Dosimetry of a $^{188}$rhenium-labeled self-expanding stent for endovascular brachytherapy in peripheral arteries

Bernd Nowak, Julius M.A. Meyer, Thomas Goergen, Dirk Fluhs, Stephan Block, Rolf W. Guenther, Hartwig Hoecker, Udalrich Buell

Department of Nuclear Medicine, Aachen University of Technology, Pauwelsstrasse 30, 52074 Aachen, Germany
Department of Diagnostic Radiology, Aachen University of Technology, Pauwelsstrasse 30, 52074 Aachen, Germany
Department of Textile and Macromolecular Chemistry, Aachen University of Technology, Pauwelsstrasse 30, 52074 Aachen, Germany
Division of Clinical Radiation Physics, Essen University Hospital, Hufelandstrasse 55, 45127 Essen, Germany

Received 8 May 2002; accepted 15 May 2002

Abstract

Purpose: Radioactive stents have been proposed as endovascular irradiation device to prevent in-stent restenosis by inhibiting neointimal proliferation. $^{32}$P-stents have been used in several studies so far, but require large-scale labeling procedures and endovascular barotrauma for stent expansion supporting the development of edge restenosis. Purpose of this study was to establish dosimetry of a self-expanding nitinol stent for peripheral vascular disease, which was radiolabeled with $^{188}$rhenium ($^{188}$Re) by a dip coating technique.

Methods and materials: The surface of nitinol Memotherm FLEXX stents was polymer-coated providing functional NH$_2$ groups for diethylenetriaminepentaacetic acid (DTPA) binding, providing the ligand for the complexation of $^{188}$Re onto the stent surface. Stability of radiolabeling was tested over 48 h using an in vitro blood circulation (Chandler Loop). Radial and longitudinal dose distributions of a radiolabeled stent were obtained with a plastic scintillator dosimetry system.

Results: Stents with a length of 30 mm and a diameter of 8 mm were labeled with up to 33 MBq $^{188}$Re. A total of 69 ± 4% of the labeled $^{188}$Re remained stable on the stent surface after 48 h. Ninety-five percent of the infinitely accumulated dose was supplied to the target tissue within 72 h. Including correction for radioactivity washout from the stent, the infinitely accumulated dose at 1 mm radial distance from the stent surface was 1.85 ± 0.19 Gy/MBq/cm stent length.

Conclusions: We developed a technique for radiolabeling of self-expanding nitinol stents with $^{188}$Re by dip coating and formation of $^{188}$Re chelate complexes. We provide dosimetry data useful for application of this $\beta$-emitting stent for endovascular brachytherapy in peripheral vascular occlusive disease.

1. Introduction

Stent placement is an accepted treatment for peripheral vascular occlusive disease [1,2]. However, long-term success of this procedure is still limited by development of chronic in-stent restenosis due to neointimal hyperplasia, which occurs in up to 40% of all patients who received stent placement in peripheral arteries [3]. Proliferation and migration of media and adventitia derived vascular smooth muscle cells responding to the initial vascular injury are thought to represent the pathophysiological correlate of this formation of vascular neointima [4–6].

It has been demonstrated in animal models and clinical studies that endovascular irradiation reduces restenosis in coronary and femoral arteries [3,7–14]. Different irradiation techniques have been proposed, including brachytherapy with radioactive sources applied intravascularly after stent implantation, external beam irradiation or the use of radioactive stents [3,7,8,10,15–18]. Most trials investigating radioactive stents so far have been performed using $^{188}$Re.
32P as pure radioactive $\beta$-emitting agent [16,17,19,20]. At 6-month follow-up in 82 patients treated with coronary stainless steel $^{32}$P-stents with stent activities ranging from 0.75 to 12 $\mu$Ci, a dose-related reduction of pure intrastent neointimal hyperplasia was observed [21].

However, two potential limitations of radioactive 32P-stents may hinder their future widespread application: First, their large-scale radioactive labeling procedure lasts several days and requires a cyclotron for neutron irradiation of red amorphous phosphorus ($^{31}$P), as well as a mass separator to separate $^{31}$P and $^{32}$P [16]. Second, balloon inflation at high pressures is necessary for expansion of stainless steel stents resulting in marked vascular injury and supporting the development of edge restenosis, which has been shown to occur frequently in $^{32}$P radioactive $\beta$-emitting stents [21].

