Electrodeposition of radioactive rhenium onto stents to prevent restenosis

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Abstract

Radioactive stents are currently being evaluated for preventing restenosis. A major difficulty to overcome is the need to load any pre-manufactured stents with defined amounts of radioactivity at the time of use. Using stents that are preloaded by the manufacturer is not ideal because the stent length usually differs from the length needed for a specific lesion and the amounts of radioactivity varies widely due to ongoing decay of the source. Thus, we have developed a novel method that allows any currently used stainless steel or tantalum stent to be coated with radioactive rhenium. The method involves placing the stent in a series of rinsing and electroplating solutions, one containing radioactive rhenium (183Re, 186Re, or both). The overall processing time is 15 min and the procedure may be conveniently applied just prior to the stent insertion. The plated stent contains radioactive rhenium in a 1.2 µm-thick cobalt layer, with an outer 2 µm layer of gold. The gold layer gives the radioactive stent excellent radiochemical stability, good bending and biocompatibility properties, and improves stent visibility during fluoroscopy. © 1998 Elsevier Science Ltd. All rights reserved

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1. Introduction

Animal studies have shown that radioactive stents reduce the rate of restenosis after coronary angioplasty [1–5]. Restenosis (the re-occlusion of vessels) occurs in a third of atherosclerosis patients who undergo balloon angioplasty or stenting of their coronary arteries [6]. The mechanism of restenosis is not clear, however, it is believed that hyperproliferation of vascular smooth muscle cells leads to scar formation inside the blood vessel, eventually blocking the blood flow [7]. Fig. 1 shows a typical cross-section of a stented coronary artery in which restenosis has occurred. Using stents to mechanically keep the vessel open in combination with local irradiation to prevent smooth muscle cell overgrowth of the stent was pioneered by the Fischell brothers [8] and is currently being tested in a clinical phase I trial involving 25 patients (the Isostent Trial). Currently, stents loaded with 32P are used. However, 32P stents must be activated in advance and therefore cannot be adjusted at the time of insertion for individual lesion characteristics, dosimetry, stent length, and stent type. In addition, using 32P leads to 75% of the radiation being delivered over 30 days (2 half-lives). However, radiobiological concerns that not only the total dose but also the dose rate are important, make delivering the radiation over a shorter time preferable [9]. Rodent experiments have shown that the irradiation of arteries between 1 h prior to and 3 days following balloon angioplasty is the most efficacious [10]. For these reasons, we are proposing the endovascular use of 186Re, a beta-emitting radioisotope with a half-life of 17 h and an average tissue penetration of 3 mm. With this radioisotope, 94% of the radiation dose will be deposited in the artery within 3 days of application. Furthermore, previous dosimetric studies showed that this isotope has the ideal treatment range in coronary arteries [11]. Smooth muscle cells thus receive doses of 15–20 Gy and the normal tissue outside the adventitia is spared.

The objective of this investigation was to develop a method that allows any currently used stainless steel stent to be coated with radioactive rhenium in a rapid
and predictable way. To obtain such stable coatings in less than 15 min, we electroplated stents using various protocols. The mechanical integrity of the plated stents was then analyzed using scanning electron microscopy (SEM).

2. Materials and methods

2.1. Electroplating

The metals were deposited on 316L stainless-steel wire (Ethicon, Somerville, NJ), from which most stents are constructed. All 0.43 mm diameter wire samples \( n = 56 \) to be electroplated were first rinsed with acetone or hexane to remove oily contaminants, followed by a cathodic acid strike [12] to activate the surface and provide a seed layer (Table 1). In all wire experiments, a length of 25 mm was immersed and plated in the strike and plating baths. The striking time was 8 min for all wire samples. Four sets of electroplating experiments were conducted: direct plating of radioactive rhenium onto the wire, codepositing radioactive rhenium with cobalt as a carrier, codepositing rhenium with gold as a carrier, and coating the cobalt and rhenium with a plated layer of gold. In addition, 2 tantalum Wiktor stents (Medtronic...

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Inc., Minneapolis, MN) were electroplated using the methods that were shown to produce the best results and then tested and analyzed similarly to the electroplated wires.

