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Optical coherence tomography: a new method to assess aneurysm healing

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Abstract

Object—Aneurysmal subarachnoid hemorrhage affects approximately 10/100,000 people per year. Endovascular coil embolization is used increasingly to treat cerebral aneurysms and its safety and durability is rapidly developing. The long-term durability of coil embolization of cerebral aneurysms remains in question; patients treated using this modality require multiple follow-up angiography studies and occasional repeated treatments.

Methods—Optical coherence tomography (OCT) is an emerging imaging modality that uses backscattered light to produce high-resolution tomography of optically accessible biological tissues such as the eye, luminal surface of blood vessels, and gastrointestinal tract. Vascular OCT probes in the form of imaging microwires are presently available—although not Food and Drug Administration-approved—and may be adapted for use in the cerebral circulation. In this study the authors describe the initial use of OCT to make visible the neck of aneurysms created in a canine model and treated with coil embolization. Optical coherence tomography images demonstrate changes that correlate with the histological findings of healing at the aneurysm neck and thus may be capable of demonstrating human cerebral aneurysm healing.

Conclusions—Optical coherence tomography may obviate the need for subsequent follow-up angiography studies as well as aid in the understanding of endovascular tissue healing. Data in this study demonstrate that further investigation of in vivo imaging with such probes is warranted.

Keywords

intracranial aneurysm; endovascular therapy; optical coherence tomography; dog

Abbreviations used in this paper

CA = carotid artery; GDC = Guglielmi detachable coil; ISAT = International Subarachnoid Aneurysm Trial; OCT = optical coherence tomography

Subarachnoid hemorrhage caused by a ruptured intracranial aneurysm is a neurologically devastating event with an annual incidence of 10/100,000 people per year.³⁸ Endovascular treatment of aneurysms has increased rapidly since the inception of aneurysm embolization by using detachable coils. The short-term advantage of minimally invasive endovascular treatment

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of ruptured aneurysms amenable to both coil or clip treatment comes with the troublesome question of long-term durability.¹⁷ Possible coil compaction and aneurysm recanalization/recurrence requires serial follow-up angiography studies.

Multiple modifications of coils as well as adjunct devices such as intracranial stents and liquid embolic agents have been developed and some have entered clinical practice. These variations are designed to improve the safety of the initial treatment and subsequent healing across the aneurysm neck, thereby reducing the rate of aneurysm recanalization/recurrence and the need for serial angiography.²⁶ To date, these incremental changes in device use have added substantial cost to the procedure with little or no documented efficacy in humans.

Optical coherence tomography is an imaging modality initially described by Huang, et al.,¹⁵ in 1991. Analogous to B-mode ultrasonography, OCT uses backscattered light to produce high-resolution tomography of optically accessible biological tissues such as the eye, blood vessels, or gastrointestinal tract.¹⁵ The OCT images have near-biopsy resolution and may be used as a nondestructive alternative to biopsy or as a screening step to reduce biopsy sampling error.

The purpose of this study was to determine the ability of OCT to demonstrate an animal model of cerebral aneurysms treated endovascularly with either standard platinum coils or bioactive-coated coils, and to correlate OCT images with results of pathological/histological examination of endovascularly treated aneurysms. A satisfactory image would reveal details of the endovascular surface of the aneurysm neck, pattern of coils within the aneurysm sac, and associated tissue growth. A correlation between OCT images and H & E-stained specimens would provide a powerful assessment tool to use during prototype development of aneurysm coils while evaluating a patient's healing response to embolotherapy.

