Preparation and characterization of radioactive Co/\(^{188}\)Re stents intended for lung cancer treatment using an electrodeposition method

H. Zhang and U. O. Häfeli*
Department of Radiation Oncology, Cleveland Clinic Foundation, 9500 Euclid Ave. T28, Cleveland, Ohio 44195, USA

A procedure for electroplating a Co/\(^{188}\)Re alloy layer on metal coils (stents) at room temperature was developed. The electroplating of the Co/\(^{188}\)Re alloy layer was carried out at a current density of 93 A m\(^{-2}\) and produced a physically strong Co/\(^{188}\)Re alloy layer that adhered well to a thin gold strike layer on top of the stent material. The final gold layer was also stable. An empirically-found equation correlates the radioactive electroplating efficiency factor to the concentration of the radioisotope and was used to deposit predetermined amounts of radioactivity on the stent surface. Radioactive stents can be prepared and quality control performed within 2 hours using an automated electroplater and dosimetric quality control system. The radioactivity was homogeneously distributed on the stent surface. The in vitro stability in human plasma at 37°C was found to be greater than 95% for both Wallstent and Ultraflex stent after 72 hours of incubation. A clinical pilot trial is planned after successful completion of animal testing.

Introduction

Advanced lung cancer often invades the major airways of the afflicted cancer patients making breathing difficult. To prevent breathing problems and improve patient quality of life, stent support as shown in figure 1 is commonly used to keep airways open mechanically [1]. To add a therapeutic component which can potentially kill the tumour or slow down its growth, the lung tumour is sometimes irradiated either by external radiation [2] or by endobronchial (inside the airways) brachytherapy (radiotherapy with a radioactive source applied close to the target) [3].

External irradiation in addition to bronchial stent placement requires many weeks of daily treatment, and the outcome is questionable [2]. Bronchial brachytherapy of lung cancer patients with stents, on the other hand, has been shown to be effective [3]. The drawback of this approach is that it normally requires at least two additional treatment sessions and extensive dosimetric treatment planning, thus making it time-consuming and expensive. To limit these drawbacks, we propose using radioactive stents that could eliminate the additional procedures and reduce dosimetric treatment planning, since the stents placed in the bronchial tree adhere closely to the airways and will thus automatically deliver the precalculated treatment dose to the correct region. Furthermore, it might be possible to give higher radiation doses, since the radioactive stents deliver the dose in a more accurate way and thus irradiate less non-cancerous tissue.

We recently developed a method of coating metallic stents with a radioactive cobalt/rhenium-188 (Co/\(^{188}\)Re) alloy [4]. The most commonly used bronchial stents are the Ultraflex stent and the Wallstent, both shown in figure 2 and available from Boston Scientific, Boston, MA. The radioactive component \(^{188}\)Re can deliver a defined radiation dose and kill the tumour cells within the range of the \(\beta\)-particles of 3–4 mm, while at the same time mechanically keeping the airways open. For clinical use, such radioactive stents must be guaranteed to be coated first with a defined amount of homogenous radioactivity, and second with a physically strong layer which will not be damaged during and after implantation in the patient’s body. The aim of our work was to optimize the electroplating conditions and to be able to predict the electroplated activities with high accuracy. An additional aim was to automate the whole procedure such that it could be run remotely and fully computer controlled, and to keep radiation exposure of the operator minimal both during the electroplating and the subsequent quality control of the radioactive stent.

Experimental setup and procedures

Instruments developed for the radioactive stent preparation and quality control

Since the operation of the electroplating process includes the handling of radioactive materials, we attempted to prepare the stents under remote computer control as much as possible. For this purpose, two automated instruments were developed for the preparation of radioactive stents. The first instrument, an automated electroplater (figure 3a), precisely controls the electroplating time and current and thus is able to deposit preset activities onto the stents. During the setup, the user has to fill four chambers with sterile solutions (strike solution, radioactive electroplating solution, acid gold solution, and water), connect the stent to the cathode and then hang it into the electroplating chamber (figure 3b). The radioactive solution and the plating chamber are covered with lead

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*Author for correspondence, e-mail: hafeliu@ccf.org
shielding, and the entire electroplater is further placed behind lead bricks. Once the start button is pressed, it takes about 15–20 minutes before the rinsed stent can be removed, analysed and used.

The second instrument, the ‘dosimetry tower’ (figure 3c), analyses and records the radioactivity distribution on the stent surfaces. The stent is moved onto a rod of nominal stent diameter which is connected to the axis of a dual stepper motor (Haydon Switch & Instrument Inc., Waterbury, CO, USA) providing rotational and linear movement. Under computer control, the stent is moved to defined positions in front of an Optidos beta-scintillation detector (Optidos system, PTW Freiburg, Germany) [5] and the radiation dose rates are measured around and along the entire stent.