The initial rhenium plating was attempted using the strike procedure described above followed by plating from a sulfate bath (0.1 M H₂SO₄) as described in the literature [13]. However, the absence of rhenium deposit, as measured by X-ray spectroscopy (see below) led to modifications. Cobalt and rhenium were plated individually from borate electroplating solutions [14], and gold was plated from a buffered phosphate solution (Table 1) using a current-controlled regulated DC power supply (Kenwood, PR18-1.2A, Davis Instruments, Baltimore, MD). When electroplating rhenium along with one of these metals, a buffered solution of Re₂O₇ (perrenate solution) was added to the plating solution to yield a rhenium concentration of 0.23 M. The acetone rinse, the striking, and the plating were all performed by immersing the wire sample sequentially into 1.5 ml polystyrene cuvettes (Fisher Scientific, Pittsburgh, PA) containing the appropriate solutions. Platinum wires 0.20 mm in diameter (Alfa Aesar, Ward Hill, MA) were used as anodes and placed vertically along the inside wall of the strike and plating cuvettes.

In the experiments involving a final gold layer, cobalt and gold were plated sequentially on the same wire sample. Here, the wire first underwent a cobalt strike (Table 1), followed by cobalt plating for 2 min at a current density of either 400 or 87.5 A/m². Finally, the wire was plated in the gold-plating solution for 5 min at a current density of 102 A/m².

For placement in a patient's artery, the stent is mounted onto a deflated balloon catheter, inserted into the artery, and then expanded by inflating the balloon generally to pressures between 0.6 and 1.0 MPa (6-10 atm). To detect possible mechanical damage to a coated stent, which may be caused by this procedure, deflated Wiktor stents (1.5 mm in diameter) made from tantalum (Medtronic Inc., Minneapolis, MN) were plated using the procedure that was found most successful for the steel wires. The stents were then mounted on a balloon catheter, and expanded at 2 MPa (the maximum pressure for inflating this stent). The stent diameter after expansion was about 3.5 mm. The stents were then examined for surface damage using SEM as described below.

2.2. Bending and mechanical stability tests

Bending tests were performed on the plated wires. In each case, a reference picture of the wire before bending was taken on a scanning electron microscope (JSM-5310, Jeol Ltd., Tokyo, Japan) at an accelerating voltage of 15 kV after rinsing in acetone. Each wire was then bent sequentially to approximately 30°, 60°, 90°, 120°, and 150° over a sharp corner of an aluminum block using teflon-coated tweezers. After each bending step, the bent section was inspected by SEM. In addition, X-ray analysis was performed on selected wire areas by a TN-5500 X-ray microanalysis system (Noran Instruments, Middleton, WI) directly under the SEM. Putting adhesive tape on the wire, pulling it off and observing its surface under the microscope tested the adhesion of the coating to the substrate. Additionally, the coated wire surface was scratched first with a fingernail, and then with a razor blade and inspected for damage.

2.3. Radiosotope preparation and measurement of uptake

To measure the uptake of radioactive rhenium on the wire, radioactive perrenate was added to the plating solutions during direct, gold, and cobalt plating, and layered Co/Au plating. At the Ohio State University Reactor in Columbus, Ohio, 2 mg of Re₂O₇ was directly neutron-activated for 1 h at a neutron flux of 1.5 x 10¹³ n/cm²/s, yielding 22.2 MBq ¹⁸⁸Re and 133.2 MBq ¹⁸⁷Re. Neutron-activation of naturally occurring rhenium always yields such mixtures because stable rhenium consists of two isotopes, ¹⁸⁷Re (37.1%) and ¹⁸⁸Re (62.9%). For the layered Co/Au plating, the radioactive rhenium was added to the cuvette containing the cobalt plating solution to a final rhenium concentration of 1 mM rhenium. The amount of radioactivity added was between 4 kBq and 42 MBq. Subsequent to plating, each wire was rinsed three times with 2 ml of phosphate buffer (pH = 7.4) and the activity of each of these rinses measured in a gamma counter (Auto-Logic, Abbott Laboratories, Abbott Park, IL). The plated wires with the higher activity, as well as the remaining plating bath were measured in a radionuclide calibrator (Model 4050, Radecal Corporation, Monrovia, CA). The amount of activity deposited was then calculated by dividing the stent/wire activity by the sum of both the plating bath and stent/wire activity, and expressed in percent of the initial activity.

