Bipolar radiofrequency ablation of aneurysm remnants after coil embolization can improve endovascular treatment of experimental bifurcation aneurysms

Xavier Boileau, MD,1 Han Zeng, MD,1 Robert Fahed, MD,1 Fabrice Bing, MD,1,2 Alina Makoyeva, MD,1 Tim E. Darsaut, MD,3 Pierre Savard, PhD,4 Benoit Coutu, MD,5 Igor Salazkin, MD,1 and Jean Raymond, MD1,2

1Centre Hospitalier de l’Université de Montréal Research Centre (CRCHUM), Notre-Dame Hospital, Interventional Neuroradiology Research Laboratory, Montreal, Quebec; 2Centre Hospitalier de l’Université de Montréal (CHUM), Notre-Dame Hospital, Department of Radiology, Service of Neuroradiology, Montreal, Quebec; 3University of Alberta Hospital, Mackenzie Health Sciences Centre, Department of Surgery, Division of Neurosurgery, Edmonton, Alberta; 4Institute of Biomedical Engineering, École Polytechnique de Montréal; and 5Centre Hospitalier de l’Université de Montréal (CHUM), Notre-Dame Hospital, Department of Medicine, Service of Cardiology, Montreal, Quebec, Canada

OBJECTIVE Endovascular treatment of aneurysms may result in incomplete initial occlusion and aneurysm recurrence at angiographic follow-up studies. This study aimed to assess the feasibility and efficacy of bipolar radiofrequency ablation (RFA) of aneurysm remnants after coil embolization.

METHODS Bipolar RFA was accomplished using the coil mass as 1 electrode, while the second electrode was a stent placed across the aneurysmal neck. After preliminary experiments and protocol approval from the Animal Care committee, wide-necked bifurcation aneurysms were constructed in 24 animals. Aneurysms were allocated to 1 of 3 groups: partial intraoperative coil embolization, followed by RFA (n = 12; treated group) or without RFA (n = 6; control group 1); or attempted complete endovascular coil embolization 2–4 weeks later (n = 6; control group 2). Angiographic results were compared at baseline, immediately after RFA, and at 12 weeks, using an ordinal scale. Pathological results and neo-intima formation at the neck were compared using a semiquantitative grading scale.

RESULTS Bipolar RFA was able to reliably target the aneurysm neck when the coil mass and stent were used as electrodes. RFA improved angiographic results immediately after partial coiling (p = 0.0024). Two RFA-related complications occurred, involving transient occlusion of 1 carotid artery and 1 hemorrhage from an adventitial arterial blister. At 12 weeks, angiographic results were improved with RFA (median score of 0), when compared with controls (median score of 2; p = 0.0013). Neointimal closure of the aneurysm neck was better with RFA compared with controls (p = 0.0003).

CONCLUSIONS Bipolar RFA can improve results of embolization in experimental models by selectively ablating residual lesions after coil embolization.

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KEY WORDS intracranial aneurysm; endovascular therapy; stent; animal model; radiofrequency ablation; vascular disorders

Endovascular coiling has revolutionized the treatment of intracranial aneurysms.7,16 The main drawback of this approach is the incidence of aneurysm recurrence, reported to occur in as many as 20% of patients, with 10% eventually requiring retreatment.18 Second-generation coils have not convincingly shown better results.4,14,17,24,26,31 The main risk factors for aneurysm recurrence include aneurysm size, rupture status, and incomplete initial occlusion of the aneurysm.5,6,14,23 Stent-assisted coiling and flow diversion are increasingly used adjunctive or alternative approaches that have shifted the emphasis of treatment from occlusion of the aneurysmal sac to repairing the parent vessel.2 While some have suggested that stent placement or flow diversion
may improve angiographic occlusion of aneurysms, they may carry increased risks\(^9,10\) and evidence of the benefits of this approach in a randomized study is still lacking.\(^3,21\)

One drawback of implanting stents or flow diverters is the double antiplatelet regimen needed to prevent parent vessel occlusion, which also hinders their use in ruptured aneurysms.\(^10\)

Radiofrequency (RF) ablation (RFA) is an interventional technique used in other clinical arenas, including treatment of cardiac arrhythmias or tumor eradication.\(^1,8,11–13,15,30\) We have previously explored the use of RFA to treat aneurysms.\(^28\) Bipolar RFA passes electrical current through biological tissues, causing a controlled thermal injury to the tissues between the electrodes. We hypothesized that a bipolar radiofrequency strategy that employed the intraaneurysmal coil mass as 1 electrode and a stent or flow diverter as the second electrode could focus the current density selectively to target the effects at the aneurysm neck, ablate residual aneurysms, and durably improve results of coil embolization. An RFA strategy could be used in ruptured aneurysms because the stent or flow diverter electrode could be removed at the end of treatment.

