

## Endovascular Biologic Aneurysm Management

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In 1991, platinum Guglielmi detachable coils (GDCs) were introduced and in 1995 approved by the U.S. Food and Drug Administration to treat intracranial aneurysms unsuited for surgical clipping using an endovascular approach. The placement of these coils in an aneurysm is designed to enhance intra-aneurysmal thrombosis, fibrosis, and finally endothelial cell formation over the aneurysm neck to obliterate it from the intracranial arterial circulation. However, not all aneurysms can be coiled, and some that are may recur. This and the relative "noninvasiveness" of the coil technique have generated interest in using coils as drug, gene, or cell delivery devices to enhance aneurysm stabilization and obliteration using biologic techniques.

In this chapter, new approaches using synthetic and biopolymer coatings, growth factor delivery, biodegradable coils, and cell and gene delivery are reviewed briefly in the context of biologic and biomechanical design goals. In most studies to date with polymer-coated platinum coils, collagen coating appears to provide the largest benefit. However, release of growth factors, such as vascular endothelial cell growth factor (VEGF), from a collagen-coated platinum coil can dramatically promote wall thickening and coil integration when compared with collagen-coated coils without any growth factor. Fully biodegradable coils also provide unique advantages with respect to wall thickening without metal-based interference of magnetic resonance imaging follow-up. Finally, new opportunities for linking viral vectors to coils for local gene therapy on the aneurysm are discussed.

### Aneurysm Changes after Guglielmi Detachable Coil Treatment

Microcoil placement in an aneurysm reduces blood flow velocities within the aneurysm. The coils provide regions of stasis or slow flow, an artificial surface area to promote coagulation, and endothelial disruption to expose thrombogenic intima (i.e., tissue factor). The rate and extent of thrombosis depend on a number of factors including coil composition, surface charge density, surface texture, and extent of intimal injury. Dense coil packing is considered necessary to promote aneurysm thrombosis. However, even with what on angiography appears to be maximal coil packing, the total volume of coil material is less than 50% of the total aneurysm volume.<sup>1</sup> Packed coils have also been proposed to absorb the systolic blood pressure normally transmitted to the aneurysm dome, thus protecting it from expansion or rupture.<sup>2</sup> However, pressures on the dome of a coiled aneurysm have never been measured. Because blood (either fluid or clotted) is incompressible, the coiled aneurysm wall also experiences the arterial pressure dynamics of the parent artery and so remains predisposed to rupture. Rather than the proposed mechanical effects on pressure dynamics or wall stresses, it is likely that the main benefit of coils is derived from the biologic progression of the thrombosed aneurysm as a result of the stasis created by the platinum coils. In addition, micromechanical motions of the coil against the aneurysm wall through endothelial denudation may drive the

biologic response by up-regulating factors that may promote thrombosis or vascular fibrosis. Because platinum is relatively inert in terms of biologic activity, opportunities exist to explore biologically active coatings or materials to enhance aneurysm obliteration.

There is limited information about the histopathologic results following human GDC therapy. However, a database is emerging, based on a small number of case reports.<sup>3-9</sup> Table 63-1 summarizes the major time course and histopathologic evolution after coil therapy. Endothelium over the aneurysm neck is needed for complete exclusion of the aneurysm from the circulation. A thin membrane is observed within days over the aneurysm neck. Endothelium over the aneurysm neck is observed only after about 12 months. In part, this may explain why GDC embolization is generally less effective in wide-necked or larger aneurysms, or both.<sup>10-14</sup> In fact, endothelialization of the aneurysm neck is uncommon as aneurysm size increases. Furthermore, open spaces between the coils are apparent with incomplete membranes over the aneurysm ostium. For example, Bavinkzi and colleagues<sup>3</sup> observed that 50% of aneurysms thought to be 100% occluded by angiography were not completely occluded on histopathologic evaluation. Therefore, coils modified with synthetic or natural polymers, growth factors, cells, or genes

that stimulate fibrosis or other biologic repair processes may have the potential to provide a better meshwork for cellular migration, matrix production, and endothelial cell formation across the aneurysm ostium.

### Polymer and Biopolymer Coatings

Modification of the coil surface is directed at enhancing thrombosis, fibrosis, and endothelial cell formation after GDC therapy. For example, Ahuja and coworkers<sup>15</sup> modified GDCs with three different polyurethanes to improve thrombogenicity and placed these coils into the common carotid artery (CCA). Histologically, coated coils showed more cellularity and thrombogenicity. Tamatani and associates<sup>16</sup> 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 up to 16 weeks showed that collagen-coated coils produced a better cellular response with more endothelium directly over the coil surface. Collagen provides a potent thrombogenic signal and a matrix for remodeling.

