



TOPIC REVIEW: SURFACE MODIFICATIONS ENHANCING BIOLOGICAL ACTIVITY OF GUGLIELMI DETACHABLE COILS IN TREATING INTRACRANIAL ANEURYSMS

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BACKGROUND

Endovascular therapy with Guglielmi detachable coils is an accepted treatment option for patients with intracranial aneurysms. However, an emerging technology in the realm of endovascular tools is the use of traditional Guglielmi detachable coils with biologically active substances complexed to the coil surface to enhance aneurysm occlusion.

METHODS

We review the literature and current trends in modified Guglielmi detachable coils. Surface modifications with extracellular matrix proteins, growth factors, ion impregnation, and genetically altered cells have been used in animal studies to improve the cellular response of Guglielmi detachable coils. Similarly, coronary artery stents have been modified in several different ways to maintain vessel patency, contrary to the goal of endovascular therapy. We comparatively reviewed this literature to add insight into the evolution of the research on modified Guglielmi detachable coils.

CONCLUSIONS

Guglielmi detachable coil modifications have the potential to enhance aneurysm obliteration with directed cellular responses. This may allow aneurysm occlusion with coils in less time than untreated coils, thus decreasing the risks of aneurysm enlargement and hemorrhage. © 2000 by Elsevier Science Inc.

KEY WORDS

Aneurysm, biologically active devices, coil embolization, coil modification, endovascular therapy, Guglielmi detachable coils.

Endovascular techniques have revolutionized the treatment of cerebrovascular disease and their impact has nowhere been as significant as in the management of intracranial aneurysms. Endovascular treatment of intracranial aneurysms initially used detachable balloons to occlude the aneurysm lumen. Risk of aneurysmal rupture and concerns about long-term patency led to the replacement of balloons with coils as the preferred embolic agent in the treatment of intracranial aneurysms. Nevertheless, the difficulty of precise coil positioning continued to pose problems in effective endovascular treatment.

In 1991, platinum Guglielmi detachable coils (GDCs) were added as a significant measure of safety to endovascular treatment [18,20]. GDCs remain attached to the delivery wire until they are properly positioned within the aneurysm lumen, where they are released by an electrical detachment mechanism. Since their approval by the U.S. Food and Drug Administration in 1995, GDCs have become the most utilized device for endovascular aneurysm treatment. Recent advances in biomaterials and genetics have generated interest in modifying the materials from which endovascular coils are constructed to enhance their effects in achieving aneurysm closure. This review will discuss some of the current laboratory and clinical investigations directed toward improving aneurysm treatment by modification of endovascular coils. While GDC modifications enhance aneurysm occlusion, coronary artery stents have been modified in several different ways to prevent restenosis. Although the goals of GDC therapy and coronary artery stent

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placement are quite different, paradigms to modify stents are comparatively reviewed to gain insight into those for GDCs.

HISTOPATHOLOGY AFTER GDC THERAPY

The presence of a microcoil changes flow dynamics within an aneurysm and enhances thrombus formation by providing regions of stasis or slow flow and surface area to promote coagulation. Rate and extent of thrombosis depend on a number of factors including coil composition, surface charge density, surface texture, and extent of intimal injury [16]. Dense packing of the aneurysm with coils is considered essential to promote blood stasis and endothelial denudation necessary for thrombosis [18-20]. Even with maximal coil packing, the total volume of coil material usually accounts for less than 50% of the total aneurysm volume [25,28]. This can be appreciated by assuming an ideal spherical configuration for an aneurysm with an arbitrary fundal diameter of 4 mm and volume ($= 4\pi r^3/3$) of 33.5 mm³. Using the enclosed coil volume, $V = (\pi d^2)/4 * \text{coil length}$, a coil of 0.254 mm in diameter, and 100 mm in length, the coil would occupy a volume of 5.06 mm³. Therefore, each coil of this size would occupy approximately 15% of the total aneurysm volume. Given these calculations, it would be necessary to pack 6-7 coils into the dome to completely fill this 4-mm diameter aneurysm. In most clinical situations, however, an aneurysm of this size would be treated with 2 to 4 coils, or 30-60% of the total volume, to insure a patent parent artery.

