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Physical aspects of endovascular brachytherapy

ABSTRACT

Recent data suggest that intraluminal irradiation of coronary arteries in conjunction with balloon angioplasty and/or stent implantation reduces the proliferation of smooth muscle cells and neointima formation, thereby inhibiting restenosis. Irradiation of peripheral arteries in humans has yielded similar results. In this article, a review of dosimetric requirements for the irradiation of coronary arteries and peripheral blood vessels, and the physical and dosimetric characteristics of several proposed irradiation techniques will be presented. Also, current approaches to the problem of dose prescription and choice of different radioactive isotopes convenient for endovascular brachytherapy treatment will be discussed.

Key words: *Endovascular brachytherapy; Restenosis; Gamma emitters; Beta emitters; Radioactive stents*

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INTRODUCTION

Angioplasty or balloon dilation of the coronary vessels was developed as a nonsurgical means of improving the vascular supply to the myocardium and as an alternative to coronary artery bypass grafting. Restenosis or renarrowing after angioplasty of intracoronary vessels today remains the most common complication and limitation to the successful use of this clinical procedure (1). Several therapeutic approaches have been suggested: pharmaceutical agents, mechanical and physical devices, and recently, gene therapy has been proposed (2), although the problems of over exuberant cell proliferation after intervention leading to restenosis, are better understood, it still remains the Achilles heel of this field.

Since the discovery of X-rays by Röntgen in 1895 and of radium by M. Curie in 1898, ionizing radiation is well known as potential antiproliferative agent for benign and malignant disorders. It is also documented that proliferative cells are radiosensitive to low doses of ionizing radiation. Therefore several investigators have suggested that local treatment with radioactive sources placed at the angioplasty site (brachytherapy) will inhibit restenosis. This has led to an evolution of a new field in medicine entitled endovascular brachytherapy.

Currently there are over one million coronary interventional procedures worldwide each year (3). Current projections suggest that 80-90% of these patients might be eligible to receive an adjunctive therapy such as radiation, to reduce the frequency of restenosis. Was this to occur, it would have a major impact on the specialty of radiation oncology. This group of patients would represent almost as many patients as seen annually by radiation oncology departments and would require a large number of radiation therapists and radiation physicists devoted to this service.

A review of dosimetric requirements for the irradiation of coronary arteries and peripheral blood vessels, and the physical and dosimetric characteristics of several proposed irradiation techniques will be presented in this article.

For effective treatments, the dose distribution must be confined to the region of the angioplasty, with reduced doses to normal vessels and myocardium. Irradiation times should be no more than several minutes in order to reduce the risk of thrombosis and other coronary complications during the treatment. This will require relatively high activity radioactive sources, meaning that the patient's whole body dose and radiation safety of staff are important concerns.

Several techniques are utilized for the delivery of radiation to the vessel wall. The most promising of them such as temporary intraluminal insertion of high activity beta or gamma seeds and wires, inflation of dilation balloon catheter with radioactive liquid and permanent implantation of radioactive stents, will be described here. Also, calculations of required activities and dose distributions are presented for different radioactive isotopes and for various source geometries as well as effects of source size and positioning on treatment accuracy.

Rationale for radiation therapy to reduce restenosis

Restenosis is a complex process comprising immediate vascular recoil, neointimal hyperplasia, and late vascular remodelling (4). The contribution of these elements to the restenotic process varies from case to case and among devices.

Radiation has been shown to be highly effective and safe in treating benign vascular malformations and also in preventing keloid formation. Radiation delays normal wound healing by impairing smooth muscle function. In animal models of coronary restenosis, radiation reduced the intimal hyperplasia associated with restenosis following balloon injury. Radiation exerts many biological effects. It inhibits smooth muscle proliferation, reduces macrophage infiltration, exerts a beneficial effect on apoptosis, inhibits expression of prostaglandin growth factors alpha and beta,

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and may lead to a reduction in thrombosis. One desirable feature of radiation is that it interferes with the proliferative processes while fixed postmitotic tissue is spared.

Technical considerations in endovascular brachytherapy

There are several potential endovascular radiation systems and techniques for the coronary application. In general, there are two classes of devices for coronary use: catheter based

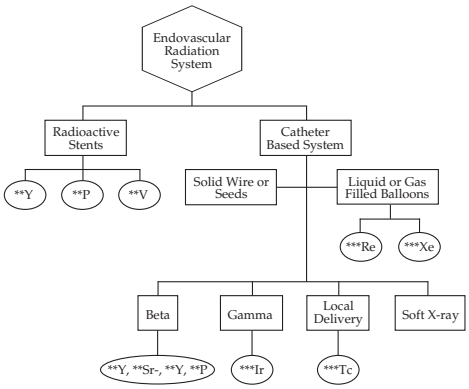

Figure 1. Review of potential endovascular radiation systems

systems, and radioactive implants (Figure1).

