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Healing of Intracranial Aneurysms with Bioactive Coils

Lei Feng, MD, PhD*, Fernando Vinuela, MD, Yuichi Murayama, MD

Department of Radiological Sciences, University of California at Los Angeles, 10833 Le Conte Avenue, Los Angeles, CA 90095–1721, USA

The birth of Guglielmi detachable coils (GDCs) a decade ago [1,2] has injected new life into the treatment of cerebral aneurysms, gradually changing the management of subarachnoid hemorrhage. More and more medical centers have adopted coil embolization as the first treatment of choice for ruptured aneurysms, particularly after the International Subarachnoid Aneurysm Trial (ISAT) demonstrated the superior safety of endovascular treatment over surgical clipping in patients with ruptured intracranial aneurysms that can be treated with either technique [3]. As this technology goes through its puberty, a shortcoming has become evident, undermining our confidence in its long-term efficacy: large clinical series have shown a high recanalization rate of embolized aneurysms. In 11 years' experience of treating 916 aneurysms at the University of California at Los Angeles (UCLA) [4], the overall recanalization rate is 20.9%. Other groups have reported recanalization rates between 14.7% and 30% [5–7], consistent with the UCLA experience. Large and giant aneurysms are at higher risk of recanalization than small aneurysms. Aneurysms with a wide neck are also more likely to recanalize than small-neck aneurysms. Because the long term follow-up data are still sparse, we do not know the clinical implications of recanalization. Most of the delayed ruptures have been observed in large or giant aneurysms, which are frequently incompletely treated and suffer coil compaction, suggesting that improved obliteration of the aneurysm neck and prevention of coil compaction may be required to treat patients with aneurysms in a definitive manner.

Bioactive (Matrix; Boston Scientific Inc., Fumont, California) coils mark the maturation of this technology from mechanical occlusion to biologic healing of aneurysms. Although the refining of GDC technology produced softer, smaller, and stretch-resistant coils, which allow easier and tighter packing of the aneurysms, no more than 30% of the aneurysm lumen is packed by the coil mass. The rest of the aneurysm lumen is filled with thrombus, which undergoes biologic changes over the first 2 to 3 weeks after treatment to become organized thrombus or fibrous scar. This biologic process thus plays an important role in eliminating the aneurysm and preventing recanalization. The bioactive coils are designed to augment the healing response and promote collagen synthesis, thus reducing the risk of coil compaction and aneurysm recanalization. They are not intended to replace dense packing of the aneurysm, which is necessary to resist the impact of blood flow on the aneurysm. Elimination of the water-hammer effect of blood flow is crucial to create a milieu for the healing process to be effective. In this article, we review our current understanding of aneurysm growth, the mechanisms of tissue scarring, the effect of biodegradable polymers on healing, and the experiments supporting the augmented healing response by Matrix coils. We hope to stimulate new ideas and encourage the development of new generations of bioactive coils for the further advancement of endovascular treatment of aneurysms. Finally, we present some typical cases and the UCLA experience to illustrate the biologic effect of Matrix coils. The long-term efficacy data on Matrix coils

* Corresponding author.
E-mail address: lfeng@mednet.ucla.edu (L. Feng).

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are not available at this point and are thus beyond the scope of this article. Because fusiform aneurysms are usually treated with parent vessel occlusion, the discussions in this article only involve saccular aneurysms.

Yin and yang of aneurysm growth: injury versus healing

Understanding the cellular and molecular pathogenesis of intracranial aneurysms is essential for developing new treatment strategies. Disrupted internal elastic lamina is the pathologic hallmark of intracranial aneurysms. The blood vessel wall contains intima, media, and adventitia. Intima is lined by endothelial cells on the luminal surface and consists of extracellular matrix and a few smooth muscle cells. The internal elastic lamina, which contains collagen type III and elastin, separates intima from media. Smooth muscle cells and collagen fibers comprise most media. The intracranial arteries have relatively thin media and little adventitia compared with coronary arteries of similar size. Injury and repair are constantly at play in the vascular wall and may lead to various types of vascular diseases, including aneurysms.

Risk factors for intracranial aneurysms and subarachnoid hemorrhage

A genetic defect in the collagen or extracellular matrix synthesis can lead to weakness in the blood vessels. According to several epidemiology studies [8–10], the first-degree relatives of patients with intracranial aneurysms have a higher incidence of intracranial aneurysms than the normal population, suggesting the presence of hereditary factors in the development of intracranial aneurysms. A recent Finnish study identified 346 families with intracranial aneurysms: an autosomal recessive inheritance pattern was noted in 57.2% of the families, 36.4% of the families showed autosomal dominance, and another 5.5% of the families were consistent with autosomal dominance with incomplete penetrance [9]. These studies support the existence of major genetic defects in at least a subpopulation of patients with intracranial aneurysms. The associations of aneurysms with inherited diseases [11], particularly polycystic kidney disease [12,13] and Ehlers-Danlos syndrome [14], have been reported; however, the denominators of these observations are not known, and a prospective study failed to establish a statistically significant association between polycystic kidney disease and intracranial aneurysms [15]. So far, no candidate gene has been convincingly identified. The potential underlying gene mutations may interact or require additional environmental factors as well. It is also difficult to identify all family members with intracranial aneurysms for linkage analysis. The improvement of noninvasive imaging techniques to detect intracranial aneurysms may facilitate future genetic studies.

