyperplasia 4 weeks after delivery of 8 Gy in pigs with coronary stent injury.[46] However in this particular study there was substantially and statistically significant greater vessel injury in the radiation group than in the control group, which may likely explain the increase neointima seen in the radiated group. Subsequently, in three different experimental models of restenosis, a single dose of externally applied radiation energy has been shown effective against neointima formation.[72,75,78]

There were several possible explanations to reconcile these conflicting results among the small number of studies. It may be that dose, mass of tissue radiated, timing of delivery and the type of injury are important contributing factors. The doses used by Schwartz, *et al*. may have been

too low to produce cell killing and could have been stimulatory to the restenosis process. Also, stenting causes more severe injury than simple balloon dilatation, and invokes a different healing response which may be somewhat less reliant on local arterial wall response.

Recently, Marijianowski, *et al.* and Styles, *et al.* reported that external beam irradiation before or at 0 or 2 days was ineffective for decreasing the absolute size of the neointima. Furthermore, the myocardium was substantially damaged by the 14 Gy external irradiation as evidenced by increased myocyte necrosis, inflammatory infiltrates, and interstitial fibrosis.[43,44] However, when neointima was corrected for overall vessel size as well as extent of balloon injury, it was shown that external irradiation indeed decreased neointima formation. More recently, Robinson, *et al.* reported the results from a study performed at Emory University using 21 Gy external irradiation to the heart of pig coronary arteries after either angioplasty or stenting that indicate a profound and consistent suppression of neointima formation.[79]

STUDIES OF ENDOVASCULAR IRRADIATION

Several groups have subsequently demonstrated remarkable inhibition of post-angioplasty cellular proliferation and neointimal formation in rabbit and pig models of restenosis, using the gamma emitter ^{192}Ir by an endovascular approach.[6,7,70,71,75] Wiedermann and co-workers found suppression of neointima 4 weeks after angioplasty when 20 Gy was delivered at a radial depth of 1.5 mm just before arterial injury and demonstrated that this effect persisted at 6 months. Similarly, Waksman and co-workers demonstrated profound suppression of neointima using ^{192}Ir with a dose-response effect in vessels treated with 3.5, 7, and 14 Gy at a radial depth of 2 mm. Additionally, they showed that delay of the radiation treatment for two days resulted in greater suppression of neointima when compared with radiation immediately post angioplasty. This study also indicated the durability of the radiation effect at 6 months. Using a high-dose rate afterloader, Mazur and colleagues found that 10-25 Gy from ^{192}Ir at 1.5 mm depth inhibited late lumen loss and intimal proliferation at 4 weeks in the balloon injured pig coronary artery. However, we need to point out that a four week end point is not likely to be an adequate end point in most animal models to assess the neointima formation due to the profound effect on delay of healing.

Verin and co-workers reported the use of a beta emitter at a dose of 18 Gy with a guide wire-deployed, flexible yttrium coil activated in the

neutron flux of a nuclear reactor. This isotope was shown to be effective for neointima reduction at 2 months in a hypercholesterolemic rabbit model of restenosis.[53] The Emory group also examined the use of stainless steel-encapsulated sources containing a pure beta-emitter (^{90}Sr / Y) to deliver one of four doses at 2 mm depth: 7, 14, 28, 56 Gy, to determine whether the use of the beta-emitting radioisotope would have similar effects as gamma irradiation and to examine the dose-response relationship. This isotope has the advantage over ^{90}Y of a much longer half-life (27 years as opposed to 64 hours) and has sufficient energy to deliver therapeutic doses within a few minutes. A dose-response relation was demonstrated, but no additional benefit was seen beyond 28 Gy since neointima formation was nearly eliminated at that dose.[66] Scanning electron microscopy of 14 Gy irradiated arteries showed no morphologic differences from controls at 2 weeks; a confluent layer of endothelial or endothelial-like cells was present throughout the region of angioplasty injury. However, delayed re-endothelialization in ballooned coronary arteries compared with controls at 4 weeks is observed at higher doses, along with the appearance of fresh mural thrombus composed of platelet aggregates and leukocytes which might have induced thrombotic vessel occlusion. A later study in adult Yucatan miniature pigs by Salame, *et al*. found that coronary arteries irradiated at 15 or 30 Gy at 2 mm from the ^{90}Sr / Y source had areas within the injured segment that had not been fully re-endothelialized by 1 month and this was associated with a significant increase in platelet recruitment at the angioplasty site compared to balloon injured non-irradiated controls even at 1 month post injury.[80]

