In Situ Beta Radiation to Prevent Recanalization After Coil Embolization of Cerebral Aneurysms

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Background and Purpose—Endovascular treatment of cerebral aneurysms, a minimally invasive alternative to surgery, is too often followed by recanalization and recurrences. The purpose of this work was to assess if in situ beta radiation can inhibit recanalization after coil embolization.

Methods—Radioactive platinum coils (^{32}P-coils) were produced by ion implantation of ^{32}P. A single-coil arterial occlusion model was used to compare angiographic and pathological results at 1 to 12 weeks after nonradioactive and ^{32}P-coil embolization of maxillary, cervical, and vertebral arteries in 26 dogs. Coils of varying activities were used and results compared to define the minimal activity required to inhibit recanalization. Similar experiments were performed in 16 porcine maxillary and lingual and 8 rabbit axillary arteries. Results of ^{32}P-coil embolization of bifurcation aneurysms were then compared with embolization with nonradioactive coils in 12 dogs at 3 months.

Results—Nonradioactive coil embolization of canine arteries led to occlusion at 1 week, followed by recanalization at 2 weeks, which persisted at 3 months in all cases. ^{32}P-coils, ion-implanted with activities above 0.13 μCi/cm, led to persistent occlusion at 3 months in 80% of arteries. ^{32}P-coils ion-implanted with the same activity inhibited recanalization in porcine and rabbit arteries. Bifurcation aneurysms treated with ^{32}P-coils had better angiographic results at 3 months ($P=0.006$) than aneurysms treated with nonradioactive coils. Arteries occluded were filled with fibrous tissue at 3 months. Aneurysms embolized with ^{32}P-coils showed more complete neointimal coverage of the neck, without recanalization, as compared with aneurysms treated with nonradioactive coils.

Conclusion—In situ low-dose beta radiation inhibits recanalization after coil embolization and may improve long-term results of endovascular treatment of aneurysms. (***Stroke***. 2002;33:421-427.)

Key Words: aneurysms ■ animal models ■ endovascular therapy ■ radiation ■ dogs

Intracranial aneurysms are a frequent cause of intracranial hemorrhage, a condition responsible for many deaths and disabilities.[1] Surgical clipping of the lesion at the neck has been the cornerstone of therapy for more than 30 years. Endovascular treatment is a minimally invasive alternative that uses catheters introduced through the femoral artery to reach and occlude aneurysms, most often with small-caliber platinum wires or "coils" (Guglielmi's detachable coils[2]). While this technique (sometimes called coil embolization) is effective in preventing rebleeding following aneurysmal rupture, follow-up angiography has revealed recanalization of aneurysms with recurrences in 10% to 20% of patients so far.[3–5] This drawback is the main reason why endovascular treatment remains underused as compared with surgery.

 Mechanisms involved in recurrences after coil embolization of human aneurysms have not been determined,[6] but similar recurrences can be reproduced in experimental models.[7–9] Platinum coils lead to occlusion of arteries or aneu-

rysms by clot formation.[8] The fate of this clot, if it is not lysed by the fibrinolytic system, depends on 2 phenomena: recanalization and neointimal tissue formation. We hypothesized that in situ beta radiation could inhibit recanalization and lead to permanent occlusion of arteries or aneurysms.

 The first goal of the present study was to activate the surface of platinum coils with the beta emitter ^{32}P using ion implantation. We then assessed the effects of this local beta radiation on recanalization of canine arteries embolized with platinum coils. We next wanted to determine the minimal dose necessary to inhibit recanalization by testing coils of various activities in the same experimental model. Since vascular healing phenomena may vary from one species to another,[4] we assessed if recanalization after coil occlusion, and its inhibition by beta irradiation, could be reproduced in porcine and rabbit arteries. We finally compared radioactive and nonradioactive coil embolization of canine bifurcation aneurysms, a model prone to recanalization.[9] Here we show

that the addition of ^{32}P to the coils used for occlusion inhibits recanalization and leads to permanent occlusion of arteries or aneurysms.

