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Ion-implantation and characterization of ^{32}P-radioactive platinum coils for endovascular treatment of intracranial aneurysms

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Abstract

We produced and measured over 800 ^{32}P-ion-implanted coils for pre-clinical and clinical studies. Platinum coils are intravascular implants most frequently used in the treatment of intracranial aneurysms. This less invasive endovascular approach is safer than conventional surgery, but a frequent drawback is the recurrence of the aneurysm, associated with recanalization, a phenomenon that can be inhibited by the local application of beta radiation. Total coil activities, uniformity, reproducibility and ^{32}P binding to platinum were determined and found to be adequate for this application.

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Keywords: ^{32}P; Beta radiation; Aneurysm; Ion-implantation; Endovascular brachytherapy

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1. Introduction

Aneurysms are abnormal, outward dilatations of arteries most often related to a weakness of their walls. Intracranial aneurysms are present in 1–5% of the adult population. Their rupture, which remains unpredictable, causes an intracranial hemorrhage, an event that occurs in 28 000 patients per year in North America [1,2]. Aneurysms have been treated by surgical clipping for many years but a minimally invasive endovascular alternative exists since 1991 [3]. The endovascular approach uses catheters introduced through the femoral artery to reach and occlude the aneurysm with small calibre platinum wires or coils. The goal of treatment is to pack the aneurysmal sac as completely as possible with multiple coils of various sizes, shapes and lengths. A randomized trial comparing surgical and endovascular treatments has shown that patients had a significantly better chance of surviving without disability when they were treated using platinum coils [4]. Despite this immediate advantage, coils are still underused as compared to surgery, mainly because recanalization of occluded aneurysms, as shown by imaging studies, can occur in the following months or years in 10–30% of patients [5]. These recurrences may necessitate retreatment or may lead to intracranial bleeding in 0.1–1% of patients [4,5].

Recanalization after coil occlusion can be reproduced in animal models, and beta radiation emitted from ^{32}P impregnated coils can reliably inhibit recanalization in such models [6,7]. The choice of ^{32}P is made because of its half-life (14.3 days) and because it is a pure beta emitter. The average and maximum range of the emitted electrons in water are a few mm and 0.76 cm, respectively. A number of methods can be used to impregnate the coils with radioisotopes [8–10]. Among those methods, we have used direct ion-implantation of ^{32}P because it can produce devices emitting pure beta radiation with, at least theoretically, minimal in vivo leaching of radioactive material, while

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preserving the coil mechanical characteristics essential to the safety of treatment.

In this paper, we report on the methods we have used to produce and characterize ^{32}P-ion-implanted platinum coils.

2. Materials and methods

2.1. Platinum coils

The platinum coils were made from a platinum–tungsten alloy wire. They come in various shapes and lengths to conform to the aneurysm morphology. Coils were selected for their wire gauge or thickness (0.010–0.015 in.), helical diameter (2–20 mm) and length (1–30 cm). An example is shown in Fig. 1.

Each coil was attached to a 145 cm long stainless steel delivery wire until it is detached, using an electrical current, into an aneurysm.

2.2. Description of the ion implanter

The ion beam accelerator and facilities are located at the Rene J.A. Levesque Laboratory of the Université de Montréal. For considerations regarding safety, and to prevent any radioactive contamination, a dedicated ion implanter was designed and built, to allow for the production and transport of the radioactive beam. The principal sections of the 75 keV implanter are: a Middleton type, cesium sputtering negative ion source that produces negative ions from a solid copper cathode containing ^{32}P, a beam focusing and shaping section which comprises an Einzel lens, magnetic beam deflectors and an $E \times B$ ion mass selection filter, and an acceleration section. Once the ions reach their final energy of 45 keV, a second magnetic deflector and electrostatic raster scanner direct the beam towards the implantation chamber where the platinum coils are mounted and pumped to 10^{-3} Pa. Behind the coil-holder, and visible only in the absence of coils, sits a Faraday cup, used to measure and optimize the ion beam current.

