

Beta Radiation and Inhibition of Recanalization After Coil Embolization of Canine Arteries and Experimental Aneurysms

How Should Radiation Be Delivered?

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Background and Purpose—Beta radiation prevents recanalization after coil embolization. We sought to determine the effects of varying coil caliber, length, activity of ^{32}P per centimeter of coil or per volume, and spatial distribution of coils on recanalization.

Methods—We studied the angiographic evolution of 81 canine maxillary, cervical, and vertebral arteries implanted with a variety of nonradioactive (n=29 arteries) or radioactive (n=52) devices. We compared 1- or 2-caliber 0.015 or 0.010 coils ion-implanted or not with 3 different activity levels (0.05 to 0.08, 0.06 to 0.12, 0.18 to 0.32 $\mu\text{Ci}/\text{cm}$) of ^{32}P and totaling 4, 8, and 16 cm in length for the same arterial volume. We also compared inhibition of recanalization by beta radiation delivered by stents, after coil occlusion proximal to or within the stent, with that delivered by coils placed within nonradioactive stents. We finally studied the angiographic evolution of canine lateral wall carotid aneurysms treated with 1 or 2 stents of various activity levels positioned inside the parent artery across the neck. Animals were killed at 4 and 12 weeks for macroscopic photography and pathological examination.

Results—All arteries (29 of 29) occluded with nonradioactive devices were recanalized, while 49 of 52 arteries (94%) implanted with ^{32}P devices were occluded at 4 weeks. All aneurysms treated with stents, radioactive or not, demonstrated residual filling of the sac or of channels leading to the aneurysms at follow-up angiography at 4 weeks.

Conclusions—The recanalization process found in the canine arterial occlusion model is minimally affected by coil caliber, number, and length or packing density. Beta radiation reliably inhibits this process, but thrombosis is an essential condition for the efficacy of a radioactive coil strategy. (*Stroke*. 2003;34:1262-1268.)

Key Words: aneurysm ■ angiography ■ cerebral aneurysm ■ endovascular therapy ■ radiation ■ dogs

Beta radiation prevents recanalization after coil embolization, but the exact mechanism responsible for this effect remains unknown. While an effective linear (per centimeter of platinum coil) therapeutic activity has been determined in an arterial occlusion model, the precise nature of the target tissue and the dose to be applied to this target are still unknown.¹ We proposed to embolize aneurysms with coils ion-implanted with a predetermined linear activity of ^{32}P .^{1,2} In addition to the aforementioned fundamental questions, this strategy raises practical issues: Should beta radiation be applied to the endothelium, to the vessel wall, or to the clot that forms over the surface and within the mesh of coils? Should it be targeted to the neck region, or should the entire aneurysmal cavity be exposed? Do all coils need to be radioactive, or is the addition of nonradioactive coils likely to shield the target and decrease efficacy? What are the effects of coil caliber, coil length, and linear or total ^{32}P activity on recanalization rates?

To address these questions, we have resorted to modifications of the arterial occlusion model that we previously described.¹ By varying coil caliber, number, and length and by studying coil-occluded arteries implanted with radioactive or nonradioactive stents, we confirm that recanalization is a potent biological process that can be reliably inhibited by beta radiation.

We also compared radioactive and nonradioactive stents positioned inside the parent artery at the level of canine lateral wall aneurysms to assess whether the presence of an “electron fence”³ emitted from the stent wires at the neck would be sufficient to cause permanent neck closure.

