

## Safety and Effectiveness of Radioactive Coil Embolization of Aneurysms : Effects of Radiation on Recanalization, Clot Organization, Neointima Formation, and Surrounding Nerves in Experimental Models

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*Stroke*. 2006;37:2147-2152; originally published online June 29, 2006;

doi: 10.1161/01.STR.0000231724.18357.68

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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# Safety and Effectiveness of Radioactive Coil Embolization of Aneurysms

## Effects of Radiation on Recanalization, Clot Organization, Neointima Formation, and Surrounding Nerves in Experimental Models

Jean Raymond, MD; Charbel Mounayer, MD; Igor Salazkin, MD; Annick Metcalfe, MSc; Guylaine Gevry, BSc; Christian Janicki, PhD; Sjoerd Roorda, PhD; Philippe Leblanc, PhD

**Background and Purpose**—Recanalization after coil embolization can be prevented by radiation emitted from  $^{32}\text{P}$  coils.

We wanted to determine the upper limits of  $^{32}\text{P}$  activities that could be implanted onto coils with respect to the potential injury to nearby nerves, delay in organization of the clot, and effects on neointima formation and recanalization.

**Methods**—We studied the effects of various  $^{32}\text{P}$  activities on recanalization and organization of thrombus after coil occlusion of canine arteries and on neointima formation at the neck of canine carotid bifurcation aneurysms. We also tested potential injury to nerves in the vicinity of radioactive or nonradioactive coils in 3 models: the brachial plexus (near proximal vertebral arteries) and the lingual nerve in a lingual artery bifurcation aneurysm model, both models being treated by radioactive or standard coil occlusion. Finally, we wrapped lingual nerves with nonradioactive or high-activity coils and studied their effects on lingual nerves and tongues. Results were assessed with a pathological scoring system and compared with Mann-Whitney and Kruskal-Wallis tests.

**Results**—No deleterious effect of radiation on nerves could be detected. Neointima formation was not hampered, scores of aneurysms treated with  $^{32}\text{P}$ -coils being significantly better when compared with treatments with standard coils ( $P=0.002$ ). Arteries treated with high-activity coils ( $>3.39\ \mu\text{Ci}$ ) showed absent recanalization but delayed organization of the clot at 3 months compared with low-activity or nonradioactive coils ( $P<0.05$ ).

**Conclusions**— $\beta$ -Radiation can prevent recanalization after coil occlusion. We could not demonstrate any deleterious effects of radioactivity on nervous structure or on neointima formation. Delayed organization of thrombus provides a rational basis to establish an upper limit for  $^{32}\text{P}$  activities to be implanted onto coils. (*Stroke*. 2006;37:2147-2152.)

**Key Words:** animal models ■ nerve degeneration ■ radiation ■ recanalization

In situ  $\beta$ -radiation emitted from  $^{32}\text{P}$  coils can prevent recanalization after coil embolization in experimental models.<sup>1,2</sup> This strategy does not modify the mechanical characteristics of the device, but we hoped to decrease the incidence of recurrences that have been found in 15% to 33% of patients at follow-up angiography.<sup>3,4</sup>

Because  $^{32}\text{P}$  activities introduced into aneurysms have to be tailored to the size of the lesion, we defined a minimal therapeutic activity according to the volume of the lesion. This volumic activity ( $0.018\ \mu\text{Ci}/\text{mm}^3$ ) derives from mathematical calculations of activities effective in preventing recanalization in preclinical studies.<sup>1,2</sup> We also arbitrarily chose maximal volumic activities as the ones prescribed in the treatment for cystic craniopharyngiomas with colloidal  $^{32}\text{P}$ .<sup>5-8</sup> We have shown the feasibility of such an approach in virtual series as well as in a pilot clinical study.<sup>5,7,9</sup>

We now wanted to better circumscribe the safety of such an approach. Main concerns regarding in situ vascular  $\beta$ -radiation include delayed healing of aneurysms and radiation damage to neighboring structures, particularly cranial nerves that may be in the vicinity of intracranial aneurysms. Thus, we studied and compared the organization of the clot and the maturity of the neointima formed in arteries (Figure 1a) and in experimental bifurcation aneurysms (Figure 1b) treated by standard or radioactive coils of various activities. Because the vertebral artery lies in the vicinity of the brachial plexus, we compared animals in which vertebral arteries were treated with radioactive versus standard coil embolization (Figure 1c). We also constructed bifurcation aneurysms in contact with the lingual nerve and verified potential effects of embolization by normal or radioactive coils on nerve structure and function<sup>8</sup> (Figure 1d). In additional experiments, we

Received October 7, 2005; final revision received March 23, 2006; accepted March 31, 2006.