To explore how RFA could be achieved with aneurysms of different dimensions, coil masses, sizes of parent vessels, and interelectrode distances, we studied electrical fields in a simplified virtual aneurysm model. Preliminary acute porcine lateral wall aneurysm experiments were followed by tests of feasibility and efficacy in a canine bifurcation aneurysm model that is known to recur after endovascular coiling.\(^27\) We aimed to assess the feasibility and efficacy of bipolar RFA of aneurysm remnants after coil embolization.

### Methods

#### Simulations

Electrical fields were studied using a simplified virtual lateral wall aneurysm model that assumed geometrical electrodes and uniform tissue resistance (200 \(\Omega/cm\)). RFA applications using electrodes schematized as polygons or cylinders were analyzed using finite element software (QuickField Student; Tera Analysis). Maps of dissipated power density (W/m\(^3\)) were generated. Simulations were repeated (n = 72) to study the impact of the following changes: 1) coil mass diameter (5, 10, and 20 mm); 2) stent diameter (2.5 and 5 mm) and length (25 and 50 cm); 3) interelectrode distance (1.25, 2.5, 5, and 10 mm); and 4) generator output (5 and 10 W). Three efficacy regions of interest (ROIs) were chosen at the aneurysm neck while 4 safety ROIs were chosen (3 on the aneurysm fundus and 1 at the level of the parent artery) to study current heterogeneity and estimate the “safety window,” or how well the current density was focused at the target aneurysm neck.

#### Animal Studies

Protocols for animal experimentation were approved by the institutional Animal Committee in accordance with guidelines of the Canadian Council on Animal Care. Lateral wall porcine aneurysms (n = 6) were used to observe the effects of RFA on the aneurysm neck and wall per-operatively and to explore the generator output parameters necessary to ablate residual lesions after coil embolization. Briefly, bilateral wide-necked carotid aneurysms were constructed using the external jugular vein as the venous pouch, as previously described.\(^20\) Coil masses were composed of 45 cm of 0.010-in platinum coils. Contacts between the generator and the electrodes (the coil mass and the endovascular stent) were ensured using 0.010-in copper wires, which exited the aneurysm fundus or were affixed to the stent. The stents (4-mm balloon-expandable stents 28–38 mm in length; Omnilink, Abbott) were deployed through a right femoral approach. Generator settings and time of exposure were varied, effects being directly visualized when aneurysms became electrocoagulated. Aneurysms were then resected en bloc with the carotid arteries, photographed, and the extent of the radiofrequency lesion examined under a stereomicroscope.

To confirm computer simulations, resected aneurysms were immersed in Petri dishes filled with 80 ml of 0.9% NaCl. Temperature probes were positioned at the level of the ROIs defined in the virtual model, and a data logger (Graphitec, GL220) was used to record temperature readings during RF applications of 2.5 and 5 W for 5–60 seconds.

To test whether RFA improved angiographic results of coil embolization, wide-necked venous pouch aneurysms were constructed in 24 Beagle dogs using a Y-type bifurcation model.\(^27\) A segment of the left external jugular vein was used as the aneurysm fundus. In this model, bifurcation aneurysms have 13- to 17-mm sacs and the “surgical neck” (7- to 9-mm) forms a dysplastic bifurcation that incorporates the origin of the left carotid artery.