To overcome these limitations, we developed a method, which allows radioactive stent labeling with the $\beta$- and $\gamma$-emitting isotope $^{188}$rhenium ($^{188}$Re) by dip coating within 2 h. As self-expanding stents are proposed to minimize vascular injury [22], we decided to use nitinol Memotherm-FLEXX stents. The purpose of this study was to evaluate stability of our radioactive labeling technique and to obtain dose distributions of a $^{188}$Re-labeled nitinol Memotherm-FLEXX stent using plastic scintillation detectors.

2. Methods

2.1. Stent description

The brachytherapy source consisted of a nickel–titanium alloy (nitinol) stent activated with $^{188}$Re (Memotherm-FLEXX vascular stent, Bard International Products, Billerica, MA). This stent is composed of 55% nickel and 45% titanium. It is formed as a one-segment nickel–titanium cylinder. The pre-expanded nominal length is 30 mm with an outside diameter of 1.9 mm mounted on a 7F deployment catheter for delivery. The expanded nominal diameter at body temperature is 8.0 mm. The final diameter of the stent is determined by the diameter of the artery.

2.2. Radiolabeling (stent activation process and properties)

The principle of the radioactive labeling procedure was as follows (Fig. 1): First, surface coating of the nitinol stent by chemical vapour deposition (CVD) polymerization was performed to create a new polymer surface, which provides NH$_2$ groups for covalent immobilization of a chelating agent. The CVD polymerization process was developed to improve surface biocompatibility of medical devices [23, 24]: Polymerization of 4-amino-[2.2]-paracyclophane to

---

Fig. 1. Principle of the radioactive labeling procedure with $^{188}$Re. CVD polymerization of the stent surface creates functional NH$_2$ groups. Covalently immobilized DTPA acts as chelating agent for $^{188}$Re.
form poly(amino-p-xylylene) directly onto the stent surface was performed using a self designed CVD installation. The pyrolysis of the 4-amino-[2.2]-paracyclophane was carried out in a glass tube of 320 mm length. The first 120 mm served as sublimation zone (220 °C, 0.2 mbar), followed by a 240-mm section as pyrolysis zone (750 °C, 0.04 mbar). The pyrolysis tube was connected to the stainless steel polymerization chamber, which was equipped with a rotatable cooled sample holder. CVD polymerization yielded a completely closed polymer layer of about 50-nm thickness on nitinol stents. Integrity of the polymer layer was not affected by loading and expanding procedures of the stents, as determined by scanning electron microscopy.

After reaction of the amino groups with hexamethylene-diisocyanate (HDI) as a spacer, diethylenetriaminepentaacetic acid (DTPA) as chelating agent was immobilized. This surface coating was performed prior to the radioactive labeling procedure.

188Re-perrenenate ($t_{1/2} = 16.98$ h) as radiation device was chosen due to its superior physical characteristics. The high-energy $\beta$-radiation ($E_{\beta_{\text{max}}} = 2.12$ MeV) is therapeutically effective and the $\gamma$-radiation of 155 keV (15.8%) allows imaging with conventional gamma cameras. 188Re-perrenenate was eluted with 0.9% saline carrier-free from an alumina-based 188Re/188W generator (Oak Ridge National Laboratory, Oak Ridge, TN, USA). Inclusion of a 0.20-μm Minisart filter (Sartorius, Goettingen, Germany) ensured trapping of any alumina fines or other particles, which may be eluted from the generator. An in-line alumina SepPak (CS-Chromatographie, Germany) trapped the low levels of 188W breakthrough ($< 10^{-6}$/bolus) [25]. Radiochemical impurities of this generator system have been reported to be $< 0.00125\%$ for 191iridium and $< 0.00025\%$ for 191osmium [25].

The solution for the complexation of 188Re onto the stents consisted of 4-ml 188Re-perrenenate in 0.9% saline (200 MBq ml$^{-1}$), 80-mg SnCl$_2$·2H$_2$O and 16-mg Natrarate in 1 ml of water and 50 μl of aqueous Na-acetate solution (100 mg ml$^{-1}$). Stents were incubated in this solution for 120 min at 85 °C and washed four times in 20 ml of 0.9% saline. Radioactivity of the labeled stents was measured with a calibrated radioisotope calibrator CRC-15R, Capintec, Ramsey, NJ, USA.

### 2.3. The plastic scintillator dosimetry system

The dose distribution for the radioactive stent was measured in a water phantom using plastic scintillation detector coupled to an optical fiber conveying the scintillation light to a photomultiplier tube [26]. The detectors had a diameter of 1 mm and a thickness of 1 mm. This dosimetry system allows the three-dimensional measurement of the dose distributions in water of $\beta$-sources, appropriate for the application in the cardiovascular brachytherapy.