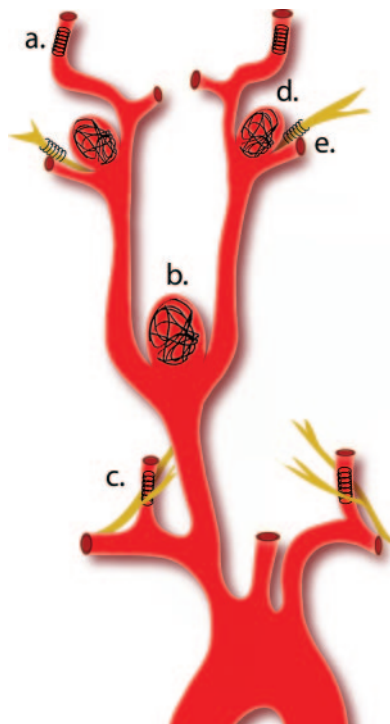
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Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000231724.18357.68



**Figure 1.** Experimental groups. Schematic illustration of experiments and groups. a, Maxillary artery coil occlusion model; b, venous pouch carotid bifurcation aneurysm model; c, coil occlusion model in vertebral arteries near the brachial plexus; d, lingual bifurcation aneurysm model; e, lingual nerve coiling.

wrapped the lingual nerve with high-activity or nonradioactive coils in an effort to increase exposure and document the effects on tissues and function (Figure 1e). We did not find deleterious effects of radiation on nerves, but we propose an objective upper limit of activities to be implanted onto coils based on potential delay in organization of the clot that forms after embolization.

## Materials and Methods

### 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. Experimental groups are summarized in Figure 1. All surgical and endovascular procedures were performed under general anesthesia.

### Arterial Occlusion Model

The arterial occlusion model has previously been described.<sup>1,2</sup> In brief, a percutaneous femoral puncture was used to reach the bilateral maxillary or vertebral arteries with 2F microcatheters introduced coaxially through 5F catheters. A 3-mm caliber 0.015 platinum coil, 10 cm long, radioactive or not, was implanted into a 10-mm segment

of each artery. Coils were made radioactive by ion implantation of <sup>32</sup>P, as described.<sup>1,2</sup>

The first centimeters of the vertebral arteries are in the vicinity of the proximal divisions of the brachial plexus (Figure 1). Thus, we compared clinical and pathological effects on the brachial plexus of radioactive (n=30) or nonradioactive (n=26) coil embolization at 3 months.

Follow-up angiography was performed immediately after embolization and at 1 hour, 4 weeks, and 12 weeks. Multiple projections after selective injections were interpreted without knowledge of the nature or activities of the coils used. Occlusion was defined as the absence of antegrade blood flow through the arterial segment treated by coiling. Any antegrade contrast opacification was sufficient to label the artery recanalized.

We studied the effects of coils of various activities (total n=122, summarized in Table 1) on angiographic recanalization, as well as on the quality of the endoluminal tissue at pathology at 3 months, and compared them with results obtained with nonradioactive coils. Coils were of low ( $0 < x < 1.13 \mu\text{Ci}$ ), medium ( $1.13 \leq x < 3.39 \mu\text{Ci}$ ), or high ( $3.39 \leq x < 6.80 \mu\text{Ci}$ ; mean,  $0.50 \mu\text{Ci/cm}$ ) activity. To translate this information into data that could be useful for aneurysmal applications, we estimated the doses corresponding to the highest activities with the use of dose-point kernel calculations in a cylindrical model that does not take into account shielding by platinum<sup>1</sup> (Figure 2).