Appropriate contacts between the generator and the electrodes were established by inserting small copper wires into the right common carotid artery (to eventually contact the endothelial stent electrode) or into the aneurysm to contact the platinum coil mass, composed of two 0.010-in or 0.015-in coils (ranging in length from 25 to 45 cm), inserted into the fundus to only partially occlude the aneurysm, leaving a large residual lesion, and leaving the copper wire exiting the fundus. RFA of residual aneurysms was performed under angiographic surveillance, performed by right common carotid artery injections using 5-Fr catheters inserted through a right femoral approach. The parent artery electrode was a braided self-expandable stent, constructed of nitinol wires (56 \(\mu\)m in caliber), nominal diameter and length (3.5 × 40 mm), 89% porosity, 16 struts, 0.6 ± 0.5 pores per \(\text{mm}^2\) (LVIS, gifts from Microvent Inc.), deployed from the left carotid branch to the right carotid artery proximal to the bifurcation. Partial deployment of the stent allowed contact to be made with the copper wire inserted at the time of aneurysm construction. Satisfactory contacts were ensured by measuring the resistance of the system using a commercial ohmmeter. Experiments were performed with an RF generator (HAT 200, Osypka GmbH Medizintechnik) supplying 500-kHz alternating current for periods of 10 seconds, starting at a power energy of 5 W and increasing by 2.5-W increments, until the coil mass was observed to decrease in size and move toward the stented parent artery (with aneurysm shrinking) under fluoroscopy. This process was repeated.
until the aneurysm was completely or nearly completely occluded. The stent, the microcatheter, and the connecting wires were retrieved, and the femoral artery ligated. Control group 1 animals were treated in the same fashion, but without application of RFA. Control group 2 animals were embolized under general anesthesia 2–4 weeks after surgical construction of the same bifurcation aneurysms, by maximal packing of the sac with 0.015-caliber platinum coils of decreasing diameters, followed by smaller caliber 0.010-in coils, until coils could no longer be introduced without protruding at the level of the bifurcation.

Angiography was performed at 4 and 12 weeks, using a single-plane coronary angiography unit (HiCor, Siemens). Angiograms were independently graded using a 4-point ordinal scale by 2 experienced observers (J.R. and I.S.) to assess the degree of aneurysm occlusion.27

After euthanasia, aneurysms were removed en bloc and fixed in formalin for 1 week. The right carotid artery was opened to visualize and photograph the aneurysm neck fixed in formalin for 1 week. The right carotid artery was fixed in formalin for 1 week. The right carotid artery was opened to visualize and photograph the aneurysm neck fixed in formalin for 1 week. The right carotid artery was fixed in formalin for 1 week. The right carotid artery was opened to visualize and photograph the aneurysm neck.

Statistical Analyses

Angiographic results before and after RFA were compared using the Wilcoxon signed-rank test for paired samples. Angiographic results at 3 months and neointimal scores were compared between groups using the Mann-Whitney-Wilcoxon test for independent samples. Pathological findings were compared between groups using Fisher’s exact test. All hypotheses were 2-tailed and statistical significance was set at p = 0.05.

Results

Simulations

Bipolar current application effectively concentrated current densities at the target neck area. Current densities were maximal at the level of the coil surface facing the stent. Heterogeneity in power densities at the efficacy points (ratios between maximal and minimal densities) increased from 1.0 to 2.1 as the coil mass increased from 5 to 20 mm in size, and as interelectrode distance increased from 1.25 to 10 mm. The safety window between the efficacy points at the level of the neck and the safety points on the aneurysm fundus or parent vessel varied from 2 to more than 2000. Varying the stent length or diameter had little or no effect. Output variations (from 5 to 10 W) led to a proportional doubling of power densities, without modifying current density ratios. The most important effects were observed when the diameter of the coil mass was decreased and the interelectrode distance was increased, both factors decreasing the safety window. That is, the smaller the stent-coil distance, and the larger the coil mass, the wider the safety window of the RFA strategy (Fig. 1).

Ex Vivo Studies

Thermal injuries affected the aneurysm neck with the lesion extending up the aneurysmal sac for 1–2 mm in all cases. The parent artery and the aneurysm fundus appeared intact in all cases (Fig. 2). Temperature recordings during ex vivo RFA confirmed the safety window shown in virtual simulations, with a significant gradient between temperature changes recorded at the target neck area and the ones recorded at the safety points.

RFA in Bifurcation Aneurysms

All animals of the experimental treatment group had residual aneurysms after coil embolization (n = 12). The coil mass was observed to “contract” when the power reached 10–12.5 W, with ablation of the residual lesion and complete or near-complete occlusion achieved with 10-second applications between 10 and 15 W in 7 of 12 animals (range 7.5–22.5 W). The residual aneurysms could be ablated in all cases, leading to immediate complete occlusions (n = 9) or residual necks (n = 3; median score 0; p = 0.0024; Wilcoxon signed-rank test). Two of 10 followed-up aneurysms went from complete occlusion to a small recurrent neck at 3 months, while 8 of 10 aneurysms remained completely occluded (n = 6) or with a stable residual neck (n = 2; Fig. 3). Control group 1 (residual necks = 4, residual aneurysm = 2) or control group 2 animals (complete occlusion = 3, residual neck = 3) had better initial angiographic results (p = 0.0013), but all aneurysms recurred at 3 months. Angiographic results were significantly better at 3 months in the RFA group (median score 0) as compared with control group 1 or 2 (median score 2; p = 0.00018; Mann-Whitney-Wilcoxon test for independent samples; Supplemental Table 1).