Coil configuration within an aneurysm is important in preventing displacement of thrombus into the parent artery. It has been proposed that intra-aneurysmal coils absorb the systolic pressure normally transmitted to the dome, thus protecting it from rupture [17]. Pressures on the dome of a coiled aneurysm have not been measured. However, because blood (either fluid or clotted) is incompressible, the aneurysm wall will also experience the arterial pressure dynamics of the parent artery, and still remain predisposed to rupture. Partial coiling usually leads to insufficient thrombus formation within an aneurysm and possibly recanalization [49]. Therefore, coils modified with collagen or any other growth factor that stimulates fibrosis may have the potential to provide a better meshwork for fibroblast migration and endothelial cell formation.

There have been six human case reports of eight aneurysms [4,26,33,34,41,43] and more recently a

1 Summary of GDC Histopathology

TIME AFTER GDC	HISTOPATHOLOGY
0-48 h	Organized clot; fibrin over neck
48-72 h	Organized clot; uncovered coils
4-7 days	Organized clot; covered coils and uncovered coils; thin membrane over ostium
8-14 days	Covered and uncovered coils; incomplete thin membrane over the ostium
15-28 days	Covered and uncovered coils; incomplete thin membrane over the ostium
1-3 months	Covered coils; some fibrous tissue at periphery; some endothelium
2-12 months	Covered coils; some fibrous tissue; no endothelium
> 12 months	Coils embedded in fibrous tissue; endothelium over neck

Summary of histopathologic findings at autopsy from cerebral aneurysms after GDC therapy.

larger series of 18 aneurysms [3] with documented histopathological results after GDC therapy. Table 1 summarizes the major time course and histopathologic evolution after GDC. There was evidence of a thin membrane over the neck as early as 3 to 7 days, fibrous tissue as early as 1 month, and endothelium covering the neck was not observed until 12 months. However, the presence of peripheral fibrosis does not determine whether there is endothelium over the ostium, a necessity for complete aneurysm obliteration.

CORONARY ARTERY STENT MODIFICATIONS

As in modifying platinum coils, considerable research has been dedicated to modifying coronary artery stents. Both areas of research are directed at modifying an intravascular device to enhance its biologic effect. However, the goal of each therapy is entirely different. Coronary artery stents are used to maintain vessel patency, whereas GDCs are used to induce aneurysmal thrombosis, fibrosis, and endothelial cell formation. Although percutaneous transluminal coronary stents are widely used for coronary artery revascularization, restenosis occurs in approximately 30 to 50% of cases [10,48]. Stent surface modifications to reduce intimal hyperplasia include polymeric coatings, biodegradable stents, radioactive coatings, gene therapy, endothelial cell coating, protein coatings, and drug-polymer composites (Table 2).

2 A Comparison of Coronary Artery Stent and GDC Modifications

STENT MODIFICATIONS	GDC MODIFICATIONS
Protein coatings	Protein coatings
• Fibrin	• Collagen/laminin
• Heparin	• Fibronectin
• Collagen/laminin	
• Phosphorylcholine	
• Monoclonal antibodies to rabbit platelet integrin	
Biodegradable polymers	Biodegradable polymers
• Poly-L-lactic acid	• Cellulose Acetate
• Polyethylene glycol	
• Poly ϵ -caprolactone	
• Polyphosphate ester	
• Cellulose ester	
Biostable polymers	Biostable polymers
• Polyurethane	• Polyurethane
• Polyurethaneurea + heparin	• Dacron
Biodegradable stents	Fibroblasts with plasmid
Endothelial cell coatings	Ion-impregnation
Drug-polymer composites	
Gene therapy	
Radioactive stents	

Biodegradable polymers such as polylactic acid and polyethylene glycol were introduced as stent coatings to prevent thrombus formation [8,23,42]. In addition, these polymers were also tried as completely resorbable stents [14,47,48]. A further innovation was to use polylactic acid coating incorporated with thrombin inhibitors and platelet aggregation inhibitors [23]. Nonbiodegradable polymers such as polyurethane, silicone, and polyethylene terephthalate have been used and may reduce thrombus formation and inflammatory response [13]. Biocompatible hybrids consisting of metallic stents with polymer coatings offer mechanical stability with the potential for drug delivery [48].