Materials and Methods

Experimental Design

We studied recanalization of canine maxillary, cervical, and vertebral arteries embolized with various coils and stents, as summarized in Table 1. In each animal 4 to 6 arteries were implanted with a

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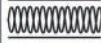
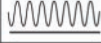


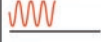
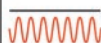




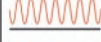




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TABLE 1. Devices, Activities, and Angiographic Results in Arterial Model

Devices	Description	Total activity (μCi)	Linear activity (μCi/cm)	Volumetric activity (μCi/mm ³)	Occlusion rate
	3mm x 8cm calibre 0.015	0	0	0	0/8
	2- 3mm x 8cm calibre 0.015	0	0	0	0/8
	3mm x 8cm calibre 0.010	0	0	0	0/4
	3mm x 8cm calibre 0.015 Stent: 3mm x 16 mm	0	0	0	0/6
	3mm x 10cm calibre 0.015 Stent: 3mm x 16 mm	0	0	0	0/3
	3mm x 4cm calibre 0.015	1.15-1.16	0.29	0.016	4/4
	3mm x 8cm calibre 0.015	1.44-2.25	0.18-0.32	0.020-0.036	4/5
	2-3mm x 8cm calibre 0.015	1.59-2.50	0 0.20-0.31	0.020-0.035	4/4
	2-3mm x 8cm calibre 0.015	1.15-1.23	0.05-0.08 0.06-0.09	0.016-0.017	3/4
	2-3mm x 8cm calibre 0.015	1.80-1.89	0.10-0.12 0.10-0.12	0.025-0.026	8/8
	3mm x 8cm calibre 0.010	1.28-1.34	0.16-0.17	0.018-0.019	4/4
	3mm x 8cm calibre 0.010	1.80-2.26	0.23-0.27	0.026-0.032	4/4
	2-3mm x 8cm calibre 0.010	1.31-1.45	0.08-0.09 0.08-0.09	0.018-0.020	4/4
	3mm x 10cm calibre 0.015 Stent: 3mm x 16 mm	2.28-2.89	0.21-0.26	0.030-0.037	3/4
	3mm x 10cm calibre 0.015 Stent: 3mm x 16 mm	2.75-2.93	-	0.035-0.037	7/7
	3mm x 10cm calibre 0.015 Stent: 3mm x 16 mm	2.66-3.35	-	0.034-0.043	4/4

variety of coils or with combinations of coils and stents, nonradioactive or implanted with various activities of ³²P, including at least 1 control artery expected to recanalize after coil occlusion. Radioactive endovascular devices were assigned a location, the contralateral artery was used to implant the control nonradioactive device or combination of devices, and positions were permuted from one animal to the other. The operator was blinded to the radioactive nature of endovascular tools, and all materials were manipulated as if radioactive.





To assess the effects of total coil length on the evolution of arterial occlusions, we compared 1- to 2-caliber 0.015 coils ion-implanted or not with 3 different activity levels (0.05 to 0.08, 0.06 to 0.12, 0.18 to 0.32 μCi/cm) of ³²P and totaling 4, 8, and 16 cm in length for the same arterial volume. A double-coil arterial occlusion model was used to exclude the potential shielding effect of 1 nonradioactive coil on beta radiation delivered by an identical coil ion-implanted with 0.20 to 0.31 μCi/cm. To determine the respective importance of total activity per volume compared with linear activity, arteries within the same animal were also embolized with 2 identical coils ion-implanted with half the

“effective linear activity,” both totaling the “effective volumetric activity” near or above 0.018 μCi/mm³. To assess the effects of changing the caliber of platinum coils on recanalization rates, we repeated previous experiments, performed with 0.015-inch coils, using caliber 0.010 in coils, radioactive or not (Table 1).

To explore potential targets of beta radiation or to test whether the location of radioactive devices within the artery is critical, we used a stent plus coil model (Table 1). We compared inhibition of recanalization by beta radiation delivered by stents, which are closer to the endothelium and vessel wall, with that delivered by coils placed within nonradioactive stents and thus emitting beta radiation at a distance from the vessel wall. In some arteries, the nonradioactive coil was positioned proximal to the radioactive stent so that it would not interfere with recanalization through the stent.

We finally studied the angiographic evolution of canine lateral wall carotid aneurysms treated with 1 or 2 stents of various activity levels positioned inside the parent artery across the neck, as summarized in Table 2.