Additionally, Waksman, *et al*. investigated potential mechanisms of the radiation effects detected as suppression of neointima formation and inhibition of post-angioplasty vessel chronic constriction.[81,82] Cell proliferation, as detected by quantitative immunohistochemistry for incorporated BrdU, was found to be significantly attenuated in the arterial media and adventitia at 3 days following injury in a dose-dependent manner. By 7 days, there was no difference in BrdU staining and cell density in any arterial wall region. A subsequent investigation suggested that radiation reduced the restenosis-like response of pig coronaries to angioplasty by inhibiting the first wave of cell proliferation in the adventitia and media, and by a favorable effect on late remodeling. In this study, estimation of cellular apoptosis by terminal transferase dUTP-biotin nick-end labeling was performed and was found to be strikingly positive in the adventitia at the balloon injury site, however, no differences between irradiated arteries and controls were seen. As indices of negative remodeling, smooth

muscle cell alpha-actin immunohistochemistry as well as histomorphometry for vessel perimeter were measured. Irradiation (28 Gy) substantially decreased staining of alpha-actin marker of myofibroblast differentiation in the adventitia at 2 weeks. This study demonstrated that beta-irradiation at 28 Gy inhibited adventitial myofibroblastic transformation and post-angioplasty chronic vessel constriction or overall shrinkage (negative remodeling). The group with 28 Gy-irradiated arteries showed significantly larger vessel perimeter than controls 4 weeks after overstretch angioplasty injury.

A combination of catheter-based radiation at the time of conventional stent placement has also been evaluated in experimental studies.[83-85] Waksman, *et al.* showed that endovascular irradiation (14 Gy: ^{192}Ir and ^{90}Sr/Y) of the coronary artery before stenting effectively reduces neointimal hyperplasia.[83] This study demonstrated the first successful use of intracoronary low-dose radiation treatment as an adjunct to stent implantation. The beneficial effect was evident at 1 month with both gamma and beta sources when 14 Gy was administered to the treatment site prior to stent implantation. Compared with radiation applied after stenting, radiation before stenting has been shown more effective in reducing intimal hyperplasia. This effect was probably due to the larger vessel diameter created by the stents, resulting in a lower dose being delivered to the target tissues in this study.[85]

RADIOACTIVE STENTS IN ANIMAL STUDIES

Hehrlein and co-workers initially studied implantation of stents made radioactive by neutron bombardment.[68] PS stents were made radioactive in a cyclotron by proton bombardment, which produced stents with a very low activity (μCi level), with a maximum of 35 μCi. The predominant form of radiation was beta-particles, but this radioactive stent also emitted low-energy x-radiation and high-energy gamma-radiation via the plethora of isotopes generated from the stent metal alloy (i.e. ^{55}Fe, ^{55}Co, ^{56}Co, ^{51}Cr, ^{52}Mn, and ^{57}Ni); these may not have contributed to the observed biologic effect because the amount of gamma radiation emitted by this stent was small, only 0.7% of the total dose within 5 days. The low-dose / low-dose-rate radioactive endovascular stents were implanted in rabbit iliac arteries and shown to significantly reduce intimal hyperplasia.[68,86,87] Consequently, this same group investigated the effects of stents bombarded with ^{32}P ions via a mass separator and showed efficacy at 4 weeks and at 12 weeks.[88]

A similar technique was independently developed and tested by Fis-

chell and co-workers.[67] ^{31}P was ion-implanted beneath the outer surface of the titanium wire of stents, which were exposed for several hours to a flux of slow neutrons to produce a pure beta-emitter. It offers the advantages of no associated gamma radiation, a short half-life (14.3 days), and limited range of the beta particles in tissue (3 to 4 mm). This stent wire with an activity as low as 0.006 μCi / cm of wire completely inhibited SMC proliferation within 6.0 mm of the wire in cell culture. These stents were also effective in inhibiting neointimal proliferation at 28 days in iliac arteries of miniature pigs.[69] In this study, neointimal proliferation was significantly reduced without excess inflammation or fibrosis compared to control, non-radioactive stents. There was a 37% reduction in neointimal area and a 32% reduction in percent area stenosis. Subsequently, this stent was tested in pig coronary arteries at various levels of radioactivity. Curiously, a U-shaped dose response effect on neointimal proliferation was demonstrated. It was found that a greater magnitude of reduction in neointimal cellularity was observed at stent activities over 1.0 μCi (3.0 to 23.0 μCi) and stent activities under 1.0 μCi (0.15 to 0.5 μCi) than control. However, stent activities of 1.0 μCi promoted rather than decreased intimal proliferation.[63] This puzzling finding may be explained by speculations that either delayed endothelialization or a complex effect on the extracellular matrix production might be implicated.[89] Vessels in which radioactive stents have been implanted also display delayed re-endothelialization. Using scanning electron microscopy, Farb, *et al.*[90] showed the endothelium still to be incomplete in rabbit iliac arteries after implantation of BX stents (6 and 24 μCi) at the late time point of 3 months. Taylor, *et al.*[91] also demonstrated that ^{32}P stents implanted in coronary arteries resulted in delayed healing with persistent fibrin in the neointima and incomplete re-endothelialization in vessels with the higher dose stents, suggesting that the delay in re-endothelialization was dose dependent. Another explanation is that the vascular response to different radiation doses is complex. There are considerable difficulties with dosimetry of radioactive stents, including substantial heterogeneity of dose due to the irregular shape of the expanded metallic stent structure. Further investigation is clearly needed to understand the radiation dosimetry in this complex setting.

