

Intracoronary Brachytherapy: The Beginning of the End of Restenosis?

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Abstract

Restenosis remains a major problem 20 years after the introduction of coronary angioplasty. Pharmacological therapy has generally been disappointing in reducing the incidence of neointimal hyperplasia. Intracoronary brachytherapy is the latest anti proliferative agent that is showing promise in the fight against restenosis. Radiation therapy has been used for decades in the treatment of benign proliferative disorders. Animal studies have consistently demonstrated the efficacy of radiation therapy in inhibiting neointimal hyperplasia. Clinical trials, using different radioactive isotopes and radiation sources, are now showing dramatic reduction in neointimal hyperplasia and restenosis rates following balloon angioplasty and stenting. Intracoronary brachytherapy is beginning to show promise as one of the truly effective agent against neointimal hyperplasia and restenosis.

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Introduction

Restenosis remains a major clinical problem 20 years after the introduction of coronary angioplasty by Andreas Gruentzig in the treatment of coronary artery disease.¹ Recent randomised studies showed a persistent 32% to 57% incidence of angiographic restenosis following successful balloon angioplasty, usually within the first 6 months, despite increased operators proficiency and improved angioplasty equipment.²⁻⁴ Furthermore, numerous randomised pharmacological trials have been carried out in an effort to reduce the restenosis rate following balloon angioplasty (Table I).⁵⁻⁷ Despite initial promises in animal models in reducing excessive neointimal hyperplasia, these trials have invariably ended in disappointing or conflicting clinical results. Only coronary stents and the use of the antioxidant agent, Probucol, have been shown to reduce the incidence of restenosis.^{3,4,8,9} In the STRESS and Benestent trials, the use of a single Palmaz-Schatz stent was associated with a 30% restenosis rate.^{3,4} As pointed out by Teirstein and others, the impact of stents on restenosis is purely mechanical.¹⁰⁻¹² Stent implantation creates a larger lumen than the use of balloon angioplasty alone can.^{3,4} Stents do not diminish the neointimal hyperplasia response to injury; rather, they cause a more proliferative response.^{3,4,13} It is simply the larger lumen created by the stent that increases the capacity of the vessel to accommodate the excess neointimal hyperplasia, which thus

lead to a reduction in restenosis rate. Tardiff et al⁸ showed that pre-treatment with the antioxidant and weakly hypocholesterolaemic agent, Probucol, for one month prior to elective balloon angioplasty reduced the restenosis rate from 39% in placebo to 21% at 6 months. Yokoi et al⁹ reported similar results with an angiographic restenosis rate of 23% in the group pretreated with Probucol compared with 58% in the control group at 24 weeks. The mechanisms behind these good results have not been fully explained. It is unlikely to be due solely to the powerful antioxidant effort of Probucol or its weak hypocholesterolaemic effort and may be due more to its inhibition of the secretion of interleukin-1 by macrophages causing a decrease in the secretion of metalloproteinases by smooth muscle cells and remodelling of the extracellular matrix.⁸

Brachytherapy is the latest in a long line of antiproliferative agents that is showing increasing promise in the fight against restenosis. Very low doses (<1 Gy) and intermediate doses (e.g. 6 to 20 Gy) of radiation have been used for many decades for the treatment of a host of non-malignant conditions like eczema, psoriasis, peri-arthritis humeroscapularis, epicondylitis, parotiditis, prevention of keloid, heterotopic bone formation after hip arthroplasty, desmoid/aggressive fibromatosis, Peyronie's disease and pterygium (Table II).¹⁴⁻¹⁹ Furthermore, in benign proliferative disorders, treatment with doses of 7 to 10 Gy have proven to be effective in

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TABLE 1: RANDOMIZED, PLACEBO-CONTROLLED CLINICAL RESTENOSIS TRIALS

Agents/Studies	End point	P value
Aspirin		
Schwartz, White, Chesebro, Finci	Angiographic	ns
Thromboxane inhibitors		
Serruys, Serruys	Angiographic	ns
Savage, Hattori	Angiographic	ns
Feldman	Clinical event rate	ns
Serotonin inhibitor		
Serruys	Angiographic	ns
Prostacyclin/analog		
Knudston	Angiographic	ns
Raizner	Angiographic	0.055
Abciximab		
Top01	Clinical event rate	0.001
Heparins		
Ellis, Faxon	Angiographic	ns
Fish Oils		
Dehmer	Angiographic	<0.026
Grigg, Franzen, Reis, Leaf	Angiographic	ns
Nye	Angiographic	<0.05
Bairati	Angiographic	<0.05
Calcium channel blockers		
O' Keefe	Angiographic	ns
Whitworth	Angiographic	ns
ACE inhibitors		
Mercator, Marcator,	Angiographic	ns
Desmet	Angiographic	ns
Lipid Lowering Agents		
Weintraub, Beigel	Angiographic	ns
Anti-inflammatory		
Pepine	Angiographic	ns
Antiproliferative		
O' Keefe	Angiographic	ns
Grines	Clinical	ns
Kent	Angiographic	ns
Emanuelsson	1. Angiographic	ns
	2. Clinical	0.046
Eriksen	Angiographic	0.003
Maresta	Angiographic	0.01
Magnesium		
Roth	Angiographic	ns