The principal of the catheter based systems, is to deliver the source via a catheter to the angioplasty site post-procedure (without affecting the angioplasty results) and the source having a sufficient dwell time to deliver the prescribed dose. Once the dose has been delivered, both the source and the catheter are removed from the artery and the lesion may undergo further work until optimal result is obtained. In contrast, permanent implants such as radioactive stents incorporate two technologies, because they are used as a frame set inside vessel wall (stent) inhibiting neointima formation (radiation). One of the main limitations of the stent technology is that the source will remain in the artery until it decays completely.

The dosimetric requirements for intraluminal treatment via the temporary insertion of radioactive sources can be summarized as follows.

1. Single fraction acute dose of 15-20 Gy to a length of 2-3 cm of arterial wall, approximately 2-5 mm diameter and 0.5 mm thick.

2. High dose volume tightly confined to the region of angioplasty, with minimum dose to normal vessels and myocardium.

3. Dose rates bigger than 5 Gy/min, in order to maintain treatment times of less than five minutes, thus reducing the probability of thrombosis or other cardiac complications.

4. The radioactive source must have dimensions, stiffness and flexibility compatible for use with angioplasty catheters. Source diameter must therefore be smaller than 0.5 mm, yet stiff enough to negotiate multiple bends in the coronary tree. Source integrity is of great importance as dislodgement into a coronary artery could be fatal.

The above requirements could be met with a high energy beta emitter, with transition energy of more than 1.7 MeV, and activity of more than 20 mCi or a low energy gamma emitter of less than 100 keV, and activity of more than 1 Ci. Higher energy gamma emitters (>100 keV) are also feasible, although the high dose region will be less well defined. For gamma emitters there will be radiation safety concerns with regard to patient's whole body dose and dose to personnel. However, for a pure beta emitter there will be a negligible dose beyond the range of the beta particles rendering radiation safety a much easier problem.

Unfortunately few isotopes meet these requirements. Most beta emitting isotopes with suitably high energy either have very short half-lives, or also emit significant amounts of gamma radiation. Because of very high activities required for gamma sources, few can be produced in a small enough volume or at a low enough cost. A list of isotopes, which either have been, or are being considered for use in endovascular brachytherapy is presented in Table 1. ^{90}Sr is listed in Table 1 even though its transition energy is 0.5 MeV because ^{90}Sr always exists in equilibrium with its daughter product ^{90}Y, which is also a pure beta emitter with the therapeutically useful transition energy of 2.3 MeV. Thus either pure ^{90}Y, with a half-life of 64 hours, or the combination ^{90}Sr-^{90}Y in radioactive equilibrium, with a half-life of 28 years, are being considered as possible irradiation sources,

Table 1. Properties of radioisotopes used for endovascular brachytherapy

Isotope	Emission	Maximum energy (MeV)	Average energy (MeV)	Half-life
^{192}Ir	Gamma	0.6	0.37	74 days
^{32}P	Beta	1.7	0.60	14 days
^{90}Sr	Beta	0.5	0.20	28 years
^{90}Y	Beta	2.3	0.90	64 hours
^{144}Pr	Beta	3.0	1.00	17 minutes
^{166}Ho	Beta	1.9	0.63	27 hours

Catheter based techniques

Issues that need to be taken into account when evaluating the use of endovascular irradiation employing catheter based techniques are: treatment time, total body dose received by the patient, dose received by the staff, the need for modification of current catheterization laboratory (cath lab) procedures and accuracy of treatment delivery.

Gamma emitters

The most frequently used gamma emitter in catheter based techniques is ^{192}Ir that could be utilized in two modalities: Medium dose rate (MDR) ^{192}Ir seeds and high dose rate (HDR) afterloading ^{192}Ir source.

Most intraluminal studies to date have used an array of 5-7 ^{192}Ir seeds of total activity 50-200 mCi. Typical seed dimensions are 0.5 mm in diameter and 3 mm in length. The seeds are embedded in a linear array inside a 1 mm diameter plastic catheter to yield an active length of 2-3 cm. Although neither the high gamma energy nor low activity of these seeds are ideal, ^{192}Ir has proven useful for preliminary studies and until recently has been the only practical source readily available. This type of therapy can be safely carried out in the clinical catheterization laboratory but the treatment times are relatively long (20 minutes), during which time the source is continuously within the coronary artery. The treatment times reported by Condado (5) using a manually delivered ^{192}Ir wire were considerably shorter, (4-12 minutes) but the radiation safety concerns about manually handling such a high activity wire caused the study to be terminated after 21 patients were treated.