Cigarette smoking and hypertension are exogenous factors that have been associated with the development of intracranial aneurysms and subarachnoid hemorrhage [16–19]. Heavy alcohol consumption has been associated with aneurysmal subarachnoid hemorrhage in case-control studies [20,21], but this association has not been convincingly proven in longitudinal studies [22,23]. Although many case series and the cooperative study showed a higher incidence of subarachnoid hemorrhage in women than in men [24], male preponderance has been observed in some geographic areas [8]. Population-based studies are required to establish gender further as an independent risk factor [25].

Vascular injury and repair

Repetitive vascular injury leads to chronic inflammation and continuous remodeling in the vessel wall. Leukocytes, particularly monocytes, infiltrate into the vessel wall and secrete various degradative enzymes, including many matrix metalloproteinases (MMPs), causing destruction of the extracellular matrix. Conversely, these inflammatory cells release several cytokines and growth factors to promote the infiltration of macrophages and proliferation of smooth muscle cells and fibroblasts. Macrophages engulf the degraded extracellular matrix and cellular debris, whereas smooth muscle cells and fibroblasts synthesize new collagen and elastin. This destruction and rebuilding process ebbs and flows and is modulated by the endothelial cells, which sense the physical and chemical milieu of the blood vessel. This process is collectively called vascular remodeling and forms the basis for the development of many vascular diseases.

Cigarette smoking and hypertension, established risk factors for chronic vascular injury leading to the development of atherosclerosis, can predispose patients to intracranial aneurysms as well. Cigarette smoking increases the oxidative

stress in the vessel wall and induces an inflammatory response, which can undermine the structural integrity of blood vessels [26,27]. Hypertension increases the mechanical stress on the vessel wall and induces vascular remodeling [28,29]. In response to excessive mechanical stretch, the activities of MMPs are increased, destroying the old extracellular matrix scaffold to allow the synthesis and organization of new extracellular matrix [30,31].

Intracranial aneurysms frequently arise from bifurcation sites, where the turbulent flow generates high shear stress. High shear stress can induce the remodeling process involving the destruction of old cellular components and extracellular matrix structure and the synthesis of a vessel segment adaptive to the rheotology [32,33]. Stagnation may also occur in the shoulder of turbulent flow, resulting in oxidative stress and the induction of nitric oxide, leading to degenerative changes in the vessel wall [34]. Inhibition of nitric oxide synthase has been shown to attenuate early aneurysmal changes and aneurysm formation in a rat model [35]. The water-hammer effect exerted on the aneurysm inflow zone can result in mechanical injury and continuous growth of the aneurysm [36,37].

Endothelial denudation, infiltration of inflammatory cells, smooth muscle proliferation, destruction of extracellular matrix, and apoptosis, the hallmarks of vascular remodeling, have all been observed in histologic specimens of intracranial aneurysms [38–41]. Increased activities of MMPs have been observed in aneurysm walls [40,42,43]. Although this process frequently leads to atherosclerosis and intimal hyperplasia [30], deficient synthesis of the extracellular matrix and failed regulation of cellular proliferation and the overproduction of degradative enzymes can all result in inadequate repair, leaving an anatomic defect in the vessel wall. The enhanced vessel wall destruction can thus interact with a genetic or acquired deficiency in extracellular matrix synthesis to create an aneurysm (Fig. 1). Once a small defect occurs in the vessel wall, the altered flow dynamic may prompt additional vascular injury, a constant remodeling reaction, and repetition of the same deficient repair, leading to the gradual growth of the aneurysm.

Because of this dynamic process in the vessel wall, treatment of an aneurysm can be achieved by promoting a healing response to increase smooth muscle proliferation and extracellular matrix deposition. This healing process results in thickening of the intima and media to counteract the hemodynamic stress and prevent the aneurysm from further growth or rupture.

Organization of thrombus and aneurysm recanalization

Aneurysm recanalization may occur immediately after embolization or during thrombus organization or later remodeling of the aneurysm neck. During embolization, stasis and thrombogenicity of GDCs promote thrombosis in the lumen of an aneurysm. In the meantime, the thrombolytic pathway is activated and may dissolve part of the thrombus. Because the coil mass and stasis hinder the access of plasminogen and plasmin to the newly formed thrombus, the dynamic process usually tilts toward thrombosis. Recanalization of the aneurysm from thrombolysis is thus only a theoretic concern unless the aneurysm is severely underpacked or the patient is placed on anticoagulation therapy. The newly formed fibrin meshwork in the thrombus continues to polymerize and becomes densely compacted and resistant to thrombolysis within the first 24 hours. The remaining thrombus undergoes organization to become a scar or partially recanalized through neovascularity. Coil compaction may occur during thrombus organization, which takes a few weeks to complete, resulting in partial recanalization of the aneurysm. Once a tough fibrous scar forms, the coil masses are fixed in space and less likely to compact. Even after a stable fibrous tissue forms, the remodeling process can continue for many years in a fashion similar to de novo growth of an aneurysm if the original vascular insult remains uncorrected and the turbulent flow at the aneurysm neck maintains significant mechanical stress on the vessel wall.