### Effects of Radiation on Neointima Formation at the Neck of Treated Aneurysms

To look for potential effects of radiation on neointima formation at the neck of treated aneurysms, we studied bifurcation aneurysms treated with standard or radioactive coils, some of which (12) have previously been published.<sup>1,2</sup> Venous pouch, carotid wide-necked bifurcation aneurysms (n=44) were constructed as described<sup>10,11</sup> and embolized with radioactive (n=21) or nonradioactive coils (n=23). The effects on angiographic results as well as the quality of the neointimal tissue at the neck were compared at 3 months (Figure 3). Transfemoral angiography was undertaken immediately after embolization, at 3 weeks, and at 3 months. Angiographic results were scored according to a previously described classification.<sup>12</sup> A score of 0 indicated complete obliteration; 1, "dog ears"; 2, residual or recurrent neck; and 3, residual or recurrent aneurysm; a score of 4 indicated large saccular recurrences. Neointimal scores were determined as explained next.

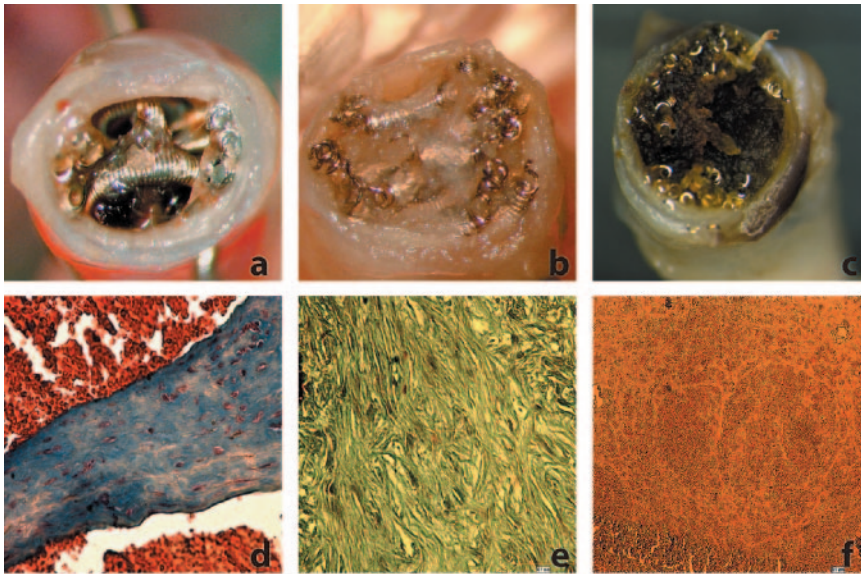
### Effects of Radiation on Lingual Nerves

Bifurcation aneurysms were constructed with venous pouches in 8 animals on the external carotid arteries, at the origin of the lingual arteries, as previously described.<sup>13</sup> In this model, the lingual nerve is in contact with the aneurysm. We compared the effects of radioactive ( $0.024$  to  $0.63 \mu\text{Ci/mm}^3$ ; mean,  $0.054 \mu\text{Ci/mm}^3$ ) and nonradioactive embolization on the function and histological appearance of the ipsilateral lingual nerve and on the tongue at 3 months (n=6) and 1 year (n=2 animals). We also performed autoradiographs at 3 months in 2 animals with calibrated films (MD55-2; Gafchromic, Nuclear Associates, Fluke biomedical, Cleveland, Ohio). To reach higher doses on the nerve, we also studied the effects of banding the lingual nerve with high-activity (2.99, 3.43, 4.43, or  $4.46 \mu\text{Ci}$ ) or nonradioactive coils in 4 animals followed up for 3 months (n=2) or 1 year (n=2).