ns: not significant.

Modified from: Hong M K, et al⁷

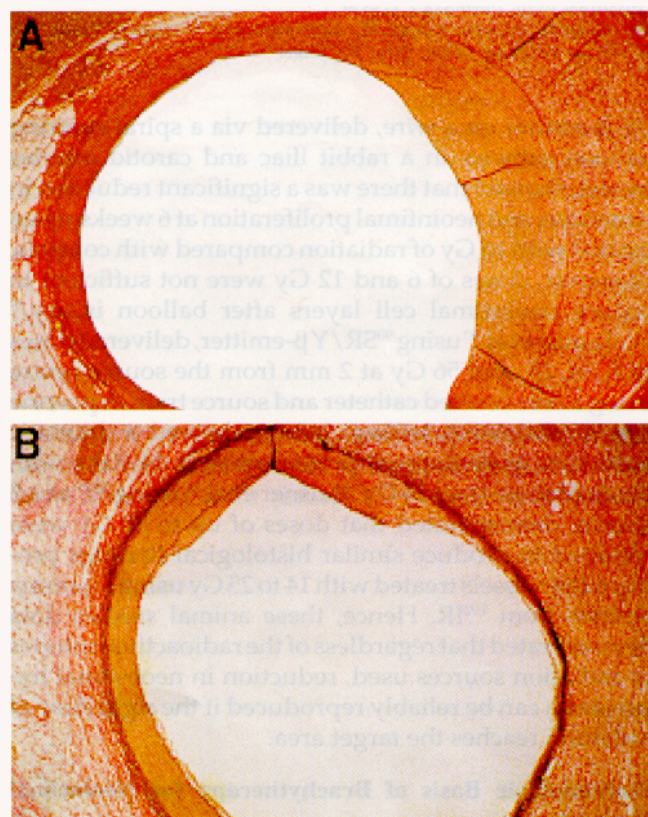
inhibiting fibroblastic activity without significantly interfering with the healing process.¹⁴⁻¹⁹

Fibrocellular tissue (neointimal hyperplasia) is a central component of the restenosis process and probably contributes 25% to 50% (with the rest explained by early elastic recoil and late pathological geometric remodeling) to late lumen loss following balloon angioplasty and is almost the sole contributor to restenosis after stent implantation.²⁰⁻²⁴ This neointimal tissue is derived from proliferating smooth muscle cells (SMCs) and newly produced extracellular matrix. The histology of this tissue is very similar to keloid tissue and smooth muscle cell tumours.²⁵ Hence, it is reasonable to consider using

brachytherapy as a new treatment modality to reduce neointimal hyperplasia through its effect on proliferating SMCs and matrix deposition.

Brachytherapy Studies in Animal Models

Early investigators have found that the porcine coronary artery injury model was the most reliable for studying the effect of cardiovascular radiation in inhibiting neointimal proliferation (Fig.1).²⁶⁻²⁸ Using this model, Mazur et al²⁸ demonstrated that neointimal formation was reduced following treatment with intraluminal Se with doses of 14 to 20 Gy using hand loading source via a perfusion delivery catheter after a dwell time of 30 to 60 min. Similar inhibitory effects were seen at 2 to 4 weeks with a higher dose rate, a delivered dose of 15 to 25 Gy and a shorter dwell time of 5 to 10 min.²⁸ Waksman et al²⁶ and Wiederman et al²⁷ showed that the inhibitory effect of radiation on neointimal hyperplasia at these doses were maintained at 6 months without causing any excess fibrosis or other adverse effects in the treated arteries and their adjacent segments. Following these encouraging results with gamma radiation, other investigators soon demonstrated similar results using different isotopes and radiation sources. Verin et al²⁹ using a

Fig 1. King SB III²⁹

(A) Porcine coronary artery two weeks after balloon overstretch injury showing exuberant proliferative response filling the crater created by the broken ends of the media. (B) Similar porcine coronary model two weeks after balloon overstretch injury with the application of endovascular radiation showing inhibition of the neointima formation between the broken ends of the media.