Methods

Ion Implantation of Coils

^{32}P-coils were produce on a dedicated radioactive ion implanter at the René J.A. Lévesque Laboratory of the Université de Montréal. The implanter consists of an ion source, where the radioactive phosphorous is ionized; a mass selection filter; an acceleration section; a final focus and steering section; and a target zone, where the coils are loaded onto a special support. A radiation-detection apparatus is located in the target region to monitor deposition of ^{32}P as it is being implanted. Platinum coils (interlocking detachable coils [IDC], 3 mm×10 cm, Target Therapeutics) were ion-implanted at 65 keV with ^{32}P (Perkin Elmer Life Sciences). The maximum penetration depth of 65-keV ^{32}P ions into platinum is 40 nm. The activity of coil was measured using a Canberra-Packard Tri-Carb scintillation counter, relying on the Cerenkov effect produced by the beta radiation in the glass vial. The accuracy of the method was confirmed independently using 3 different techniques on 3 coils: Geiger counter, counting using direct liquid scintillation, and counting after coil dissolution in acid. Measurements were within 10% of each other and in agreement with the Cerenkov counting method. To assess their integrity, coils were inspected with a binocular microscope. Their behavior on passage through microcatheters (Excelsior, Target Therapeutics) was also compared with standard coils. To assess leaching, 10 coils ion-implanted with 0.10 to 0.13 μCi/cm were submitted to a sonication bath in saline at 45°C for 50 minutes. In 7 coils, this test was followed by immersion in saline at 45°C with constant agitation for 5 days.

Dosimetry

A dose-point kernel method[10] was used to estimate the theoretical dose delivered to tissues surrounding 3 ml×10 cm coils ion-implanted with 0.13 μCi/cm of ^{32}P in the arterial model detailed below.

Animal Models

Protocols for animal experimentation were approved by the Institutional Animal Care Committee in accordance with guidelines of the Canadian Council on Animal Care. All surgical and endovascular procedures were performed under general anesthesia. Thirty-eight beagles weighing 10 to 15 kg were sedated with an intramuscular injection of acepromazine (0.1 mg/kg), glycopyrrolate (0.01 mg/kg), and butorphanol (0.1 mg/kg), and anesthetized with intravenous thiopental (15 mg/kg). Animals were ventilated artificially and maintained under surgical anesthesia with 2% isoflurane. Postoperative analgesia was provided for 3 days by a 50-μg fentanyl skin patch. Pigs and rabbits were similarly anesthetized for endovascular interventions and control angiograms, following preanesthetic cocktails specific to their species.

Single-Coil Arterial Occlusion Model

A percutaneous femoral puncture was used to reach bilateral maxillary arteries with 2F microcatheters (Excelsior, Target Therapeutics) introduced coaxially through 5F catheters. A platinum coil (IDC, 3 mm in diameter, 10 cm in length), nonradioactive or ion-implanted with an activity of 0.13 to 0.15 μCi/cm of ^{32}P, was deposited in each artery in a blind fashion. (All coils were considered potentially radioactive.) Angiograms were performed immediately after embolization, at 1 hour, at 1 week, and before sacrifice in all animals. Animals kept for 3 months were also followed by angiography at 2 and 3 weeks. Multiple projections following selective injections were interpreted in a blind fashion. Occlusion was defined as the absence of antegrade blood flow through the coil. Any antegrade contrast opacification was sufficient to label the artery recanalized. This experiment was performed in 14 dogs followed for 1 week (n=2), 10 days (n=2), 2 weeks (n=2), 4 weeks (n=2), and

12 weeks (n=6). We then compared standard coils and coils submitted to the implantation process but without ^{32}P in both maxillary arteries of 3 dogs followed for 12 weeks and studied by angiography at 1, 2, 3, and 12 weeks. To define the minimal activity necessary to inhibit recanalization, we compared, in another experiment, 50 coils ion-implanted with 5 different activities of ^{32}P (<0.02, 0.04 to 0.06, 0.08 to 0.13, 0.13 to 0.15, and 0.40 to 0.50 μCi/cm) and inserted in both maxillary, cervical, and vertebral arteries of 9 dogs followed for 3 months. This model was also used in similar experiments performed in 16 porcine maxillary and lingual arteries (4 Yorkshire pigs, weighing 25 to 30 kg) followed for 3 weeks and 8 rabbit axillary arteries (4 New Zealand rabbits, 2.5 to 3 kg) followed for 12 weeks using control or ^{32}P-coils (0.13 μCi/cm).