Both instruments are computer controlled through an ADAC MF5500 data acquisition board (IOtech Inc, Cleveland, OH, USA) using user-friendly interfaces programmed in Visual Basic 6.0 (Microsoft, Redmond, CA, USA). During the electroplating steps, all currents are time-logged and saved into a log file for documentation. The dosimetric results are also saved to file and then automatically graphed with Origin 7.0 (Origin Lab, Northampton, MA, USA). More technical, process automation and software details of the electroplating and dosimetry system are given elsewhere [6].
Surface preparation and cleaning of stents

Caustic permanganate solution is used to loosen the scale on the stent and consists of 0.5 M KMnO₄ and 1 M NaOH solution. The highly oxidizing pickling solution made from 3.33 M HCl and 5.13 M HNO₃ reacts with the base metal and removes the loosened scale from the stent. Pickling should not exceed 5 minutes at room temperature to avoid weakening of the base metal. The 2 M HCl strike solution is not directly useful in the electroplating process, but serves to freshly prepare the 0.007 M gold strike solution for the strike step. The gold strike solution is mixed directly in the electroplating chamber at a ratio of 2:1 (strike: acid gold), thus avoiding instability problems. The acid gold solution [7] is made from CoSO₄·6H₂O (1.35 g l⁻¹), KAu(CN)₂ (6.00 g l⁻¹), citric acid (56.0 g l⁻¹) and Na₂EDTA·2H₂O (2.16 g l⁻¹), and adjusted with 10 N NaOH to a pH of 4.0. The radioactive Co²¹⁸Re electroplating solution is composed of 0.44 M CoCl₂, 0.5 M boric acid and up to 7.4 GBq L⁻¹²¹⁸Re.

Surface preparation and cleaning of stents. Stents need to be clean of scale and oxidation layers to result in reliable coatings. Both stent types used for lung cancer therapy are prone to oxidation. The Ultraflex stents are made from a single nitinol wire, and just clamping it to an alligator clip provides a good connection (figure 4a). Additionally coating the clip with a gold layer prevented rusting and allowed reuse for several months. The Wallstents are made from 24 to 36 separate wires (depending on their diameter) which cross each other several times, but the crossings at these connections are not reliable. To overcome this problem, we developed a special holder for the Wallstent (figure 4b), which contains a metal wire that is pressed onto all the wires and connects directly to the cathode.

Electroplating procedure. During the pretreatment of the stent in the caustic permanganate solution followed by the pickling solution, the plating chamber in the electroplater was automatically filled with the gold strike solution. The stent was taken straight from the pickling solution (without rinsing), connected to the cathode, and placed in the filled plating chamber. After hitting the button ‘Proceed’ in the software, the electroplater applied currents and rinsed the stent fully automatically, starting with a current density of 100 A m⁻² for 60 seconds to strike the stent with the gold strike solution. The plating chamber was emptied, rinsed three times with water (volume equal to the plating chamber size), three times with small amounts of the radioactive electroplating solution (volume = 600 µl) and then filled with the radioactive Co²¹⁸Re electroplating solution. A current density of 93 A m⁻² was applied for the time calculated by the software program using the radioactivity electroplating efficiency factor as given in figure 5. The plating chamber was then rinsed three times with water (volume equal to the plating chamber size), three times with acid gold solution (volume = 600 µl) and filled with acid gold solution. The stent was finally electroplated at a current density of 35 A m⁻² for 300 seconds with the acid gold solution to give a 1-µm thick gold layer and rinsed with water (volume = plating chamber size) three times before it was taken out for dosimetry measurements.

Testing of the radioactive stents

Stability testing in vitro. To measure how much radioactivity is leaking from the stents after electroplating, one Ultraflex and one Wallstent were placed in a vial containing 3 ml of human plasma (Sigma Chemical Co., St. Louis, MO, USA). At different time points (1 h, 1 d, 3 d, 7 d), the vial with the Co²¹⁸Re-stents was removed from the 37°C shaking water bath and the total radioactivity was measured in a Radcal dose calibrator (Radcal Corp., Monrovia, CA, USA). Two 1 ml aliquots of supernatant were then removed and transferred to clean vials. The activities of the two vials of supernatant were measured using a γ-counter (HP Minaxi Autogamma 5000 counter, Packard, Meriden, CT, USA). The volume of plasma taken from the samples was replaced by adding 2 ml of fresh plasma to the sample vial. The stability of the stent-bound activity was calculated by subtracting from 1 the supernatant activity divided by the total radioactivity at each time point.