CLINICAL STUDIES

Based on these results of several animal studies, clinical experiences with endovascular irradiation to prevent restenosis are accumulating.

PERIPHERAL SYSTEM

Preceding the coronary trials, endovascular brachytherapy was first applied in the peripheral vascular system. Preliminary clinical studies using gamma radiation in the human iliac restenotic artery, human AV hemodialysis shunt, and human coronary artery have been completed.[92-96] One of the earliest clinical studies demonstrated a beneficial effect of endovascular irradiation in the peripheral circulation. Liermann and co-workers reported preliminary results using endovascular radiation therapy in 35 patients with restenosis after initial stenting in the superficial femoral artery. Restenotic lesions were ballooned and treated with a prescribed dose of 12 Gy from ^{192}Ir delivered to the vessel wall by a high-dose-rate afterloader. Twenty-eight patients showed no restenosis or adverse effects at follow-up of 7-60 months (mean 38 months) after irradiation. Four cases showed complete occlusion or a significant restenosis.[97] Clinical follow-up detected a patency of 80% at the treated site at 5 years and none of them reported any adverse effects as a result of the radiation treatment at follow-up of up to 7 years.

Regarding endovascular radiation therapy for the prevention of restenosis following angioplasty of peripheral artery blockade, PARIS (Peripheral Artery Radiation Investigational Study) is the first multicenter, randomized double-blind study to compare the late patency of superficial artery PTCA in 300 patients with or without adjunctive gamma radiation using ^{192}Ir. The feasibility study was finished and the results showed that target lesion revascularization (TLR) was 7% and target vessel revascularization (TVR) was 12%, respectively.

CLINICAL TRIALS USING GAMMA-IRRADIATION (TABLE II)

In human coronary artery disease, several groups have reported their results using gamma irradiation. Mazur, *et al.* found that 10-25 Gy of ^{192}Ir using a high dose-rate afterloader inhibited the 4-week post-injury intimal thickening in left coronary arteries treated by balloon angioplasty but had no effect on the stented right coronary artery.[98] Wiedermann, *et al.* also reported that neointima from aggressive oversize stenting did not respond to radiation therapy. The mixed results of these preliminary studies may be due either to the differences in doses or dose rates, variance in the healing response to stent injury, or some combination of these factors.

An intracoronary radiation study with long-term clinical and angiographic follow-up was reported by Condado and co-workers.[99] This was

Table II. Clinical Trials Using Catheter-based γ(192Ir)-irradiation Systems in Coronary Arteries

Study, PI	Trial design	^{192}Ir Dose	Radiation system
Condado	Phase I, Open-label	20-25 Gy, (actual 19-55 Gy)	Angiorad system; 30mm ^{192}Ir wire, hand-delivered, non-centered
SCRIPPS Teirstein	Single center, Double blind, Randomized,	8-30 Gy to media by IVUS	0.03in nylon ribbon with seeds (Best Medical), hand delivered, non-centered
WRIST Waksman	Single center, randomized, double blind	15 Gy at 2 mm	Best Medical, hand delivered, non-centered, 5F close-ended (Medtronic)
WRIST-SVG Waksman	Multicenter, randomized, double blind	15 Gy to 2.4 mm in stent restenosis	Same as WRIST
WRIST-LONG Waksman	Single center, randomized, double blind in-stent restenosis	15 Gy to 2.0 mm	Same as WRIST
GAMMA-1 Leon	Multicenter, randomized, double blind, in-stent restenosis	8-30 Gy to adventitia; IVUS-guided	Same as WRIST but 4 F catheter, (Cordis)
GAMMA-2 Leon	in-stent restenosis	14Gy at 2 mm	Same as GAMMA-1
ARREST Faxon	Multicenter, double blind	12Gy to 2mm,	Angiorad system, 30mm ^{192}Ir wire, balloon centering, 3.2F catheter
ARTISTIC Waksman	In-stent restenosis, native artery	12-18Gy to 2mm from source	30mm ^{192}Ir wire, 3.2F catheter, manual delivery
GRANITE Serruys	Multicenter, European Uncontrolled	Low dose γ	Seeds in nylon ribbons 23, 39, 55mm in length
SMARTS Waksman	Multicenter, double blind	12Gy to 2 mm from vessel wall	Angiorad system
R^2: Waksman	Rotablator Radiation Trial, Multicenter, randomized, double blind	12-18 to 2.0 mm from source	Angiorad system