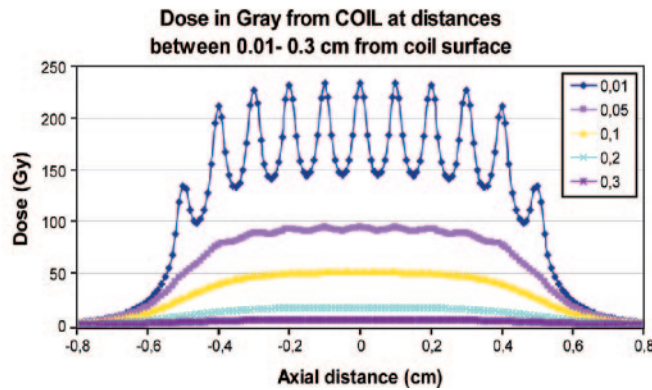
**TABLE 1. Single-Coil Arterial Occlusion Model**

	Coil Activities, $\mu\text{Ci}$			
	0	$0 < x < 1.13$	$1.13 \leq x < 3.39$	$3.39 \leq x < 6.80$
n	39	18	54	11
Recanalization at 3 months	97.44%	44.44%	12.96%	0%†
Median organization score	0	0	1	1*

\* $P < 0.05$ , † $P < 0.001$ , compared with standard coils.



**Figure 2.** Single-coil arterial occlusion model. Macroscopic photographs (a through c) and microphotographs (d through f) of arteries treated with coils of various activities showing recanalization with standard coils (a, d), no recanalization but clot organization with 1.2  $\mu\text{Ci}$  (b, e), and no recanalization but no organization with high-activity coils (6.81  $\mu\text{Ci}$ ; c, f) (Movat's pentachrome; original magnification  $\times 100$ ). A graphic illustration of doses to tissues according to distance from the coil surface is shown in g (coil of 5  $\mu\text{Ci}$ ; assuming solid coil 300  $\mu\text{m}$ /all water; 1400 days).



**Macroscopic Photography and Pathology**

Macroscopic and microscopic stereophotographs of cut sections of arteries and en face views of the neck of bifurcation aneurysms were taken with a computerized imaging system (Vision PE, Clemex). Neointima formation and recanalization at the neck of bifurcation aneurysms or at the level of the arterial section were evaluated, without knowledge of coil activities, according to a previously described scoring system.<sup>11</sup> In brief, neointima formation was labeled with a score of 0 when a thick neointima completely sealed the aneurysmal neck; a score of 1 when small areas of recanalization were seen; a score of 2 when a crescent of recanalization was present around the neointima covering the coil mass; a score of 3 when recanalization affected the coil mass; and a score of 4 when no neointima, only thrombus, was found. The same type of classification was used to assess arteries. The degree of organization of arterial

thrombus was also scored into 3 categories: completely or near completely organized (0), intermediate (1), and unorganized (2) thrombus. Arteries and aneurysms were studied after formalin fixation, axial sectioning, and staining with hematoxylin-phloxine-saffron and Movat's pentachrome stain.

The amount of fibrosis encountered during dissection of the lingual nerves treated with radioactive or nonradioactive coils was also evaluated in a blinded fashion. Lingual nerves and tongues were photographed before and after fixation and sectioning in the axial plane. Sections were embedded in paraffin for light microscopic examination of tissues after staining with hematoxylin-phloxine-saffron and Gomori's trichrome stain for nerve sections.

**Statistics**

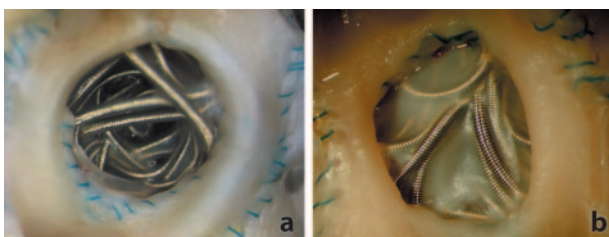
Angiographic occlusion rates and neointima formation in aneurysms treated with standard or radioactive coils were compared with *t* and Mann-Whitney tests. Angiographic and macroscopic pathological results with <sup>32</sup>P or standard coils in the arterial model were compared with the Kruskal-Wallis test. A probability value <0.05 was considered significant.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

**Arterial Occlusion Model**

In situ  $\beta$ -radiation could prevent angiographic recanalization compared with standard coils ( $P \leq 0.001$ ; Table 1) and was



**Figure 3.** Carotid bifurcation aneurysm model. Stereophotographs of en face views of the neck of aneurysms treated with nonradioactive (a) or <sup>32</sup>P (b, 0.03  $\mu\text{Ci}/\text{mm}^3$ ) coils, showing complete neointima in radioactive aneurysm.