Autoradiography of the radioactive stent. The micro-homogeneity of radioactive coating was tested by...
electroplating a 10 × 15 mm Wallstent with 3.7 MBq of 188Re. All wires that the Wallstent is made of were then pulled apart, placed on a storage phosphor screen MP (Packard) and weighed down with a piece of acrylic. After 1 hour in the dark, the autoradiograph was developed using a Cyclone Phosphor Imager (Packard). The analysis was done with Optiquant (Packard) and Image Pro Plus (Media Cybernetics, Silver Spring, MD, USA) software.

Scanning electron microscopy (SEM). Scanning electron microscopy was used to determine the mechanical integrity of the radioactive stent coating after electroplating. The stents were for this purpose mounted onto aluminum studs with double-sided tape and then viewed in a Jeol JSM 5310 scanning electron microscope (Peabody, MA, USA) at an accelerating voltage of 15 kV. The magnification range used to check the stent surface was from 35 to 20 000.

Results and discussion

There exist currently four different methods of making a stent radioactive. In the first method, a metal stent contains a non-radioactive element which can be made radioactive upon neutron bombardment in a nuclear reactor. Stents which have been produced using this method and were tested in the treatment of coronary artery disease (restenosis) were made from iron and cobalt which turned into radioactive 55Co/55Fe [10], contained holmium which produced radioactive 166Ho [11, 12], or contained gold which could be activated into 198Au [11]. The second method of preparing radioactive stents involves the adsorption of a radioactive isotope, either by itself or as part of a chelator, peptide, larger protein or polymer to the surface of a stent. This method has been used for 111In, 90Y, and 188Re [13]. The third method of making stents radioactive is ion implantation and works not only for metals, but also for plastic and polymer stents. In this procedure, the stent surface is bombarded with accelerated radioactive ions, which become embedded deep into the stent surface. Radioactive ion implantation has been used with radioactive 32P [14] and 103Pd [15]. Most clinical studies have been performed with such prepared 32P stents for the treatment or prevention of restenosis (re-occlusion of vessels due to endovascular scar formation) both in coronary arteries [16] and peripheral arteries [17]. The fourth method involves the coating of metallic stents with a radioisotope using electrodeposition [4, 13] and has been tested with the radioactive isotope 188Re in peripheral arteries [18].

The last method, electrodeposition of radioactivity onto stents, is the method we chose for the preparation of radioactive stents for lung cancer treatments. The main reason for this choice is that it gives us the flexibility of making any type and size bronchial stent radioactive on-site with the exact amount of the beta-emitting radioisotope 188Re. Lung cancer patients require the use of individualized, perfectly sized stents with exact amounts of the radioisotope 188Re. This radioisotope has a relatively short half-life of 17 hours and can present a logistic problem, since the radioactive stent has to be placed in a patient within 3 hours of the target time in order to be within the legal limit of 10% from the prescribed dose. Our solution to the logistic problem is to prepare the radioactive stents on site within less than 2 hours, using a radioactive 188Re solution obtained from an on-site 188W/188Re-generator and the automated electroplating system as described in this paper.
Electroplating efficiency factor and concentration limitations for $^{188}\text{Re}$

The electroplating efficiency factor for the radioactive $^{188}\text{Re}$ is of critical importance in preparing radioactive stents with precise and predetermined amounts of radioactivity. In our earlier research, we found that the electroplating efficiency factor for $^{188}\text{Re}$ increased almost linearly with the radioactivity concentration in the solution when a constant electroplating current density was used [4]. When applying this correlation to the preparation of radioactive stents for lung cancer patients, we found that the final stents were always less radioactive than predicted and attributed this effect to the geometry factor. Stents consist of wires crossing each other numerous times, and it seems that the rhenium ions are not deposited as efficiently as onto short straight stainless steel wires.

To be able to predict the deposited radioactivity more accurately, we electroplated a series of stents with $^{188}\text{Re}$ and calculated the electroplating efficiency factor for each of them (figure 5). Using the experimentally determined efficiency factor of $f = 2.79$ MBq/coulomb from the fitted curve in figure 5, we can calculate the plating current and plating time for a target activity. As an example, we would like to electrodeposit a target activity of 44.4 MBq on a stent with a surface area of 0.0005 m$^2$ using a $^{188}\text{Re}$-concentration $R_c$ of 18.5 MBq ml$^{-1}$. The radioactive electroplating time can then be calculated as:

$$f = \frac{R_s}{\text{electricity amount}} \Rightarrow \text{electricity amount} = \frac{R_s}{f}$$

$$= \frac{44.4 \text{ MBq}}{2.79 \text{ MBq/coulomb}} = 15.9 \text{ coulomb}$$

$$I = \frac{\text{Current density} \times \text{surface area}}{93 \frac{A}{m^2} \times 0.0005 m^2} = 0.0465 A$$

$$\text{plating time} = \frac{\text{electricity amount}}{I} = \frac{15.9 \text{ coulomb}}{0.0465 A} = 342 \text{s}$$

We therefore need a plating time of 342 seconds at a current density of 93 A m$^{-2}$ to deposit 44.4 MBq of $^{188}\text{Re}$ on the stent surface.