the first study to treat the human coronary artery with radiation (22 lesions, 21 patients) using ^{192}Ir (prescribed dose 20-25 Gy, actual dose; 19-55 Gy). At 60 days, repeat angiography showed 2 total occlusions and one pseudo-aneurysm; the binary restenosis rate was 18%. At over 6 months follow-up, 20 remaining arteries sustained patency with a lack of late lumen loss and a binary restenosis rate of 28% with a late loss index of 0.19 with favorable remodeling in 10 (45%) arteries. Recently, three-year follow-up data demonstrated that the clinical benefits of the treated group remained and no major adverse coronary events were seen.[100)]

Several controlled clinical studies have shown that stents prevent restenosis more effectively by dilating the lesion and inhibiting chronic vascular constriction;[4,5,32)] stent restenosis, which occurs in 20 to 30% of patients, is due solely to neointimal proliferation.[101-103)] In this setting, endovascular irradiation therapy might be a promising strategy to treat in-stent restenosis. Teirstein and co-workers showed that treatment of in-stent

restenosis followed by catheter-based radiotherapy using ^{192}Ir substantially reduced the rate of recurrence in patients with previous coronary in-stent restenosis.[104] This SCRIPPS trial[94] is the first report of a catheter-based ^{192}Ir source applied to the human coronary artery in a prospective double-blinded randomized study. Fifty-five patients with restenotic lesions (14 in a vein graft) were randomized to receive intravascular brachytherapy at a dose of 8-30 Gy, versus placebo application. Dichotomous restenosis rate at 6 months at the stent and stent border was 54% in the control group and 17% in the radiation group and within the stent itself was 35.7% in the control versus 8.3% in the irradiated group. Follow-up vessel diameter and reduction of lumen loss was significantly greater in treated lesion[95] and in-stent neointimal hyperplasia was reduced by 65% in the irradiation group. The composite event-free survival rate was 5% in the treated versus 52% in the placebo group. At the 2-year follow-up, the clinical benefits of the treated group were maintained with a TLR of 15.4% versus 44.8% for the placebo group ($p = 0.01$).[105]

More recently, many trials such as WRIST (Washington Radiation for In-stent Restenosis Trial), WRIST SVG, WRIST LONG, GAMMA 1, ARTISTIC (Angiorad Radiation Technology for Instent Restenosis), and ARREST (Angiorad Radiation for Restenosis Trial) have been designed to evaluate the effectiveness of vascular brachytherapy using gamma radiation in patients who developed in-stent restenosis.

WRIST[106] is a randomized placebo controlled single-center double-blinded trial to evaluate the efficacy in patients with in-stent restenosis. Patients with native coronary arteries ($n = 100$) and SVG ($n = 30$) disease were randomized to receive placebo or hand delivered non-centered gamma irradiation (^{192}Ir) source wire at a dose of 15 Gy in vessels 2-4 mm in diameter and with lesions < 47 mm in length. Primary endpoints were major adverse cardiac events (MACE) and binary restenosis at 6 months. The mean dwell time was 22.3 ± 2.1 minutes. The restenosis rate was 19% in the irradiated arm compared to 58% for the placebo arm, whereas TLR was 14% and 63%, respectively ($p < 0.001$). MACE at 6 months was 29% in the irradiated group vs 68% in the placebo arm ($p < 0.001$).

GAMMA-1 is a multicenter, double-blind randomized trial to evaluate the effects of endovascular gamma-irradiation in patients ($n = 252$) with in-stent restenosis in native coronary arteries (2.75-4.0 mm in diameter) and lesion length < 45 mm. Angiographic follow-up at 6 months demonstrated a 58% reduction in in-stent restenosis ($p < 0.001$) and a 43% reduction in the in-lesion restenosis with ^{192}Ir, compared with placebo. The

results were more impressive for the shorter lesions with a 69% reduction in in-stent restenosis and a 53% reduction in in-lesion restenosis.

Thus, one of the most important contributing factors of in-stent restenosis appears to be lesion length.[107] LONG-WRIST is a randomized trial designed to assess the effectiveness of endovascular irradiation using the ^{192}Ir wire. The endpoints are MACE, TLR and angiographic binary restenosis at 6 months. Patients (n = 120) with in-stent restenosis with a lesion length 45-80 mm and a vessel size of 3.0-4.0 mm were enrolled. The results showed a significant decrease in clinical and angiographic restenosis. The restenosis rate was 38% compared with 62% in placebos in clinical restenosis and 46% vs 78% in angiographic restenosis.