A plastic scintillator coupled to a photo-multiplier tube with appropriate electronics is mounted in the vacuum chamber, in the line of sight of the target to provide real-time monitoring of the amount of ^{32}P-ions transported from the source to the target.

2.3. Ion source preparation and implanter optimization

Ortho-phosphoric acid of 100% ^{32}P was obtained from Perkin–Elmer (Woodbridge, Ont., Canada). Typically 25 mCi was diluted in water and radioactive cathodes were prepared by pipetting the acid solution into a hole drilled in each of the copper cathodes, and allowed to dry prior to use.

It was not possible to adjust the implanter parameters by using the electrical current of the ^{32}P beam. The amount of radioactive material is small; only 1 nM of ^{32}P was deposited on the cathode, and the efficiency of the source in producing negative ^{32}P-ions was in the order of 1/1000. The ^{32}P beam current, in the pA range, is also masked by other ion beams at the same M/q ratio (O_2^- and possibly Cu^{2-}) and thus extremely difficult to optimize. Therefore, we used a non-radioactive ^{28}Si beam to adjust the implanter's parameters as follows: A non-radioactive cathode containing a pure silicon powder was inserted into the source. This cathode material produced a beam of H^- and $^{28}Si^-$-ions, depending on the settings of the mass filter. With the mass of the H selected, all parameters were optimized according to the H current measured on the Faraday cup at the target. A current of tens of nA was consistently recorded at this point. The mass selection filter was then adjusted to silicon-28 and a beam of a few micro-amps was measured. The parameters were re-optimized, using two magnet currents corresponding to the magnetic beam steerers. Lastly, a raster scanning of the beam over the surface to be implanted was adjusted, by sweeping the beam through an aperture of the size corresponding to the target surface and measuring the current on the edge of the aperture. Since the raster scanner is electrostatic, the scan width is mass-independent. At this point, the magnetic settings (steerers and mass filter) were adjusted for ^{32}P production and transport. A radioactive cathode containing the ^{32}P salt was loaded into the source of the implanter. The coils to be implanted were loaded in the target section and the high voltage was switched on without making any further beam adjustments.

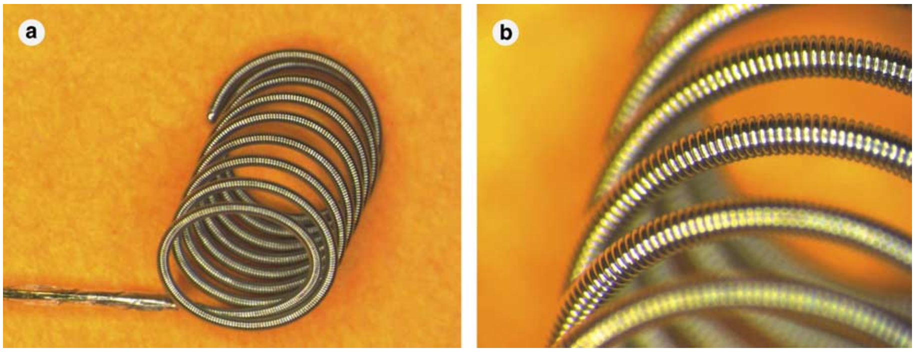

Fig. 1. Close-up view of wire showing (a) helical structure and (b) gauge.