Fibrin was proposed as providing a platform for the recolonization of endothelial cells [24,32]. Polymer-coated metallic stents bound to heparin successfully reduced the thrombogenic potential inherent in metallic stents [22,40]. Phosphorylcholine, a major phospholipid component of biological membranes, when added to stents may result in a reduction of subacute occlusion rates [15,29]. In addition, nitric oxide synthase or nitric oxide donors have also been suggested as therapeutic coatings [12].

Because cardiac stents lose their thrombogenic potential once they become covered with endothelial cells, they could be seeded with cell lines ge-

netically modified to create immortalized endothelial cells [39], or genetically modified cell lines that secrete tissue plasminogen activator [9,11]. Topol et al [48] reviewed the use of stents as a platform to deliver radiation to the vessel wall; preliminary studies with these stents showed encouraging results in reducing neointimal hyperplasia in animal models.

It has already been shown that recombinant defective adenoviral vectors are an efficient method for arterial gene transfer [2,5,21,31,36,38]. Several investigators have fabricated resorbable endoluminal stents from biodegradable polymers such as poly-L-lactic acid and poly ϵ -caprolactone blends impregnated with recombinant adenovirus [37,50,51].

GDC SURFACE MODIFICATIONS

Altering the coil surface is directed at enhancing fibrosis and endothelial cell formation after GDC therapy. While similar techniques have been applied to coat coronary artery stents, coil modifications are meant to enhance, not suppress cellular growth responses. The difference between stenting and coiling is significant because the geometry of the coil is designed to actually enhance thrombosis. Both in vitro [27,45] and in vivo [6,7,28,35,44,46] models evaluate the clinical efficacy of these modifications (Table 3).

IN VITRO

Tamatani et al [45] cultured canine carotid artery endothelial cells with platinum microcoils, polyvinyl alcohol particles, silicon balloons, and silk threads that were either uncoated or coated with type I collagen or fibronectin. Their results showed that collagen-coated materials had much higher endothelial cell densities. Kallmes et al [27] evaluated GDCs in vitro with laminin, poly-L-lysine, fibronectin, and types I and IV collagen. Coils were coated and cultured with fibroblasts that could secrete basic fibroblast growth factor. Rates of cellular proliferation were better for those coils coated with type I collagen, laminin, and fibronectin as compared to type IV collagen.

IN VIVO

Ahuja et al [1] modified GDCs with three different polyurethanes to improve thrombogenicity. Coils were endovascularly placed into the common carotid artery and blood flow was measured using Doppler ultrasound before and after coil placement.

3 Histopathologic Follow-up of Animal Data with Modified Coils

STUDY [REF]	ANIMAL	MODEL	MODIFICATION	No. ANIMALS	FOLLOW-UP (WEEKS)	RADIOGRAPHIC OCCLUSION	HISTOLOGIC OCCLUSION	ENDOTHELIUM
Kwan [30]	Rabbit	Bifurcation	Polyester	9	4-12	4	1	1
Dawson [6]	Swine	Sidewall	Collagen	9	3-12	9	9	9
Dawson [6]	Swine	Sidewall	Polyester	5	3-12	5	0	0
Dawson [7]	Swine	Sidewall	Collagen-filled	4	10	3	N/A	N/A
Muramaya [35]	Swine	Sidewall	Protein/Ion	2	4	N/A	2	2
Szikora [44]	Canine	Sidewall	Collagen-filled	9	12	6	N/A	N/A
Szikora [44]	Canine	Sidewall	Polyester	6	12	3	N/A	N/A
Totals				44		30/33 (91%)	12/25 (48%)	12/25 (35%)

Abbreviations: N/A = not available; No. = number.