Canine Bifurcation Aneurysm Model

Terminal bifurcation aneurysms were constructed in 12 dogs using external jugular venous pouches sutured with 8-0 Prolene to a T-type bifurcation created by anastomosis between the 2 common carotid arteries according to a modification of the technique of Graves et al.[9,11] In this model, the width of the neck that can be constructed is limited by the diameter of the carotid artery used for the construction of the horizontal segment of the T-type bifurcation. Necks were oval-shaped and measured approximately 5 mm in diameter (5.3±0.8 mm and 5.0±0.7 mm for control and ^{32}P-treated aneurysms, respectively). Aneurysms measured approximately 10 mm in their longest axis (10.4±0.7 mm and 9.7±1.2 mm for control and ^{32}P-treated aneurysms, respectively) as assessed by angiography. Endovascular treatment was performed at least 2 weeks after aneurysm construction through a transfemoral approach routinely used in clinical practice. Maximal coil packing of the aneurysm was performed after the first coils had formed a retaining "basket" bridging the neck.[3] In aneurysms treated with beta radiation, the first 2 coils (5 mm×15 or 20 cm) bridging the neck were implanted with a mean activity of 0.22 μCi/cm of ^{32}P, and the operator was not blinded to the radioactive nature of these coils. Because aneurysms were larger than the size of the radioactive coils, the lesion was often embolized in 2 steps, the fundus region being packed first to allow positioning of the radioactive coils at the neck. Healing of the aneurysms was assessed in vivo by angiography at 3 weeks and 12 weeks, with the results being scored according to a previously described classification.[7,9] A score of 0 indicated complete obliteration; 1, "dog ears"; 2, residual or recurrent neck; 3, residual or recurrent aneurysm; 4, large saccular recurrences. Mean angiographic scores were compared using Student's t test.

Pathology

Arteries implanted with coils or common carotid arteries bearing aneurysms were excised after sacrifice. Arteries harboring coils were sectioned in the axial plane. The wall of the carotid artery was longitudinally opened to expose the luminal surface of the neck of aneurysms. After fixation, cut sections of arteries and the necks of aneurysms were photographed "en face" using an operating microscope. Pathological specimens were studied after formalin fixation, axial sectioning, and staining including immunohistochemical stains for α-actin and factor VIII, as previously described.[7,9]

Results

Platinum Coils Can Be Made Radioactive Using ^{32}P Ion Implantation

A total of 103 platinum coils were ion-implanted with activities varying from 0 to 0.5 μCi/cm. Coils were unchanged in their morphology and in their mechanical properties after ion implantation and could be delivered similarly to nonradioactive coils through standard microcatheters.

The loss of activity of ^{32}P-coils submitted to a sonication bath was <10% in all cases. Activities measured after immersion with constant agitation for 5 days were compatible with the natural decay of ^{32}P.
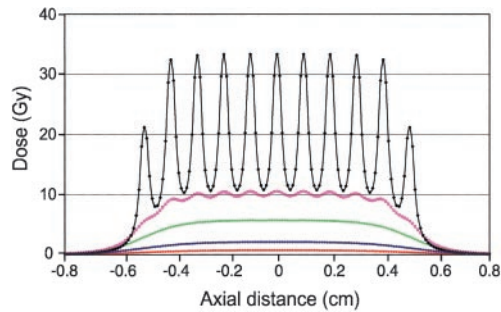
Figure 1. Dosimetry of ^{32}P-coil in arterial model. Graph showing theoretical dose after 1 half-life to tissues at 0.1 (black line), 0.5 (pink line), 1 (green line), 2 (blue line), and 3 mm (red line) of a 3 mm×10 cm platinum coil, ion-implanted with 0.13 μCi/cm of ^{32}P and used to embolize a 3-mm maxillary artery, according to the dose-point kernel method.[10]

## Dosimetry

Doses delivered during 1 half-life were calculated to be 33, 10, 5, 2, and 0.07 Gy at 0.1, 0.5, 1, 2, and 3 mm, respectively, from the coil surface (Figure 1). At distances greater than 0.5 mm from the coil surface, the effect of the coil geometry on doses vanishes.

Beta Radiation Inhibits Recanalization After Single-Coil Occlusion of Arteries

We first studied single-coil embolization of canine maxillary arteries. In 8 animals, ^{32}P-coils (0.13 μCi/cm) were used to embolize 1 maxillary artery, while the contralateral maxillary artery was treated with an identical but nonradioactive coil. Arterial implantation of a single coil was followed by occlusion within 1 hour in all cases. The occlusion persisted for 1 week, but serial angiographic studies revealed recanalization of arteries treated with nonradioactive coils at 2, 3, 4, and 12 weeks (Figure 2). The recanalization process was completely inhibited with ^{32}P, and arteries remained occluded for 2 (n=2/2), 3 (n=2/2), 4 (n=4/4), and 12 weeks (n=6/6), while arteries treated with nonradioactive coils were recanalized and patent at all dates (Figures 2 and 3). This phenomenon could not be reproduced with 3 coils processed in the implanter without ^{32}P. Arteries embolized with these coils *implanted* without ^{32}P showed the same evolution as contralateral intact coils, with complete occlusions at 1 hour and 1 week but full recanalization at 2, 3, and 12 weeks. To determine the minimal activity of ^{32}P required to prevent recanalization, the experiment was repeated in 9 animals followed for 12 weeks using coils ion-implanted with different activities in maxillary, cervical, or vertebral arteries of each animal. The results of these experiments are summarized in Figure 4. An activity of 0.13 μCi/cm is sufficient to prevent recanalization in 80% of arteries. The rate of recanalization after coil occlusion is related to the activity of ^{32}P following an exponential curve (Figure 4b).