TABLE II: RADIOLOGIC QUANTITIES*

Radiation quantity (conventional term)	Description of quantity	Conventional units (Abbreviations)	SI units (abbreviation)	Symbol	Equivalent expressions-relationship between quantities
Exposure	Amount of ionization per mass of air due to X and gamma rays	Roentgen(R)	coulombs/kg (C/kg)	X	1R=2.58 x 10 ⁻⁴ C/kg
Absorbed dose	Amount of energy imparted by radiation per mass	Radiation absorbed dose (rad)	Gray (Gy)	D	1 rad = 100 erg/g 1 rad = 10 mGy 100 rad = 1 Gy 1 J/kg = 1 Gy
Kerma	Kinetic energy released per unit mass	Radiation absorbed dose (rad)	Gray(Gy)	K	K(mGy) = 3.39 x 10 ⁻⁴ x X(C kg)
Dose equivalent	A measure of radiation-specific biological damage in humans	rem	Sievert (Sv)	H	H(Sv) = W _R x D (Gy) H(rem) = QF x D (rad) 1 rem= 10 mSv 100 rem = 1 Sv
Effective dose equivalent	A measure of radiation and organ system-specific damage in humans	rem	Sievert (Sv)	H _E	H _E (Sv) = ΣW _T H _T (Sv) H _E (rem)~ΣW _T H _T (rem)
Activity	Amount of radioactivity expressed as the nuclear transformation rate	Curie (Ci)	Bequerel (Bq)	A	1 Ci + 3.7 x 10 ¹⁰ Bq 1 Bq = 1 s ⁻¹ (dps) 37 kBq = 1 μCi 37 MBq = 1 mCi 37 GBq = 1 Ci

*Modified from: Bushberg J T, et al⁵⁸.
 dsp: disintergration per second; H_T: equivalent dose to organ or tissue; QF: quality factor; W_R: radiation weighing factor;
 W_T: tissue weighing factor; 1erg: 10⁻⁷ joule.

⁹⁰Y P-emitter on a wire, delivered via a spiral centring balloon catheter in a rabbit iliac and carotid arteries model, showed that there was a significant reduction in restenosis and neointimal proliferation at 6 weeks when treated with 18 Gy of radiation compared with controls. However, doses of 6 and 12 Gy were not sufficient to reduce neointimal cell layers after balloon injury.²⁹ Waksman et al,³⁰ using ⁹⁰SR/Y p-emitter, delivered doses of 7, 14, 28, and 56 Gy at 2 mm from the source centre using a non-centred catheter and source train in porcine arteries following balloon injury, showed a dramatic reduction in neointimal proliferation at 14 days with doses of more than 14 Gy. Raisner et al,³¹ using ³²P as a β source, demonstrated that doses of up to 32 Gy were required to produce similar histological findings produced by vessels treated with 14 to 25 Gy using a gamma emitter from ¹⁹²IR. Hence, these animal studies data demonstrated that regardless of the radioactive isotopes or radiation sources used, reduction in neointimal hyperplasia can be reliably reproduced if the right dose of radiation reaches the target area.

Radiobiologic Basis of Brachytherapy for Neointimal Hyperplasia

These animal experiments and clinical observations showed that treatment with doses of 12 to 20 Gy appeared to be effective in reducing neointimal hyperplasia following balloon injury. Based on *in vitro* models of

human SMCs, Brenner et al³² put forward various mechanistic interpretations to explain why radiation doses of between 12 and 20 Gy should be efficacious in reducing restenosis. Doses of greater than 25 Gy are required to completely eliminate the SMC population which has the potential to cause restenosis. However, this is too large a dose to use in practice as treatment doses at these levels are likely to produce late complications. In external-beam treatment of Hodgkin’s disease, doses of above 30 to 40 Gy produce significantly increased risk of late cardiac complications.^{33,34} It is postulated that in the dose range used in animal studies, the reduction in restenosis may be due to a relatively small reduction in the potentially clonogenic SMCs population. However, this reduction may be sufficient to prevent the surviving SMCs to proliferate sufficiently to cause restenosis as normal SMCs have a finite proliferation capacity before senescence occurs. With the doses used in animal studies, potentially clonogenic SMC population are not entirely eliminated. Bertrand et al³³ showed that following irradiation with doses of 2 to 12 Gy, human SMCs showed a dose-dependent reduction in clonogenic survival. The remaining surviving SMCs will grow back, and, if not halted by senescence, will eventually cause restenosis but with a time delay compared to if no depopulation with radiation was carried out. Brenner’s model suggested that without irradiation, restenosis will be completed in 4 months. With a 12 Gy dose, restenosis is

expected in 22 months and with a 20 Gy dose restenosis will be postponed to 34 months, assuming senescence does not occur.³² However, it is unclear whether, with doses of <20 Gy, restenosis will be permanently prevented as this depends critically on the assumption that the SMC population that survive irradiation will reach senescence after a finite proliferative expansion.