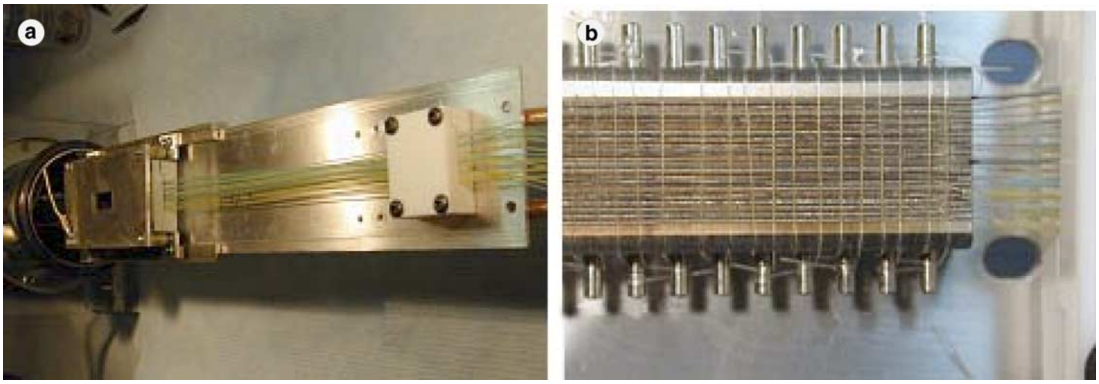

Fig. 2. (a) Coils mounted in their support in its vacuum tube. (b) Close-up view of the coils inserted in grooves with the retaining piano type wire.

2.3.1. Description of the coil support

Treatment of an intracranial aneurysm may necessitate the use of 2–40 coils of multiple sizes and shapes. Coils are fragile and expensive. A special coil support that would allow the simultaneous implantation of multiple coils of various sizes and shapes, all attached to 175 cm long delivery wires, had to be designed. The configuration of the support should minimize coil damage during manipulations and expose a high number of coils per surface area to maximize the efficiency of implantation.

The design of the coil support is shown in Fig. 2. It consists of a stainless steel plate with multiple parallel grooves 0.015 in. wide and interspersed by 0.010 in. walls machined to high accuracy to insure a smooth insertion of coils into the grooves. Platinum coils are maintained straight, uncoiled, in a plane perpendicular to the beam. During the mounting step, the coils were slid into their respective groove and retained by fine piano type wires placed perpendicularly to the grooves. One 30 cm coil or two 15 cm coils were mounted in each groove. A maximum of 40 coils (total length: 600 cm) can be implanted simultaneously. This support is mounted on a mobile system that allows traveling for up to 30 cm with respect to the center of the vacuum tube. An aperture delimiting a surface of 1×6 cm was used in front of the coil support and the rastering of the radioactive beam in the X–Y plane was adjusted accordingly. To permit implantation along a length of 30 cm, the coil support was moved successively 5 times, 6 cm at a time, in the coil direction with respect to the center of the aperture. At each position, implantation took place until the pre-defined level of activity was reached using the in situ beta counting system.

2.4. Activity measurements

2.4.1. Total coil activity

The total activity of each radioactive coil was measured (ex situ) with a 40 cm long plastic scintillator BC-400 (Bicron, Newbury, OH) in a well type geometry coupled to a photo-multiplier tube. The coil was slid into the well inside the plastic scintillator and counted for a period of time. To correct for detection inefficiency and discriminator threshold, a calibration factor was used to convert to an absolute activity measurement. This factor was obtained by comparing the count rate obtained with the plastic scintillator to the count rate obtained from a liquid scintillation counter (Canberra-Packard Tri-Carb Model 2100) which is nearly 100% efficient for ^{32}P counting.

The measured activity for a number of gauge 10 and gauge 18 coils of different length and ion implanted at the same time is shown in Fig. 3 as a function of coil length. The results for the 10 gauge coils were normalized to account for the smaller surface area. The dashed line represents a linear fit showing that the linear activity of these coils is, on average, 0.23 μCi/cm. The vertical spread of the data points corresponds to coil-to-coil variations in received activity.

2.4.2. Measurement of implantation uniformity

A stainless steel rod was used alongside the coils to monitor the implantation uniformity, because it is believed give a better impression of the performance of the raster scanning system. Coils, when stretched out as required for the