Materials and Methods

The institutional animal research committee approved the experimental protocol. The study involved the surgical creation of experimental sidewall CA aneurysms in adult dogs, as previously described.^{9–11,31,35} Four Beagles (1–3 years old) weighing 20 to 25 kg were placed in a state of general anesthesia (intravenous Pentothal/1.5% isoflurane inhalation) with electrocardiography and peripheral oxygen saturation monitoring. Bilateral exposure of the CAs was performed using an incision along the medial border of the sternocleidomastoid muscle. A long segment of the external jugular vein was harvested to fashion multiple sidewall aneurysms.^{11,29,30,32} An intravenous dose of heparin (80 U/kg) was given prior to arteriotomy with a 4-mm arterial punch. An attempt was made to create two side-wall aneurysms on each CA. After creation of the aneurysms, each dog convalesced for 1 week prior to transfemoral angiography studies and coil embolization of patent aneurysms.

One week later—after using the same regimen to anesthetize the dogs—the aneurysms were endovascularly treated using conventional platinum GDCs or with biopolymer-coated (polyglycolic acid 90%/polylactic acid 10%) Matrix coils (both coil types obtained from Boston Scientific Neurovascular, Fremont, CA). The animals were allowed to recover and the aneurysms permitted to heal for variable periods. The animals were again anesthetized, angiography was performed, and the animals were killed at one of the following intervals: 7, 15, 21, or 27 days. Angiograms obtained before death were evaluated for vessel occlusion, coil compaction, and radiolucency separating the coil mass from the contrast lumen of the parent artery. The animals were then killed while in a state of anesthesia (20 mg/kg intravenous Pentothal followed by 80 mEq intravenous potassium chloride) and the aneurysms harvested en bloc. The CA segments were carefully opened longitudinally opposite the aneurysm sac and then sutured onto clear acrylic blocks with a central well (for the aneurysm dome) such that the luminal surface of the neck faced outward (Figs. 1 and 2) and fixed in 2% formaldehyde.

All harvested aneurysms were evaluated using bench-top OCT to determine whether the technology is capable of providing diagnostic images depicting the adequacy of coil treatment. A sample arm scanner was mounted on a vibration-isolated optical bench where it could be configured to scan vertical or horizontal surfaces at a rate of eight images/second. A wavelength of 1310 nm was used to optimize penetration of the OCT beam into the vessel wall. The OCT studies were performed as line scans traversing the neck of the aneurysm. Each line scan covered a surface of 9.8 mm (parallel to the long axis of the artery) by 3.2 mm to a depth of 2.3 mm with a resolution of 20 μ m in both axial and transverse dimensions (Fig. 3). Line scans were evaluated for the detection of the neck of the aneurysm, visualization of the platinum coils and/or coating, and the presence of surface endothelium or fibrous response. Measurements of the tissue thickness on the endoluminal side of the coils were performed at four different points along the scan traversing the central, longest portion of the aneurysm neck. The measurements were calibrated using standard targets. The mean tissue thickness covering bare platinum compared with biopolymer-coated coils was plotted and analyzed using a two-tailed t-test with equal variance.

The depth measured on OCT scans is the optical path length, so it is magnified by the refractive index of the tissue. The refractive index of the tissue surrounding the coils is unknown, but we have assumed a value of 1.40 based on 1310-nm index measurements of various types of tissues.³⁴ Therefore, all measured thicknesses were divided by 1.40 to obtain the values quoted in this manuscript. Because all results were scaled by this assumed value for the refractive index, the trends reported in this study do not depend on this assumption.

A neuropathologist then reviewed the specimens grossly and histologically. The aneurysms were embedded in methylmethacrylate, cut into 40- to 50- μ m sections by using a diamond band saw, polished, and surface stained with H & E, as previously described.²⁶ Microscopic images of the aneurysm necks were digitized and analyzed in comparison with the OCT images of the same specimen.

Results

Four dogs underwent successful unilateral external jugular vein harvest with creation of two to four sidewall aneurysms per dog. Fourteen aneurysms were surgically created and after a 1-week convalescence, all animals underwent transfemoral angiography with coil embolization of the 10 remaining patent aneurysms (Fig. 4). After the appropriate time interval, all animals underwent follow-up angiography and were killed. After harvesting the aneurysms and securing them in acrylic blocks, bench-top OCT images were generated and measurements were made of the tissue overlying coils at the aneurysm neck (Fig. 5 and Table 1). The OCT images were correlated with the histological findings at each interval of healing (Fig. 6).