These considerations suggest that current follow-up times may be too short for animal experiments and clinical studies to address some of the key issues in this area. At present, not enough information has been collected to predict if radiation doses used in current clinical studies would eliminate restenosis completely or merely delay the onset of restenosis.

The other key issue that needs further clarification is that of the "therapeutic window" of intracoronary brachytherapy.³⁵ Earlier animal studies and data from external beam irradiation therapy indicated that doses of less than 6 Gy to 14 Gy may not be sufficient to inhibit neointimal hyperplasia and doses of greater than 30 Gy to 40 Gy may lead to long-term complications and excessive neointimal formation.^{29,30,34,36-38} However, Waksman et al³⁰ demonstrated that porcine intimal tissues showed a dose-related response to P-radiation over a range of 7 Gy to 56 Gy with no acute injury nor excessive neointimal formation at any of these doses. Furthermore, with intracoronary radiation therapy, it is possible that some parts of the irregular intraluminal surface may have received up to 55 Gy adjacent to the small, non-centred catheter system. The fact that no late effects from radiation have been reported may suggest that periluminal tissues can tolerate a high dose of radiation and that it is structures deep to the lumen that determine post radiation sequelae.^{35,39} Teirstein's study showed that effective neointimal hyperplasia inhibition can be achieved with doses of ≤ 8 Gy.⁴⁰ It is possible that the effectiveness of therapeutic dose for intracoronary radiation therapy may even be lower than this.

Gamma, Beta or External Radiation

In coronary brachytherapy, the area of interest, the intima, medial and adventitia of the arterial wall, is generally within a few millimetres of the catheter or stent-base radiation source. Previous animal studies have demonstrated that the effectiveness of brachytherapy is dependent on the delivery of an appropriate dose of radiation to this small area of interest rather than to the different isotopes or types of radiation employed.

Gamma (X-Ray) Sources

Gamma sources are commercially available with ¹⁹²Ir and ¹²⁵I. As they have been in use in oncology radiotherapy for many years, their handling characteristics and calibration are well understood. However, the dose

rates required in endo-vascular brachytherapy are in the range of 50 to 250 cGy/min. The source range is thus high, for instance, an ¹⁹²Ir source would have tens of mCi per seed in a linear array. Thus, radiation exposure to both operator and total patient body exposure is an issue that need to be addressed. However, dosimetry calculation is relatively simple and precise centring of the source ribbon is not essential. Furthermore, because of its deep penetration, it is effective in large vessels.^{40,41}

Beta Sources

Beta emitters such as ⁹⁰Sr, ⁹⁰Y and ³²P in the form of sealed linear sources are new to the radiotherapy community. These have been developed specifically for the purpose of vascular irradiation. The dose rates from these β emitters are high enough to limit treatment or dwell time to a few minutes. Another major advantage of β sources is that it requires little radiation protection measures. Furthermore, conventional stents can be transformed into radioactive ones using this source and conventional balloon catheters can be filled with a liquid or gaseous β emitter for dose delivery.⁴²⁻⁴⁵ However, dosimetric calculation is complex and delivering a prescribed dose to the region of the arterial wall containing actively proliferating cells may be difficult with a β emitter despite the use of centring balloons.⁴² In addition, because of its dose-depth curve characteristics, its use in large vessels may be problematic. The advantages and disadvantages of gamma and beta sources are tabulated in Table III.