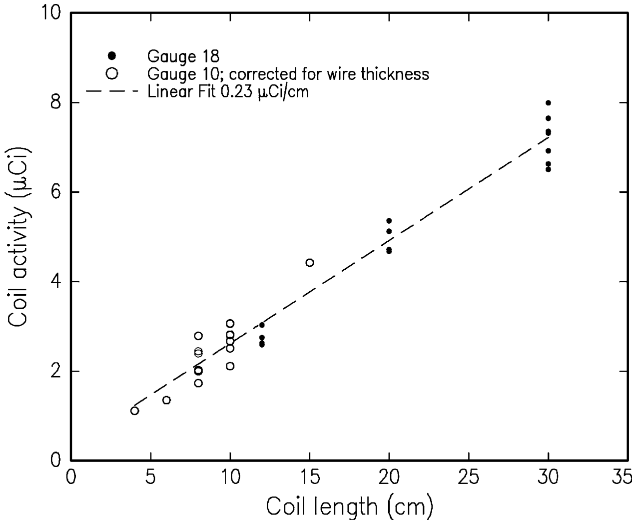

Fig. 3. Total coil activity for coils of different lengths. Activities measured on gauge 10 coils have been normalized to gauge 18.

uniformity measurements, have a tendency to twist and since only one side was implanted, this may lead to apparent non-uniformity along the coil's length.

A beta detection system with spatial resolution was built to measure the uniformity of implantation of ^{32}P along. It consists of four surface barrier silicon detectors with their associated electronics disposed symmetrically around the principal axis of the object. The detectors were individually shielded by 5 mm thick Plexiglas. A slit 2 mm wide and 10 mm long machined in the Plexiglas was placed in front of each detector to limit the radioactive area being counted. The detector assembly was mounted on a computer controllable *x*-table that can be moved over the entire object length. A uniformity measurement was performed by moving the detector assembly in successive steps along the object length and recording at each step the number of beta disintegrations going through the slit. We routinely scanned objects with a step of 2 mm and a collimator width of 2 mm. A typical uniformity measurement of a 30 cm stainless steel rod is shown in Fig. 4. The 60 mm wide regions marked I–V correspond to the stepping intervals used during implantation. The inset shows a scan along a rod which had received a single irradiation, i.e. no interval stepping. The single-implant rms uniformity is well within 5%. The rms uniformity along the entire 30 cm coil length, disregarding 1 cm on each extremity, amounted to 10%. When deployed, the coils will be curled up in a volume of a few mm diameter, a size which is comparable to the mean range of the electrons emitted by the radio-isotopes. Therefore, the uniformity of the irradiation field during aneurysm treatment is not expected to be adversely affected by such a 10% variation.

2.4.3. Estimation of the efficiency of the implanter

A typical implantation session required 150 mCi of ^{32}P pipetted into 12 cathodes to implant 600 cm of coils with an activity of 0.26 μCi/cm. Thus the overall efficiency is in the 0.1% range. Typically half of the ^{32}P was not sputtered by the cesium and remained on the copper cathodes, and half remained in the source region.

2.5. Assessment of loss of ^{32}P from radioactive coils

The release of ^{32}P from the coil was evaluated both in vitro and in vivo. In vitro, 14 coil pieces were sonicated in a saline bath for up to 5 h using a temperature at start-up of 37 °C. The coil pieces and a sample of the elution were measured using a liquid scintillation counter before and after sonication. After 60 and 380 min of sonication the mean loss amounted to $2.0 \pm 0.9\%$ and $5.2 \pm 0.9\%$ respectively. For sonication times greater than 30 min the bath temperature rose to 50 °C due to the energy supplied by sonication. The activity loss as a function of sonication time for a number of coil pieces is shown in Fig. 5. The non-zero values at 0 sonication times correspond to activities measured in the scintillation liquid after the coils had been immersed for the first time. Most of the loss occurs during the first 20 min. The small loss at longer times is tentatively attributed to erosion of the Pt coils themselves under the energetic sonication. (The depth distribution of implanted ^{32}P-ions along the curved surface of the coils is such that 2% of the radioisotopes comes to rest within 12 Å of the outer surface even if sputter erosion during the irradiation is not taken into account.) Fig. 5 also shows an anomalously large loss from one coil piece after more than 100 min. This particular value was omitted in the calculation of the average loss.