Cellular mechanisms of thrombus organization

As the first step of thrombus organization, mesenchymal cells infiltrate into the thrombus to form granulation tissue. Leukocytes and platelets trapped in the thrombus release degradative enzymes to break down the fibrin meshwork. If the thrombus is large, as is usually the case in underpacked large aneurysms, the center of the thrombus may be liquefied, allowing coil compaction to occur. Endothelial precursor cells migrate into the thrombus and coalesce into a capillary network, which connects with the blood flow and brings in more inflammatory cells. Macrophages

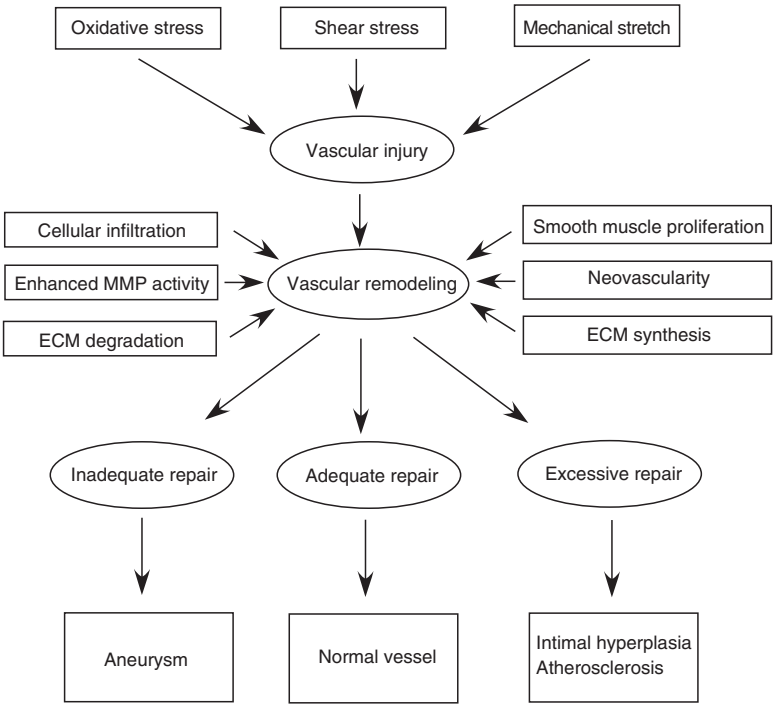

Fig. 1. Vascular remodeling. Oxidative stress caused by cigarette smoking, excessive mechanical stretch of the arterial wall in patients with hypertension, and increased shear stress at vascular bifurcation points can all lead to vascular injury, triggering vascular remodeling, which involves further destruction and rebuilding of the vessel wall. Infiltration of inflammatory cells and increased activity of matrix metalloproteinase (MMP) activities remove cellular debris and dissolve the old extracellular matrix (ECM) scaffold. Smooth muscle proliferation and neovascularization take place at the site of vascular remodeling, followed by the synthesis of new ECM. The integrity of the vessel wall is restored with adequate repair. When repair is inadequate, an anatomic defect may result, leading to the formation of an aneurysm. Conversely, excessive repair can contribute to intimal hyperplasia and atherosclerosis.

engulf the fibrin degradation products and cellular debris as fibroblasts and smooth muscle cells proliferate and synthesize new extracellular matrix, including collagen, fibronectin, and elastin. Smooth muscle cells are the major cellular component of neointima, which covers the neck of an embolized aneurysm. Their activation and proliferation are critical for adequate healing of the aneurysm [44]. The thrombus is gradually replaced by fibrous scar tissue, which is strengthened by extracellular matrix proteins, particularly collagen fibers, rendering the scar tissue resistant to the flow dynamic effect at the aneurysm neck. If the synthesis of extracellular matrix proteins is reduced, the scar tissue may contract, causing additional coil compaction and aneurysm recanalization. In addition, the capillary network, which usually disappears in the later stage of the healing reaction, may enlarge and become incorporated into the parent vessel, resulting in partial or even complete recanalization.

Because healing is intimately related to destruction, promoting the healing response can be a double-edged sword. Increased cellular infiltrate at the early stage of the healing response can result in rapid softening and destruction of the fibrin thrombus, thus facilitating coil compaction. Angiogenesis enhances the healing response but risks recanalization at a later stage. Adequate packing of the aneurysm is crucial in preventing recanalization by limiting early thrombolysis, reducing the size of the thrombus, and modifying flow dynamics at the aneurysm neck. Modulating the healing response, particularly the synthesis of extracellular matrix proteins, may promote the formation of dense scar tissue to reduce the risk of recanalization.