The scintillator dosimeter system was absolutely calibrated in terms of absorbed dose rate to water with a precision of $\pm 15\%$ (2 S.D.) at the National Institute of Standards and Technology (NIST). The relative precision achievable is $\pm 2.5\%$. The response of the system is linear within $\pm 2\%$ for dose rates from 0.5 mGy s$^{-1}$ to 500 mGy s$^{-1}$. The dosemeter calibration can be controlled by means of a 90Sr-source of which the absolute dose rate distribution was also determined at the NIST [27]. This system fulfills the requirements for dosimetry of cardiovascular brachytherapy sources published by the Task Group 60 of the American Association of Physicists in Medicine (AAPM).

### 2.4. The set-up for the dosimetry of a radioactive stent

To prevent the risk of possible radioactive contamination of the detector, the radioactive stent was welded into a plastic tube with a wall thickness of 0.05 ± 0.005 mm. The water-equivalent plastic consisted of polyethylene-terephthalate (BOPET) and polypropylene with a density of 1.04 g cm$^{-3}$. The stent was positioned at the bottom of a water phantom by fixing the ends of the plastic tube. Fig. 2 shows the water phantom with a Memotherm stent and the plastic scintillator in position.

### Table 1

Mean dose rates of a 13-MBq 188Re Memotherm stent (8 × 30 mm) at various radial distances from the stent surface

<table>
<thead>
<tr>
<th>Radial distance from stent surface (mm)</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>2.5</th>
<th>3.0</th>
<th>3.5</th>
<th>4.0</th>
<th>4.5</th>
<th>5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose rate (Gy/h)</td>
<td>0.664</td>
<td>0.445</td>
<td>0.298</td>
<td>0.195</td>
<td>0.128</td>
<td>0.082</td>
<td>0.053</td>
<td>0.033</td>
<td>0.020</td>
<td>0.011</td>
</tr>
<tr>
<td>± S.D.</td>
<td>0.074</td>
<td>0.047</td>
<td>0.032</td>
<td>0.022</td>
<td>0.015</td>
<td>0.009</td>
<td>0.005</td>
<td>0.003</td>
<td>0.002</td>
<td>0.001</td>
</tr>
</tbody>
</table>
A two-dimensional dose distribution was based on matrix spacing 1 mm in both directions. This matrix consisted of line measurements parallel to the stent axis at depths between 0.5 and 9.5 mm from the stent surface. The dose at a total number of about 400 measuring points was hence determined for a matrix length of 40 mm. At a single measuring point, the detector signal was integrated for a mean time of approximately 9 s in order to obtain a sufficient measuring accuracy of 3–5% within the β-range. As a cross check, also a depth dose curve, i.e., a linear dose profile in radial direction at the mid position of the stent, was measured.

To position the detector accurately in direction of the stent diameter (x direction), it was carefully moved towards the surface of the plastic tube up to the contact point, which was then defined as zero position. In the two other directions (y, z), an overview measurement of the linear dose distribution was performed. The zero position was determined by the mean of the position values with 50% dose fall-off, i.e., the symmetry axis of these distributions.

2.5. Stability testing of the system in blood contact (Chandler Loop)

Stability of radiolabeling was tested using an in vitro blood circulation (Chandler Loop, Fig. 3). Five radiolabeled stents (30 mm in length with a diameter of 8 mm) were expanded in plastic rings of 20 cm diameter and inner luminal diameter of 7 mm. The rings were filled with heparinized human blood (10 ml/ring) and mounted on a rotating device. Pulsating forward and backward rotations of 120° with 60 rotations min⁻¹ were performed in a heated chamber (37 °C) for 48 h. During these rotations the stents were continuously covered with blood.

The plastic rings were placed on the collimator of a gamma camera (Multispect-3, Siemens, Erlangen, Germany) after 1, 4 and 48 h to measure radioactive washout from the stent in the blood. During acquisition the head of the gamma camera was rotated in a slight oblique position (10° rotation from the horizontal plane) to ensure separation of the fixed stent on the upper side of the ring and blood on the lower side of the ring. Acquisition parameters were as follows: High-resolution collimator, matrix 256 × 256, zoom 1.0, photopeak 155 keV (energy window width 15%), acquisition time 15 min. Using regions of interest, the relative remaining stent activity as indicator of radioactive washout was calculated by comparison of the total counts of the stent (cts(stent)) and blood (cts(blood)):

\[
\text{Remaining stent activity (\%)} = \frac{\text{cts(stent)}}{\text{cts(stent)} + \text{cts(blood)}} \times 100\%
\]