Healing Time: 7 Days

In the 7-day animal, both CAs remained patent. Angiograms obtained before death compared with those obtained postembolization did not demonstrate thrombosis/occlusion, coil compaction/residual neck, or radiolucency separating the aneurysm neck from the contrast lumen.

With harvesting and opening of the vessel, uncoated coils could be seen at the aneurysm neck on gross inspection. After OCT scanning of all four aneurysms, one pair of aneurysms was used to refine the technique of histological sectioning and staining. Sections of these aneurysms were not suitable for comparison with OCT. Histological examination of the other two aneurysms demonstrated organized thrombus without significant inflammatory response or tissue growth on the endoluminal side of the coils at the neck of the aneurysm (Fig. 6).

Bench-top OCT demonstrated similar findings for the uncoated platinum and coated coils. The vessel wall and aneurysm neck could be identified on a series of line scans as a bright linear surface interrupted by a shallow depression. Coils were seen as a series of bright points or arcs within or projecting above this crater, depending on whether the coils were imaged transversely or longitudinally. There was significant optical shadowing beneath the coils that permitted ready identification of the coils but limited imaging of tissue beneath. The resolution of the image was sufficient to delineate the individual windings on the uncoated platinum coils. Perhaps due to the polyglycolic acid/polylactic acid, this pattern was less visible on the coated coils. There was little or no tissue visible between the lumen and the coils in either the uncoated platinum or coated coil-treated aneurysm (Fig. 7 and Table 2).

Healing Time: 14 Days

In the 14-day animal, one CA thrombosed prior to coil placement without clinical consequence. The remaining two aneurysms were harvested from the contralateral vessel and analyzed 2 weeks after coil embolization. Angiograms obtained before death compared with postembolization angiograms did not demonstrate thrombosis/occlusion, coil compaction/residual neck, or radiolucency separating the aneurysm neck from the contrast lumen.

With harvesting and opening of the vessel, uncoated coils were visible at the aneurysm neck. A giant cell inflammatory response appeared within the organizing thrombus. No definitive tissue was seen at the aneurysm neck interposed between the coils and the vessel lumen. The polyglycolic acid/polylactic acid coating on the bioactive coils was easily demonstrated in each specimen. The coating appeared to be the epicenter of the inflammatory response.

Bench-top OCT demonstrated similar findings for the uncoated platinum and coated coils, as seen in the 7-day animal. The vessel wall and aneurysm neck could be identified as an irregular, shallow depression. Coils were seen as a series of bright points or arcs within or above this crater. There was significant optical shadowing beneath the coils. There was little or no tissue seen between the lumen and the coils in either the bare platinum or coated coil-treated aneurysm (Table 2).

Healing Time: 21 Days

In the third animal, one CA thrombosed prior to coil insertion without clinical consequence. The remaining two aneurysms were harvested and analyzed 3 weeks after embolization. Angiograms obtained before death compared with those obtained postembolization did not demonstrate thrombosis/occlusion, coil compaction/residual neck, or radiolucency separating the aneurysm neck from the contrast lumen.

With harvesting and opening of the vessel, uncoated coils were visible at the aneurysm neck of only those treated with conventional platinum coils. The neck of the aneurysm treated with coated coils demonstrated a grayish-white translucent layer covering the coils on the luminal surface. Specimens continued to demonstrate a progressive giant cell inflammatory response. Again, the coating appeared to be the epicenter of the inflammatory response. Progressive fibrosis with increasing fibroblastic response was also noted. In the uncoated platinum coil specimen, coils protruded into the vessel lumen, whereas the coated-coil specimen demonstrated many coils covered by the inflammatory fibroblastic response. An endothelial surface per se was not visible.

