INVITED COMMENTARY

Intravascular Radiation Therapy with Radioactive Liquid-Filled Balloons for Inhibition of Restenosis After Angioplasty: A New Opportunity for Nuclear Medicine?

Over the past decade, the introduction of coronary stents brought a quantum improvement in postangiographic treatment of diseased coronary arteries by providing a scaffolding that maintains vessel patency. However, the relatively high incidence of coronary restenosis after percutaneous transluminal angioplasty (PTCA) and stent implantation (20%–40%) has required the pursuit of additional techniques that minimize the neointimal hyperplasia underlying coronary restenosis. Despite >200 separate trials evaluating a range of pharmacologic and other methods, the intracoronary postangiographic use of high-dose–rate radiation is the only method shown to be effective in reducing the incidence of restenosis. The article by Stoll et al. (*1*) in this issue of *The Journal of Nuclear Medicine* describes the use of the positron-emitting ^{68}Ga liquid-filled balloons (which offers an alternative to high-dose–rate delivery of radiation for postangiographic therapy) and the anticipated involvement of nuclear medicine.

USE OF SOLID RADIOACTIVE SOURCES FOR INHIBITION OF CORONARY RESTENOSIS

The well-established, effective use of radiation for the treatment of keloids (*2*) and other hyperplastic processes has been expanded to include high-dose–rate radiation therapy with ^{192}Ir sources to reduce the incidence of restenosis after angioplastic procedures in iliac and popliteal vessels (*3*). Based on these promising results, the intracoronary use of high-dose–rate ionizing radiation from catheter-based γ- and β-emitting radioisotope sources was subsequently evaluated in animal models and reported in the early 1990s (*4–6*).

The first 2 commercial systems for coronary irradiation, the Beta-Cath System (Novoste, Inc., Norcross, GA) and the CHECKMATE System (Cordis Corp., Miami, FL), were approved by the Food and Drug Administration in November 2000 for routine use. The Novoste system is a manually operated hydraulic system that uses a noncentered radioactive seed source train (2.3-mm diameter) of ^{90}Sr pellets, which emit high-energy β-particles (β_{max} 2.28 MeV) by decay of the ^{90}Y daughter. By contrast, the Cordis system consists of a high-activity (7.4–18.5 GBq) ^{192}Ir wire source, which is advanced using an automated afterloader device. Both systems use a high-dose rate, with a 3- to 6-min vessel dwell time (i.e., time required for placement of the radioactive source in the vessel target region for delivery of radiation) for the Novoste source and a 15- to 20-min dwell time for the Cordis device. The total dose prescriptions for the Beta-Cath System, for example, are 18.4 Gy in small vessels and 23.0 Gy in larger vessels, measured at 2 mm radially from the center of the source, and 8–30 Gy at 2 mm from the center of the source for the CHECKMATE system. Although a discussion of the relative advantages and disadvantages of using these and other systems is beyond the scope of this commentary, the commercial introduction and rapidly increasing use of the Beta-Cath and CHECKMATE systems represents an important application of therapeutic radioisotopes for the treatment of this widespread clinical problem. The treatment of restenosis with radioactive materials has thus encouraged new alliances between the interventional cardiology and radiation oncology communities for use of solid radioactive sources, and nuclear medicine for use of radioactive liquid-filled balloons, as discussed in the article by Stoll et al (*1*).

Remodeling and intimal hyperplasia are the 2 main causes of restenosis after PTCA. Stenting of the vessel during the initial PTCA has nearly eliminated the possibility of negative restenosis caused by remodeling, because the stent acts as a scaffold to hold the artery patent. Intimal hyperplasia, however, is an abnormal wound healing response. When balloon angioplasty is performed, the intimal surface of the vessel is disrupted and immediate repair begins. Experimental evidence indicates that the mechanism of inhibition results from the antiproliferative effects of radiation on target cells in the outer regions of the vessel wall (*7*). Both macrophages (*8*) and myofibroblasts (*9*) have been implicated in this process. In addition, radiation is considered to be antiinflammatory and to modulate growth factors, nitric oxide, and apoptosis, leading to a positive remodeling of the vessel.

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For correspondence contact: F.F. Knapp, PhD, Oak Ridge National Laboratory, Nuclear Medicine Group, Bldg. 4501, MS6229, P.O. Box 2008, Oak Ridge, TN 37831-6229.