Another difficult condition to treat with angioplasty is disease in saphenous vein grafts (SVG), which, apart from the periprocedural distal embolism, is the relatively high rate of restenosis after balloon angioplasty. WRIST-SVG is a randomized, placebo-controlled trial that focuses on in-stent restenosis in SVG. Patients (n = 120) with SVG in-stent restenosis are to be randomized to placebo or gamma irradiation (^{192}Ir) at a dose of 15 Gy (2 mm from the source center) in lesions less than 45 mm in length in vessels 3.0-4.0 mm in diameter. Primary endpoints are the same as LONG WRIST.

ARTISTIC (Angiorad Radiation Therapy for In-Stent Restenosis Intra-Coronary trial) is now ongoing and a two-center randomized study in 290 patients will concentrate on in-stent restenosis. Randomization is performed after successful angioplasty and the dose of radiation at 2 mm from the source center is 12-18 Gy depending on the vessel size. Interim data on the first 26 patients[108] showed that the clinical restenosis at 6 months was 4 / 25 (16%) whereas MACE at 9 months was 11.5% (death 2 / 26 and CABG 1 / 26) with PTCA to TLR 1 / 26 and PTCA to non-TLR 1 / 26.

ARREST is a multicenter randomized trial designed to evaluate the effectiveness of a gamma-emitter for preventing restenosis following balloon angioplasty or provisional stenting in native or in-stent restenotic coronary arteries (lesion length < 20 mm, reference diameter 2.5-5.0 mm) in 800 patients. The Angiorad™ irradiation system (Vascular Therapies, CT) uses a 0.014 inch fixed-wire 30 mm radiation source with high activity (500 mCi) which is mechanically delivered into a closed end lumen balloon centering catheter. The randomization step to radiation (12 Gy at 2 mm from source center) or placebo is performed. MACE and target vessel failure at 9 months and angiographic binary restenosis rate at 6 months are the endpoints.

The GRANITE study is a multicenter open label European study in 100 patients designed to document the safety and effectiveness of low-dose gamma-irradiation as an adjunct to PTCA for in-stent restenosis. Source lengths are 23, 39 and 55 mm in vessels 2.75-4.0 mm in diameter. Endpoints will be MACE at 1, 9 and 36 months and angiographic binary restenosis at 6 and 36 months.

Small vessel intervention also appears to be another problem which have relatively high restenosis rates.[109] The SMART (Small Artery Radiation Therapy) study is a multicenter, double blind, placebo controlled non-randomized trial conducted to evaluate the safety and efficacy of ^{192}Ir (12 Gy at 2 mm from source center) for the prevention of restenosis with provisional stenting in 180 patients with vessels less than 2.75 mm in diameter. The primary endpoins are MACE at 6 months and 2 years and binary restenosis at 6 months.

CLINICAL TRIALS USING BETA-IRRADIATION (TABLE III)

Subsequently, early experience with beta-radiation has been reported by Verin and colleagues (Geneva trial).[110] Based on the experimental work,[53] a study using 18 Gy beta irradiation targeted to the luminal surface from a ^{90}Y-impregnated wire (Yttrium coil) hand-delivered through a segmented balloon centering catheter has been completed in 15 patients. The clinical event rate (4 / 15 patients underwent further target lesion revascularization) and the angiographic follow-up (6 / 15 patients had a greater than 50% stenosis at the previously treated site) did not suggest a significant impact on the expected restenosis rate. It seems likely that an insufficient dose delivered to the media or adventitia may have contributed to the discrepancy between the experimental and clinical results. A dose-response study to determine the effective dose in 160 patients following PTCA using this system with an automatic afterloader was initiated in Europe in three centers beginning in September 1997.

Novoste Beta-Cath™, an over the wire 5.0 French non-centering catheter with a closed end delivery and retrieval channel for hydraulic transfer of a 30 mm ^{90}Sr / Y source train, has been applied in human trials at Emory University and Brown University. The Beta Energy Restenosis Trial (BERT) is a feasibility study approved by the FDA and has followed 23 patients angiographically with single-vessel application of beta-irradiation after balloon angioplasty. The prescribed dose in this trial was 12-16 Gy and the radiation was successfully delivered to 21 out of 23 patients following successful PTCA without any complications or adverse events at

Table III. Clinical Trials Using Catheter-based β Radiation Systems in Coronary Arteries