Since vascular healing phenomena may vary from one species to another, we finally wanted to assess if the recanalization process described above and its inhibition by beta radiation were specific to canine arteries. Control and ^{32}P-coils were used to occlude porcine lingual and maxillary arteries and rabbit subclavian arteries. Recanalization after
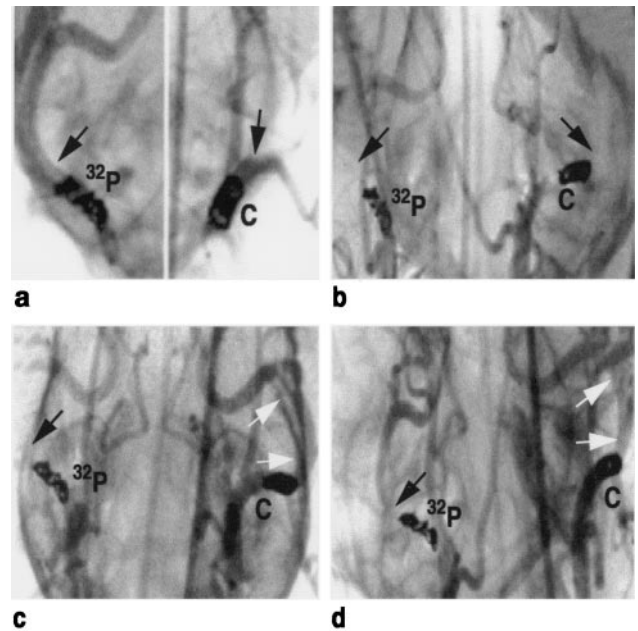

Figure 2. Angiographic demonstration of inhibition of arterial recanalization with ^{32}P-coils (0.13 μCi/cm). Selected images from sequential angiograms performed immediately (panel a), 1 week (panel b), 3 weeks (panel c), and 12 weeks (panel d) after control (C) or ^{32}P-coil (^{32}P) embolization of both maxillary arteries in the same dog. Immediately after embolization, both arteries are patent (arrows in panel a). Both arteries are occluded at 1 week (arrows in panel b). At 3 and 12 weeks, the artery embolized with ^{32}P-coil remains occluded (black arrows in panels c and d) while the artery embolized with a control coil has recanalized at 3 weeks and remains patent at 12 weeks (white arrows in panels c and d). Note that arteries distal to the occlusion are opacified in a retrograde fashion through collateral circulation.

coil embolization was reproduced in both species. Recanalization after nonradioactive coil embolization was less frequent (6/8 instead of 100%) and the recanalized lumen more narrowed in porcine as compared with canine arteries. The same activity of ^{32}P (0.13 μCi/cm) was effective to inhibit recanalization in the 3 species studied. All porcine arteries embolized with ^{32}P-coils (8/8) were occluded at 3 weeks; all rabbit arteries embolized with ^{32}P-coils (4/4) were occluded at 3 months (Figure 5).

Sequential pathological studies performed 1, 1.5, and 2 weeks after ^{32}P-coil embolization of canine maxillary arteries (n=2 for each time point) showed, within the clot, the absence of endothelialized channels found in contralateral maxillary arteries embolized with nonradioactive coils. Recanalized artery harvested at 12 weeks showed that coils were embedded in neointima, with large endothelialized channels in between coils or between the coils and the vascular wall. The lumen of arteries embolized with radioactive coils was fully replaced with vascularized connective tissue, consisting of fibroblasts or α-actin positive myofibroblasts in a dense collagenous matrix, at 12 weeks (Figure 3).

