Development Of A Metallic Radioactive Rhenium Source
For The Treatment Of Restenosis After Angioplasty

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Abstract:

Radioactive Rhenium sources can be prepared in a nuclear reactor by bombarding the non-radioactive metal with neutrons. In a n,p-reaction, the two β-emitters $^{186}$Re and $^{188}$Re are produced with high yield. One application of these prepared radioactive Rhenium wires is the prevention and treatment of restenosis after balloon angioplasty. For this brachytherapeutic application, the source must be very stable, sealed and safe to handle. The necessary sealing of the radioactive Rhenium source was done by plasma coating with a 2400 Å layer of titanium and confirmed by scanning electron microscopy.

Our results confirmed that radioactive sources made from $^{185}$Re and, even more so, $^{188}$Re, are excellent candidates for restenosis inhibition due to their narrow treatment range, sharp dose gradient, inexpensive preparation, excellent stability, easy shielding and short treatment times.

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Introduction:

Atherosclerotic vascular disease is the most common cause of mortality in developed countries. A highly effective way of treating patients with this vascular disease is percutaneous transluminal angioplasty (PTA). Approximately 500,000 such procedures will be performed in the U.S. this year. This procedure involves the insertion of a catheter into a blood vessel which has narrowed due to atherosclerosis and the expansion of a balloon in this narrowed area. The vessel is thus widened and greater blood flow is possible. These vessels, however, become re-narrowed in about 30-40% of the patients 6 months after the procedure (1,2), making additional interventions necessary. This re-narrowing of the treated blood vessel is called restenosis.

It is widely believed that restenosis is due to endovascular scar formation. The vessel wall is damaged during balloon angioplasty and reacts by attracting blood platelets and leukocytes, both of which release growth factors into the damaged area. These growth factors stimulate smooth muscle cells to migrate from deeper vessel wall areas to an area called the intima, just below the endothelial layer, where they additionally start to divide. The smooth muscle cells then proliferate and form new tissue called the neointima (see Figure 1).

![Image](image.png)

Figure 1: Human coronary artery in a) a healthy person (H&E stain) and b) in a 70-year old atherosclerotic person 7 weeks after performing a balloon angioplasty (Mevat stain). The arrow points at neointima which consists of hyperproliferating smooth muscle cells, currently believed to be the main culprit for restenosis.

The idea of treating restenosis with locally applied radiation was born when Grünzig, the founder of the balloon angioplasty, reported the first cases of restenosis and noted that it could be regarded as endovascular scar formation (3). That scars (keloids), which are hyperproliferative skin diseases, can be successfully treated with irradiation, was first shown by Freund in 1898 (4), just three years after Roentgen's discovery of x-rays (5). The first attempts to use radiation for the prevention of restenosis started about 6 years ago. The two general methods used are externally applied irradiation with photons or electrons and irradiation from inside the vessel with a local radioactive source. A first clinical trial with external irradiation has resulted in successful prevention of restenosis (6), but the internal method is favored by most physicians since much less normal tissue is irradiated.

The prevention of restenosis through the use of radiation applied directly in the vessel is commonly called endovascular brachytherapy. A radioactive catheter emitting either beta- or gamma-radiation is inserted through a previously placed catheter, moved to the target area and left there for several minutes. During this time, the vessel wall is irradiated with a therapeutic dose of between 12-18 Gy. It should be noted that the optimal dose as well as the area to be treated is still under investigation. Several clinical trials have used endovascular brachytherapy with radioisotopes such as the gamma-emitter $^{198}$Ir (7) or the beta-emitter $^{90}$Y (8). Under evaluation is also a variant of this approach, the delivery of the endovascular radiation dose using a radioactive stent. This stent consists of a metal coil containing low amounts of radiation and delivering the dose during its decay over several months (9,10). All the mentioned approaches seem to decrease the percentage of restenosis occurring within 6 months after balloon angioplasty from 30-40% to about 10-20%.