Study, PI	Trial design	Isotope / dose	Radiation system
The GENEVA study Verin	Phase I, de novo or restenosis	^{90}Y, 18 Gy to balloon surface	Manual delivery of Yttrium wire. Centered with 30mm balloon
BERT King	Phase I, de novo lesions	^{90}Sr / Y, 12,14,16 Gy to 2mm from source	Novoste beta-cath system. Non-balloon centered
BERT Canadian Bonan	Phase I	^{90}Sr / Y, 12,14,16 Gy to 2mm from source	Novoste Beta-cath system
BERT 1.5 European Serruys	Open label	^{90}Sr / Y, 12,14,16 Gy to 2mm from source	Novoste Beta-cath system
BETA-CATH Kuntz	Phase III, Multicenter, randomized	^{90}Sr / Y, 14,18 Gy to 2mm from source	Novoste Beta-cath System
European dose finding Verin	Multicenter, dose finding, open label	^{90}Y, 9, 18, 32 Gy to balloon surface	Schneider System. Automatic afterloading of Yttrium coil. Centered with 30mm segmented balloon
CURE Weinberger	Phase 1, Single center, open labeled	^{188}Re, 20 Gy to balloon surface	Perfusion balloon which is filled with liquid ^{188}Re
PREVENT Raizner	Phase 1, open label, Multicenter,	^{32}P, 28, 35 or 45 Gy to 1mm from wire.	Guidant ^{32}P-wire system delivered by afterloader . Centered by a helical balloon
BETA WRIST Waksman	Phase 1, single center registry, in-stent restenosis,	^{90}Y, 20. Gy at 1.2 mm	Schneider System
BRIE Serruys	Multicenter European study, de novo or restenotsis	^{90}Sr / Y, 14,18 Gy at 2mm from source	Novoste Beta-cath system
INHIBIT Waksman	Phase-III, in-stent restenosis	^{32}P, 20 Gy at 1 mm.	26mm ^{32}P source line, Nucleotron afterloader, helical centering balloon
STARTS Waksman	Phase-III, In-stent restenosis	^{90}Sr / Y, 18-20 Gy at 2 mm	Novoste Beta-cath system,
SCHNEIDER Wijns	Multicenter, randomized, dose finding	^{90}Y, 9, 12, 15, 18 Gy at 1 mm	^{90}Yttrium wire (Schneider / Boston Scientific)
MARS-1 De Scheerder	2 centers, open label, de novo lesions	^{186}Re, 20 Gy to 0.5mm into vessel wall	Mallinckrodt, Liquid filled balloon system

30 days. The results at 6-month follow-up including clinical and angiographic evaluations showed that only 3 of the 21 patients treated had angiographic restenosis (15%) and 2 required target lesion revascularization (10%). The late loss index was only 4%. This remarkable lack of late lumen loss means that the artery maintained almost all of the benefits of the initial balloon angioplasty.[111,112] The Canadian arm from the Montreal Heart Institute and the European arm of BERT at the Thoraxcenter in Rotterdam were also conducted and the results were similar. A multicenter randomized trial, the BETACATH trial, of 1450 was started in July 1997 to confirm this beneficial effect in a larger group of patients.

Expeditious approval is desired for patients with diffuse in-stent restenosis since there are no other attractive alternative modalities for the treatment of in-stent restenosis and there is definite evidence that radiation

works. However, gamma radiation is somewhat impractical to use in the clinical setting because it requires a longer dwelling time and / or special shielding due to its high penetration characteristics. In this setting, several clinical trials using beta-radiation for in-stent restenosis have already been completed. START (STents And Radiation Therapy) is a randomized multicenter (from 50 sites), placebo-controlled trial assessing the Novoste Beta-Cath system (16 and 20 Gy at 2 mm) in 476 patients with in-stent restenosis. Primary endpoints are TLR and MACE at 6 months and 2 years as well as binary restenosis at 8 months. In the stent segments, restenosis was 14% compared to 41% in the control group ($p < 0.001$). Total segment analysis showed a 29% restenosis rate in the radiation group compared with 45% in the control ($p = 0.001$). Interestingly, of the 21% of patients who were implanted with new stents, no cases of late thrombosis were reported.

The BETA-WRIST trial was an open-label study evaluating the safety and efficacy of beta-radiation using ^{90}Y (Schneider) in 50 patients with in-stent restenosis. The control group was the placebo group of the WRIST trial. The vessel sizes were 2.5-4 mm with lesion lengths being < 50 mm. The mean dwell time was 183 ± 56 seconds in the treated arm. The primary endpoints are both clinical (MACE at 6 months and 2 years) and angiographic (binary restenosis and late loss at 6 months). Restenosis at 6 months was 16% compared to 66% in the control group. MACE at 6 months was 33% compared to 72% in the control arm.

Several other trials using beta-emitters are now ongoing. The feasibility phase of PREVENT (Proliferation Reduction with Vascular Energy Trial) study was initiated in December 1977 and Phase II was started in mid 1998. Interim results[113] were encouraging with a restenosis rate in the irradiated arteries of 4% (2 / 55) compared to the placebo group having a restenosis rate of 18% (3 / 17). The late loss index was only 5% in the treated arm compared to 51% for the placebo arm ($p = 0.0001$).