The setup that was used for the successful layered Co/Au plating was also used to codeposit the radioactive rhenium for different lengths of time, using various rhenium concentrations, and various current densities for the cobalt plating step. The plating times for cobalt/rhenium codeposition ranged from 1 to 18 min. A dilution trial was performed with rhenium concentrations in the cobalt plating bath ranging from 0.05 to 500 μM. The influence of the plating current on rhenium plating efficiency was determined at current densities ranging from 20 to 420 A/m².

A Wiktor stent was electroplated using the most promising conditions (Table 1) with 29.7 MBq of radioactive rhenium in the plating solution. The stent was rinsed three times with 3 ml of distilled water each, put in a 5 ml glass vial filled with 4 ml of phosphate buffer (pH = 7.4) and placed in a 37°C shaking water bath. Serial measurements of both the stent and the buffer were performed.
daily in the gamma-counter and the released activity calculated.

3. Results

Directly plating rhenium metal onto the steel wires from the sulfate bath yielded no detectable metal on the wire surface. A strike and plating sequence from a hydrochloric acid solution (strike) followed by rhenium plating from a boric acid electrolyte (Table 1, columns 1 and 2, respectively) deposited, however, a thin layer of dark-gray metal on the surface. X-ray analysis indicated that the coating consisted of rhenium. The metal could be easily rubbed off. Scanning electron microscopy revealed that the rhenium was plated in streaks along the length of the wires, the streaks consisting of rhenium bubbles approximately 2 μm in diameter (Fig. 2A and B). The current efficiency was very low, yielding only a 0.11 μm-thick layer per minute of plating time.

The optimal plating conditions for each metal to be codeposited with rhenium were determined individually. Cobalt plated readily out of a borate plating solution, with a deposition rate of 1.2 μm/min of plating time. The light-gray coating could not be scratched with a fingernail but could be scratched with a razor blade. Gold also plated readily out of a phosphate plating solution, yielding 0.56 μm/min of plating time. The surface could not be scratched with a fingernail but could be scratched with a razor blade. The color of the plated gold ranged from light to dark brown-gold, depending on the thickness of the layer. The sequential plating of first cobalt and then gold yielded surface characteristics similar to those of the gold-only plating. All the wires were subjected to bending tests. Damage was particularly severe in the cobalt-plated wires, with cracks appearing already at an angle of 30° and further widening to broad valleys (Fig. 3B and C). Although reducing the electroplating time from 18 min (Fig. 3A–C) to 30 s resulted in a much smoother surface (Fig. 3D), it is obvious in Fig. 3E that even this cobalt layer (only 0.6 μm thick) cracks at 30°. This chipping would be unacceptable in vivo.

Bending tests of the gold-coated wire showed none of the flaking, splintering, or cracking seen in the cobalt layer. At a plating time of 2 min (a 1.1 μm-thick gold coating), wires were bent to 150° without any visible break in the layer (Fig. 4A and B).

Bending tests of layered Co/Au plated wires showed that the mechanical properties of the layers depended highly on the cobalt layer thickness. When a wire was plated with cobalt (400 A/m²) for 2 min, followed by gold (102 A/m²) for 1 min, flaking and cracking at 60° and 120° angles were visible with SEM (Fig. 4C and D). Reducing the cobalt thickness (plating at 87.5 A/m² for 2 min) and increasing the gold thickness (plating at 102 A/m² for 5 min) improved the bending test results.

Fig. 2. Stainless steel plated with rhenium metal. (A) Overview of plated area. Dark areas are bare steel, lighter areas are plated rhenium. (B) Close-up of plated rhenium showing that the streaks in (A) consist of rhenium "bubbles".

This layered Co/Au plated wire showed properties similar to those of the wire coated with gold only. Cracking was not seen at 30° (Fig. 4E), 60°, or 90°, but some small micro-fractures were distinguishable at 120° (Fig. 4F).

X-ray spectroscopy performed under the scanning electron microscope clearly showed that rhenium was codeposited with the cobalt. Measurements of radioactivity confirmed that rhenium was codeposited with cobalt (under the plating conditions investigated) at a rate of about 0.5% of the total amount of perrenhein present in the solution per minute.