External Beam Sources

Using conventional megavoltage linear accelerators, external beam radiotherapy (EXRT) has a reliable dose delivery system and carries no significant procedural

TABLE III: ADVANTAGES AND DISADVANTAGES OF BETA AND GAMMA RADIATION

Characteristics	Beta	Gamma
Radial distance from the source	short	long
Biologically effective in porcine arteries	+++	+++
Effectiveness in large vessel	?	+++
Dosimetry calculation	Complex	Simple
High specific activity	+++	+
Radial dose uniformity	+	+++
Requirement of encapsulation	Yes	No
Attenuated by the stents metal	Yes	No
Dose range variability with lack of centring	+++	+
Use for radioactive stent	Yes	Not recommended
Use of liquid and gaseous isotopes	Yes	No
Radiation exposure to the operator	+	+++
Total patient body exposure		
Radiation safety		
Require use of an afterloader system		
Effective in humans		

risks. EXRT delivers a uniform dose throughout the affected blood vessel without any of the high dose gradient problems seen with brachytherapy.^{46,47} One major drawback with EXRT, however, is that it unduly irradiates a large amount of unaffected tissue. As doses of up to 20 Gy may need to be delivered to the target tissue, a single large dose of EXRT to a large amount of tissue is unacceptable with its attendant risks of late sequelae. Schwartz et al,⁴⁶ using EXRT in an animal model, showed a surprising exacerbation of neointimal hyperplasia following treatment with doses of 4 and 8 Gy. Although these results are unexpected in light of the results of other animal studies using intraluminal irradiation, no further clinical studies in humans using EXRT are currently ongoing or are being planned to our knowledge.

Radiation Delivery Systems and Dosimetry

(1) Radioactive Wire or Ribbon

Using ¹⁹²Ir as the gamma-radiation source, both Condado and Teirstein delivered the required dose to the coronary vessel segment of interest using a wire or ribbon delivery system.

Condado et al⁴¹ used a 4F non-centred, monorail delivery catheter and a 3-cm ¹⁹²Ir ribbon source of either 0.018 or 0.14 inch diameter fused to a wire of similar calibre. Once the delivery catheter is positioned into the area of interest, the ¹⁹²Ir wire is then manually passed inside the delivery catheter to the area to be treated. Dose calculations were based on the reference lumen diameter estimated by the operator during the procedure. Dwell time in their study ranged from 164 to 929 seconds (mean 580 ± 226 seconds). Teirstein et al,⁴⁰ in their randomised control study, again used a monorail 4F infusion catheter and a 0.03-inch calibre ribbon. One end of the ribbon consisted of a train of 3 mm-long seeds of ¹⁹²Ir source separated from the next by a 1-mm gap. Ribbons with different lengths, composed of 5 to 9 ¹⁹²Ir seeds were used to treat vessels of different lengths. An essential component of this technique was the use of intravascular ultrasonography (IVUS) to obtain the maximal and minimal source-to-target (centre of the ultrasound catheter to the leading edge of the external media) distances of the vessel segment to be treated. Using this information obtained during the time of the procedure, and the specific activity of the ¹⁹²Ir source used, the dwell time can be calculated to deliver a dose of 8 Gy to the target furthest from the ribbon and a maximum dose of 30 Gy to the target closest to the source. Patients tolerated the dwell time of between 20 and 45 min required to delivered the prescribed 8 to 30 Gy doses to the vessel wall remarkably well. During the period when the delivery catheter and ribbon were in place, heparinised saline and ioxaglate, an ionic contrast material, was administered through the guiding catheter regularly.

Verin et al,⁴² choosing ⁹⁰Y (Yttrium-90) as the β emitting source, used a β radiation delivery system that consisted of the ⁹⁰Y source in the form of a 29 mm long, 0.014 inch (outer diameter) titanium-coated pure yttrium wire secured to the end of a 0.014-inch wire and a centring balloon that allowed for homogenous radiation dose distribution to the vessel wall. The centring device consisted of a 30-mm long segmented balloon with four interconnected compartments mounted on a double-lumen shaft. One lumen allowed for the introduction of this balloon into the vessel over a conventional 0.014-inch guide wire, monorail fashion. The other was a blind internal lumen of 0.016-inch calibre, large enough to accommodate the 0.014-inch ⁹⁰Y source wire. The mean exposure time was 281 seconds for the 2.5 mm, 322 seconds for the 3.0 mm and 561 seconds for the 3.5 mm diameter centring balloon. This almost doubling of the dwell time from a 2.5-mm to a 3.5-mm diameter centring balloon reflects the steep depth-dose fall-off curve of β emitting sources. Because the centring balloon used was occlusive, treatment has to be fractionated in some of the patients treated.⁴² The same group recently refined this system by using a new centring catheter and an automatic remote after-loader and successfully treated 14 porcine vessels with 18 Gy 1 mm from the balloon surface using this system.⁴⁸