Extracellular matrix synthesis

The regulation of extracellular matrix synthesis is a complex process involving many cytokines, including transforming growth factor-β (TGFβ), connective tissue growth factor (CTGF), tissue necrosis factor-α (TNFα), and interferon-γ (IFNγ) [45]. TGFβ induces fibroblasts to synthesize and contract extracellular matrix and has long been regarded as a key mediator of the healing response [46]. It also suppresses the transcription of MMPs, preventing the degradation of newly synthesized extracellular matrix. TGFβ is synthesized as a latent precursor complexed with latent TGFβ binding protein and covalently linked to the extracellular matrix [47]. Proteolytic cleavage of latent TGFβ precursor by metalloproteinases, which promote matrix degradation, activates the healing response through TGFβ. Other TGFβ activators include thrombospondin-1 (TSP-1) and integrin $\alpha_v\beta_6$. TSP-1 modulates cell adhesion, angiogenesis, and reconstruction of matrix. Transgenic mice with TSP-1 knock-out share many phenotypes with TGFβ null mutants [48]. Without integrin β_6, the transgenic mice are protected against lung fibrosis when treated with the profibrotic drug bleomycin [49]. CTGF is synthesized in the endothelial cells in response to TGFβ and is thought to carry out the downstream effects TGFβ on fibroblasts [50]. TNFα and IFNγ are the major inhibitors of extracellular matrix synthesis. TNFα released by macrophages interferes with signal transduction of TGFβ, thus suppressing the synthesis of extracellular matrix genes [51,52]. IFNγ is made by T cells and inhibits collagen production through its signal transduction pathway [53].

The complexity of these interwoven regulatory mechanisms makes it impossible to use a single cytokine or growth factor to promote a desirable healing response in aneurysms. Conversely, the counteracting factors maintain the healing response under strict control, reducing the risk of parent vessel occlusion by exaggerated fibrosis.

Modulation of healing response in animal models of cerebral aneurysm

Ever since the introduction of GDCs, various modifications of GDCs have been studied in animal models to promote the healing response in aneurysms. Based on the agents used, these modifications can be categorized as extracellular matrix proteins, growth factors and/or cytokines, and bioactive polymers.

Coils coated with extracellular matrix proteins

Extracellular matrix proteins, including type 1 collagen, fibronectin, vitronectin, fibrinogen, and laminin, have been used to coat GDCs with ion-implantation technology [54]. The protein-coated coils behaved similarly to plain GDCs in their mechanical properties when used to embolize experimental side-wall aneurysms in swine [55]. These modified coils demonstrated a faster and enhanced cellular response in the aneurysm body and dome and the formation of a fibrous and endothelialized covering of the aneurysm neck. Favorable anatomic and histologic results were also obtained with collagen-based coils in a rabbit model [56]. Because these extracellular matrix proteins are highly thrombogenic, it is not clear whether the enhanced healing response is secondary to increased thrombosis or direct integration of these extracellular matrix proteins. Nevertheless, the extracellular matrix proteins provide an excellent substrate for the adhesion and migration of inflammatory cells and endothelial cells, which may contribute to the faster and stronger inflammatory response in the aneurysm and neointima formation at the aneurysm neck.

Coils coated with cytokines and/or growth factors

Given its critical role in regulating extracellular matrix synthesis, TGFβ is a prime candidate for coating bioactive coils. When TGFβ-coated coils were compared with plain platinum coils in a rabbit model of aneurysm, increased thickness of the neointima at the aneurysm neck was noted 2 weeks after embolization [57]. The difference decreased at 6 weeks, suggesting that TGFβ coating may accelerate cellular proliferation and production of extracellular matrix at the coil-lumen interface. Because this experiment was performed with significant underpacking of the aneurysm to study the interaction between the coil surface and surrounding tissue and there was no angiographic follow-up, it remains unknown if TGFβ coating has any effect on obliterating aneurysms or preventing recanalization. To determine if TGFβ can stimulate neointima formation at the aneurysm neck, Desfaits et al [58] delivered gelatin sponges soaked with TGFβ into experimental porcine and canine aneurysms. They found that a high dose of TGFβ (600 ng) significantly increased neointima thickness at the neck of porcine aneurysms, whereas a low dose of TGFβ had no effect. Surprisingly, no difference

was seen in canine aneurysms. Similarly, the homodimer of platelet-derived growth factor B subunits (PDGF-BB) or platelet extract that contains PDGF increased neointima thickness in porcine aneurysms but failed to improve healing of canine aneurysms [58,59]. The authors attributed this discrepancy between porcine and canine aneurysms to deficient thrombosis in the canine model and the consequent lack of matrix support for cell migration and proliferation. If the thrombus is dissolved by the thrombolytic pathway before organization, there would not be any substrate for the activity of these growth factors.

Because angiogenesis accompanies the organization of thrombus, Abraham et al [51] tested the hypothesis that vascular endothelial growth factor (VEGF), which stimulates endothelial cell proliferation, could enhance fibrosis and obliteration of aneurysms when released from GDCs. These authors created a rat aneurysm model by ligating the common carotid artery and inserted coil segments without coating or coated with type I collagen or type I collagen and human recombinant VEGF into the blind-ended sac. They found increased wall thickness with VEGF-coated coils and an enhanced cellular reaction on the surface of VEGF-coated coils.

Basic fibroblast growth factor (bFGF) has been demonstrated to stimulate the proliferation and migration of endothelial cells, smooth muscle cells, and fibroblasts as well as the production of type 1 collagen by smooth muscle cells and fibroblasts [60]. Because of its short-half life in circulation, direct application of bFGF to an aneurysm is ineffective. Hatano et al [61] developed a polyethylene terephthalate (PET) fiber coil coated with gelatin hydrogel containing bFGF to release bFGF slowly into the aneurysm. They tested this coil in a rabbit venous pouch aneurysm model and demonstrated increased fibrosis, neointima formation, and closure of the aneurysm neck using bFGF-eluting gelatin hydrogel PET coils compared with gelatin hydrogel PET coils without bFGF. This prototype of drug-eluting coils opens a new dimension to modulate the healing process in aneurysms.