The activity loss from the coils shown here is somewhat larger than that from coronary stents as reported earlier [9,10]. There are several, not mutually exclusive, explanations possible. (1) The implantation energy (45 keV) is lower than that used for the stents (60 keV), and therefore

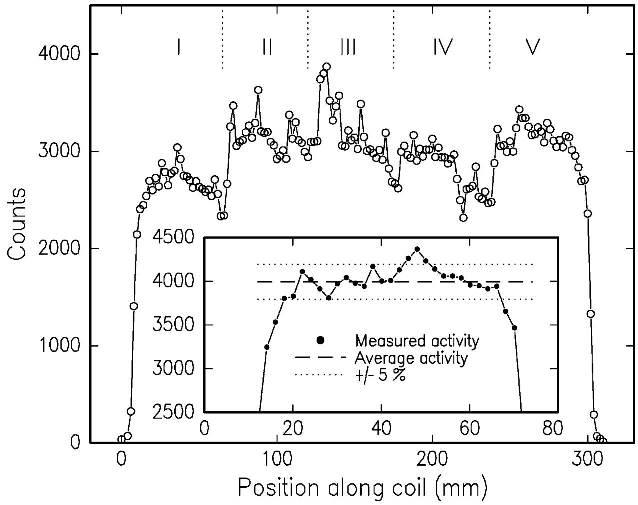

Fig. 4. Uniformity of the radioactive implantation along a 30 cm stainless steel rod. Zones marked I–V correspond to 5 irradiations of 60 mm wide regions each. The inset shows the uniformity of a similar steel rod after a single irradiation.

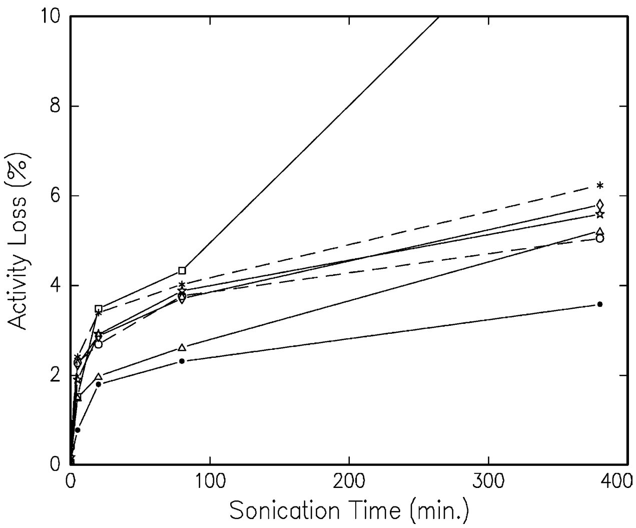

Fig. 5. Loss of activity during ultrasonic treatment in saline. The different curves correspond to different pieces of a single coil.

the penetration depth of the ^{32}P-ions into the metal is reduced. (2) The coils are Pt, whereas the stents were made from stainless steel. This implies, again, a smaller penetration depth but may also lead to faster erosion of the coil itself since Pt is softer than steel. (3) The coils were used as-received. Any surface contamination on the coils would be activated and washed off in the early stages of the ultrasonic treatment. To assess the in vivo leaching of ^{32}P from platinum coils, four 3 mm × 8 cm radioactive coils were inserted through a percutaneous femoral approach into the abdominal aorta of four anaesthetized dogs for 60 min. They were then retrieved and counted. The range of activity loss was between 0 and 10% with a mean loss of 4%.

2.6. Penetration of ^{32}P-ions into platinum

It is instructive to compare the thickness of the platinum wires with two other length scales, namely the penetration depths of the ions and the electrons involved. The projected range and range straggling of 45 keV ^{32}P-ions in platinum are 21 nm and 12 nm [11], which is much less than the wire thickness. A wire that is ion irradiated from one side only, will therefore exhibit an asymmetric beta radiation field because the implanted ions all come to rest within 70 nm of the metal surface exposed to the ion beam. The asymmetry of the radiation field depends on the energy loss of the beta-electrons as they pass through the metal of the wire. The electrons emitted by ^{32}P nuclei vary in energy between 0 and 1.7 MeV, with an average energy of about 700 keV, but considerable energy loss will occur in the Pt wire if the electrons are emitted away from the nearest surface. The asymmetry of the radiation field is not a limiting factor since multiple coils are randomly deployed to fill an aneurysm.