The use of conventional HDR afterloader with a ^{192}Ir source would require either expensive modification of the cath lab for therapy to be undertaken there or transportation of the patient to Radiation Oncology for treatment with a delivery catheter in the coronary artery. Transportation to Radiation Oncology for treatment would be unacceptable for most cardiologists but would not be of great concern for peripheral vascular cases. One alternative being considered to allow treatment within the cath lab would be to install a shield around the patient during the treatment. Also, these very high activity (>10 Ci) ^{192}Ir sources are available in HDR afterloading devices which are used in radiation oncology, but such sources are too large for use in intracoronary applications although they are suitable for use in larger peripheral vessels. Modified HDR brachytherapy units with smaller sources for use in the coronary tree are currently being developed. The prolonged time required by treatment planning with the current generation of HDR afterloaders may negate some of the advantages of HDR therapy compared to MDR. Additional problems to be solved include: navigating around the tight curves in coronary vessels and treating at a greater distance than it is done with current generation afterloaders.

The advantage of the HDR afterloader is the precision with which dose can be delivered to the target volume, the extensive knowledge and experience with the dose distribution around these sources, and the flexibility in delivering the dose to lesions of different length. Certainly for peripheral treatment where transfer of the patient to the Radiation Oncology department is

not of great concern these devices seem to be almost optimally configured as they currently exist.

Dose distribution for point or line source gamma emitters have been well studied both theoretically and experimentally, although measurements at distances of less than several millimeters are difficult due to extremely high dose gradients and due to other technical considerations. At small distances from the source dose perturbations caused by scatter and self-absorption also make theoretical calculations difficult. The AAPM (American Association of Physicists in Medicine) Task Group 43 has reviewed (6) this problem and recommended that dose should be calculated according to the following equation:

$$Dose(r, \theta) = s \cdot \Gamma \cdot G(r, \theta) \cdot g(r) \cdot F(r, \theta)$$

where,

r - radial distance from source

θ - angle from point of interest to center of source, as measured from the axial dimension of the source

s - air kerma strength

Γ - dose rate constant

G - "geometry factor" resulting from spatial distribution of the radioactivity with the source. For a 3-5 mm long line source, $G(r, \theta) = r^2$ for $\theta = 90°$

g - radial dose function given as $\Sigma a_i r^i$, where a_i represent fitted parameters to a fifth order polynomial

F - anisotropy factor describing dose variation versus angle. This function is normalized to unity at $\theta = 90°$

Although some of the terms in the equation are not accurately known at distances 1 cm, linear extrapolation of data given by AAPM Task Group 43 yields reasonably accurate results.

Beta emitters

Beta emitting sources have an advantage over gamma emitters in terms of reduced dose delivered to normal tissues of the patient and radiation safety of the attending medical staff. Furthermore, because they are directly ionizing it is possible to achieve very high dose rates with sources of modest activity.

The two beta sources described in literature include $^{90}Sr/^{90}Y$ seeds and ^{90}Y coil. Also ^{32}P may be used in the form of encapsulated ^{32}P source in HDR afterloader. Although the half-life is somewhat shorter than other sources used in HDR afterloaders, the useful life of the source is approximately one month. In the $^{90}Sr/^{90}Y$ seed preparation both strontium and yttrium emit beta particles and are in equilibrium with each other. The lower energy beta particles from the strontium are completely absorbed within the catheter lumen and the beta particles from yttrium are used for treatment of the vessel wall. $^{90}Sr/^{90}Y$ seeds have a major advantage over ^{90}Y wire in terms of half-life, 28.5 years versus 64 hours. Source handling is easily accomplished with both of these sources and they could be easily incorporated within the current cath lab environment. Both sources are of fixed length. To treat different length lesions would require a different wire or source train. This would not be a major problem in the coronary vasculature where the balloon catheters are almost invariably 2.0 cm to 2.5 cm in length.