Beta Radiation Inhibits Recanalization and Improves Results of Coil Embolization of Canine Bifurcation Aneurysms

We next tested to see if beta radiation would prevent recurrences after endovascular treatment of experimental
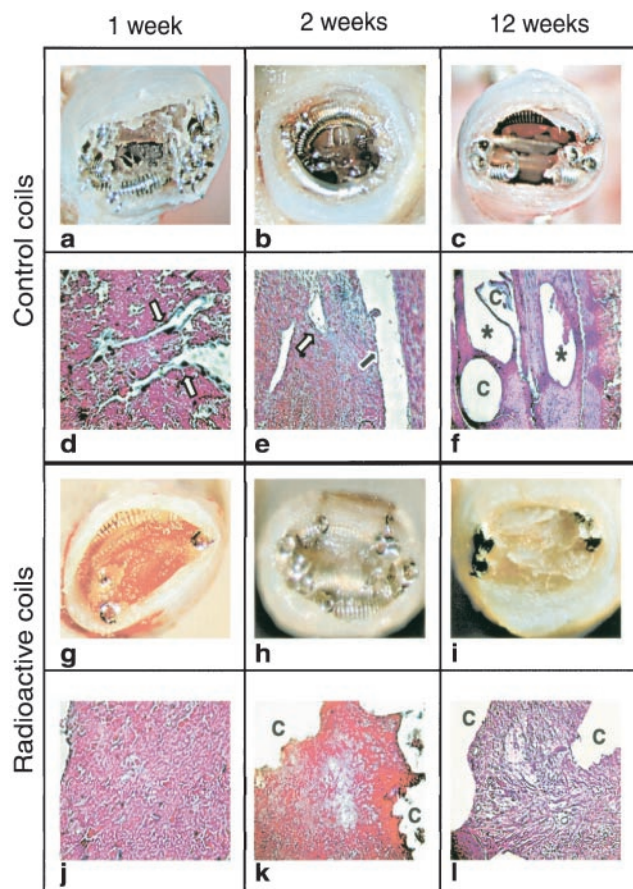
Figure 3. Arterial recanalization after coil occlusion and inhibition of recanalization with beta radiation: pathological findings. Macroscopic (panels a, b, c, g, h, and i) and microscopic studies (panels d, e, f, j, k, and l) performed 1, 2, and 12 weeks after control coil (panels a through f) and ^{32}P-coil (panels g through l) embolization of canine maxillary arteries. At 1 week (panels a, d, g, and j), both arteries are occluded (panels a and g); pathology reveals endothelial channels within the clot that formed on control coil (white arrows in panel d). Those channels are absent when the coil is radioactive (0.13 μCi/cm; panel j). At 2 weeks (panels b, e, h, and k), the artery embolized with a control coil is recanalized (panel b) and a fissure developed between the vessel wall and the clot (black arrow in panel e); channels are wider within the clot itself (white arrow in panel e). The artery embolized with a ^{32}P coil remains occluded (panel h) and the clot is not recanalized by channels (panel k). At 12 weeks (panels c, f, i, and l), the artery occluded with a control coil is recanalized (asterisk in panel f), even though the coil is covered by thick neointimal tissue, while the artery treated with a ^{32}P-coil is completely filled with fibrous tissue (panels i and l). For magnification factor in macroscopic studies ($\times$5, panels a, b, c, g, h, and i), note that coil caliber is 0.381 mm. Hematoxylin-phloxine-saffron staining was used for arterial cross sections ($\times$100, panels d and j; $\times$20, panels e, f, k, and l). C indicates a defect caused by removal of the coil.

aneurysms. Two radioactive coils (mean activity of 0.22 μCi/cm) were introduced into bifurcation aneurysms constructed in 7 animals. The core of the radioactive platinum sphere formed at the neck by these 2 coils was then packed with smaller nonradioactive coils to achieve near-complete occlusion of aneurysms. Results of this experiment were compared with 5 aneurysms embolized with nonradioactive coils only. Aneurysms treated with ^{32}P-coils were stable, without recurrence at 12 weeks, while aneurysms embolized
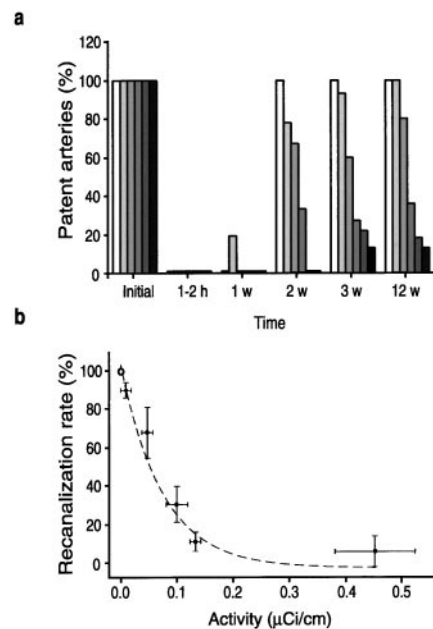