TABLE 2. Carotid Bifurcation Aneurysm Model

	Radioactive Coils	Nonradioactive Coils	P
n	21	23	
Long-axis mean size, mm	8.2±1.8	11.0±2.8	0.001*
Short-axis mean size, mm	6.9±1.6	7.7±1.7	0.123*
Neck mean size, mm	5.7±1.1	6.6±1.8	0.057*
Mean packing density	31.28±15.23	26.35±15.60	0.307*
Mean activity, $\mu\text{Ci}/\text{mm}^3$	0.036±0.028	0	...
Initial results median, $t_0$	1	1	0.526†
Angiographic results median, $t_3$ mo	0	2	0.003†
Neointimal score, median	2	2	0.002†

\* $t$  test.

†Mann-Whitney test.

more effective when activities increased. Organization of the clot at 3 months was complete in all groups, including arteries treated by radiation, except for coils of higher activities: arteries remained occluded, but histopathological results showed unorganized clot, reflecting “delayed healing” when  $^{32}\text{P}$  activities were high ( $>3.39 \mu\text{Ci}$ ; Table 1 and Figure 2). Dose-point kernel calculations revealed that these activities corresponded to a dose approaching 100 Gy at 0.5 mm from the coil surface (Figure 2).

### Bifurcation Aneurysm Models

Aneurysms treated with radioactive coils were smaller and showed better angiographic results at 3 months than aneurysms treated with standard coils. Neointima formation could proceed despite radiation. In fact, radioactively treated aneurysms showed a better median neointimal scores at 3 months ( $P=0.002$ ; Table 2 and Figure 3) compared with aneurysms treated with standard coils.

### Radiation Effects on Nervous Structures

#### Effects on Lingual Nerves

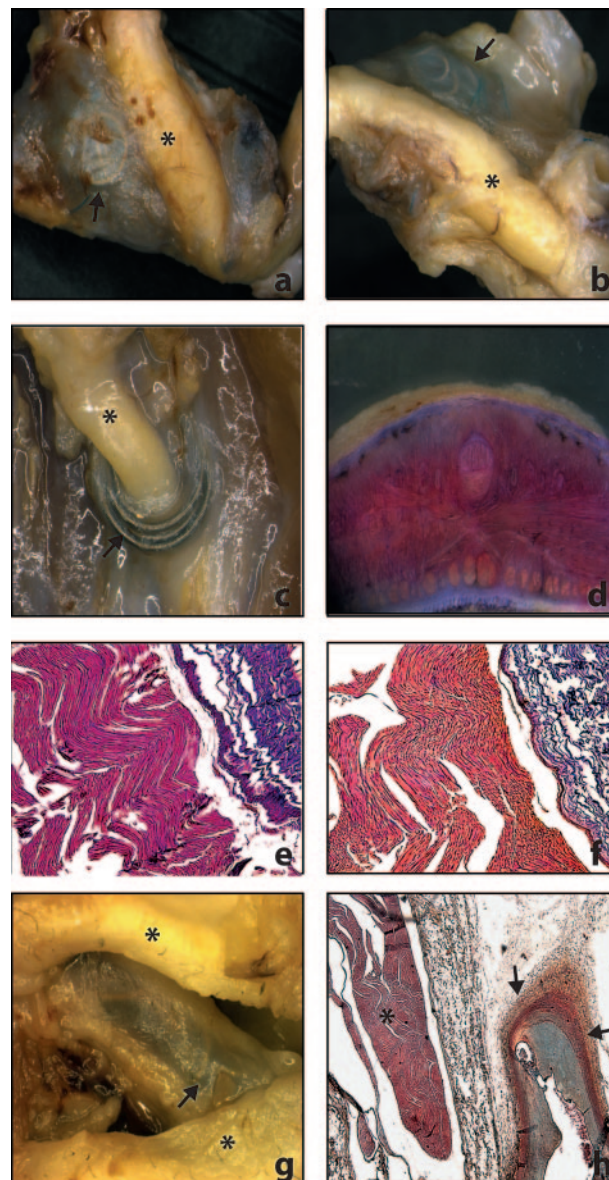
Embolization of lingual bifurcation aneurysms with radioactive or nonradioactive coils did not lead to any clinical or pathological signs of injury to lingual nerves (fibrosis or axonal degeneration) or atrophy of tongues (Figure 4). Wrapping the nerves with high-activity or nonradioactive coils did not cause any perceptible effect either (Figure 4). Fibrosis around the coil at 3 months and 1 year was judged to be more abundant on the radioactive side on 2 occasions and on the nonradioactive side on 2 other occasions.