The major disadvantage of these sources is the rapid fall-off in radial dose distribution which would result in a major decrease in dose rate at greater depths in larger arteries. The energy of the ^{90}Y beta particles would however seem to be sufficiently penetrating for irradiation of even the largest coronary arteries. However, if the clinical treatment volume is relatively thick the dose received to the endothelial surface may be excessive compared to more penetrating sources such as ^{192}Ir. One additional concern is that the dosimetry around the sources is less well established and more difficult to quantitate than with gamma sources.

Calculations of dose from internally deposited beta emitters are also a well studied problem (7,8). Dose *versus* radial distance from a point source can be calculated using the equation (9):

$$Dose(r) = \int_{E_{min}}^{E_{max}} F(E) \cdot A \cdot k \cdot S(E') \cdot dE / (4\pi\rho r^2)$$

where,

r - distance (cm)

E_{max} - maximum energy of electron

E_{min} - minimum energy of electron with range ≥ r

F(E)dE - electrons emitted per decay in the energy interval (E + dE) MeV

A - activity (mCi)

k - units conversion factor of 21.31

S(E') - mean restricted stopping power for electron of energy E'(MeV/cm)

E'- energy at distance r from the source of electron with initial energy E

ρ - density (g/cm^3)

Electron ranges and stopping powers have been given by Berger & Seltzer (10) and F(E) spectra are well known (11). However, dose calculations based on stopping power tables derived from the continuous slowing down approximation may introduce errors due to range straggling and Landau energy loss straggling. More accurate data based on Monte Carlo calculations are available in the form of dose kernel function, which give directly the dose per beta decay as function of redial distance.

Balloon systems

1. Liquid filled balloon

The main advantage of the liquid filled balloons is the uniformity in dosimetry of the beta source such as ^{32}P, ^{188}Re or ^{186}Re supplied either by a generator, which will be located in the hospital or provided as a liquid by a pharmaceutical manufacturer. This system allows optimal centering via the inflated balloon. The balloon size and length are flexible. The ideal isotopes for this technology are those with a short half-life which will be less toxic in the event of balloon rapture during inflation. While this technique clearly yields desirable dose distributions (agreement between measurements and calculations is ± 3% unlike ± 10% for other techniques), the chemical and radiological toxicity of the radioactive liquid must be considered, as there is a risk of balloon rapture with present catheter design. Since most commonly available beta emitters, including all of those listed in Table 1, are bone seeking compounds, the whole body and bone marrow doses following balloon rapture would be unacceptably high (100 - 1000 cGy).

2. Gas filled balloon

The radioactive gas filled balloon is a similar concept to the liquid filled balloon. Isotopes such as ^{133}Xe were proposed to fill the balloon during the radiation treatment. The advantages of this system would be the homogeneity of the gas distribution within the balloon, uniformity of the dose surrounding the vessel, ease of use, and a dwell time of less than two minutes to deliver the treatment dose. The major concerns regarding this concept are gas leakage or rapture and contamination of the room if such an accident happens. Preliminary animal studies suggested that the treatment with a gas filled balloon is as efficacious as shown previously with solid beta and gamma catheter based systems.

Soft X-ray system

The new innovation is designed to deliver soft X-rays *via* a miniature X-ray emitter of 1.25 mm in diameter attached to the coaxial cable which is placed inside a delivery sheath. The emitter is positioned at the distal angioplasty site and than retrieved by an automatic pullback controller that measures the dose along the lesion site. The treatment time for doses such as 15 Gy for a lesion length of 30 mm are planned to be less than or equal to 10 minutes. The system is electronically activated by high voltage

(20 kV). The advantages of such a system are that it does not require the use of isotopes, it emits radiation only when activated by the operator, and probably will not require the presence of the radiation team while performing the procedure.

Radioactive stents

Radioactive stents are balloon expendable or self-expending stents whose radioactivity is achieved by activation in a cyclotron by ion implantation with beta or gamma radiation for the purpose of inhibiting neointimal hyperplasia and restenosis after stenting in arterial, or venous conduits (12). Over one million stents were implanted in human coronaries in 1997 (13) and it is estimated that 20 % of these stents will restenose and require further intervention at the stent site. If stents with low radioactivity can prevent neointima formation than the restenosis rate may fall to less than 10%, a phenomenon which will revolutionize the field of interventional cardiology.

The use of radioactive stent to deliver the beta dose radiation has an advantage similar to the use of radioactive liquid in that the radioactive source will be in intimate contact with the vessel walls. The dose distribution however will not be uniform given the gridded structure of the stent, and the concomitant inhomogeneous distribution of the radioactive source. The dosimetric characteristics of stents are therefore, a complicated problem beyond the scope of this article but has been discussed in detail by Prestwick (14). It is not completely biologically understood why permanent radioactive stents containing 1 μCi or less of activity are effective in reducing restenosis, while for obtaining the same result with temporary beta sources activities of more than 20 mCi and doses bigger than 1500 cGy are needed. Both ^{32}P and ^{90}Y are suitable isotopes for use in radioactive stents.