Figure 4. Angiographic results of coil embolization of canine arteries according to ^{32}P activity. Panel a, bilateral maxillary, cervical, and vertebral arteries were embolized with 4 to 6 coils of varying activities (μCi/cm) in each animal: control (□), 0.002 (▨), 0.04 to 0.06 (▨), 0.08 to 0.13 (▨), 0.13 to 0.15 (■), and 0.4 to 0.55 (■). All arteries are occluded 1 to 2 hours after embolization. The occlusion persists at 1 week but recanalization occurs after 2 weeks unless the coils are radioactive. The higher the ^{32}P activity, the stronger the inhibition of recanalization. Most arteries (80%) treated with ^{32}P coils ion-implanted with activities of 0.13 μCi/cm or more, remain occluded at 12 weeks. Panel b, percentages of recanalized arteries, as shown by angiography 2 to 12 weeks after coil occlusion are plotted against ^{32}P activity. The rate of recanalization is an exponentially decreasing function of the activity of ^{32}P (reduced χ^2=1.09). Vertical bars indicate SD; horizontal bars indicate intervals of ^{32}P activity.

with nonradioactive coils, as assessed by angiography, recurred constantly (Figure 6). While initial results were similar (P=0.68), aneurysms treated with radioactive coils showed better angiographic scores at 12 weeks (P=0.006) than aneurysms treated with control coils. Morphological studies at 12 weeks showed that the necks of aneurysms embolized with ^{32}P-coils were sealed by a well-developed neointima. Conversely, the necks of control aneurysms showed numerous open crevices between coils covered by neointima, leading to large recurrent spaces (Figure 6). Pathological studies performed at 12 weeks did not show any significant difference in the nature of the vascularized connective tissue found between the coils or in the appearance of the aneurysmal wall. Patent endothelialized crescents between the aneurysmal wall and the coil mass covered by neointimal tissue, typical of recanalization, were routinely found in control aneurysms while they were absent in aneurysms treated with ^{32}P coils.

Discussion

Detachable coils permit the progressive obliteration of the aneurysmal sac with soft packing material. When coil deposition is unsatisfactory, the coils can be retrieved and repo-
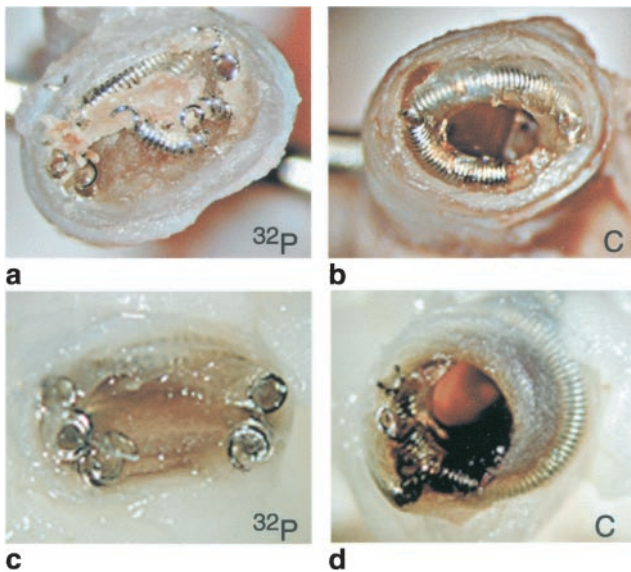
Figure 5. Inhibition of recanalization by beta radiation in other species. Cross sections of porcine maxillary (panels a and b) and rabbit axillary arteries (panels c and d) show recanalization 3 weeks after control coil occlusion (panels b and d) compared with persistent occlusion of contralateral arteries embolized with ^{32}P-coils (0.13 μCi/cm; panels a and c).

sitioned with ease and then detached when, and only when, the operator is satisfied. These characteristics, essential to the safety of the procedure, would ideally be preserved in future strategies designed to improve long-term results of endovas-
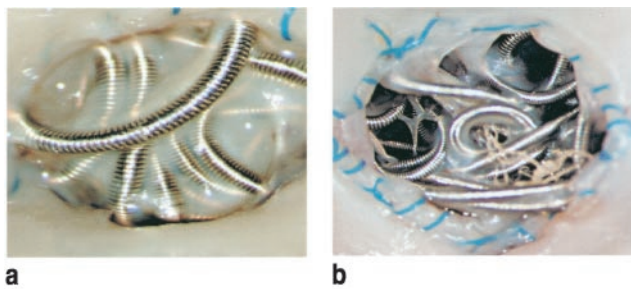
	Initial		3 weeks		12 weeks	
Control coils	0.67 ± 0.42	p=0.68	0.67 ± 0.42	p=0.60	3.00 ± 0.26	p=0.006
Radioactive coils	1.00 ± 0.31		1.14 ± 0.26		1.14 ± 0.26	