Histologic Occlusion: complete occlusion of aneurysm neck; Radiographic Occlusion: > 90%; Endothelium: any amount present.

Histologically, coated coils showed more cellularity and thrombogenicity. Tamatani et al [46] embolized both internal maxillary arteries of dogs using coils coated with type I collagen on one side and unaltered coils on the other. Histopathologic and angiographic follow-up at 30 minutes and at up to 16 weeks showed that collagen-coated coils produced a better cellular response with more endothelium directly over the coil surface.

Muramaya et al [35] created sidewall aneurysms made from jugular vein in swine and treated them with coils coated with albumin, fibronectin, or collagen and subjected to high-energy (neon ion) implantation. Ion implantation embedded proteins onto the coil structure without altering its size. Fibronectin-coated, ion-implanted coils showed the greatest acute thrombogenicity at post-treatment day 14 as measured by weight of thrombus and the greatest cellular response as demonstrated by microscopy. Kwan et al [30] created bifurcation aneurysms in rabbits and treated them with polyester fiber-coated coils. Angiography at 1 to 3 months showed complete obliteration of the aneurysm dome in most rabbits. However, histologic examination revealed extensive proliferation of endothelial cells within the dome, but endothelium across the neck in only one animal.

Dawson et al [6] created sidewall aneurysms using jugular venous pouches in swine; these were embolized with either collagen-coated or dacron-fibered platinum coils. Aneurysms treated with collagen-coated coils showed on microscopy a mature, collagen-rich fibrous scar with no evidence of thrombus, recanalization, or aneurysm growth. There was an endothelial cell layer across the neck of the aneurysms treated with the collagen-coated coils. Aneurysms treated with dacron-fibered coils showed on microscopy immature scar, thrombus, fibrin deposits, and multilayered endothelium. The same group, using a similar model in swine, treated surgically-created aneurysms with collagen-filled and unaltered interlocking detachable coils. On angiography, three of four aneurysms with collagen-filled coils were occluded compared to two of four with unaltered coils. On histopathologic review, the aneurysms treated with collagen-filled coils showed more collagen near the coil, and a greater number of fibroblasts.

Szikora et al [44] created sidewall aneurysms in the common carotid artery of canines and treated these with collagen-filled and unaltered coils. Angiographic comparisons showed no difference between unaltered coils and collagen-filled coils. Light microscopy showed an enhanced local proliferation of fibroblasts in collagen-filled coils as com-

pared to unaltered coils. Kallmes et al [28] genetically modified 3T3 fibroblasts transfected with Zipneo vector (plasmid) that contained the bFGF (basic fibroblastic growth factor) gene. Transfected fibroblasts were grown in culture medium and then coils were added until the outer surface of the coil was confluent with cells. Coils were then placed in the common carotid artery (CCA) of adult nude rats for either 14 or 35 days and then compared with uncoated coils. Coils coated with transfected fibroblasts showed marked fibroblast proliferation and collagen formation 5 weeks after insertion into the CCA as compared with uncoated coils.

DISCUSSION

Histopathological aneurysm data from autopsy series highlight some possible limitations of GDC therapy. Surface modifications may be necessary to improve occlusion rates and overall protection from aneurysm growth or rupture. While neurosurgeons and neurointerventionalists have modified platinum microcoils to enhance aneurysm wall inflammation and occlusion, cardiologists and interventional cardiologists have modified coronary artery stents to prevent local inflammation and restenosis.