(2) The Beta-Cath System

Novoste Corp developed a hydraulic-catheter-based system using ⁹⁰Sr/⁹⁰Y, a pure beta emitter as the radiation source.⁴⁹ It consists of a catheter with a double lumen hydraulic system which is entirely enclosed and completely separated from the patients' circulation. One lumen allows for the hydraulic delivery of the train of radiation source, the other for reversed fluid flow. A third lumen allows for the positioning of this catheter into the area of interest over a 0.014-inch calibre guide-wire. The catheter has 2 radio-opaque markers, 30 mm apart, for accurate positioning of the delivery catheter and hence the radioactive source to the area of interest. The other component of the system consists of a transfer mechanism which houses a small cannister of the radioactive source in a quartz chamber, a switching system and a gate. The switch allows for the hydraulic fluid flow to either transfer the source to the end of the catheter or to return the source to the transfer device. The radiation source train consists of 12 stainless steel cannisters with the ⁹⁰Sr/⁹⁰Y isotopes. The catheter diameter is about 1.5 mm and because of its large size relative to the intracoronary luminal diameter and with cardiac motion, centring was presumed.

(3) Radioactive Stents

Fischell and others⁴³ evaluated the use of radioactive stents as radiation delivery devices. Palmaz-Schatz stents were made radioactive by direct ion implantation of ³²P

beneath the metal surface. The radioisotope is actually embedded within the lattice structure of stainless steel or other metal stent. ^{32}P was chosen because it is a pure β emitter, providing radiation delivery with a maximum range in tissue of 5 to 6 mm. It has a desirable, relatively short half-life of 14 days. Hence, half the total dose is delivered within 2 weeks of implantation with negligible radioactivity at 5 months. In *vivo* studies of a porcine coronary artery model using stents with a relatively low activity range of 0.1 to 1.0 μCi have been shown to inhibit neointimal hyperplasia. A 0.5 μCi half Palmaz-Schatz stent over a 1-month period will deliver an equivalent of 2 Gy to the media and adventitia. This is, surprisingly, a much lower dose compared to that required using a catheter-based system. This may be due to the near-field dosing effect around the stent which has been calculated to deliver a dose equivalent of 30 Gy to migrating SMCs near to the plane of the stent wires.

Hermann et al⁵⁰ demonstrated the feasibility of implantation of radioactive gold-coated stainless steel stents (Inflow Dynamics) into porcine coronary arteries. The gold-coated stents were activated in the neutron beam of a nuclear reactor. Radioactive gold, Au-198, with a half-life of 2 to 7 days, may be advantageous since it may interact less with endothelial cell regrowth due to its short half-life. Stents with activity range of 0 Gy to 20 Gy were successfully implanted without any complications.

(4) Liquid Isotope-filled Balloon

Another irradiation technique under study is that of filling a balloon dilatation catheter with a high activity beta emitting fluid.⁵¹ Yttrium-90, a pure β emitter, with a half life of 64 hours in the form of yttrium chloride solution or Re-188, another β emitter with a half life of 270 days, in the form of Re-perhenate solution, may be used as the radioactive source for balloon-filled liquid irradiation therapy. The advantages with this system include the ease and accuracy of source positioning and uniform dose delivery to the vessel wall. Furthermore, existing catheters can be used as the radiation source receptacle and patient dose can be accurately measured from source activity as this is relatively easy to carry out for a liquid without the difficulties of dose distribution estimation encountered using seeds, stents, ribbons or other solid sources. However, the one potentially serious radiation safety feature of this system is that of balloon rupture. Amols et al⁵¹ showed that even in the event of balloon rupture and the release of the complete balloon content of 0.25 ml of radioactive 90 Yttrium-chelate into the balloon, rapid kidney clearance will result in whole body dose of <3 cGy and they argued that the risk-benefit ratio of the radioactive liquid-filled balloon system is still favourable despite this potential risk.

Makkar et al,⁴⁴ using ^{188}Re as the liquid β emitting source, treated 6 porcine coronary arteries with a pre-

scribed dose of 14 Gy at 0.5 mm tissue depth. Mean treatment time was 7 min. Their group showed that no radioactive material was leaked into the bloodstream and that neointimal hyperplasia was inhibited in this porcine model. Kim et al⁵² further showed that holmium-166, a liquid isotope with 94% β and 6% gamma emission can be used as another emitting source for this system.

(5) Others

Other novel delivery systems are under investigations also. Wakmans et al⁴⁵ showed that radiation can be delivered to the area of interest using a radioactive gas-filled angioplasty balloon. Radioactive 133-Xenon gas, with an activity of 300 mCi was injected into the balloon and a successful dose of 15 Gy delivered at 0.25 mm from the surface of the balloon successfully delivered to the vessel of interest in porcine coronaries.