Figure 6. Embolization of canine aneurysms with ^{32}P-coils and inhibition of recanalization. Bifurcation venous pouch aneurysms were constructed in 12 animals and embolized 2 weeks later with control (n=5) or radioactive coils (n=7). Panels a and b, photography of the neck of aneurysms treated with ^{32}P (a) or control coils (b) 12 weeks after embolization. Recanalization between coils is evident in lesions treated with control coils while ^{32}P-coils are covered with a thick neointima, sealing the neck of the aneurysm. Suture material used for aneurysm construction is visible as interrupted blue lines. Panel c, angiographic results were scored immediately, 3 weeks, and 12 weeks after the embolization, and mean scores were compared using Student's *t* test (see method; a higher score indicates a recurrence). While initial results were similar (P=0.68), aneurysms treated with radioactive coils showed better angiographic scores at 12 weeks (P=0.006) than aneurysms treated with non-radioactive coils.

cular treatment of aneurysms. We have used interlocking detachable coils for these preclinical studies because the coils can be detached from their pusher wire to be ion-implanted, and reattached before percutaneous embolization. The target zone of the implanter has now been modified to enable ion-implantation of Guglielmi detachable coils that will be used for clinical studies. Ion implantation of ^{32}P, a pure beta emitter with a half-life of 14 days, provides coils capable of inhibiting the recanalization process, a phenomenon that has been shown to be constant with standard platinum coils in our arterial occlusion model. Ion implantation permits embedding ^{32}P ions at a few nanometers within the coil surface without any mechanical alteration of the device. The coil can be considered a sealed source of beta particles, a radiation that delivers energy with a limited penetration (70% of the energy is delivered within 1 mm of the coil surface). This poor penetration, however, seems sufficient to inhibit cellular processes involved in recanalization while it ensures an important safety factor regarding normal tissues surrounding the aneurysm. Unlike other surface modifications of coils that increase their thrombogenicity[8] or stimulate an inflammatory reaction,[12,13] ion-implanted radioactive coils are not susceptible to shedding of material and subsequent embolic risks. The activity decays according to a constant, without the variability intrinsic to biodegradable materials.[13] Finally, a radioactive strategy is unique in its potential to affect biological phenomena at a distance from the coil using infinitesimal quantities of material at the coil surface.

Platinum coils lead to occlusion of arteries or aneurysms by secondary clot formation. The fate of this clot and the outcome of embolization depends on 2 synchronous phenomena that occur at the level of the provisional matrix provided by this clot. One is the recanalization process, which involves endothelial cells that attempt to restore a patent lumen and a nonthrombogenic surface. The other is neointimal tissue formation, with mesenchymal cells invading the provisional fibrin matrix to secrete collagen. The neointima, a nonspecific vascular response fundamental to vascular healing, is composed of mesenchymal cells and extracellular matrix covered by a single layer of endothelial cells.[14] The endothelium itself, the biologically active inner lining of blood vessels, is a living nonthrombogenic surface that rapidly regenerates after injury.[15] Histological studies performed after coil embolization of arteries show that clot invasion by α-actin positive mesenchymal cells (with deposition of new collagen) is preceded by endothelialization of channels that restore circulation in the occluded vessel (Figure 2).[16] This mechanism differs from the one related to the fibrinolytic system, which occurs at a molecular level earlier on and which does not necessitate cellular invasion of the clot. We have shown that this cellular recanalization process that occurs between 10 and 14 days of occlusion in our animal model is inhibited by low activities of ^{32}P. Although ^{32}P stents have been designed to inhibit restenosis, numerous animal studies have shown a paradoxical increase in neointimal thickness with low-dose stents.[17,18] Endothelialization of the clot formed on the surface of the device may be involved in decreasing neointima thickness following arterial implantation of stents. Inhibition of endothelialization by beta radia-