#### Effects on Brachial Plexus

None of the animals in which vertebral arteries were treated with  $^{32}\text{P}$  or nonradioactive coils developed a neurological deficit. There was no pathological abnormality in nerves nearby radioactive or nonradioactive coils.

### Discussion

The rate of recanalization after coil occlusion of canine arteries is related to the activity of  $^{32}\text{P}$  following an exponential curve. An activity of  $0.018 \mu\text{Ci}/\text{mm}^3$  is sufficient to prevent recanalization in 87% of arteries, whereas arteries



**Figure 4.** Effects of radiation on nearby nerves. Photographs of bilateral lingual bifurcation aneurysm model 3 months after embolization with nonradioactive (a) or radioactive (b) coils (arrow) showing close relationship with lingual nerve (\*). In another experiment, the coil was wrapped around the lingual nerve itself (c). Nerves and tongues (d) were studied by photography and histopathology (e, f). Gomori's trichrome staining of nerves wrapped with nonradioactive (e) or  $^{32}\text{P}$  (f) coils shows no injury. Macro and microphotographs of the proximal vertebral artery (arrow in h) show the proximity of the radioactive coil to the brachial plexus (\*) (g, h). (Movat's pentachrome; original magnification  $\times 20$ ).

occluded with nonradioactive coils showed almost constant recanalization.<sup>1,2</sup> Having defined a minimal activity to prevent recanalization, we wanted to determine a maximal activity to prevent complications.

One empiric choice was to limit the total activity to the prescribed dose in the treatment of craniopharyngiomas.<sup>14–16</sup> Tables have been designed to prescribe activities/volumes necessary to treat intracranial cysts; they aim at 3 times the activities to prevent recanalization, or  $0.06 \mu\text{Ci}/\text{mm}^3$ .<sup>3,17</sup> For centers equipped with 3-dimensional volumetric equipment, the thera-

peutic “window”  $A$  would be  $0.018 \mu\text{Ci}/\text{mm}^3 < A < 0.06 \mu\text{Ci}/\text{mm}^3$ .

However, is it possible to find objective ways to define maximal activities by an experimental, observational approach? The main concerns are (1) the risk of radiation damage to neighboring nervous structures, as well as (2) the potential to prevent neointima formation at the neck of treated aneurysms, or delayed organization of aneurysmal thrombus, with the theoretical risks of embolic complications and delayed recurrences.

### Risk to Nervous Structures

There is no recognized model to study the effects of  $\beta$ -radiation on nervous tissues. The literature mainly concerns conventional radiotherapy. Pertinent factors involved in increasing the risks of radiation are a large total dose, a large irradiated volume, and a small number of fractions given over a short period of time.<sup>18,19</sup> Conventional radiotherapy has been associated with brain injury in 0.04% to 0.4% of cases.<sup>19</sup> Maximal doses given in 1 fraction by stereotactic radiosurgery for arteriovenous malformations have been associated with a higher risk (1% to 4%).<sup>20–22</sup> Local  $\beta$ -radiation minimizes risks because intrinsic safety factors include small total activities, small irradiated volumes (consisting of a rim of a few millimeters surrounding the coil mass), long treatment time, and above all, low dose rates. Multiplying fractions used to deliver the total dose during weeks is the most important factor to reduce radiation injury with conventional radiotherapy.  $\beta$ -Radiation delivers the total dose in an infinite number of small “fractions” during the lifetime of the isotope. Thus, we believe that the risks associated with  $^{32}\text{P}$  coils should be negligible or  $<1\%$ .