2.7. Summary of pre-clinical results

A single coil canine arterial occlusion model was used to test the effects of radiation on arterial recanalization. Through a percutaneous femoral approach, 3 mm arteries were catheterized and a single 3 mm coil was inserted and detached into each artery. Paired arteries were used to compare the evolution of the occlusion with time using radioactive or non-radioactive coils. Radiographic contrast arterial injections were used to monitor the patency of embolized vessels. While all coils led to arterial occlusion at one week, recanalization of arteries treated with standard platinum coils was 100% at 2 weeks. The occlusion persisted at all times studied (up to12 weeks) when the coil was radioactive. Inhibition of this recanalization phenomenon was achieved in more than 90% of cases when activities exceed 0.13 μCi/cm of coil or 0.018 μCi/mm^3 of arterial volume [6]. Pathological studies have shown that arteries treated with standard coils are recanalized while those treated with radioactive coils are filled by fibrous tissue at 12 weeks. This is illustrated in Fig. 6, which shows photos of arterial occlusions with standard (top) and radioactive coils (bottom).

2.8. Clinical study

An initial clinical study [12] was performed on 45 intracranial aneurysms in 41 patients with lesions at high risk of recurrence after endovascular treatment. Manipulations of radioactive coils and their mechanical characteristics were unchanged as compared to standard platinum coils. More than 800 coils were ion implanted in preparation for these procedures, and 242 were actually used to occlude aneurysms. This initial experience confirmed the feasibility of

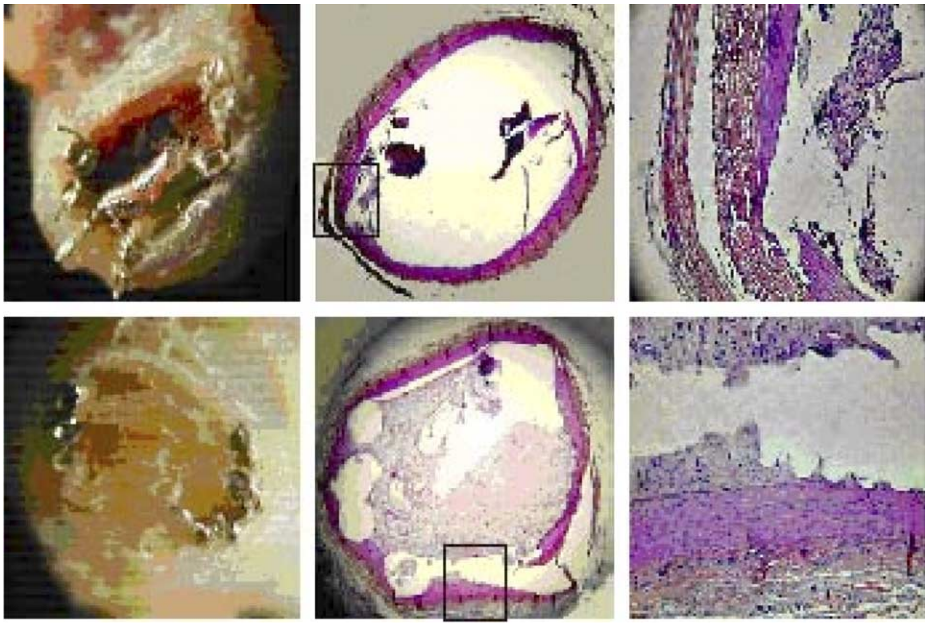

Fig. 6. Macro photography of arterial occlusions using standard (top) and radioactive coil (bottom).

radioactive embolization of human aneurysms. A randomized clinical trial comparing radioactive and non-radioactive coil embolization is now necessary to assess if this strategy can improve long-term results of endovascular treatment of intracranial aneurysms.

3. Conclusion

We have developed effective apparatus and methods for the production and characterization of ^{32}P-radioactive platinum coils to be used in the endovascular treatment of intracranial aneurysms. Total coil activities, uniformity, reproducibility and ^{32}P retention in platinum were measured and found to be appropriate for this application.

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