Complications

Three complications occurred, 2 immediately and one 3 days after RFA: one animal died in the postoperative period, but the autopsy and microscopic examination of the aneurysm-bifurcation complex showed no abnormality. The left carotid artery was temporarily occluded in 1 case, apparently from clot formation on the endovascular stent. One animal died 3 days after RFA from the development of a cervical hematoma; autopsy revealed 2 hemorrhagic blisters arising from the adventitial side of 1 of the carotid branches. These blisters did not reach the media of the parent artery, but were obviously related to thermal injury of the outside aspect of the arterial wall (Fig. 4). These complications were associated with repeated applications at high output levels (20 and 30 W).

Pathological Studies

The neck of aneurysms treated with RFA was completely or near-completely sealed with neointima (scores of 0 in 6 cases, 1 in 2 cases) in 8 of 10 cases examined at
FIG. 1. Simulations. Computer simulations show how current densities vary within the target area (between the center [NC] and the sides [NS] of the aneurysmal neck. Color maps (A and B) show how the current densities are distributed when the coil mass is 5 mm and the distance between the coils and the stent is increased from 1.25 (A) to 2.5 mm (B). The effects of increasing distance and increasing aneurysm size on current densities at the target area (gray zone in C–E), and at the safety points (coil side [CS], aneurysm fundus [F], and parent artery) are shown in C–E. Note how the safety window decreases with increasing distance between the coil mass and the stent (interelectrode distance from 1.25 to 10 mm) and with decreasing size of the aneurysm (coil mass diameter [CMD] from 5 to 20 mm; F). Figure is available in color online only.
3 months, while neointimal closure was deficient in most control cases (scores of 3 in 10 cases, 4 in 2 cases). RFA-treated aneurysms had significantly better neointimal scores than control groups (median score 0 as compared with median score 3 for control groups 1 and 2; \( p = 0.0003 \); Fig. 3). At the level of the aneurysmal sac, the coils were embedded in organized connective tissues in all cases (Fig. 5), but regions of unorganized clot infiltrated with inflammatory cells lacking organization were present in 6 of 10 RFA specimens, as compared with 2 of 12 controls (\( p = 0.074 \)). Brown staining of the aneurysm wall and of the connective tissues between the aneurysm wall and the carotid branch was visible in 5 of 10 RFA cases, as compared with 1 in 12 controls (\( p = 0.056 \)). Histopathologically, these areas of staining were associated with persistent inflammation containing hemosiderin-laden macrophages (Fig. 5A and B). Minimal neointima formation was visible at the level of the carotid arteries in 1 case of each group (RFA and controls).

**Discussion**

The most interesting feature of this study is that bipolar RFA, using the intraaneurysmal coil mass and an endovascular stent as electrodes, can selectively ablate aneurysm remnants after coil embolization. Aneurysms had improved angiographic results as compared with controls immediately after RFA and at 3 months. However, excessive RFA applications can injure structures in the vicinity of the target, including the adventitia of arterial branches.

Preliminary studies showed that the bipolar strategy can generate current densities and hyperthermia at the neck of the aneurysm. These experiments also showed that the safety window is a function of the diameter of the coil mass and the interelectrode distance: larger coil masses and shorter interelectrode distances were safer in providing wider differences in current densities. The simulations could not take into account the cooling effect of circulating blood flow. In vivo, the temporary use of a flow diverter (as the parent artery electrode), which should affect aneurysm blood flow but preserve branch blood flow, could also help to selectively control the thermal lesion at the target site where the cooling effects of blood flow will be minimized.

A number of challenges need to be addressed before considering a clinical application. First, if currently available platinum coils, braided stents, and flow diverters can serve as electrodes by themselves, they cannot directly be used by connecting pusher wires to the generator (for example) without some modifications. All endovascular tools that we have tested so far are constructed in such a fashion that there is excessive resistance to the electrical current (and consequently heating within microcatheters) when the current is applied through the pusher wires. This problem was circumvented in the present work by the surgical implantation of copper connectors. Dedicated devices will be needed for future clinical applications, to ensure resistance-free contacts.

Second, variability in aneurysm size and shape, coil mass size, and interelectrode distance, and the cooling effects of aneurysm and branch flows, prevent the use of a constant prescription of power output and time of applications. Our virtual simulations have shown that there is a safety window between effective and dangerous applications, but RFA will need to be tailored to each case. Exacting preoperative imaging studies may be needed to exclude the presence of important structures, such as a cranial nerve, in the target zone between the coil mass and the stent.