The codeposition of gold with rhenium could not be confirmed by X-ray spectroscopy because the spectroscopic peaks for gold overlapped those for rhenium. Using radioactive rhenium, however, proved that no codeposition of rhenium with gold took place under the conditions used. In fact, rhenium was virtually excluded. This could be expected due to the much more noble nature of gold vs. rhenium.
4. Discussion

Both radioactive rhenium isotopes $^{188}$Re and $^{188}$Re are currently only available in aqueous solution in the form of the highly water- (and ethanol-) soluble perrenate. For our work, we used dirhenium heptoxide, Re$_2$O$_7$, which can be activated in a nuclear reactor and dissociates in aqueous buffer immediately into perrenate, ReO$_4$. This anion has been routinely used in studies of rhenium plating since the early 1930s, being obtained primarily from potassium perrenate [16, 17].

The plating bath most commonly used for rhenium metal is a low-pH sulfuric acid bath, and rhenium has been plated onto brass, copper, iron, nickel, chromium, and rhodium [18]. However, our attempts to electroplate stainless-steel wire in this manner produced only insignificant amounts of rhenium metal. Plating from sulfuric acid solutions, even at the higher concentrations described by Root [15], was unsuccessful. We therefore adapted a strike and a plating solution based on hydrochloric and boric acids, respectively, somewhat similar to the cobalt plating system (Table 1). These hydrochloric acid and borate solutions yielded a thin, spotty rhenium layer (Fig. 2). The grayish rhenium layer consisted of small, microsphere-like rhenium particles that could be easily brushed off with adhesive tape. Obtaining a stable, even layer of rhenium using this plating method would require heating the substrate to 1000°C so as to anneal the rhenium to the substrate [15]. For a stent plating process, such temperatures would not be practical.

Because rhenium did not electroplate well by itself, we considered codepositing rhenium with other metals, a possibility that Fink and Deren had raised in 1934 [16], and that Netherton and Holt had further explored in 1952 [19]. We chose to test the codeposition of rhenium with cobalt for two reasons: cobalt is a biocompatible material [20, 21], and it is an excellent carrier for rhenium because of its relatively lower standard potential ($-0.280$ V for cobalt as compared to $+0.368$ V for...
rhenium) [22]. In such cases, the metal with the higher, more noble potential should plate more readily, as our experiments confirmed. Unfortunately, the plated cobalt is not very ductile, making it susceptible to cracking when bent. The plated layer splits and splinters, even when the layers are thinner than 1 μm (Fig. 3E). Because of this fragility, cobalt cannot be used alone as a carrier for rhenium deposition onto a flexible stainless steel stent.

A metal with better mechanical properties as well as good biocompatibility, due to its near complete resistance to corrosion in vivo, is gold [23–25]. Gold, a dense but much softer metal than cobalt, will not crack when subjected to the same bending stress (Fig. 4A and B). Gold’s standard potential (+0.959 V) [22], however, is higher than that of rhenium, explaining why the direct codeposition of gold with rhenium was not successful; the rhenium was completely excluded from the electroplated layer. Plating and mechanical testing yielded good results when a two-step plating procedure was used. In the first step, rhenium was electroplated together with cobalt for a short time (2 min) and at a low current density (87.5 A/m²), thus minimizing the cobalt layer thickness (0.4 μm). In the second step, a relatively thick, crack-resistant coating of gold was plated on top of the cobalt/rhenium layer (2.5 μm gold layer when plated for
5 min). Such a procedure incorporates both the ductility of gold and the acceptable rhenium uptake when codeposited with cobalt. Bending tests indicate that the outer gold coating prevents the layer from cracking (Fig. 4E). The cobalt layer may be fracturing beneath the gold surface, but the damage becomes visible only when the wire is bent to a much higher degree (Fig. 4F). Such bending angles will never be reached in vivo, and we thus believe that the currently available stents made radioactive with this layered Co/Au plating method can be mounted on a balloon catheter, inserted into a patient’s artery and expanded into the artery wall without cracking or chipping.

Radioactive rhenium can be codeposited with the layered Co/Au plating method in a reliable, predictable and reproducible way. Under the tested conditions and concentrations, the rate of rhenium uptake does not depend on the plating time or rhenium concentration in the plating solution. This allows to easily ‘pre-set’ the amount of radioactivity loaded on the stent by either altering the amount of rhenium in the solution or adjusting the plating time (Figs. 6 and 7). The plating efficiency, however, depends on the plating current, and the percent yield of radioactive rhenium may drop sharply if the current density falls below a threshold limit. For practical purposes, this limit is about 60 A/m² (Fig. 5).