TABLE 2. Stents, Activities, and Angiographic Results in Lateral Wall Aneurysm Model

Devices	Description	Total activity (μCi)	Occlusion rate
	Stent: 3mm x 16 mm	0	0/8
	2 Stents: 3mm x 16 mm	0	0/1
	Stent: 3mm x 16 mm	0.59-0.62	0/6
		3.92-4.38	0/8
		7.95-12.36	0/3
	2 Stents: 3mm x 16 mm	16.29	0/2
		16.49	

Ion Implantation of Coils and Stents

³²P coils and stents were produced 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 or stents are loaded onto a special support. A radiation detection apparatus is located in the target region for monitoring ³²P as it is being implanted. ³²P was purchased from Perkin Elmer Life Sciences. The activity levels of endovascular devices were measured with a Canberra-Packard Tri-Carb scintillation counter, relying on the Cerenkov effect produced by the beta radiation in the glass vial.¹

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. Twenty-six 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.

Arterial Occlusion Model

The arterial occlusion model has previously been described.¹ Briefly, a percutaneous femoral puncture was used to reach bilateral maxillary, vertebral, or cervical arteries with 2F microcatheters (Excelsior, Target Therapeutics) introduced coaxially through 5F catheters. Platinum coils were a gift from Target Therapeutics. Coils, non-radioactive or ion-implanted with various activity levels of ³²P, were deployed in each artery in a blinded fashion (all devices were considered potentially radioactive). In some arteries, 3-mm stents (NIR on Ranger, 16 mm, Boston Scientific), radioactive or not, were first deployed before coil deposition inside or proximal to the stents (Table 1). A total of 81 arteries were studied in 20 dogs. Control

angiography was performed immediately after embolization and at 1 hour and 1 and 4 weeks, immediately before the animals were killed. Twenty-four arteries in 4 animals were followed for 12 weeks. Multiple projections following selective injections were interpreted in a blinded fashion. Occlusion was defined as the absence of antegrade blood flow through the arterial segment carrying the device. Any antegrade contrast opacification was sufficient to label the artery recanalized.

Lateral Wall Aneurysms and Carotid Stenting

Lateral wall aneurysms were constructed on each common carotid artery by the technique of German and Black as modified by Graves et al.⁴ Two segments of the same external jugular vein were harvested for construction of the venous pouches. After temporary occlusion of the common carotid artery, an oval 5-mm arteriotomy was performed, and the venous pouch was sutured to the arterial wall with 8-0 polypropylene suture (Prolene). Aneurysms measured approximately 10 mm with a 5-mm neck. Transfemoral angiography was undertaken immediately after surgery in all animals. During recovery, the dogs were fed a normal diet, and their activities were not restricted. Stents (3.5 mm, 16 mm long; ACS Multilink Rx Duet, Guidant), radioactive or not, were introduced through 7F guiding catheters and deployed in front of the aneurysmal neck, by balloon inflation at nominal pressure, at least 2 weeks after aneurysm construction. Experiments are summarized in Table 2. We studied 3 different levels of activity, ie, 0.59 to 0.62 μCi or 0.004 μCi/mm³ (n=6), 3.92 to 4.38 μCi or 0.026 to 0.028 μCi/mm³ (n=8), and 7.95 to 12.36 or 0.053 to 0.08 μCi/mm³ (n=3) and compared results with nonradioactive stents (n=8). To increase the density of stent struts crossing the neck of aneurysms, in some experiments 2 stents totaling 16.29 or 16.49 μCi or 0.106 to 0.118 μCi/mm³ (n=2) or 2 nonradioactive stents (n=1) were overlapped in front of the neck of aneurysms. A total of 28 aneurysms were studied in 14 animals. Some animals were also used for the aforementioned arterial occlusion experiments. Carotid angiography was repeated at 1 and 4 weeks (immediately before euthanasia by barbiturate overdose) in anesthetized animals to document the degree of aneurysmal obliteration and the absence or persistence of communicating channels between the parent artery and the aneurysm.