The lingual bifurcation aneurysm model provides an experimental situation wherein a cranial nerve is in contact with the aneurysmal sac.<sup>13</sup> Aneurysms can be embolized with  $^{32}\text{P}$  coils, and the animal may be observed for neurological symptoms or the appearance of lingual atrophy. Because the dose varies according to the distance from the source, we also ensured delivery of the highest possible dose by wrapping high-activity coils around the nerve itself. We did not observe any clinical or histopathological evidence of nerve damage, tissue atrophy, or fatty replacement of the tongue. However, the absence of any deleterious effects could be explained by a lack of sensitivity of our experimental model.

Another means of assessing the safety of radioactive embolization is to study the effects of radiation emitted from proximal vertebral arteries on the adjacent brachial plexus. In this experiment, we have a positive historical control in the same model: the frequent occurrence of clinical brachial plexus injury and axonal degeneration by endovascular balloon cryoablation before coil occlusion, found in 3 of 5 animals in which this strategy was used to prevent recanalization in another study.<sup>23</sup> Radioactive coils (with activities  $>1.13 \mu\text{Ci}$ ) could prevent recanalization without nerve injury. Although this finding is reassuring, such an approach can only exclude the occurrence of a constant or frequent event and cannot be used to predict stochastic phenomena that could occur in clinical practice. Thus, this preclinical work does not establish the safety of the approach that ultimately would need to be assessed in a clinical trial.<sup>1</sup>

### Effects on Thrombus Organization

The tissue that will constantly be in closest contact with the radioactive coils is the organizing clot and neointima that forms at the surface of the coil mass at the neck of treated aneurysm. Because  $\beta$ -radiation has been proposed to prevent restenosis in coronary stents, delayed healing or poor neointima formation at the neck of treated aneurysms is a concern. However, neointima formation was increased and more complete in aneurysms treated with  $^{32}\text{P}$  coils compared with standard coils.

The 2 groups that were compared differed in mean sizes, and nonradioactive aneurysms tended to have a wider neck (Table 2). These facts alone could explain the better angiographic results at 3 months in aneurysms treated with radioactive coils. Because there is also a relation between angiographic result and neointima formation,<sup>24</sup> we can only claim that neointima formation at the neck was not hampered by activities within the range used for this study ( $0.036 \pm 0.028 \mu\text{Ci}/\text{mm}^3$ ).

We do not subscribe to the theory that a small dose stimulates whereas a large dose inhibits neointima formation. We rather believe that neointima formation at the neck is the result of 2 concurrent phenomena responsible for the evolution of thrombus after coil deposition, recanalization and organization.<sup>25</sup> Activities between 0.018 and  $0.048 \mu\text{Ci}/\text{mm}^3$  are sufficient to prevent recanalization but do not prevent organization by 3 months. However, higher activities approaching those prescribed in the treatment of craniopharyngiomas were shown to delay organization in the arterial model.

The single-coil arterial occlusion model that was used to study the effects of radiation on recanalization and organization of thrombus is not meant to mimic clinical embolization of aneurysms. It is a valuable scientific tool because it permits the study of a repeatable phenomenon in a reliable fashion and the determination of dose-effect relations without confounding factors, such as differences in aneurysm construction, size, or shape; extent of embolization; and packing density. This experimental testing was thus performed in a very different context than the clinical situation, wherein recanalization is much less prevalent and expectable.<sup>4</sup> It is always uncertain whether experimental findings can be extrapolated to clinical problems.

### Conclusion

$\beta$ -Radiation prevents recanalization after coil occlusion. We could not demonstrate deleterious effects of radioactivity on nervous structure or on neointima formation. High activities can delay organization, and this phenomenon provides a rational basis to fix an upper limit for  $^{32}\text{P}$  activities to be implanted onto coils.

### Sources of Funding

This study was supported by grants from the Canadian Institutes of Health Research (MOP-44062) and the Heart and Stroke Foundation of Canada.

### Disclosures

None.

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