In the case of the 21-day specimen, bench-top OCT demonstrated disparate findings for the uncoated platinum and coated coils. With the former coils, the findings were similar to the 1- and 2-week specimens: the vessel wall and aneurysm neck could be seen as a bright surface interrupted by a shallow depression, and coils appeared as a series of bright points or arcs at

the lumen with shadowing beneath. The coated coils were likewise seen as bright points and arcs; however, the majority of those made visible were below the surface line of the aneurysm neck. The appearance of the surface was also more shallow and smoother than had been observed on earlier specimens treated with coated coils (Table 2).

Healing Time: 27 Days

In the fourth animal, one CA thrombosed prior to coil placement without clinical consequence. The remaining two aneurysms were harvested and analyzed 27 days after embolization. Angiograms obtained before death compared with those obtained postembolization did not demonstrate thrombosis/occlusion, coil compaction/residual neck, or radiolucency separating the aneurysm neck from the contrast lumen.

With harvesting and opening of the vessel, uncoated coils were visible at the aneurysm neck of only those treated with uncoated platinum coils. The neck of the aneurysm treated with coated coils demonstrated an opaque, white layer covering the coils on the luminal surface. Histological specimens again continued to demonstrate a progressive giant cell inflammatory response around the coils, especially those that were coated. Progressive fibrosis with increasing fibroblastic response was noted at the luminal surface of the aneurysm neck. With the uncoated platinum specimen, coils protruded past the luminal surface. An endothelial surface per se was not demonstrated.

The 27-day specimens demonstrated similar, albeit more pronounced, findings on OCT compared with the 21-day specimen. The appearance with the uncoated platinum coils was unchanged, whereas the coated coils were seen as bright points and arcs below the ever-thickening surface line of the aneurysm neck. The appearance of the surface was progressively smoother than had been observed earlier (Table 2).

Summary of Results

Biopolymer-coated coils demonstrated greater mean tissue thickness along the endoluminal side of the coils when compared with the uncoated platinum coils in three of four dogs. The dogs whose aneurysms were harvested 15 days after coil embolization seemed to have less tissue on the endoluminal side, and there was no difference between the two types of coils (Table 1 and Fig. 8).

Discussion

Data from several large autopsy series have indicated that the prevalence of intracranial aneurysms in the general population is 5%.^{16,22} The incidence of subarachnoid hemorrhage is approximately 10/100,000 persons per year.³⁸ The frequency of significant neurological morbidity and death as a consequence of intracranial aneurysm rupture remains high. Historically, the treatment of intracranial aneurysms has required craniotomy together with microsurgical clip application to exclude aneurysms from the cerebral circulation.³⁶ Alternative treatments, including wire coil-induced electrothrombosis, have been attempted but never successfully popularized.^{23–25,37} In 1974 Serbinenko²⁸ described aneurysm obliteration with the use of detachable balloons. In 1991 the first descriptions of the revolutionary aneurysm treatment of controlled embolization and electrothrombosis using platinum GDCs appeared.^{13,14}

More recently, the results of the ISAT indicated that patients with ruptured cerebral aneurysms who are suitable candidates for either microsurgery or endovascular therapy and actually undergo endovascular treatment may experience less short-term morbidity and death.¹⁷ Nevertheless, even after the ISAT study, the long-term durability of GDC treatment remains

a serious concern.¹⁷ Possible coil compaction and aneurysm recanalization/recurrence necessitates serial follow-up angiograms—and in the ISAT there was indeed a trend toward repetitive treatments as well as recurrent hemorrhage in the endovascular cohort. These findings reflect not only the limitations of the noninvasive methods *in vivo* but also the knowledge gap that exists in defining the histological features and time course of aneurysm healing after endovascular therapy.^{2,3,6,7,21,29–31,35}

Several modifications of coils have been and continue to be developed to improve healing (that is, aneurysm fibrosis and endothelialization) across the neck of aneurysms, thereby reducing the rate of recanalization/recurrence and the need for serial angiography.²⁶ Developmental costs of these coils can be substantial. Confounding these issues is the fact that human histological data with both first-generation and modified coils are sparse or nonexistent given that patients with prior coil placement have rarely undergone autopsy.^{1,12, 27,31} Finally, the biological features of venous pouch side-wall aneurysms do not necessarily reflect the true physiology of human cerebral aneurysms, and results in these types of studies may very well reflect a species-dependent phenomenon.