Ideally, endovascular brachytherapy should be performed immediately after balloon angioplasty, directly in the angiography suite. To allow for this, a radiation source should be used where shielding by the patient's body is sufficient. This will also eliminate the need to transfer the patient to a specially shielded brachytherapy room, as is currently necessary with the $^{198}$Ir source. Furthermore, since the catheter containing the source will very likely block the blood flow, the procedure should take no longer than 3 minutes. Additionally, the radioactive source must be a sealed source (completely covered with another, non-radioactive material), reusable, easily sterilizable, very small in diameter and usable for several days.

Preliminary calculations and tests have shown the initial usefulness of a radioactive source made from a 3.4 cm long metallic Rhenium-wire and activated in a nuclear reactor to contain $^{186}$Re and $^{188}$Re. Both radioisotopes are beta-emitters with a maximum energy of 1.1 and 2.1 MeV, respectively. The electrons will therefore have a maximum treatment range in tissue of 5 and 11 mm, although most of the energy is deposited within 1-2 and 3-4 mm due to the spectrum of electron energies and scattering. In addition, Rhenium can easily be made into a sealed source by coating it with titanium. Due to the relatively high cross sections of 112 and 74.6 barns for $^{186}$Re and $^{188}$Re, respectively, rhenium can be easily and therefore inexpensively neutron-activated even in a low flux nuclear reactor. Once activated, the radioactive Rhenium source can be attached to the tip of a normal guide wire and then used for the prevention of restenosis.

This paper aims to examine the material and dosimetric properties of a radioactive Rhenium wire in order to determine its suitability as a radiation source in endovascular brachytherapy.

Methods:

Plasma coating of the Rhenium-wire and analysis of the titanium coat: The Rhenium-wire was plasma cleaned before a 2400 ft titanium layer was deposited in an ion beam sputtering system (Commonwealth, Alexandria, VA). The chamber was evacuated to $10^{-6}$ torr and the machine then run at 1000 V and 15 mA under argon atmosphere with a pressure of $10^{-4}$ torr. The elemental composition of the titanium coated Re-wire surface elements was analyzed by a TN-5500 X-ray Microanalysis system (Noran Instruments, Middleton, WI) connected to a JEOL-JSM-5310 scanning electron microscope (JEOL Ltd., Tokyo, Japan) at an accelerating voltage of 15 kV.

Stability tests of the radioactive Rhenium-wire: 1 cm long pieces of titanium covered Rhenium wire with an initial activity of 42.5 MBq were incubated in a vial with a bottom made from nylon sieve with 21 μm wide pores. This vial was placed inside a bottle with 60 ml of buffer PBS 7.4 or horse serum and kept on a shaking waterbath at 60 rpm at 37 °C. Three times 1 ml of the supernatant and the total radioactivity were measured daily on a gamma counter (Auto Logic, Abbott Laboratories, Abbott Park, IL) and radiation calibrator (Model 4050, RadCal Corp, Monrovia, CA), respectively.
Neutron-activation of the Rhenium wire: 0.5 to 3 cm long pieces of Rhenium wire of 99.99% purity with a diameter of 0.5 mm (Rhenium Alloys, Cleveland, OH) were sent to the Ohio State University reactor in Columbus, Ohio and placed directly in the neutron beam for 15-60 minutes at a neutron flux of 0.5 to 1.5 x 10^13 n/cm^2/sec. The amounts of the produced radioisotopes ^186Re and ^188Re and possible contaminations were determined with a high purity Germanium detector coupled to a multichannel analyzer (EG&G Ortec, Oak Ridge, TN).