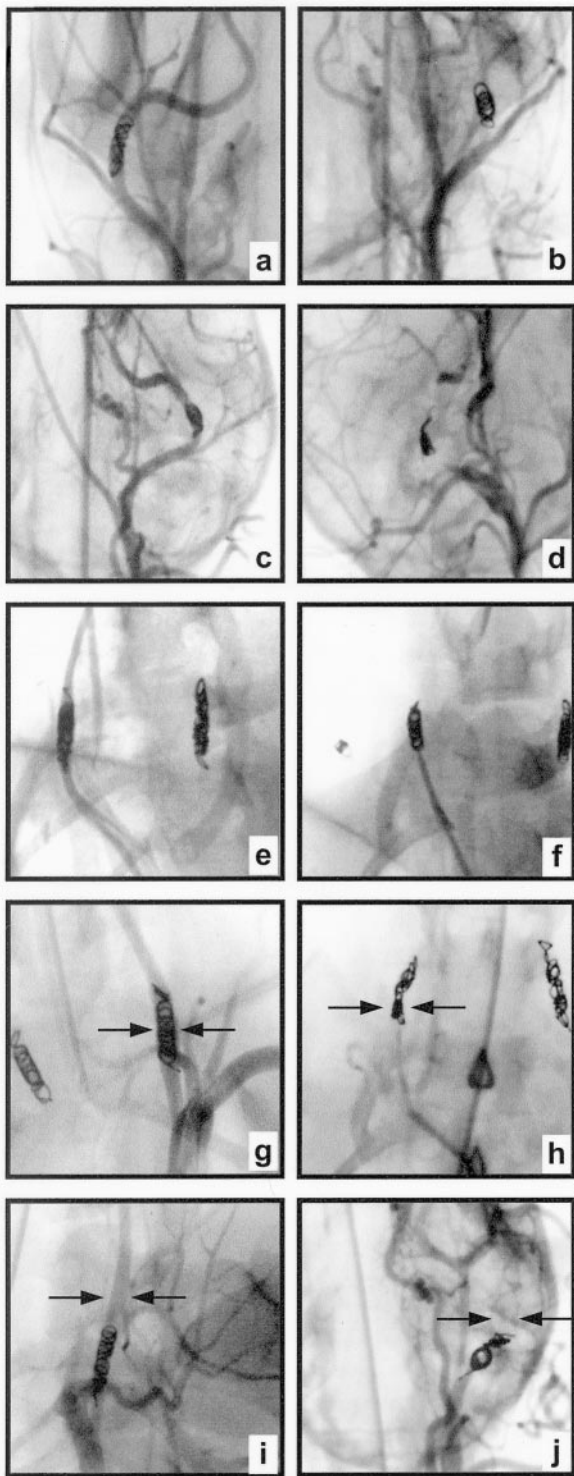


Figure 1. Recanalization in arterial occlusion model: angiographic results. Selected images are from angiograms performed 4 weeks after coil occlusion of maxillary (a to d, j) or vertebral (e to i) arteries with radioactive (b, d, f, h, j) or nonradioactive (a, c, e, g, i) devices. Arteries were occluded with one 8-cm caliber 0.015 (a, b) or one 8-cm caliber 0.010 (c, d) coil, two 8-cm caliber 0.015 coils (e, f), and one 10-cm caliber 0.015 coil within (g, h) or proximal to a 3×16-mm stent (i, j). Activity levels were 1.58 (coil in b), 1.34 (d), 0.50+0.67 (coils in f), 2.73 (stent in h), and 3.06 μ Ci (stent in j). Note that all arteries implanted with radioactive devices are occluded, while arteries occluded with nonradioactive devices recanalized. Arrows indicate intra-arterial stents.