In 1881 physicist A. A. Michelson constructed an interferometer as part of his work to measure the speed of light.²⁰ The Michelson interferometer divides a light source into a reference beam and a sample beam, and then recombines them to measure the interference between the two beams. More than 100 years later, Huang, et al.,¹⁵ described a novel digital imaging technique that uses the Michelson interferometer to measure the depth of reflections from a tissue sample by their interference with a reference beam (Fig. 2). Analysis of the interference pattern yields a cross-sectional image that is the optical analog of pulse-echo ultrasonography and radar. Optical coherence tomography is approved by the Food and Drug Administration for scanning surface and subsurface structures (microvasculature and nerves) of the retina; and despite the absorption and scattering of light by red blood cells, new flexible guidewire probes (similar to current microguidewires used for intracranial endovascular neurosurgical procedures) are currently being clinically tested in the coronary circulation for the evaluation of atherosclerotic plaques.^{4,5,8,18,19,33,39} Optical coherence tomography produces very high resolution images. The bench-top device used in this protocol and those used with other applications has a resolution of approximately 20 μm . It is possible that images with a resolution of 1 to 2 μm could be produced. This resolution compares favorably with intravascular ultrasonography, which has a resolution of approximately 100 μm , and confocal microscopy, which has a resolution of approximately 1 μm .

Data in this study confirm the ability of OCT to demonstrate an animal model of cerebral aneurysms treated using endovascular techniques. High-resolution *ex vivo* OCT images revealed the endovascular surface of the aneurysm neck as well as the pattern of coils and associated tissue growth. Optical coherence tomography was able to distinguish histological changes at the aneurysm neck of uncoated platinum and polyglycolic acid/polylactic acid-coated coils imaged serially over time. These changes were not seen on corresponding conventional angiograms. The ability to perform such imaging *in vivo* may have positive implications relative to testing future devices (that is, the need for fewer animals tested over longer time periods). Similarly, if *in vivo* OCT scanning in humans could produce images of similar resolution with little or no increase in complication rates, it may offer additional insights into competing or complementary strategies of endovascular aneurysm treatment as well as a more definitive end point of treatment than conventional angiography.

On the other hand, *in vivo* OCT would require micro-catheterization of the intracranial arteries as well as a method of briefly excluding red blood cells from the studied vessel (that is, balloon occlusion or mannitol, saline, or contrast injection). Finally, the depth of tissue penetration

with OCT is limited so that any questions about deeper tissues could not be answered with the current capabilities of the device.

Conclusions

Bench-top OCT can demonstrate tissue growth (that is, healing by fibrosis and/or endothelialization) across the neck of coiled aneurysms in a canine model. Optical coherence tomography images correlate with the histological features demonstrated at the neck of aneurysms embolized with GDCs and Matrix coils. On the basis of this preliminary work, further effort implementing OCT and confirming these results in vivo is warranted.

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Fig. 1.
Photograph depicting an aneurysm 7 days after embolization with uncoated platinum coils. After excision, the artery was opened longitudinally and sutured into an acrylic block with a central well to hold the aneurysm.

Fig. 2. Schematic of the bench-top OCT system. The aneurysm specimen is immersed in saline solution in a glass cuvette (shown from above) to minimize light reflection from the surface. SLD = super luminescent diode.

Fig. 3. Endoluminal view of 27-day aneurysm treated with Matrix coils during OCT imaging. Horizontal lines demonstrate how OCT scans across the neck of the aneurysm; the resulting nine scans are shown in Fig. 6b.

Fig. 4.

A: Carotid artery angiogram obtained 1 week after creating CA sidewall aneurysms just prior to coil embolization. B: Carotid artery angiogram obtained 1 week after creation of CA sidewall aneurysms following coil embolization.