Dosimetric evaluation of the Rhenium wire: A 17 mm long piece of radioactive Re-wire with a diameter of 0.5 mm was placed on a 3x3 cm^2 piece of gafchromic film type MD-55 (Nuclear Associates, Carle Place, NY) sitting on top of a 7 cm block of solid water RMI 457 (Gammaxe RMI, Middleton, WI) and covered with a 1 liter bag of saline. The wire contained 148 MBq of ^186Re and 37 MBq of ^188Re. After 2 hours of incubation, the piece of gafchromic film was scanned on a VXR-12 x-ray film digitizer (Vidar Systems Corporation, Hemdon, VA) and then transferred to a PC running the software Image Pro Plus for Win95 (Media Cybernetics, Silver Spring, MD). A calibration curve was taken by irradiating pieces of 1x1 cm^2 gafchromic film on top of the 7 cm thick solid water block, covered with 1.9 cm of solid water. The calibration film pieces were scanned in the same run with the Rhenium-irradiated gafchromic film, making additional background corrections unnecessary. A Clinac 2100 linear accelerator (Varian, Palo Alto, CA) using a 9x10 cm^2 irradiation field of 6 MV photons at 100 cm to the solid water surface was used for the calibration irradiation. One monitor dose equalled 1.0 cGy. The dose distribution was plotted applying the calibration to the Rhenium-irradiated gafchromic film.

Results:
The plasma coating of the Rhenium wire was without problems and Figure 2 shows the wire surface after being rubbed with a dry tissue and cleaned with water and alcohol.

![Figure 2: Scanning electron microscopy pictures of the Rhenium wire a) before and b) after plasma coating with 2400 Å of titanium. The width of the wire is 0.5 mm.](image)

Although the titanium coating in Figure 2b looks spotty, it was confirmed by scanning large parts of the surface using an X-ray spectroscopy microanalysis system that the titanium layer covered the entire surface and could not be rubbed or washed off (Figure 3b). The spotty appearance might be an artifact from the scanning electron microscopy. The observed x-ray lines coincided with titanium at 1.5, 8.6 and 10.2 keV and with aluminum at 4.5 and 4.9 keV (11). The low energy lines near the first Rhenium peak are Sulfur and Aluminum, and they are due to the aluminum stud on which the wire was mounted.

![Figure 3: Low energy x-ray spectroscopy spectrum of a) the pure Rhenium wire and b) the titanium coated Rhenium wire.](image)

The thickness of the titanium layer was confirmed by scratching the wire with a knife and then measuring the layer thickness in the electron microscope. Figure 4a shows the surface view. The thickness of about 2400 Å - probably a little more - was measured by beaming in from the side, as seen in the close-up from Figure 4b and 4c. No chipping of the titanium coat was observed when the wire was bent.

![Figure 4: Scanning electron microscopy pictures of the titanium coated Rhenium wire after scratching it with a knife. a) Surface view of the scratch b) side view of the edge of the scratch at the same location and c) close-up of this side view.](image)

The titanium coated Re-wire was neutron-activated and then analyzed for contaminants. Two hours after activation, no traces of the short-lived titanium radioisotopes ^48Ti and ^49Ti were found. No contaminants were found beside ^186Re and ^188Re. The radiochemical stability of the radioactive Rhenium wires at 37°C can be seen in Figure 5. A small amount of radioactive perchlorate was released during the first 3 days, but none thereafter. The radioactivity never exceeded a total of 3.6 kBq. A thorough cleaning of the wire before sending it to and after receiving it from the reactor would possibly prevent this initial "burn-in" effect.

The dose distribution around the radioactive ^186Re/^188Re-wire is shown in Figure 6. It is symmetrical around the wire, both along the wire axis and perpendicular to it. Figure 6c shows the dose distribution in the center of the wire with the area directly touching the radioactive wire being the hottest spot. It is apparent that the dose fall-off is very steep. Just 1 mm away from the center, only 26% of the dose are delivered, and further declining to 8% at 2 mm. If one wanted to treat or prevent a restenotic lesion in vivo at a distance of about 2 mm away from the surface of the wire, a reasonable assumption if the diseased vessel is a coronary artery, then the tested wire containing a mixture of 148 MBq of ^186Re and 37 MBq of
Figure 5: Stability of the radioactive, titanium coated Rhenium-wire. The released radioactivity is graphed in percent of the total activity of the wire.

$^{186}$Re would deliver a dose of 13.3 Gy. A source delivering 15 Gy at 2 mm from the wire surface within 2 minutes could therefore be made by using an activity of about 586 MBq $^{186}$Re and 147 MBq of $^{188}$Re per cm wire. Such a wire can be made by neutron-activating it for 2 hours at a neutron-flux of $1.5 \times 10^{13}$ n/cm$^2$/sec.