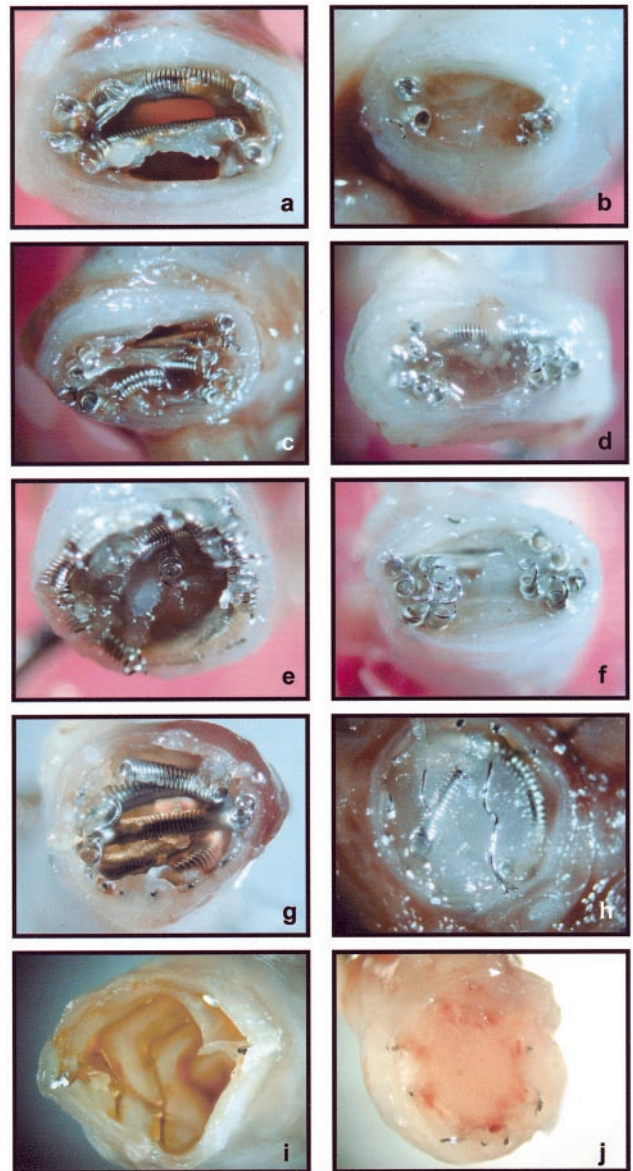


Figure 2. Recanalization in arterial occlusion model: macroscopic results. Selected photographs are cross sections of maxillary (a to d) or vertebral (e to j) arteries 4 weeks after coil occlusion of arteries with radioactive (b, d, f, h, j) or nonradioactive (a, c, e, g, i) devices. Arteries were occluded with one 8-cm caliber 0.015 (a, b) or one 8-cm caliber 0.010 (c, d) coil, two 8-cm caliber 0.015 coils (e, f), and one 10-cm caliber 0.015 coil within (g, h) or proximal to a 3×16-mm stent (i, j). Activity levels were 1.84 (coil in b), 1.28 (d), 0.55+0.68 (coils in f), 2.28 (stent in h), and 3.06 μ Ci (stent in j). Note recanalization of arteries implanted with nonradioactive devices and complete occlusion of arteries implanted with radioactive devices.

Pathology

Arteries implanted with coils or common carotid arteries bearing aneurysms were excised after the animals were killed. 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* with the use of an operating microscope. Pathological specimens were studied after formalin fixation, axial sectioning, and staining, as previously described.¹