Fig. 5. Optical coherence tomography images obtained across the central aspect of the experimental aneurysm 7 (a), 15 (b), 21 (c), and 27 (d) days after coil embolization. For scale comparison, the size of the platinum coils is shown in the lower left corner of each image.

Fig. 6. Histological specimens and corresponding OCT image, respectively, across the central aspect of the aneurysm treated with GDCs at 7 days (a and b), Matrix coils at 7 days (c and d), GDCs at 27 days (e and f), and Matrix coils at 27 days (g and h).

Fig. 7. Stacked OCT images of experimental sidewall CA aneurysms in dogs examined 7 (a) and 27 (b) days after embolization with GDCs or Matrix coils. Each image covers an area of 2.3 mm (depth) $\times$ 9.8 mm (length). The images were recorded at a separation of 0.4 mm, but are displayed here at much greater spacing to avoid visual overlap.

Fig. 8. Graph demonstrating measurements of overlying tissue thickness based on images shown in Fig. 4. These data depict the results listed in Table 1 (error bars show one standard deviation above and below the mean).

TABLE 1

Tissue thicknesses on the endoluminal side of coils based on OCT scans*

Healing Time (days)	Coil Type	No. of Aneurysms Treated & Imaged w/ OCT	No. of Measurements of Tissue Depth on OCT per Aneurysm	Mean Tissue Depth (mm) [†]	t-Test Significance Level [‡]
7	GDC	2	4 & 4	0.264 ± 0.283	0.046
	Matrix	2	4 & 4	0.535 ± 0.248	
15	GDC	1	4	0.190 ± 0.245	0.542
	Matrix	1	4	0.117 ± 0.067	
21	GDC	1	4	0.102 ± 0.110	0.017
	Matrix	1	4	0.416 ± 0.294	
27	GDC	1	4	0.124 ± 0.120	0.021
	Matrix	1	4	0.770 ± 0.432	

* The OCT scans are featured in Fig. 5.

[†] Values represent the means ± standard deviation.[‡] Two-tailed test with equal variance.

TABLE 2

Summary of results

Dog No.	Days of Healing After Embolization	No. of Patent Aneurysms Treated w/ Coils	Results of Angiography	Gross Inspection	Histological Features	OCT
1	7	4	no compaction/recurrence; no radiolucency separating the parent vessel from the aneurysm neck	coils w/no overlying tissue	organizing thrombus; no inflammation; no tissue growth across neck	neck of aneurysm easily identified; coil pattern discernible; winding of coils easily seen but less so w/Matrix coils; limited tissue btwn coils
2	15	2	no compaction/recurrence; no radiolucency separating the parent vessel from the aneurysm neck	coils w/no overlying tissue	organizing thrombus; giant cell inflammatory response; no tissue growth across neck	neck of aneurysm easily identified; coil pattern discernible; winding of coils easily seen but less so w/Matrix coils; limited tissue btwn coils
3	21	2	no compaction/recurrence; no radiolucency separating the parent vessel from the aneurysm neck	gray-white translucent layer w/Matrix coils no layer seen w/uncoated platinum coils	giant cell inflammatory response; Matrix coils covered w/fibroblastic inflammatory tissue at aneurysm neck	neck of aneurysm easily identified; coil pattern discernible; winding of coils easily seen but less so w/Matrix coils; limited tissue btwn uncoated platinum coils; Matrix coils visible beneath tissue layer
4	27	2	no compaction/recurrence; no radiolucency separating the parent vessel from the aneurysm neck	opaque white tissue layer w/Matrix coils; no layer seen w/uncoated platinum coils	giant cell inflammatory response; Matrix coils covered w/maturing fibroblastic inflammatory tissue at aneurysm neck	neck of aneurysm easily identified; coil pattern discernible; winding of coils easily seen but less so w/Matrix coils; limited tissue btwn bare platinum coils; Matrix coils visualized beneath tissue layer