Stefanadis et al,⁵³ on the other hand, irradiated venous graft segments with gamma radiation prior to mounting them on Multilink stents for implantation into porcine iliac arteries and demonstrated that this novel approach of irradiated covered stents can be safely deployed.

Clinical Studies In Intracoronary Radiation Therapy

The first intracoronary radiation study in humans was conducted by Condado using an iridium 192 wire to treat 22 patients (22 arteries) with unstable angina pectoris. Nineteen of the 22 arteries were successfully treated following balloon angioplasty. The prescribed doses were 18, 20 and 25 Gy although the actual delivered doses were 19 to 55 Gy. This discrepancy was due to the fact that the subsequent core laboratory measurements using a standard, commercial system showed consistently smaller diameters than estimation carried out during the procedure. Furthermore, due to the absence of any centring device, certain areas of the wall adjacent to the source wire may have received doses of up to 92.5 Gy. In this cohort, 2 patients developed subacute thrombosis and 1 a coronary pseudoaneurysm at 60 days. This patient may have received up to 92 Gy of radiation, far in excess of the prescribed dose. Late angiographic (8 months) follow-up showed an excellent late loss index of 0.19. This late loss advantage persisted at 2 years. Clinical events at 2 years included myocardial infarction in 1 patient, repeat angioplasty in 4 and persistent angina pectoris in 7 patients. The study was criticised on the basis that no intravascular ultrasound measurements were used to determine lumen sizes and that the late index loss was calculated using an "angiographic baseline by 24 hours" to measure minimal luminal diameter rather than at the end of the procedure as is usually the case.⁵⁴ Nevertheless, this pioneering study was the first to demonstrate that intracoronary radiation was feasible and that it led to a decrease in late lumen loss at 6 months.

In a clinical pilot study, Verin et al⁴² demonstrated the feasibility and safety of using an endoluminally segmented balloon-centred Yttrium-90, a P-emitting wire source. In this study, 15 patients were given intracoronary radiation therapy following balloon angioplasty. The prescribed 18 Gy dose was delivered in all cases with a mean exposure time of 6.5 min. Fractionation of dose was required in 4 patients because of ischaemia caused by complete vessel occlusion during balloon inflation.

At 6 months follow-up, no complications occurred that could be attributed to the radiation therapy. One patient had a fatal acute anterior myocardial infarction 5 days following treatment of the right coronary artery. The angiographic restenosis rate was 40% with a late loss index of 0.50 which did not suggest a favourable response. However, Teirstein¹⁰ argued that this may be a case of “too little, too soon”. Using a β emitter and a prescribed dose of 18 Gy, the dose delivered at a depth of 1 mm is only approximately 5.4 Gy and at a depth of 2 mm, only approximately 2.7 Gy, which is about 15% of the prescribed dose based on the dose-depth characteristics of a ⁹⁰Y wire. Furthermore, the negative result may be due to the radiotherapy being given too soon. Wakesman demonstrated an enhancement of the effects of radiotherapy if treatment is given 48 hours following balloon injury.

Teirstein et al⁴⁰ in their well-conducted double-blind randomised study, showed a substantial reduction in restenosis at 6 months in the treated group compared with control. In this cohort of 55 patients, of which 26 were assigned to the ¹⁹²Ir group, or no evidence of myocardial infarction, death or CABG were reported at 30 days. Angiographic and IVUS follow-up at 6 months showed that the angiographic restenosis rate in the ¹⁹²Ir group was 17% compared with 54% in the control group (Fig. 2). Late luminal loss index was significantly lower in the treated group (0.12 vs 0.60). These results were confirmed by IVUS assessment. The volume of tissue growth was 15 mm³ compared with 45 mm³ in the

control group. Clinical end points of death, myocardial infarction, stent thrombosis and target lesion revascularisation were lower in the iridium-192 group (15% vs 48%) also.

In the Beta Energy Restenosis Trial (BERT), King et al,⁴⁹ using the Beta-cath system treated 21 patients successfully in a cohort of 23 patients after balloon angioplasty. There were no in-hospital or 30-day morbidity or mortality. Angiographic follow-up in 20 patients showed a late lumen loss of 0.05 mm, a late loss index of 0.04 and a restenosis rate of 15%. With these encouraging results, a multi-centred randomised trial is currently being planned.