Similar to the delivery of growth factors, coils have also been used as a platform to deliver cellular grafts that secrete growth factors or are expected to integrate into the vessel wall during the healing process. When fibroblasts transformed with human bFGF gene were introduced into rat carotid arteries using a GDC as the carrier, increased fibroblast proliferation was observed in the vessel wall at 14 days [62]. At 35 days, there was an increase in fibroblast proliferation and collagen synthesis. Further studies showed that fibroblasts grown on GDCs and introduced into aneurysms in a rabbit elastase model can remain viable and proliferate in the vicinity of coils [63]. Progressive cellular proliferation and increased fibrosis were observed in the aneurysms treated with cellular grafts compared with those treated with GDCs alone.

The delivery of growth factors and cellular grafts are higher levels of modulation of the healing process than the introduction of extracellular matrix proteins. Nevertheless, many cytokines and growth factors are involved in the healing process. Which growth factor or combination of growth factors is the most effective treatment remains unknown. The timing and dosing of these growth factors require further studies as well. Cellular grafts may have the advantage of sensing the needs for these growth factors and releasing them at the appropriate time and in the appropriate amount. Nonetheless, genetic manipulation of cellular grafts may be required to activate these cells, and the creation of an appropriate milieu may be necessary for these cells to carry out the desired healing function instead of destruction or overzealous cellular proliferation and extracellular matrix synthesis, leading to parent vessel stenosis. GDCs can serve as a drug-eluting and cellular graft platform, facilitating the delivery, visualization, and controlled release of therapeutic agents.

Matrix coils

Although many of these extracellular matrix proteins and cytokines have shown beneficial effects in promoting a healing response in experimental aneurysms, none of them have passed the preclinical stage. As pointed out earlier, the healing response involves several processes that are influenced by different extracellular proteins and cytokines. Exaggeration of an individual process in the healing response, whether that is cellular proliferation, angiogenesis, or extracellular matrix synthesis, may be counterproductive and increase the risk of recanalization or parent vessel stenosis. In addition, the toxicity and long-term safety of these extracellular matrix proteins or growth factors in human beings, particularly inside blood vessels, have not been adequately studied. The regulatory hurdle for moving these agents to the clinical stage is thus high.

Furthermore, the cellular and molecular mechanisms of aneurysm development and the healing response after embolization have just begun to be elucidated. Future studies are likely to identify better therapeutic targets and better therapeutic agents for the modulation of the healing response.

In contrast, bioabsorbable polymers, such as polyglycolic acid and polyglycolic/poly-L-lactic acid copolymer (PLGA), have been well studied and widely used in tissue engineering applications [64–66]. They can regulate the healing response in the adjacent tissues during their biologic degradation: the faster the degradation, the stronger is the tissue reaction [67,68]. The degradation rate of PLGA can be altered by changing the composition of lactic and glycolic acids. A high concentration of lactic acid renders the polymer resistant to degradation enzymes [69]. This property can thus be used to control the healing response after coil embolization.

To investigate the cellular responses to different compositions of PLGA, Murayama et al [70] placed PLGA at lactide/glycolic acid ratios of 85:15, 75:25, 65:35, and 50:50 into 16 experimental aneurysms in eight swine. They found that PLGA with faster degradation rates (ie, lower lactide content [65:35 and 50:50]) induced more mature collagen deposition and fibrosis in the sac and neck of aneurysms than polymers that are more resistant to degradation. The levels of collagen formation were linearly correlated to the degradation rates of PLGA polymers. This experiment demonstrated the feasibility of using bioabsorbable polymers to accelerate the healing response in aneurysms and paved the road for the manufacture of Matrix coils.

Matrix coils comprise an inner core of plain platinum coils and an outer layer of PLGA, which is affixed to the platinum core by heating. The platinum core provides radiopacity and coil shape memory. The size and physical properties of Matrix coils are similar to those of GDCs; however, the presence of PLGA on the outside of the platinum core does increase friction during coil delivery.

Murayama et al [71,72] used a swine aneurysm model to demonstrate accelerated wound healing in aneurysms treated with Matrix coils compared with plain GDCs. They created 24 aneurysms in 12 animals. One aneurysm in each animal was randomly chosen to be embolized with Matrix coils, and the other aneurysm was embolized with plain GDCs as a control. The aneurysms treated with Matrix coils were intentionally underpacked to study the healing response, whereas the other aneurysms were packed with GDCs as densely as possible. Angiographic follow-up obtained at 14 days after embolization showed a gap between the coil mass and the contrast-filled parent vessel in 75% of aneurysms treated with Matrix coils, suggesting neointima formation at the aneurysm neck; none of the aneurysms treated with regular GDCs had this finding. At 3 months, evidence of neointima formation was observed in all aneurysms treated with Matrix coils but in none of the aneurysms treated with regular GDCs. Histologic examination revealed a higher grade of cellular response around the coils, lower percentage of unorganized thrombus, and thicker neointima in the neck of aneurysms treated with Matrix coils than of those treated with regular GDCs. The thick neointima remained 3 months after embolization. In addition, there was no incidence of parent vessel stenosis or thrombosis. It should be noted that Matrix coils have less thrombogenicity than standard GDCs; thus, their action is not based on promotion of thrombosis within the aneurysm. Retraction of the aneurysm was observed at 3 months after treatment, suggesting the possibility of reducing mass effect after embolization. These results showed great promise of Matrix coils to enhance the healing response in aneurysms and reduce the risk of recanalization.