BRIE (Beta Radiation In Europe) is a randomized multicenter European trial in 180 patients using the Novoste Beta-Cath system at doses of 14 or 18 Gy at 2 mm from source center following angioplasty or provisional stenting in lesions < 20 mm. The endpoints are angiographic restenosis and MACE at 1 and 12 months. The interim data demonstrated that the target vessel restenosis was 30%: 19% in the PTCA group and 35% in the stent group. Geographic miss was found in about 40% of the treated lesions and could be the main problem.

CURE is the first liquid-filled balloon system used in a clinical feasibility trial for 30 patients after stenting. So far no data concerning the

results or the feasibility and safety of this system have been reported. MARS-1 (Mallinckrodt Angioplasty Radiation Study) is an open-label two-center study evaluating the efficacy and safety of a liquid-filled ^{186}Re balloon delivering 20 Gy to 0.5 mm into the wall in de novo lesions ($n = 60$). A small Australian pilot study evaluated the feasibility, safety and efficacy of delivering endovascular irradiation (using a ^{188}Rh-liquid filled balloon) following conventional percutaneous coronary intervention in 28 lesions with in-stent restenosis. Angiographic follow-up demonstrated a lower-than-expected rate of restenosis in this restenosis-prone group with only 1 vessel having restenosis in the irradiated segment and 4 vessels having restenosis at the irradiation border zone.[114]

INHIBIT is a randomized, double-blind, multicenter study designed to evaluate vascular brachytherapy using the Nucleotron afterloader to deliver a ^{32}P line source 26 mm in length to in-stent restenotic lesions < 45 mm in vessels 2.4-3.7 mm in diameter in 320 patients. Primary endpoints will be MACE at 6 months and angiographic binary restenosis. The results are also expected in late 1999.

RADIOACTIVE STENT (TABLE IV)

The IRIS (Isostent for Restenosis Intervention Study) trial is a preliminary non randomized safety trial using very low activity (0.5~1.0 μCi) ^{32}P impregnated Palmaz-Schatz stents with a mean stent activity of 0.69 μCi; it began in 1996 in 32 patients with restenosis and de-novo lesions in the native coronary artery as a phase I trial. There were no adverse effects at 30 days; however, 6-month angiographic follow-up revealed a binary restenosis rate of 31% and TLR rate of 21%. The results of the phase 1 IRIS trial (IRIS 1A) were not conclusive and expanded to include an additional 25 patients using a higher activity (0.75~1.5 μCi) stent with a mean activity level of 1.14 μCi (IRIS-1B). Two other studies, Heidelberg (3 μCi) and Milan (6 μCi), using higher activity level stents were also conducted. The Heidelberg Moderate-Activity ^{32}P-Stent trial[115] evaluated a dose of 1.5-3 μCi (mean 2.2 μCi) in 11 patients with restenosis. Clinically driven TVR was 4 / 11 (36%) at 6 months. Interestingly, the restenosis was observed to occur at the articulation point of this stent and to a lesser extent at the proximal and distal edges.

The previously tested radioactive stent lacks dose homogeneity across the entire length of the stent,[94] which could affect the biologic response to radiation, especially at the edges of the stent. Studies with the BX^{TM} stent and Multilink stent as a platform are about to begin in the US. These

Table IV. Clinical Trials Using Radioactive Stents in Coronary Arteries

Study, PI	Trial design	Isotope / dose / stent	Results and Status
IRIS 1A Fischell	Multicenter, open label, Phase I, de novo or restenotic lesions	^{32}P, 0.5-1.0 μCi, Palmaz-Schatz (PS) 15 mm stent	Binary restenosis rate 31%, TLR 21%
IRIS 1B Moses	Extension of IRIS 1A, Multicenter, open label	^{32}P, 0.75-1.5 μCi, PS 15 mm stent	Binary restenosis rate 32%
Heiderberg Hehrlein	Dose response study, single center	^{32}P, 1.5-3.0 μCi, PS 15 mm stent	TVR 36%
MILANBX-1 Colombo	Dose response study, single center	^{32}P, 3-6 μCi, 15 mm BX stent	Binary restenosis rate 43-50% (Presented at AHA 1998)
	Dose response study, single center	0.75 to 20 μCi, PS 15 mm stent and 15 mm BX stent	Binary restenosis rate 39-55% (Presented at Cardiovascular radiation Therapy III, 1999)
Rotterdam Serruys	Dose response study	^{32}P, 6 and 20 μCi, BX 15 mm stent	Started in Mar 1998
Isostent Moses	Radioactive stent for in-stent restenosis	^{2}P,8-12 μCi, BX 15 mm stent	Started in the US in 1999