For optimal electroplating results, it is necessary to work under set conditions. The Co/$^{188}\text{Re}$ concentration should be kept in our experimental range (from 10 to 50 MBq ml$^{-1}$). Furthermore, the total radioactivity in the plating chamber should be at least 10 times the target stent activity, thus avoiding large concentration changes during the electroplating process.

By staying within these conditions and applying the empirically found efficiency factor shown in figure 5, several radioactive stents were prepared. The difference between targeted and measured activity of the stents was $\pm 7\%$ (figure 6), which is within the targeted 10% and would allow the use of these $^{188}\text{Re}$-stents in lung cancer patients.

Stent appearance and mechanical stability

The electroplated stents were of golden colour (figure 7), with a smooth surface, as confirmed by scanning electron microscopy (figure 8). No bridging between adjacent wires could be seen. Mechanical tests of extending and compressing the stents did not lead to surface defects, chipping, cracks, or holes in the coating. Furthermore, the crossing points of the stent wires did not show any wear. We further tested what would happen when the coating was damaged with a razor blade. The electroplated layers could be removed by this method, but no peeling occurred at the edges (figure 9). The adhesion between the electroplated layers and the base metal thus seems just as strong as the adhesion among the electroplated layers themselves. This stability is important for human use, because broken off particles can be toxic, in addition to unwanted radiation effects in non-cancerous tissue.

Stability of stent bound radioactivity

Although the radioactive rhenium has been co-deposited with cobalt and covered with a gold layer, $^{188}\text{Re}$ might still leak into the blood and other body fluids. In vivo, this radiation leakage must be kept to a minimum, because the radioisotope might reach healthy cells farther away that do not need to be irradiated. We investigated the level of leakage in blood plasma at 37 $^\circ$C (figure 10). The Wallstent released less radioactivity into the plasma and retained 99.4% after 72 hours, as compared to the Ultraflex stent which retained about 96% at that time point. The difference might be due to differences of cobalt/$^{188}\text{Re}$-layer thickness (2.6 times thicker on the Wallstent than on the Ultraflex stent). Both types of stents, however, showed levels of stability that would be sufficient to be used in a cancer patient, based on the levels of unbound radioactivity allowed in current radiopharmaceuticals.

![Figure 6. Comparison between measured and targeted stent activity (n = 4).](image-url)
Radioactivity distribution on stent

The measured radiation doses (or dose rates) from the dosimetric surface scan of the $^{188}$Re-stent is evaluated graphically and will become part of the documentation for each patient. Around the stent, the measured radiation doses should ideally be identical, independent of the angle. The radiation doses increase from the stent’s edge, where we theoretically measure 50% of the maximum, to the nominal dose within the next 5 mm. Furthermore, the dose distribution along the length of the stent should be uniform. As shown in figure 11, this is true along the axis within...
Higher resolution measurements are possible by autoradiography measurements and have been used to evaluate the $^{188}$Re microdistribution on the single wires which make up a Wallstent. Figure 12 shows a quite uniform radioactivity distribution. Having the wires directly touch the phosphor screen avoids measurement errors and should thus reflect the reality most closely. The wires cannot be combined back into a stent, and this destructive method is thus only useful for developmental purposes. Autoradiography thus further confirms that the radioactivity coated on the radioactive stents by our technique is uniform.

Figure 11. Surface plot of a 46.88 MBq $^{188}$Re-Wallstent (10 $\times$ 30 mm) measured with the Optidos system. The 'box' on the purple back wall indicates the placement and true length of the stent.

Figure 12. Homogeneity of the radioactive coating on single wires of a 10 mm diameter Wallstent electroplated with 3.70 MBq of $^{188}$Re, as measured by autoradiography.

Conclusions

$^{188}$Re radioactive stents (Wallstent and Ultraflex stents) were prepared using an electrodeposition technique. The radioactive layer on the stents showed good physical strength, appropriate in vitro stability, and uniform radioactivity distribution. A specifically developed automated electroplater enabled precise control of the electroplating procedure and facilitated the documentation of the radioactive stent preparation information. The developed dosimetry tower system provided a way to check the surface radioactivity distribution of the radioactive stents and document it for the treatment of patients. The radioactive stents prepared with this system are currently undergoing in vivo testing and will then be evaluated clinically in patients with inoperable lung cancer.

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