Dose prescription

When prescribing endovascular radiation therapy one needs to consider what is the target tissue and what dose will be delivered to it. Determining the target point for catheter-based therapy is problematic and a number of alternatives are possible as it could be seen in Figure 2.

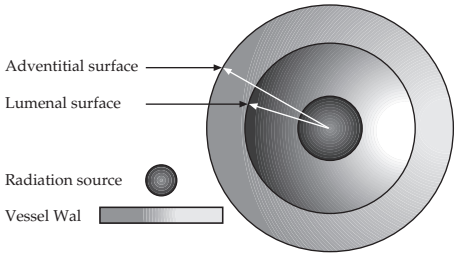

Figure 2. Radiation dose prescription in endovascular brachytherapy

Important issues are:

1. Whether to prescribe the dose to the lumenal surface or to the adventitia of the artery

2. Whether the reference or treated vessel segment should be considered in prescribing treatment.

Reports from different researchers were being done using different prescription points, so the dose-response relationships that are cited often are not comparable from study to study. Most researchers feel that the target cell in the restenotic process migrates from the adventitia of the artery into the media. Delivering dose to this point would require the use of intravascular ultrasound to establish the distance from the source to the prescription point. The American Association of Physicists in Medicine (AAPM) Task Group-69 has dealt with the issues such as prescription of dose in endovascular brachytherapy (15). The effect of curvatures, non-centering and variability in the thickness of the clinical target volume are the issues that have to be fully addressed.

Most stent therapy has been prescribed based on the activity of the radioactive stent with only rudimentary evaluation of the dose delivered to the target tissues. Because the dose delivered is variable depending on the degree of expansion and the geometric structure of the stent, it may be impossible to know in advance exactly what the absorbed dose will be in the target tissues. Even if the stent or balloon centering device results in uniform dose to the vessel lumen this does not ensure that the target volume receives a uniform dose which is shown in Figure 3.

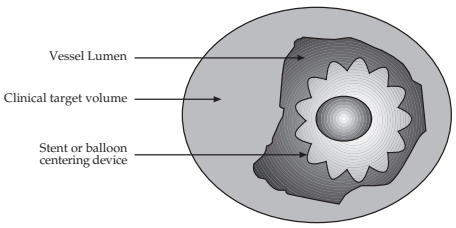

Figure 3. Potential dose inhomogeneity within the clinical target volume even though the stent or balloon centering device gives uniform dose to the vessel lumen

Calibration of sources

Calibration of ^{192}Ir or other gamma sources presents no new challenges to the radiation physicist involved in a treatment programme of this type. The strength of a brachytherapy source of this kind should be known with accuracy better than ± 5 % prior to its medical use (16-19). To achieve this, various calibration techniques have been proposed (20-29). On the other hand, the measurement of the activity of pure beta emitters poses considerably greater difficulty. For both source types Monte Carlo type calculations of the dose distribution surrounding these sources may be carried out. Physical measurement of the dose rate at distances less than 5mm pose significantly greater problems and guidelines for use of the sources in this new environment have to be established.

CONCLUSION

Currently there are majority of evidences supporting the notion that endovascular radiation can alter the natural history of coronary interventional procedures. Therapeutic effect is very dependent upon the prescribed dose and the dose distribution. Different isotopes have been proposed for use and found to be effective in preclinical studies. Endovascular brachytherapy will most likely be performed with high energy gamma or beta emitters. The ideal source would have a high specific activity, long half-life, uniform dose over treatment distances of at least 2-3 mm, and low cost. No available isotope is ideal. Beta emitters such as ^{32}P and ^{90}Sr-^{90}Y have advantages in terms of high specific activity and dose rate, radiation safety, and half-life, while gamma emitters such as ^{192}Ir have advantages in terms of radial dose uniformity. Each isotope could be fabricated at the required specific activities and size using current technology. Because of the high required activity for gamma emitters it is likely that safety considerations will mandate that gamma emitters could be used only with specially designed HDR units. Beta emitters, on the other hand may be usable via manually loaded techniques, thus reducing costs.

And last but not least, the expertise of an experienced radiation oncologist with excellent back up of a medical physicist is crucial to the initiation and continuation of a high quality program.

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