second generation stents will give a better stent geometry which will result in superior uniform dosing across the stent. European trials conducted by Colombo et al in Milan on a second generation radioactive stent, the ^{32}P-Isostent BX™ stent, found a significant reduction in tissue within the stent; however, a 43-50% binary restenosis due to an increase in restenosis at the stent edges, the so-called 'candy wrapper' effect[116,117] where pronounced luminal narrowing occurred, was observed and is a problem which needs to be solved. The angiographic appearance of these vessels is quite unique, with narrowing at the site just proximal or just distal to the stent. Extremely low dose radiation was emitted at the periphery of the ^{32}P radioactive stent and injured vessels were not fully covered by the radioactive source that may be the main cause of this unique phenomenon. This phenomenon was seen in 5 of 6 cases that underwent TLR (5 of 29 patients treated, 20.7%).[117] Though they reported that neo-intimal proliferation was inhibited within the stent dose-dependently, the binary restenosis rate was not overly different with the control group. A recent study with a higher dose rate, 12-24 μCi, using the BX™ 15 mm stent conducted in Milan demonstrated that in-stent neointimal hyperplasia was also reduced in a dose related manner while intra-lesion restenosis was 39-55% due to late loss proximal and distal to the stent edges.[118] So far the results of all these studies have revealed similar restenosis rates of about 30-50% and TVR of around 20%.

CONCLUSION AND FUTURE PERSPECTIVE

Early results of the feasibility and phase 1 clinical trials are encouraging and confirm the predictive value of the preclinical studies. However, a large number of issues still remain, and further basic and applied investigation needs to be done. The target tissue for treatment is not yet determined, however adventitia must be targeted; the ideal isotope and efficient method of application, the timing, and the minimum and maximum doses of radiation including the toxic dose are still unknown. The studies with both beta and gamma radiation serve to prove the principle of the technology that if the right dose is delivered to the right target tissue then radiation will work to prevent restenosis regardless of the type of isotope and the difference of delivery method used. Which patients should be treated with radiation is also an important practical issue. Patients with high risk factors of recurrence who have many anatomical lesion characteristics, such as ostial, small, long, diffuse, bifurcation and venous graft lesions or underlying disease such as diabetes mellitus with a well-known propensity for restenosis could be potential populations for brachytherapy. Subanalysis of the BERT trial demonstrated that favorable remodeling was seen more commonly in small sized vessels.[119] Considering the great impact of the results in the SCRIPPS, WRIST and GAMMA-1 trials, gamma radiation is an important and viable therapeutic option for in-stent restenosis, especially diffuse type in-stent restenosis.

Thus, an initial impression of the results of clinical trials may lead to the conclusion that brachytherapy appears to be safe for clinical use and may be highly effective for restenosis prevention and a breakthrough adjunctive therapy to interventional cardiology. However, the late vascular complications related to radiation such as fibrosis or aneurysm formation or edge effect and late thrombosis as a new iatrogenic disease remain major concerns. Evidence is accumulating that delayed re-endothelialization leaving a chronically thrombogenic luminal surface may also create late thrombosis that requires resolution. The incidence of thrombotic occlusion after PTCA was dramatically reduced to $< 1.5\%$ by improvements in angioplasty techniques as well as the combined use of antiplatelet therapy. However, late and sudden thrombosis after angioplasty followed by intracoronary radiotherapy is now becoming a new phenomenon in interventional cardiology. Costa, *et al.*[120] reported that the incidence is 6.6% comfirmed by angiography 2 to 15 months after intervention and the rates appear to be higher in patients treated with stents plus radiation (8.8%) versus patients treated with balloons alone plus radiation (3.2%).

The effect of radiation on delaying the healing process and maintaining a thrombogenic surface may have triggered the thrombotic process and the timing is extremely unusual. Prolonged antiplatelet therapy and limiting stent use in conjunction with radiation are recommended.[121] One of the possible long-term sequelae of vascular radiation is the ability of radiation to increase the risk of a second malignancy. The risk of carcinogenesis depends on the volume and types of tissue as well as the radiation dose. From the data of the Swedish Cancer Registry,[122,123] the incidence is 0.02% per year in patients who had undergone local external irradiation for breast cancer. The radiation dose received by brachytherapy is nil compared with the radiation exposure during cancer treatment, therefore, it is unlikely we will see a sudden burst of brachytherapy induced cancers in 10 to 20 years time. Another important observation in recent clinical trials is the increased rate of revascularization in the irradiated group only during follow-up.[105,106] This late "catch-up" phenomena may minimize the long-term benefit of radiation.

The future of this technology still raises questions that are being addressed in well-designed and controlled clinical trials as well as mechanistic arrival studies that are underway.

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