USE OF RADIOACTIVE LIQUID FILLED BALLOONS FOR RESTENOSIS THERAPY IS FEASIBLE AND PROVIDES UNIFORM DOSE DELIVERY

The use of liquid-filled balloons was first considered from a theoretical perspective (*10*): A uniform dose of radiation would be delivered to the vessel wall and the balloon itself would function as a convenient self-centering system. Centering of the radiation source is not considered essential with high-energy γ-emitting radioisotopes such as ^{192}Ir, because the dose fall-off with radial distance is not so steep. However, with high-energy β-emitting radioisotopes such as ^{90}Y, many investigators feel that uniform dose delivery is an important issue, because of the rapid decrease of dose with radial distance. Use of β-emitting radioisotopes greatly simplifies the radiation protection issues. Whereas high-energy γ-emitters such as ^{192}Ir (average, 871 keV) require special shielding in the catheterization laboratory to protect the operator and staff, the use of high-energy β-emitters represents localized radiation delivery with minimal exposure to the operator and patient.

The first liquid-filled balloon studies for coronary radiation therapy were proposed using ^{188}Re (*11–14*), a high-energy (β_{max} 2.12 MeV) β-emitting radioisotope conveniently obtained from the ^{188}W–^{188}Re generator system (*15,16*). The use of ^{188}Re provides the advantages of ready and inexpensive availability from a generator with a long useful shelf life for an application of 3–4 mo, a high β-energy that delivers sufficient radiation to target sites deep in the vessel wall while minimizing the dose to the lumen wall, and stable chemical forms that are rapidly excreted by the urinary bladder in the unlikely event of balloon rupture (*17,18*). Initial studies in swine using the balloon coronary injury overstretch model (*19,20*) and stent implantation (*21,22*) have clearly shown that the ^{188}Re liquid-filled balloon approach, in a dose-dependent manner, is a simple and cost-effective method for inhibition of restenosis. Adventitial doses (>0.5-mm depth) of 18–20 Gy reduced the 30-d incidence of restenosis from 30%–40% to 5%–10% in injured and irradiated arterial segments. Physician-sponsored clinical trials quickly followed these promising preclinical studies and have successfully shown the usefulness of this technique (*23–30*).

With the rapid industry-driven introduction in the United States of the solid sources for coronary radiation therapy, clinical studies of the ^{188}Re liquid-filled balloon approach are no longer in progress at Columbia University (New York, NY) (*23*) and Cedars Sinai Medical Center (Los Angeles, CA) (*24*). However, there are currently more than 30 clinical studies in progress outside the United States using the ^{188}Re liquid-filled balloon technology, including studies in Germany (*25–27*), Korea (*28,29*), Taiwan (*30*), and Australia (*31*). In addition to a recently initiated, 10-center trial using the ^{188}Re liquid-filled balloon method in Korea, the International Atomic Energy Agency will sponsor a multicenter trial with this technology beginning in 2001 at 12 institutions in developing regions. Typical balloon activity levels using efficient ^{188}Re bolus concentration methods are 1.11–1.85 GBq (30–50 mCi) (*16,17*). The intracoronary balloon dwell times depend on the levels of activity and are usually 3–8 min, from single or multiple inflation/deflation cycles. Because of the long, useful shelf life, the ^{188}W–^{188}Re generator is particularly well suited for use in developing regions.

Use of liquid-filled angioplasty balloons for such therapy, however, has special safety concerns, such as potential balloon rupture. The possibility of leakage would only be expected to occur at either end of the catheter—that is, within the patient or at the proximal connection. Protection of the operator and staff and minimization of any contamination of the catheterization laboratory can be controlled through appropriate engineering measures. However, potential balloon rupture—although not commonly encountered at the low 1- to 3-atmosphere pressures required for compliant balloon inflation with radioactive liquids—and accidental release of the radioisotope cannot be overlooked. Appropriate pharmacologic, biokinetic, and excretion properties of the radioactive species that may be released into circulation must, therefore, be carefully considered and have been evaluated in appropriate laboratory animal models.

Excretion studies and organ dose estimates in animals with ^{188}Re-perrhenate and Re(V)-MAG3 (*17*) and Re(V)-DTPA complexes (*32*) reveal that these species show rapid urinary excretion and no skeletal uptake, and that the adsorbed tissue doses in the event of balloon rupture are within acceptable limits, especially with hydration, urinary bladder catheterization, and diuretics. In addition, thyroid uptake of perrhenate can be avoided by prophylactic treatment with perchlorate (*17,33*) or perrhenate can be subsequently rapidly discharged by perchlorate, as shown by administration in animals (*17,33*). Gamma camera imaging of perrhenate distribution and clearance data in one clinical case of balloon leakage of ^{188}Re-perrhenate showed that absorbed tissue doses were within the acceptable range (*34*). Knowledge of the ICRP and MIRD data related to the radioisotopes used will help when limiting the contents of the system to a safe specific volume so that in the unlikely event of balloon rupture and release of the total content of the system into the patient, clinical symptoms can be avoided.