Figure 6: Dosimetry of a radioactive Rhenium-wire measured with Gafchromic film. The activity at the time of measurement was 4 mCi of $^{188}$Re and 1 mCi of $^{186}$Re. a) Photograph of the gafchromic film after incubation with the wire for 120 minutes. b) Dose distribution around the wire. The darkest area in the middle received 200 Gy or more. c) Relative dose distribution perpendicular through the center of the wire.

Discussion:

The appropriateness of radioactive Rhenium as a source in endovascular brachytherapy is indicated by its mechanical properties and biochemical stability after coating with titanium. Mechanical bending tests detected no chipping in the neutron-activated wires. Furthermore, an even coating with titanium was achieved by plasma coating, as seen by scanning electron microscopy and x-ray detection. The inflexibility of the tested Rhenium wire of 0.5 mm diameter and 2-4 cm length would not allow for its use in vivo applications. In order to circumvent this problem, a more flexible source of this diameter and length could be produced by braiding smaller wires, such as 0.1 mm Rhenium wires, to form a cable of 0.5 mm diameter. Such a cable would be able to negotiate the narrow turns inside a catheter, and would be expected to have dosimetric properties similar to those of the solid wire.

Our results confirmed that metallic Rhenium sources containing a mixture of the two radioisotopes $^{186}$Re and $^{188}$Re are excellent candidates for restenosis inhibition. Their dosimetric profile exhibits a sharp dose gradient which results in a narrow treatment range. This narrow range leads to a substantial decrease in the radiation received by normal tissue and assists in keeping the treatment times short. Within 2 minutes, a Rhenium wire containing about 6 GBq of $^{186}$Re and 1.5 GBq of $^{188}$Re per cm of wire will deliver the currently believed to be optimal dose of 15 Gy at 2 mm from the wire surface. If the design of the catheter or the anatomy of the vessel allow for shorter treatment distances, the necessary amount of radioactivity could be reduced to an even greater degree. Using the same amount of radioactivity, a reduction of the distance from 2 mm to 1.5 mm will, for example, increase the relative dose delivered from 8.3% to 15%. And at just 1 mm from the source surface, 27.3% of the dose will be delivered. The narrow treatment range of the beta-emitting Rhenium source, unfortunately, makes the homogeneous treatment of the different vessel layers difficult. Atherosclerotic plaque, for example, which is often eccentric and more than 1 mm thick, leads to the displacement of the radioactive source away from the center of the vessel, thus irradiating the different vessel wall layers unequally.

In conclusion, our results indicate that radioactive Rhenium wire sources are excellent candidates for restenosis inhibition due to their stability, narrow treatment range and short treatment times. Additional research into the mechanisms of restenosis and the molecular targets of the endovascular brachytherapy is needed, to allow for restenosis prevention with minimal side effects and no late radiotoxic effects.

References:

Production Of Rhenium - Powder With A Jet Mill And Its Incorporation In Radioactive Microspheres For The Treatment Of Liver Tumors

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Abstract:

Metallic rhenium powder of 325 mesh is readily available, but well characterized powder of micrometer size is less easy to obtain. This paper describes the preparation of rhenium powder with an average particle size of 2 μm through the application of a jet mill to 325 mesh material. The particle size distribution was confirmed by light and scanning electron microscopy, and laser diffraction. The change in density and surface characteristics (porosity) was also analyzed.

Jet-milled Rhenium particles were then incorporated into biodegradable poly(lactic acid) microspheres using a solvent-evaporation method. After neutron-activation in a nuclear reactor, 186/188Re-microspheres were directly obtained with no need for further processing before their employment in radiotherapy. The usefulness of the Rhenium microspheres for the treatment of liver tumors was tested by determining their biodistribution in rats. The results were a time-dependent, up to five fold increase in Novikoff liver tumor uptake as compared to normal liver tissue.

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