Third, hemorrhagic and thrombotic complications in some animals are precisely the issues that could limit the use of such a strategy in human applications. Potential thrombotic complications related to the delivery of RF currents through stents or flow diverters would need to be thoroughly studied in vivo once specific endovascular devices, dedicated to that task, are designed.

The blister injuries that occurred in at least 1 animal were clearly related to excessive RFA application. In these inaugural experiments, we deliberately aimed to obtain immediate eradication of all residual lesions, to show the potential efficacy of the technique at the risk of encountering complications. More work is needed to better define the therapeutic window of the strategy.

We had initially conceived RF as a way to ablate the endothelial lining to prevent recanalization after coil embolization. This may be true where the endothelial lining is in contact with the coil mass. At a distance from the coil mass, the bipolar strategy barely affects the intima where the endothelial lining is maximally cooled by blood flow. In the present experiments the main effect of RFA was to shrink tissues and ablate residual lesions.

**Limitations of the Study**

We used per-operative coil embolization in the RFA and control 1 groups, a technique that differs from standard transfemoral embolization performed weeks after
aneurysm construction. In both of these groups, the aneurysms were deliberately undertreated. We also included a comparison group treated 2–4 weeks later, using a more conventional and more complete coiling technique. We studied only 1 stent in vivo, a braided device, but in vitro studies have shown that any stent or flow diverter that conducts electrical currents can be used as the parent vessel electrode. The number of animals studied in this work is small, and follow-up angiography beyond 3 months was not performed. Experimental aneurysms were surgical constructions and results may differ significantly from spontaneous intracranial aneurysms. Canine biology differs from human biology. Extrapolation to human applications should be conducted with great caution. The occurrence of adventitial blisters in preliminary experiments speaks to the need to refine methods to titrate RFA to prevent unintended injury to perianeurysmal tissues.

**Practical Application**

Bipolar RFA of residual lesions after coil embolization can improve angiographic results in experimental aneurysms. Dedicated devices, preoperative high-resolution imaging of the aneurysm environment, and further safety experiments are needed before considering a clinical application.

**FIG. 3.** Results of bipolar RFA. Bifurcation aneurysms were constructed and coiled partially during surgery (A–F) or completely occluded 3 weeks later using an endovascular approach (I and J). Immediate results of RFA show ablation of the residual aneurysm (A and B) but no change in the control group (E and F). At 3 months, angiography shows stable results of ablation (C), while control aneurysms recur with coil compaction (G and K) and neointimal closure of the aneurysmal neck was improved (D) as compared with control aneurysms (H and L).
Conclusions

RFA of aneurysm remnants after coil embolization can be successfully applied using the coil mass and a partially deployed endovascular stent as electrodes. This innovative method has the potential to improve results of coil embolization, but further safety experiments are needed before considering a clinical application.

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References


FIG. 4. Treatment-related complication. Excessive RF applications led to thermal injury of the adventitia of the right carotid artery, with 2 blisters (arrows in A, magnified view in B). The arterial intima remained intact (endoluminal view in D), while the adventitial blister did not reach the medial layer, as shown after cross-section (C).

FIG. 5. Pathological results. Photographs and histopathology of cross-sections of aneurysms 3 months after RFA (A and B), sham RF application (C and D), or endovascular coil occlusion (E and F). Hemosiderin-laden macrophages were found in RFA aneurysms (arrow in B). A residual aneurysm is shown in a control group aneurysm (asterisk in C and D). Control group 2 aneurysms show coils embedded in organized connective tissue (E and F). Figure is available in color online only.
Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Raymond, Darsaut, Savard, Coutu, Salazkin. Acquisition of data: Raymond, Boileau, Zheng, Bing, Makoyeva, Darsaut, Savard, Coutu, Salazkin. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critical revision of the article: all authors. Final version of the manuscript: all authors. Approved the final version of manuscript on behalf of all authors: Raymond. Statistical analysis: Raymond, Boileau, Fahed. Administrative/technical/material support: Fahed. Study supervision: Raymond.

Supplemental Information
Online-Only Content
Supplemental material is available with the online version of this article.

Supplemental Table 1. https://thejns.org/doi/suppl/10.3171/2016.3.JNS152871.

Correspondence
Jean Raymond, Interventional Neuroradiology, CHUM, Notre-Dame Hospital, 1560 Sherbrooke East, Pavilion Simard, Rm. Z12909, Montreal, QC H2L 4M1, Canada. email: jean.raymond@umontreal.ca.