Most coil modification studies have been limited to animal research, which still lacks an accurate model for intracerebral aneurysms. Current aneurysm models (bifurcation and sidewall) are based on arterial and venous manipulation of the extracranial vessels, usually the common carotid artery. Most investigators use different species (canine, monkey, rabbit, and swine) and different techniques (with or without postembolization heparin). In Table 2, we compared only those aneurysms evaluated at maximal follow-up for the reported period. Though given the study differences, those coils modified with collagen (type I), fibronectin, ion impregnation, and bFGF showed a better overall cellular response when compared to controls.

Compared to stent modifications, coil modifications are in the very early stages of development. The majority of research in coil modification has thus far been limited to the extracellular matrix proteins, laminin, collagen, and fibronectin. Of these, collagen (Type I) seems to have the greatest potential as a coating and may be considered as a medium to release other pharmacologic agents into the aneurysm dome. However, it is important for these modifications not to destabilize the aneurysm wall. In addition, an important design constraint with any surface modification is to maintain the integrity of the coil surface while using catheter

delivery systems. Added factors or cells may be sheared off as the coil is manipulated through the catheter. More importantly, added modifications could induce thrombosis near the parent artery, thus increasing the risk of post-treatment stroke.

CONCLUSION

Guglielmi detachable coil surface modifications may enhance the matrix formation needed to cross the aneurysm dome, and improve fibrosis. In general, current work with GDC modification parallels that with coronary stents, although with different endpoints: aneurysm occlusion and vessel patency. Although coil modifications are in the early stage of development, stent technology may add new information to current research initiatives.

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endovascular embolization has again become the focus of aneurysm treatment.

However, some probable deficiencies of GDC embolization have recently been pointed out. The most considerable problem is that an unexpectedly low rate of complete aneurysmal obliteration has been achieved with GDC embolization. This article describes surface modifications of GDCs intended to resolve this problem. Similar principles of surface modification of platinum coils have been used in a variety of clinical and basic studies of coronary stents. This knowledge of coronary stent modifications could be applicable to the surface modifications of GDCs, although the goals of the two therapies are conflicting. These basic and clinical studies will aid in the therapeutic advancement of treating cerebral aneurysms by GDC embolization.

The basic concept of GDC treatment—"obliteration of an aneurysm using merely helical-shaped platinum coils"—makes it difficult to achieve complete cure of all aneurysms, which have a wide variety of sizes and shapes. No improvement, including surface modifications of coils, will resolve this basic problem. A significant breakthrough, such as liquid embolization material [1,2] will be necessary to achieve complete cure of cerebral aneurysms by less invasive endovascular techniques.

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The actual research on modifications of the surface of stents and coils is extremely important for the future of these two techniques. The research on stents is far more advanced than the research on coils. The goals of stent and coil treatments are totally different, as the authors clearly state. In the case of stents, the goal of surface modification is to decrease the risk of thrombosis and intimal hyperplasia. As soon as the stent is covered by epithelial cells, the risk of thrombus formation is eliminated.

COMMENTARY

The endovascular approach to cerebral aneurysms with detachable balloons has not been as widely accepted as might be expected, because this technique is not considered to have much merit compared to radical aneurysm surgery. Since the development of Guglielmi detachable coils (GDC) in 1991,

In the case of coils, the research is still in its infancy and is limited to in vitro and animal studies. The goal of coil treatment is to induce more thrombosis and fibrosis within the aneurysm and more epithelialization of the aneurysm neck. For stents, surface modification *decreases* the undesired thrombogenic reaction without the anticipated side effects. For coils, surface modification *increases* the thrombo-

genic reaction, which is desired within the aneurysm but may cause increased risk of thrombogenic complications in the parent artery. This is the dilemma.

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Without a unified approach, I fear that academic health centers are doomed to extinction or to become pure for-profit businesses. What will it take to reunify medicine so we can get back to taking care of patients, educating our successors, and making new discoveries without expending so much time and energy on fighting managed care businesses and each other?

—CATHERINE D. DEANGELIS, M.D., MPH
“THE PLIGHT OF ACADEMIC HEALTH CENTERS”
JAMA 2000;283:2438-9