Hydrocoils

To improve packing of the aneurysm, which is another important factor in preventing recanalization, coils coated with expandable hydrogels (Hydrocoils; Microvention Inc., Aliso Viejo, California) have been developed and approved by US Food and Drug Administration (FDA) for clinical use. Hydrocoils consists of platinum coils coated with a synthetic polyalcohol, which can swell to nine times its original volume when placed into blood. The hydration process is slow enough to allow deployment and retraction of the coil for at least 5 minutes. Animal studies in a rabbit aneurysm model showed that Hydrocoils can improve aneurysm filling from the historical 20% to 30% with standard GDCs to a mean of 68% [73]. Hydrogel was biologically inert and did not stimulate an inflammatory reaction or healing response. Poor organized thrombus remained in the aneurysm after 14 days, and the aneurysm neck was covered with a thin fibrous layer as often seen in aneurysms treated with standard GDCs. Initial clinical experience with Hydrocoils

confirmed improved packing of aneurysms from 32% in aneurysms treated with standard GDCs to 72% in aneurysms treated with Hydrocoils [74]. Although Hydrocoils have no effect on the healing response, improved packing of aneurysms, particularly in large and giant aneurysms, can have significant beneficial effects on preventing recanalization.

Preliminary clinical experience with Matrix coils

Since the first patient received Matrix coils in June 2002, a total of 150 saccular aneurysms in 140 patients have been treated with Matrix coils at UCLA. These patients include 116 women and 24 men, with an average age of 57 ± 1 years. Fifty-three patients presented with acute subarachnoid hemorrhage, 14 patients had subarachnoid hemorrhage but came to our service after the acute phase, and the other 77 patients had unruptured aneurysms. Among the patients with unruptured aneurysms, seven were symptomatic from mass effects, and the other 70 patients had incidental aneurysms. The distribution of these aneurysms is shown in Table 1. One hundred eighteen aneurysms were in the anterior circulation, including 32 posterior communicating artery aneurysms and 29 anterior communicating artery aneurysms, the two most common sites. Thirty-three aneurysms were in the posterior circulation, including 20 basilar artery aneurysms. There were 99 (66.0%) small (≤10 mm), 50 (33.3%) large (11–25 mm), and 1 (0.7%) giant (>25 mm) aneurysms. Sixty-nine of these aneurysms (46.0%) had a small neck, and 81 (54.0%) had a wide neck. A total of 157 embolization procedures were performed on these aneurysms. Complete obliteration of the aneurysm was achieved at the end of the procedure in 60 (38.2%) cases, and 14 (8.9%) aneurysms were partially coiled. The remaining aneurysms (52.9%) had small neck remnants. The high percentage of neck remnants may be related to the increased sensitivity of using a three-dimensional rotational angiogram to detect small neck remnants; most of these aneurysms would have been considered completely obliterated by planar angiography. There were six intraoperative ruptures and eight thromboembolic complications. Parent vessel narrowing after embolization occurred in only 1 patient, who had a small loop of coil herniating into the parent vessel.

Eighty patients with 90 aneurysms have had follow-up angiograms, with an average interval of 8 ± 0.6 months. Based on preliminary analysis of the data, 21 patients showed progressive thrombosis and reduction of the residual neck, suggesting successful healing of the aneurysms. A white-collar sign was observed in several cases (Fig. 2), indicating the formation of thick fibrous intima at the aneurysm neck. Most aneurysms remained stable during follow-up. Durable results were obtained in many large and wide-neck aneurysms, which are at high risk of recanalization (Fig. 3). Twelve aneurysms (13.3%) showed significant recanalization, requiring further treatment. Only 1 patient had repeat subarachnoid hemorrhage after embolization. This patient had a basilar artery aneurysm with a wide neck and received dome protection during the acute phase of her first subarachnoid hemorrhage. She rebled in 2 months, before scheduled definitive therapy with stent assistance.

Table 1
Distribution of aneurysms in Matrix coil series at the University of California at Los Angeles

Location	Number	Percentage
Anterior circulation		
Anterior choroidal	3	2.0%
Anterior communicating	29	19.3%
Cavernous carotid	7	4.7%
Carotid cave	10	6.7%
Internal carotid bifurcation	3	2.0%
Middle cerebral	7	4.7%
Ophthalmic	15	10.0%
Posterior communicating	32	21.3%
Superior hypophyseal	11	7.3%
Posterior circulation		
Anterior inferior cerebellar	1	0.7%
Basilar	20	13.3%
Posterior cerebral	3	2.0%
Posterior inferior cerebellar	3	2.0%
Superior cerebellar	6	4.0%
Total	150	