tion could explain these paradoxical results. Radioactive coils, with activities within the range chosen for this study (0.1 to 0.5 μCi/cm), did not prevent mesenchymal cell invasion of the clot, fibrous replacement of the lumen of arteries, or neointima formation at the neck of treated aneurysms. The neointima at the neck of aneurysms treated with radioactive coils was more complete than the one found in aneurysms treated with nonradioactive coils only (Figure 5). The modification of the embolization technique, designed to allow the use of 5-mm coils in large aneurysms, or the variation in aneurysm sizes is, in our opinion, insufficient to explain the improvement in the angiographic scores and the more complete neointimas found at pathology at 12 weeks. We propose that inhibition of recanalization by beta radiation, as demonstrated in the arterial occlusion model, is responsible for the difference observed. We hypothesize that higher doses, distributed to the entire thickness of the vessel wall, are necessary to prevent neointima formation in a radioactive stent strategy, while lower doses, confined to the luminal clot, are sufficient to prevent recanalization after coil occlusion. In any event, in situ beta radiation inhibited recanalization of arteries and aneurysms, while it did not prevent fibrous tissue transformation of the clot, leading to permanent occlusion of arteries or aneurysms in our animal models.

The recanalization phenomenon is not specific to canine arteries and can be found in 2 other species frequently used in the evaluation of pathological reactions to endovascular interventions.[7,14] Recanalization seems to be less effective in restoring arterial patency in pigs. This diminished potential for recanalization after coil embolization may explain the strong tendency for healing and the absence of recurrence in porcine aneurysmal models as compared with dogs and rabbits.[7,19] The lumen of nonrecanalized porcine arteries, occluded with nonradioactive coils, was filled with fibrous tissue that was similar to the one found in arteries permanently occluded with ^{32}P-coils. This observation gives credence to the hypothesis that the outcome of vascular device implantation depends on a balance between recanalization and neointima formation.

Even though the recanalization process may vary in potency from one species to the other, it could be inhibited by ^{32}P-coils implanted with the same activity (0.13 μCi/cm) in the 3 species studied. It is yet unknown if the same level of activity would be effective in human arteries. Serial angiographic results obtained with coils of various activities in canine arteries lead to 2 important observations. It is apparent from Figure 4 that if recanalization cannot proceed normally within the first few weeks after occlusion in this animal model, it will not occur in a delayed fashion once the clot has been replaced with fibrous tissue. Another observation is that even though an activity of 0.13 μCi/cm is sufficient to prevent recanalization in 80% of arteries, the higher the activity, the more effective the inhibition of recanalization. The therapeutic window must be relatively wide, since activities above 0.13 μCi/cm could inhibit recanalization in most arteries, while the topography of the coil, and ensuing dosimetry, must have varied dramatically from one artery to the other.

Because it is impossible to predict or to track the exact position of coils, dosimetry would be impossible to obtain before and even after radioactive coil embolization of intracranial aneurysms. In fact, we have not yet identified the target tissue that has to be irradiated to prevent recanalization. We hypothesize that the clot formed between and over the coils cannot be recanalized if it is subjected to a sufficient dose of radiation. For this reason we propose, for a clinical application on human aneurysms, to use coils that are all radioactive, to ensure inhibition of recanalization everywhere the coils have caused thrombosis. Since coil packing in clinical practice is commonly performed in a much denser fashion than in our arterial occlusion model,[20] a strategy that would use activities per centimeter of coils in the range shown to be effective in the arterial model (0.13 μCi/cm) could reach sufficient levels to prevent recanalization after coil embolization of aneurysms. The operator would then be limited to a maximum number of ^{32}P-coils, to prevent excessive exposure to tissues surrounding the aneurysm. Colloidal ^{32}P has been used to treat certain craniopharyngiomas, by intracystic injection under stereotactic guidance.[21] These cysts grow in the suprasellar cistern, a common location for intracranial aneurysms. Tables have been designed to measure the activity of ^{32}P necessary to irradiate the cyst epithelium, responsible for fluid secretion, without harming surrounding nerves and tissues, according to the size of the cyst.[21] These tables could provide an upper limit of activities to be inserted into aneurysms, according to their sizes.

Conclusions

We have shown that coils implanted with low activities of ^{32}P can prevent recanalization after coil embolization and improve angiographic results 3 months after endovascular treatment of canine bifurcation aneurysms. The effects of ^{32}P on the recanalization process after coil embolization are reproducible, and this discovery may have a strong impact on endovascular treatment of aneurysms. A method that uses coils enhanced to prevent recanalization is expected to improve long-term results of the endovascular procedure without increasing thromboembolic complications. This alternative treatment to surgery could then be offered more frequently to patients with aneurysms.

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