3. Results

3.1. Radiolabeling

After radiolabeling in a solution with 200 MBq ml⁻¹ ¹⁸⁸Re-perrhenate and washing procedure 16–18 MBq of ¹⁸⁸Re were fixed onto the surface of the stents. Due to
physical decay, the radioactivity of the stent was 13 MBq when dosimetric evaluation was performed. Radiolabeling in a higher concentrated solution with 400 MBq ml\(^{-1}\) \(^{188}\)Re-perrhenate yielded stent activities of 30–33 MBq \(^{188}\)Re. A total of 97.3 ± 1.4% of the radiolabeled \(^{188}\)Re remained stable on the stent surface after washing for 24 h in 0.9% saline.

3.2. Dosimetry

Fig. 4 demonstrates two-dimensional dose rate profiles measured along the long axis of a Memotherm stent labeled with 13 MBq \(^{188}\)Re. Dose rate profiles at various radial distances ranging from 0.5 to 5.0 mm from the stent surface are shown. Stent struts are reflected by the wavy dose rate profile at 0.5 mm distance. With increasing distance rather uniform dose rates are delivered to the target tissue. Dependent on the radial distance from the stent surface mean dose rates (± S.D.) were as demonstrated in Table 1. At all radial distances, approximately 94% of the soft tissue mass in the respective radial distance received between 80% and 120% (± 2 S.D.) of the given mean dose rates.

Infinite integration of the dose rate at 1 mm radial distance is shown in Fig. 5 for the 13 MBq stent. Due to the physical half-life time of \(^{188}\)Re (16.98 h), 95% of the accumulated dose was delivered to the target tissue within the first 72 h. After an infinite time interval, a mean dose of 10.84 ± 1.14 Gy was supplied to the soft tissue at 1 mm distance from the stent surface.

Transfer of these washout data to the physical radioactive decay resulted in the washout corrected effective decay of the labeled \(^{188}\)Re as shown in Fig. 8. Data of the time points 12 and 24 h were interpolated. Integration of both decay curves revealed that the washout of labeled \(^{188}\)Re was responsible for a 26% reduction of the theoretically calculated dose.

The accumulated doses at various radial distances from the stent surface — calculated as dose supplied per MBq \(^{188}\)Re per cm stent length with and without correction for washout — are summarized in Table 2. Including the correction for washout, a stent labeled with 30 MBq \(^{188}\)Re was calculated to supply 18.5 ± 1.9 Gy to the vessel wall at 1 mm distance from the stent surface.

4. Discussion

4.1. Dosimetry

Endovascular brachytherapy in coronary and peripheral vascular disease using different types of irradiation techniques has been shown to be effective for the prevention of neointimal hyperplasia following percutaneous transluminal angioplasty and intravascular stent placement [28,29]. Intraluminal irradiation with 12 Gy applied to the vessel wall using an \(^{192}\)Ir source after sufficient angioplasty and stent placement in 40 patients suffering from peripheral arterial occlusive disease was performed by Liemann et al. [30]. After a follow-up period ranging from 4 months to 7.5 years in 33 out of these 40 patients, there was no deterioration of
the clinical stage and no restenosis [30]. A significant reduction of restenosis rate 6 months after intraarterial 
192Ir brachytherapy (12 Gy) following femoropopliteal percutaneous transluminal angioplasty was observed in the Vienna-2-trial comprising 113 patients [31].

As our radioactive stent supplies 1.85 ± 0.19 Gy/MBq 
188Re/cm stent length to the vessel wall in 1 mm depth, a stent with 30 mm in length and 8 mm in diameter needs to be labeled with 30 MBq 
188Re to apply a mean dose of 18.5 Gy. Our radiolabeling procedure turned out to be sufficient to fix this amount of 
188Re onto the stent surface and therefore provides an applicable tool for endovascular brachytherapy.

Endovascular stents for peripheral arteries usually measure 5–10 mm in diameter. Our dosimetric results show that at 5 mm distance from the stent wire only 0.04 ± 0.01 Gy/MBq 
188Re/cm stent length are supplied (2% of the dose supplied at 1 mm distance). This means that there is negligible contribution of the stent wire across the vessel to the therapeutic dose delivered to the opposite vessel wall. Therefore, our dosimetry of the 8-mm stent can be transferred to 5–10-mm stents with negligible errors in dosimetry.