Patient selection bias could have masked some of the beneficial effects of Matrix coils. Matrix coils were more likely to be used in large and wide-neck aneurysms, which are more likely to recanalize than small aneurysms. The percentage of large aneurysms in this case series is almost twice as high as in our previously published series [4]. Multivariate analysis is thus required to draw a conclusion. In addition, the friction of Matrix coils could have contributed to underpacking of the aneurysms. Despite its healing effect, the strong water-hammer effect of blood flow can still compact the coils in partially coiled aneurysms. The follow-up period is still too short to assess the

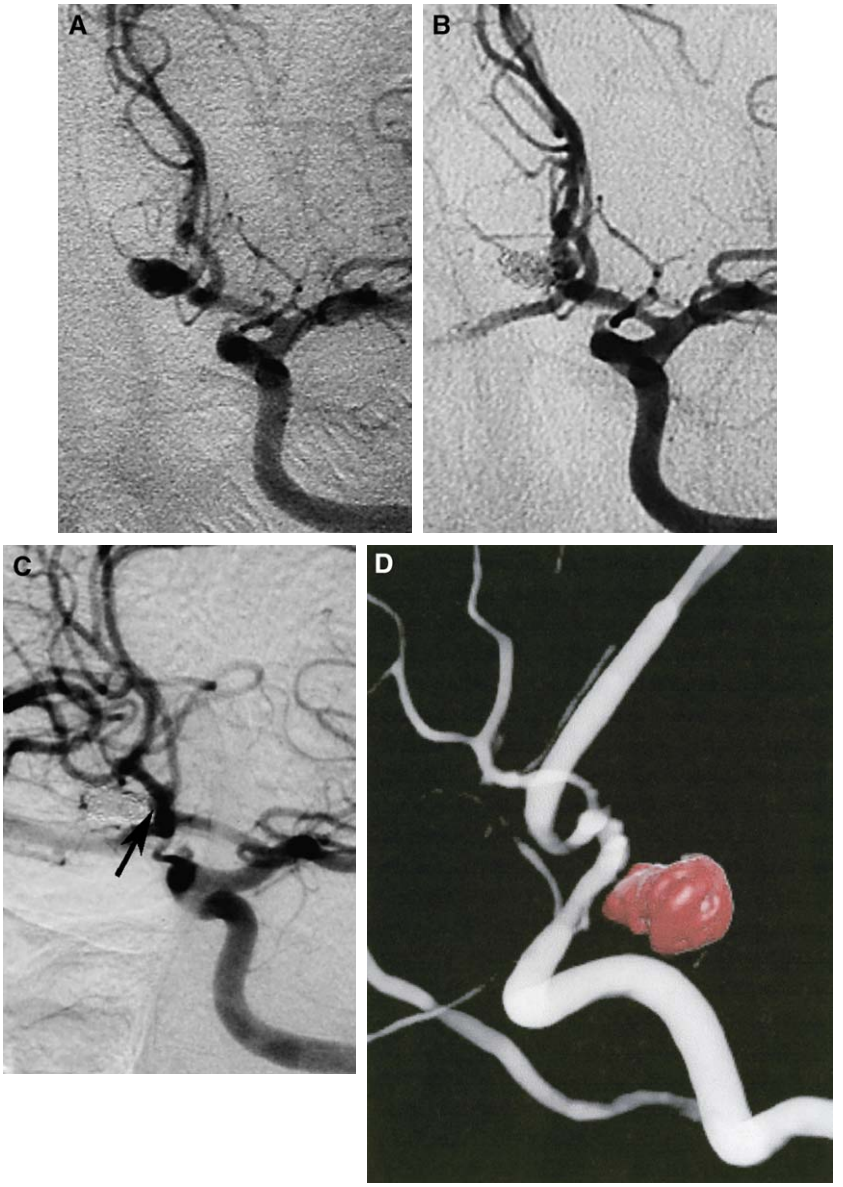

Fig. 2. White-collar sign. (*A*) This patient presents with a ruptured anterior communicating artery aneurysm. (*B*) At the end of Matrix coil embolization, the dome of the aneurysm is obliterated but there is still a small amount of contrast filling at the neck of the aneurysm. (*C*) Follow-up angiogram 3 months later reveals complete occlusion of the aneurysm neck. The coil mass is separated from the parent vessel by a thin white line (*arrow*), the white-collar sign, suggesting fibrous neointima at the aneurysm neck. (*D*) Three-dimensional angiography illustrates another example of the white-collar sign at 13 months of follow-up in a patient with a ruptured posterior communicating artery aneurysm. The coil mass is depicted in red.

long-term clinical outcome and rebleed rate of Matrix coil embolization.

In our experience, patients with unruptured aneurysms sometimes develop headaches in the first few days after embolization with Matrix coils. These headaches usually subside after 1 week and respond to nonsteroidal anti-inflammatory drugs or rapid-taper steroid therapy, suggesting that they are related to inflammation incited by the Matrix coils. Whether anti-inflammatory therapy interferes with healing or not remains unknown.