Most tests in this study were performed with 316L stainless-steel wires. The successful layered Co/Au plating, however, was also tested with Wiktor stents, which are made of 0.1 mm-thick surgical tantalum wire. The stent was coated with a 0.4 μm thick, rhenium-cobalt layer, followed by a 2 μm-thick gold layer. The SEM surface scan showed a smooth surface, and no cracks were found after the stent was expanded with a balloon catheter at maximum pressure.

The incubation of the radioactive stent in phosphate buffer at 37°C showed that the radiochemical stability is not optimal yet. However, the radiobiological implications of the release of 2% of ¹⁸⁸Re within the first two days after implantaion are very small: Rhenium is
excreted rapidly with a biological half-life of less than 12 h and does not accumulate in the body [26, 27]. The safety margin therefore is much higher than for $^{32}$P or $^{90}$Y, which accumulate in the bones and are toxic to the bone marrow. Based on the MIRD approach [28], a dosimetric scheme for calculating organ and whole body doses often used in nuclear medicine, the dose from the released activity to the body can be calculated. The tested stent of 492,1 kBq releasing 3% of its activity would thus give a whole body dose of 0.08 μGy, an amount comparable to the 0.1 μGy given to the ovaries or testes by a single dental X-ray [29] and is thus of little concern. The exact method of dose calculation is described in detail in a forthcoming paper [30]. It covers the release of radioactive rhenium from intrahepatic glass microspheres for the purpose of liver tumor treatment.

The dose necessary to inhibit restenosis is, on the basis of animal experiments, currently believed to be about 15 Gy [31, 32]. However, neither the exact dose nor the exact target (media, adventitia, smooth muscle cells, matrix substances) is known [33]. In coronary arteries, the radioactive restenosis treatment with stents would require the radioactive stent to deliver the 15 Gy at an average distance of 1 mm from the vessel surface. A stent loaded with about 1 MBq of radioactive rhenium would deliver such a target dose. The electrodeposition of such amounts can be easily reached with the method discussed here, using either a mixture of $^{188}$Re/$^{188}$Re as used for our work, or preferably pure $^{188}$Re from a $^{188}$W/$^{188}$Re generator [34]. The recently developed and now available $^{188}$W/$^{188}$Re generator works like a $^{99}$Mo/$^{99m}$Tc generator, which is currently used in most nuclear medicine departments. The radioactive $^{188}$Re is extracted daily in amounts of up to 37 GBq, and the half-life of the parent nuclide $^{188}$W is such that the generator can be used for at least 3 months. The generator will thus allow every hospital doing angioplasty to produce radioactive stents shortly before the stenting procedure in a reliable way, using the stent and radioactive dose appropriate for the lesion to be treated.

The procedure has been done under sterile conditions. An apparatus is currently being developed which will minimize handling during electroplating. After placing a stent and the radioactivity in the electroplating apparatus, no additional work will be required before the coated, rinsed and sterilized stent is produced. It should also be noted that the set up used in this procedure requires relatively little space. The needed designated laminar flow hood containing the $^{188}$Re-generator, dose calibrator, electroplating apparatus and small radiation shield can be set up adjacent to the cardiac catheterization lab or in the radiation oncology department, depending on the number of daily radioactive stent placements. The preferred location, however, might be the hospital radiopharmacy as it already is prepared, both legally and with respect to radiation safety and manufacturing expertise, to work with radioactive substances and radiopharmaceuticals. One concern to be addressed is whether metals deposited on a stent influence the healing response to stent implantation. Although gold, the final layer on the stent, is generally considered to be highly biocompatible, there have been reports that small sheets of gold implanted in rats caused a tumor [35]. In vivo studies of the coated stents are thus necessary, and work is underway to test the described stents in a swine over-stretch model.

5. Conclusions

We have shown that a procedure involving the sequential electroplating of cobalt and gold may be suitable for codepositing radioactive rhenium onto surgical stainless steel wire as well as tantalum of the type used for endovascular stents. Such an electroplated stent could be relied on to easily deliver a given dose of radiation to a target area inside a vessel. No damage to the stent coating resulting from cracking and splintering is expected. The plating procedure is quick (about 15 min from start to finish), it can be performed at the time of stent insertion, and the process can be adapted to stents of any manufacture or size. The gold layer gives the radioactive stent not only excellent radiochemical stability, good bonding and biocompatibility properties, but also will improve its visibility during fluoroscopy performed in angioplasty.

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References