The Isostent for Restenosis Intervention Study (IRIS) is another feasibility study currently underway.⁵⁵ An earlier study using radioactive ³²P Palmaz-Schatz stents with activity of 0.5 μ Ci to 0.1 μ Ci showed no major adverse events at 30 days but the activity used may be insufficient to reduce restenosis in patients with *de novo* lesions. ³²P Palmaz-Schatz stents with a higher activity of 0.75 μ Ci to 1.5 μ Ci were subsequently used. The initial report showed that this was successfully implanted in 22 *de novo* and 3 restenotic lesion in 25 patients. No adverse events were reported at 1 month.⁵⁵

The Washington Radiation for In-stent Restenosis Trial (WRIST) is another randomised trial in 130 patients with in-stent restenosis currently in progress.⁵⁶ Prescribed radiation doses of 15 Gy, 2 mm from the source centre will be delivered to the target using ribbons with ¹⁹²Ir seeds. Lesions length of up to 50 mm will be treated. Seventy-five patients have been successfully treated in the initial report with no procedural or 30-days adverse events.

Radiation Safety Issue

A major consideration in intracoronary radiation therapy, particularly with the use of ¹⁹²Ir with its high energy gamma rays (206 keV), is that of radiation safety of both operations and patients. Teirstein et al⁴⁰ ensured minimum radiation exposure to the laboratory staff by ensuring that all personnel leave the fluoroscopic room during the treatment period and the placement of a portable 25-mm thick lead-shield between the patient and the control room. With these precautions, additional radiation exposure to laboratory staff was insignificant. The radiation oncologist who manually positioned the ribbon into place received 4 mR (whole body) per procedure. In most instances, this is less than the radiation exposure received during a typical fluoro/cine procedure.^{56,57}

The other unknown long-term safety issue is that of the risks of accelerated coronary artery disease over a period of 5 to 20 years seen in patients receiving much higher doses of radiation for the treatment of certain cancers and the exposure of radiosensitive tissues such

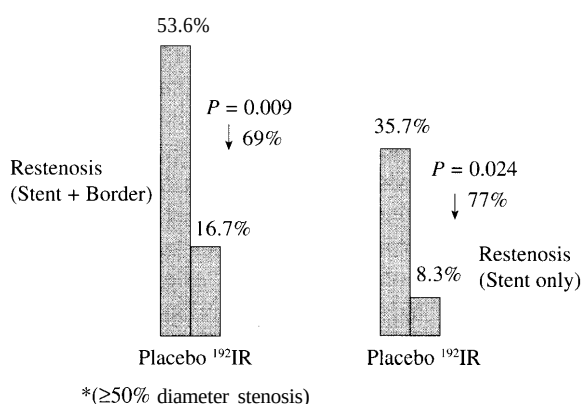


Fig. 2. Angiographic follow-up.

as sternal bone marrow and lymph nodes during intracoronary brachytherapy. This risk may be mitigated by the low calculated dose (1.0 to 2.5 cGy) delivered at a distance of 5 cm to 10 cm from the gamma source. These issues will only be settled with long-term follow-up data from the current brachytherapy trials using gamma radiation as the radiation source.

The use of pure β emitters, however, has a much safer radiation profile compared with gamma emitters as they have limited penetration in tissue. Furthermore, because of their rapid dose-depth fall off in tissue, they deliver a significantly lower dose beyond the prescription point. As a result, the total body exposures of both operators and patient to radiation are much lower compared with gamma emitters. King et al⁴⁹ showed that with a ⁹⁰Sr/Y beta emitting source, dose-equivalent rates were 2.1mrem/h at the patient's chest, 0.3 mrem/h at the groin and 0.3mrem/h at the position of the cardiologist. This was a 2×10^4 smaller absorbed dose by the cardiologist compared with gamma radiation (Table IV).

TABLE IV: DOSE EQUIVALENT LEVEL WITH γ - AND β -ISOTOPES, μ SV

	SCRIPPS Trial ⁴⁰	BERT ⁴⁹
Dose equivalent at chest surface	Not measured	0.95
Dose equivalent at groin	Not measured	0.25
Dose equivalent to patient	6410	0.43
Dose equivalent to operator per procedure	4000	0.20

*Based on a 3-minute patient exposure time.

Modified from: King S B et al⁴⁹

Conclusion

Endovascular gamma or beta radiation has now been shown to be effective in substantially inhibiting neointimal hyperplasia and in reducing the incidence of restenosis following balloon angioplasty.⁵⁹ A number of large, randomised trials of intracoronary radiation therapy are currently ongoing or are being planned. These will add enormously to our understanding of the efficacy of this modality of therapy for restenosis over the next few years. We believe that intracoronary radiotherapy will prove to be a major advance in our effort in reducing the incidence of restenosis following balloon angioplasty. After 20 years of effort, this may herald the beginning of the end of restenosis.

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