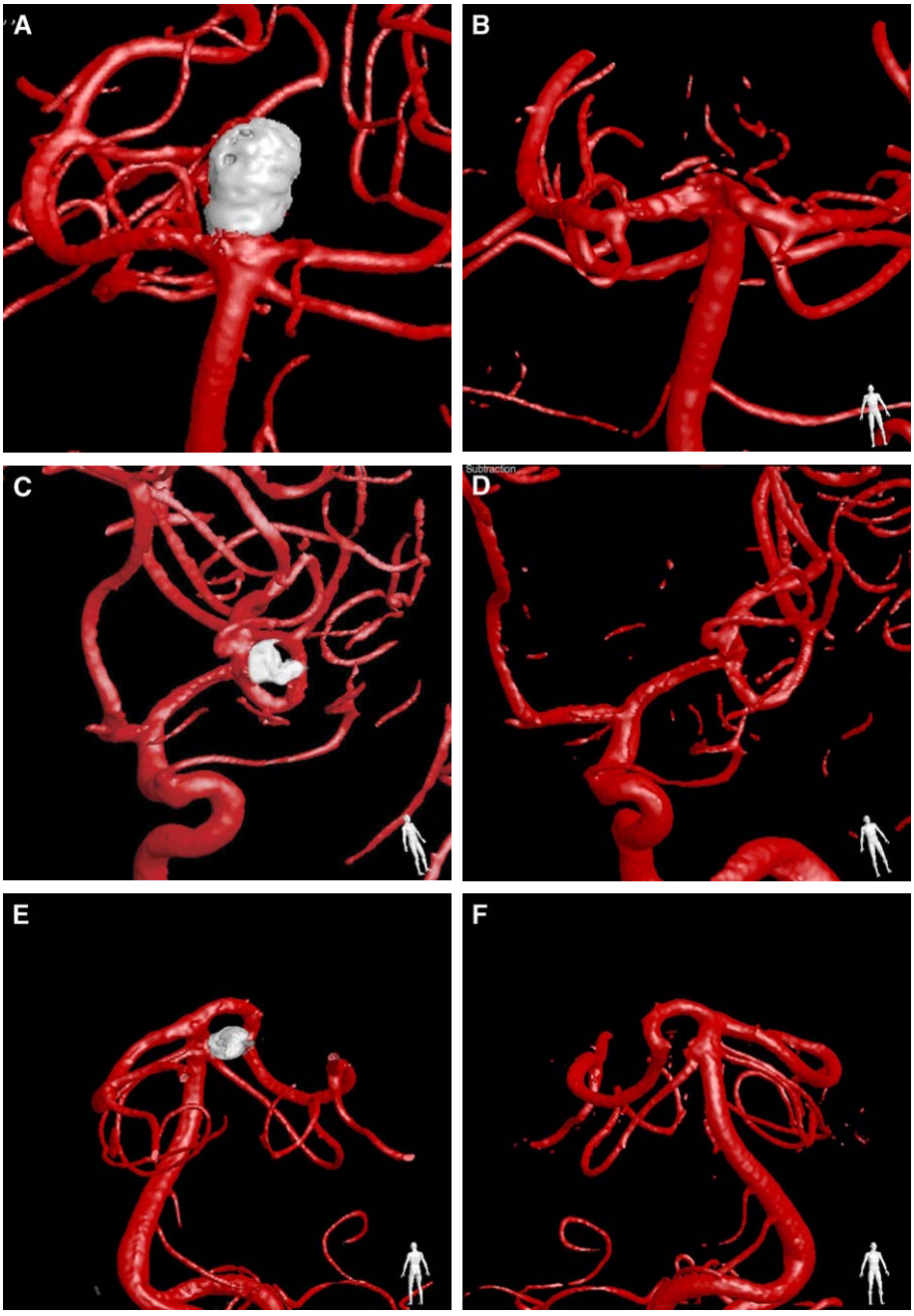

Fig. 3. Durable Matrix coil embolization of aneurysms. (*A*) Anterior-posterior projection of a three-dimensional rotational angiogram shows a completely occluded wide-neck basilar tip aneurysm at 14 months of follow-up. The coil mass is depicted in white. (*B*) After subtraction of the white coil mass, the angiogram shows no evidence of a residual neck. (*C*) Left anterior oblique projection of a three-dimensional rotation angiogram reveals near-complete obliteration of a wide-neck left middle cerebral artery bifurcation aneurysm at 18 months of follow-up. The subtracted image is shown in *D*. (*E*) Twelve months after embolization, this wide-neck right superior cerebellar artery aneurysm remains completely occluded (posterior-anterior projection). (*F*) The subtracted image (anterior-posterior projection) shows preservation of the right superior cerebellar artery.

In summary, Matrix coils are designed to promote healing and reduce recanalization in well-embolized aneurysms; they are not meant to replace dense packing of aneurysms. Although we have observed evidence of a healing response in our preliminary clinical experience using Matrix coils, the benefit of Matrix coils is not dramatic and requires further studies for confirmation. Friction of the coils may limit dense packing of aneurysms. For this reason, we usually use Matrix coils as framing or filling coils and use regular GDCs as the last few finishing coils. Nonetheless, the Matrix coil is the first step in the future direction of improving endovascular treatment of aneurysms. Although it may be tempting to conduct a clinical trial to prove the efficacy of Matrix coils, resources can probably be better used in developing new generations of bioactive coils based on an understanding of the molecular pathogenesis of aneurysms and on the cellular and molecular mechanisms of tissue healing.

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