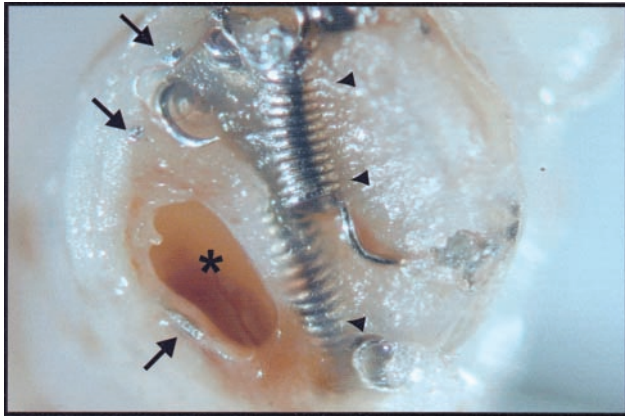


Figure 3. Recanalization despite beta radiation. Macroscopic photography shows arterial section 4 weeks after occlusion of vertebral artery with a 3×10-cm caliber 0.015 coil (arrowheads) ion-implanted with 2.65 μCi and deployed within a nonradioactive stent (arrows). This is 1 of the 3 of 52 arteries that recanalized despite beta radiation. Note that this phenomenon occurred within the stent in an area devoid of radioactive coil loops (asterisk).

Results

Arterial Occlusion Model

The recanalization rates of arteries occluded with coils and stents of various activity levels are summarized in Table 1 and illustrated in Figures 1 and 2.

All arteries remained occluded 1 week after device implantation. All arteries (29 of 29) occluded with nonradioactive devices were recanalized at 4 weeks.

Overall recanalization was inhibited in 49 of 52 arteries (94%) implanted with ^{32}P devices, and these arteries remained occluded at 4 ($n=49$) and 12 ($n=18$) weeks. This difference with nonradioactive devices was significant ($P<0.01$, χ^2 test). Recanalized arteries occluded with radioactive coils (3 of 52) had been subjected to volumetric activity levels of 0.016, 0.020, and 0.030 $\mu\text{Ci}/\text{mm}^3$. In this last case, recanalization occurred within a space delimited by the nonradioactive stent, outside the coil mesh of the radioactive coil (Figure 3).

Macroscopic photography of axial sections confirmed the complete occlusion of arteries implanted with radioactive devices and the presence of large recanalizing channels in arteries initially occluded with nonradioactive devices (Fig-

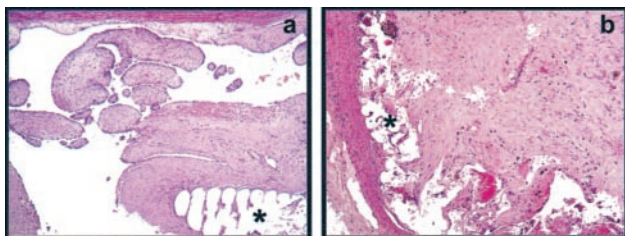


Figure 4. Histological findings. Microscopic photography shows arterial sections stained with hematoxylin and eosin 4 weeks after embolization with nonradioactive (a) or radioactive (b) coils. Note defects from coil loops (asterisk) and extensive recanalization with polypoid appearance of residual tissues covered with endothelium (a). Arteries occluded with radioactive coils are filled with fibrous tissue (b). Magnification $\times 100$.

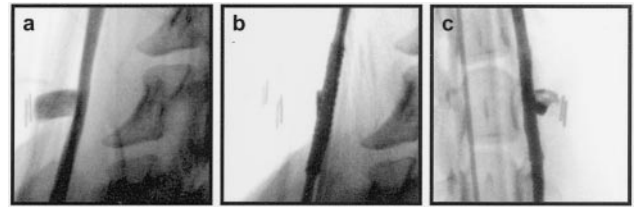


Figure 5. Stents and lateral wall aneurysms. Angiographic results before (a), immediately after (b), and 4 weeks after (c) deployment of 2 overlapping radioactive stents (totaling 16.49 μCi) in front of left carotid aneurysm are shown. Note persistent opacification of aneurysm despite partial thrombosis.

ure 2). These channels were endothelialized at histopathology, and the neointima covering coils and stents was of variable thickness (Figures 2 to 5). Transverse sections of arteries occluded with radioactive devices showed variable organization of the clot, which was more evident at 12 weeks (Figure 4).