The use of the liquid-filled method for coronary irradiation with short-lived radioisotopes such as ^{188}Re (half-life, 16.9 h), and especially with the shorter-lived ^{68}Ga (half-life, 1.13 h), also requires special procedures for dose planning because an understanding of the exact level of activity in the balloon is necessary. Several effective and easy-to-use PC-based spreadsheet methods have been designed to accurately calculate the required vascular balloon inflation dwell time based on the radioisotope specific volume (mBq/mL) and balloon dimensions (*35,36*). Because of the use of these relatively

rapidly decaying sources and the uncertainty of when vessel irradiation will commence, the availability of such robust methods that can be used in real time is very important.

In addition to the various clinical trials currently in progress using the ^{188}Re liquid-filled balloon, initial patient studies with ^{186}Re have been reported (*37*) and application of balloons filled with liquids of the high-energy β-emitting radioisotopes ^{166}Ho (*38*) and ^{32}P (*42*) has been discussed. The use of ^{68}Ga (*1*) as a high-energy γ-emitting candidate resulting from positron decay offers another alternative for postangiographic therapy. The long useful shelf life of the ^{68}Ge–^{68}Ga generator resulting from the long 288-d physical half-life of the ^{68}Ge parent would suggest that use of this ^{68}Ga for restenosis therapy could be cost effective and readily available on an acute basis. The rapidly increasing number of clinical trials using ^{188}Re in conjunction with the potential use of the positron-emitting ^{68}Ga and the other β-emitting radioisotopes being studied illustrates the rapidly growing interest in the use of balloons filled with radioactive liquids for restenosis therapy.

A key question is how the use of angioplasty balloons inflated at low pressure with radioactive liquids would compare with the use of solid radioactive sources. Although the issue of source centering and the subsequent consequences of uniform radiation dose delivery to the vessel wall continue to be controversial, the rapid dose fall-off with radial distance for high-energy β-emitting radioisotopes is well established. The use of a liquid-filled balloon is automatically centered, circumventing this issue and ensuring uniform dose delivery. In addition, the source radial dimension (i.e., diameter) is not an issue with liquid-filled balloons; any diameter vessel can be irradiated if the deflated balloon or catheter can be passed through the vessel obstruction (*35*). Because normal angioplasty balloons can be used for the radioactive liquids, only a simple shielded radioactive liquid transfer or administration device is required, thus eliminating the need for capital investments. Finally, the issue of cost is important, especially in developing countries, and the use of a generator-derived radioisotope such as ^{68}Ga or ^{188}Re offers the benefit of being cost effective and readily available from a radiopharmacy on an acute basis. Similar to ^{68}Ga, the incremental cost of ^{188}Re for treatment of restenosis is expected to be in the $100–$200 range per case. This is in stark contrast to the current incremental cost of the CHECKMATE and Beta-Cath Systems, which can add U.S. $3,000 or more to the cost of PTCA.

Approaches being considered as alternatives to radiation include drug-treated coronary stents, balloons, or other devices for the site-specific release of these pharmacologic substances that would inhibit the hyperplastic response to vessel injury (*39*). But concern persists about the high incidence of late thrombosis and late effects if stent implantation and radiation are combined. Investigators have recommended that stenting and radiation not be used together because of delayed reendothelialization or impaired endothelialization of the stent, which would require the antiplatelet therapy to be prolonged (*40*). Future developments may reduce radiation doses, which is highly desirable, by radiosensitization methods such as the use of molecular oxygen. The success and the future of the intracoronary radiation therapy technology might depend on the ability to solve its major complications from edge effects, late thrombosis, and late effects.

It remains to be seen how long high-dose–rate, catheter-based radioactive systems will be used for restenosis therapy. However, this approach works well, is currently the only method of choice for restenosis therapy, and is most beneficial in patients with in-stent restenosis or de novo lesions with a high risk of restenosis after PTCA alone. The clinical use of radioactive liquid-filled balloons would also be expected to represent an important opportunity for the nuclear medicine community, because licensed nuclear medicine physicians are required for the handling and administration of radioactive liquids in most countries. Although radiation oncologists are responsible for dose planning and prescription and advancing the solid sources such as ^{90}Sr/^{90}Y and ^{192}Ir for vascular brachytherapy, the use of radioactive liquids would represent an opportunity for nuclear medicine for intravenous radiation therapy. In the same context, one could envision that such radioactive liquid-filled balloons could have applications for the inhibition of hyperplasia associated with other procedures, such as for AV shunts and biliary stents, and for the treatment of some cancers, where new therapeutic approaches with such cost-effective, radioactive liquid-filled devices would be possible.

Furn F. (Russ) Knapp, Jr.
Oak Ridge National Laboratory
Oak Ridge, Tennessee

Robert H. Spencer
Knoxville Cardiovascular Group, PC
University of Tennessee Hospital
Knoxville, Tennessee

Joachim Kropp
University Hospital
Technical University
Dresden, Germany

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