Our dose measurements predict that although peaks in the dose distribution are observed in areas adjacent to the stent wire as reflection of stent geometry, a relatively uniform dose can be delivered to the target tissue of the media and adventitia. This feature is essential to yield therapeutic effects for the inhibition of smooth muscle cell proliferation responsible for neointimal hyperplasia.

4.2. Edge restenosis

Stent-edge re-narrowing occurs after conventional stent implantation [32]. After radioactive stenting, a visual gradient at the extremities becomes apparent, called the “candy wrapper” effect [22]. The pathophysiology of this edge restenosis might be explained by effects secondary to low-dose radiation at the margin of the stent, or due to balloon injury at the stent edges, or a combination of both [22]. High-dose irradiation using 12–21-μCi 
32P-labeled radioactive coronary stents did not reduce the edge restenosis, which occurred mainly due to remodeling [33], whereas edge restenosis in 3–12-μCi 
32P coronary stents was mainly due to tissue growth [21].

Several aspects let us believe that this “candy wrapper” problem might be less severe in our radioactive stent for peripheral arteries: First, aggressive stent placement strategies with high pressure balloon inflation are being discussed to support development of edge restenosis (“geographic miss”) [22]. Our self-expanding stent allows implantation while eliminating barotrauma beyond the stent edge, thereby preventing “geographic miss” [34]. Second, 
\[ E_{\text{max}} \] of 
188Re (2.12 MeV) used for our stent is higher than that of 
32P (1.71 MeV) used in other trials and therefore ensures greater reach of the β-radiation, which diminishes the effect of low-dose radiation at the margin of the stent [35]. Third, in a large trial using 
32P coronary stents [21], apart from a high balloon-to-artery ratio (as indicator of an aggressive approach to stenting), a small vessel size was the only predictor of edge restenosis. This favours the chance that in general edge restenosis may play a less important role in larger peripheral arteries than in smaller coronary arteries.

Furthermore, up to now, edge effects have been described for 
32P-stents only. However, proportions of doses and dose rates supplied by 
32P and 
188Re differ particularly due to their extremely different half-life times of 14.3 days and 16.98 h, respectively. As dose rate may play a critical role in the efficacy of endovascular irradiation [36,37], it is not imperative that edge effects observed with 
32P-stents will occur in the same dimensions when using 
188Re-stents. It is of no doubt that these theories have to be confirmed in animal studies using our stent.

4.3. Radioactive washout — radiation exposure

We have demonstrated that approximately 31% of the originally labeled 
188Re were released from the stent within 48 h. This rises the question of radiation exposure to the patient resulting from this released radioactivity. Kotzerke et al. [38] performed dosimetric evaluations after intravenous application of 
188Re-perrhenate in humans. Based on MIRD Dose Estimate Report No. 8, assuming the kinetic model for 
99mTc-pertechnetate, the authors calculated an effective dose equivalent of 0.42 mSv MBq
−1 
188Re-perrhenate, which decreased to 0.16 mSv MBq
−1 after oral administration of 600-mg perchlorate. Therefore, a therapeutically effective stent labeled with 30 MBq would release approximately 9.3 MBq resulting in an effective dose equivalent of 3.91 mSv without and 1.49 mSv with accompanied administration of perchlorate. Both effective dose equivalents are within the range of dose equivalents of usual diagnostic nuclear medicine procedures and far below the dose equivalents of angiographic procedures required for stent implantation.

4.4. Delayed endothelialization

Radioactive stents have been accused to cause delayed endothelialization with the consequent risk for late thrombosis [39]. Recently, several investigators proposed prolonged courses of antiplatelet agents to avoid the thrombotic sequelae of late endothelialization in patients treated with radioactive stents [21], as well as in patients treated with endoluminal brachytherapy sources in combination with stents [40,41].

5. Conclusion

We developed a polymer-coated vascular stent which can be labeled with 
188Re by means of dipping and formation of stable chelate complexes. The labeling procedure can be performed at the site of stent implantation and overcomes
the limitation of $^{32}$P-stents, which have to be produced in advance and have to be shipped to the angiography lab. Dosimetry proves that therapeutic effective doses can be delivered to the vascular wall by this radioactive stent and that radioactive burden caused by radioactive washout from the stent is low and within the range of diagnostic nuclear medicine procedures.

Acknowledgments

The authors thank Michael Kohnen for data processing. This study was supported by the interdisciplinary center for clinical research in biomaterials and tissue–material interaction in implants (BMBF project no. 01/KS 9503/9).

References