Lateral Wall Aneurysm Model

All aneurysms showed residual filling of the sac by persisting although altered flow channels through the stent struts immediately after stent implantation into the carotid arteries. All aneurysms treated with stents, radioactive or not, demonstrated residual filling of the sac or of channels leading to the aneurysmal sac at follow-up angiography at 1 or 4 weeks, provided that the carotid artery remained patent (Figure 5). None of the 9 control carotid arteries implanted with nonradioactive stents but 6 of 19 carotid arteries implanted with radioactive stents showed nonocclusive endoluminal clots 1 week after treatment. This difference was significant ($P<0.01$, χ^2 test). Four of those 6 carotid arteries were occluded at 4 weeks, all treated with stents of moderate or high total activity (4.02, 4.08, 8.12, and 16.36 μCi). None of the carotid arteries treated with control stents were occluded at 4 weeks. On macroscopic photography, the neointima covering the stent was “perforated” by endothelialized channels that were continuous with residual cavities inside the aneurysmal sac in some specimens and with “neovessels” in others (Figure 6). Some of the high-activity stents were covered with an incomplete or immature neointima still containing unorganized clot. The aneurysmal sacs themselves were most often occluded with richly vascularized connective

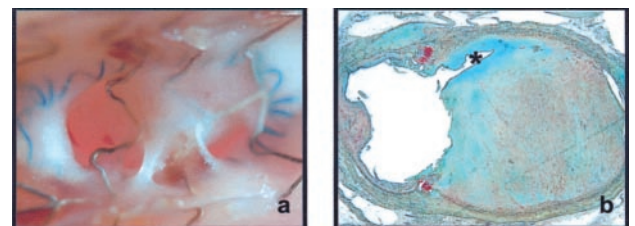


Figure 6. Evolution of aneurysmal neck after stent implantation. Macroscopic photograph (a) and microscopic photograph (b) of aneurysmal neck 4 weeks after radioactive stent implantation (4.38 μCi) are shown. While neointima formed on the stent struts (a), endothelialized spaces persisted through the stent, communicating with residual aneurysmal cavity (asterisk in panel b). The aneurysmal sac is filled with connective tissue.

tissue (Figure 6). Large residual aneurysms containing unorganized clot were present in others. Treatment with 2 overlapping nonradioactive stents led to better but still incomplete neointimal coverage of the neck (n=1). Neointimal coverage of 2 overlapping high-activity stents was incomplete in some areas (n=2).

Discussion

Recanalization and Variations in Coil Caliber, Length, Number, and Activity

We have previously shown that *in situ* beta radiation prevents recanalization after coil embolization.¹ This process seems to occur soon after coil implantation into canine arteries, and if recanalization is inhibited for 3 weeks, arteries remain occluded at 3 months.¹ We thus limited the period of observation to 4 weeks for most animals of the present experiments. The coil arterial occlusion model is simple and reliable. Multiple devices (up to 6) can be compared within the same animal. Coil occlusions routinely recanalize, and, as such, this model is well suited to evaluate coil modification strategies designed to inhibit recanalization. This model is not subject to variations of residual flow found after embolization at the neck of aneurysmal models, which can confuse follow-up results.

The present study emphasizes the strength of the recanalization process after coil occlusion of canine arteries, which occurred routinely regardless of coil caliber, coil length, resulting packing density, and with or without stainless steel stents adding to the bulk of the embolic agents.

Beta radiation is effective in inhibiting recanalization, and this effect is robust; provided that an "effective volumetric activity" is reached, it is effective whether the total activity is delivered by a single coil of various length or caliber, 2 coils of half the total activity each, or 1 radioactive coil deployed with a nonradioactive coil or shielded by a stainless steel stent.

These observations are reassuring for the clinical use of radioactive coils in endovascular treatment of aneurysms. To a certain extent, the use of nonradioactive coils that may be more appropriate at a certain phase of the intervention is feasible without jeopardizing the efficacy of radioactive coils in inhibiting recanalization. Furthermore, 2 low-activity coils can replace a single high-activity coil provided that the volumetric activity reaches $0.018 \mu\text{Ci}/\text{mm}^3$.² These experiments support the clinical use of effective volumetric activity (the total activity distributed throughout the aneurysm), which should be $>0.018 \mu\text{Ci}/\text{mm}^3$, as a guide to radioactive embolization of aneurysms.¹ This "effective level" of activity was extracted from our previous study in the arterial occlusion model by dividing the activity necessary to prevent recanalization by the volume of the arterial segment occupied by the coil.^{1,2} To maximize the radioactive coil strategy and ensure inhibition of recanalization anywhere coils have caused thrombosis, however, we believe that the aneurysm should be filled with coils that are all radioactive to the extent that this is possible.¹

Stent-Coil Experiments

With this modification of our model, we wished to explore the importance of the distribution of the radioactive device on the recanalization phenomenon. In theory, stents would apply radiation closer to the vessel wall compared with endoluminal coils. We anticipated that, because of the low penetration of beta radiation (70% of the energy is deposited within 1 mm), radioactive stents could have shown a narrow recanalizing channel in the center of the lumen after proximal coil occlusion. Conversely, with the other modification of the model, radiation emitted from endoluminal coils could have been shielded away from the vessel wall by stainless steel stents. However, all arteries implanted with the nonradioactive stent-coil combination recanalized, while most (14 of 15) arteries implanted with the radioactive combination remain occluded whether the radiation was delivered by the coil within the stent or by the stent itself.

Radioactive Stents and Lateral Wall Canine Aneurysms

Stents positioned across the neck of lateral wall aneurysms modify blood flow inside the sac. With time, the aneurysm partially thromboses, and the thrombus is progressively organized. However, residual channels through the stent struts remain patent and become endothelialized, in effect preventing complete closure of the aneurysmal neck.^{5,6} This phenomenon could not be inhibited by beta radiation emitted from radioactive stents. Some of the stents were implanted with ³²P activity levels that were sufficient to cause other biological effects such as late thrombotic phenomena probably related to delayed re-endothelialization.⁷ Although radioactive stents were intended to prevent neointima formation, a number of preclinical studies have shown a paradoxical increase in neointima formation.⁸ A simple explanation for the lack of effect of radioactive stents on neck closure is that residual channels through the stent struts persisted for the entire duration of the experiment, without the temporary 1-week occlusion observed in the arterial occlusion model. Beta radiation prevents recanalization, and thrombus formation is a prerequisite for this phenomenon.

One of the goals of a radioactive coil strategy is to preserve the safety of coil embolization while attempting to improve long-term efficacy by inhibition of recanalization. This is possible because mechanical aspects of the procedure remain unchanged. We expect the same advantages but also the same drawbacks, including suboptimal mechanical closure of the aneurysmal neck, in a significant proportion of patients.⁹ In clinical practice, coils are often loosely packed near the parent artery, leaving residual blood flow at the neck of treated aneurysms. The present experiment suggests that applying radiation exclusively at the neck-parent vessel interface would be insufficient. The persistence of residual channels through the struts of radioactive stents suggests that beta radiation will not cause closure of the neck if coils are poorly occlusive. The expectation is that recanalization, which may be related to early endothelial invasion,^{1,10} will be inhibited by radiation deeper inside the neck, where coils are effective in producing thrombosis, thus stopping the evolution toward recurrences.

Conclusion

The recanalization process is minimally affected by coil caliber, number, length, or packing density in the canine arterial occlusion model. Beta radiation with volumetric activity levels $>0.018 \mu\text{Ci}/\text{mm}^3$ reliably inhibits this process. Radioactive stents deployed across the neck of aneurysms did not prevent the formation of endothelialized channels leading to residual aneurysms and routinely found after implantation of nonradioactive stents.

Acknowledgments

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