The efficacy of several biologic modifications in various in vitro and in vivo animal aneurysm models is summarized in Table 63-2. First, Murayama and colleagues<sup>20</sup> created sidewall aneurysms in swine made from the jugular vein and treated these lesions with coils coated with albumin, fibronectin, or collagen and subjected to high-energy (neon) ions before use. Fibronectin-coated, ion-treated coils displayed the greatest acute thrombogenicity at post-treatment day 14 as measured by weight of thrombus and the greater cellular response demonstrated by microscopy. Second, Kwan and coworkers<sup>17</sup> created bifurcation aneurysms in rabbits and treated them with polyester fiber-coated coils. Angiography 1 to 3 months later showed complete obliteration of the aneurysm dome in most rabbits. However, histologic examination demonstrated extensive proliferation of endothelial cells within the dome but endothelium across the neck in only one animal. Third, Dawson and associates<sup>18</sup> created sidewall aneurysms using jugular venous pouches in swine that were embolized using collagen-coated or Dacron-fibered platinum coils. On microscopic examination, aneurysms treated with collagen-coated coils demonstrated a mature, collagen-rich fibrous scar with no evidence of thrombus, recanalization, or aneurysm growth. In addition, an endothelial cell layer across the neck of the aneurysms treated with the collagen-coated coils

**TABLE 63-1**

| Time Course of Histopathology of Human Cerebral Aneurysms after Placement of Platinum Coil |  |
|--|--|
| Time   | Histopathology   |
| 0-48 hr  | Organized clot; fibrin over neck   |
| 48-72 hr   | Organized clot; uncovered coils  |
| 2-7 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 mo   | Covered coils; some fibrous tissue at periphery; some endothelium            |
| 3-12 mo  | Covered coils; some fibrous tissue; no endothelium                           |
| >12 mo   | Coils embedded in fibrous tissue; endothelium over neck                      |

TABLE 63-2

| Histopathologic Follow-up of Animal Data with Surface Modified Coils |        |             |                 |                |      |     |             |
|--|--------|-------------|-----------------|----------------|------|-----|-------------|
| Study  | Animal | Model       | Modification    | Follow-up (wk) | RO   | HO  | Endothelium |
| Kwan <sup>7</sup>  | Rabbit | Bifurcation | Polyester       | 4-12           | 4/4  | 1/4 | 1/4         |
| Dawson <sup>8</sup>  | Swine  | Sidewall    | Collagen        | 3-12           | 9/9  | 9/9 | 9/9         |
| Dawson <sup>8</sup>  | Swine  | Sidewall    | Polyester       | 3-12           | 5/5  | 0/5 | 0/5         |
| Dawson <sup>9</sup>  | Swine  | Sidewall    | Collagen filled | 10             | 3/4  | N/A | N/A         |
| Murayama <sup>20</sup>   | Swine  | Sidewall    | Protein/ion     | 4              | N/A  | 2/2 | 2/2         |
| Szikora <sup>21</sup>  | Canine | Sidewall    | Collagen filled | 12             | 6/12 | N/A | N/A         |
| Szikora <sup>21</sup>  | Canine | Sidewall    | Polyester       | 12             | 3/12 | N/A | N/A         |
| Overall  |        |             |                 |                | 91%  | 48% | 35%         |

HO = histologic occlusion (complete occlusion of aneurysm neck); N/A, not available; RO = radiographic occlusion (> 90%); Endothelium, any amount present.

was observed. The Dacron-fibered coils demonstrated an immature scar, thrombus, and a multi-layered endothelium. Fourth, Szikora and coauthors<sup>21</sup> created sidewall aneurysms in the canine CCA and treated them with collagen-filled or unaltered coils. Angiographic comparisons showed no difference between unaltered coils and collagen-filled coils. On examination using light microscopy, enhanced local fibroblast proliferation in the collagen-filled coils was observed when compared with aneurysms treated using unaltered coils.

Polymer coatings can alter the interaction of cells with the coil surface. To date, the majority of research in coil modification has 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 also may be considered as a medium to release other pharmacologic agents into the aneurysm dome. These effects have been tested in cell culture models. For example, Tamatani and coworkers<sup>22</sup> 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 greater endothelial cell densities than the other substances. Kallmes and colleagues<sup>23</sup> evaluated GDCs coated with laminin, poly-L-lysine, fibronectin, and types I and IV collagen and cultured with fibroblasts that could secrete basic fibroblast growth factor in vitro. Cellular proliferation rates were better for the coils coated

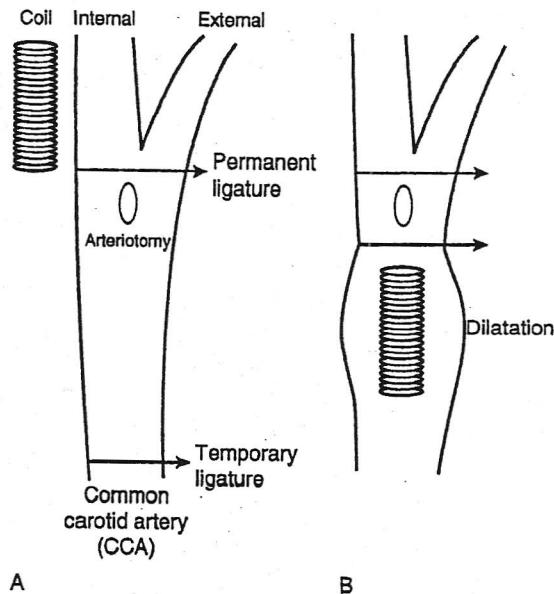
with type I collagen, laminin, and fibronectin than those coated with type IV collagen.

#### Device-Based Growth Factor Therapies

Various growth factors have been attached to coils including transforming growth factor  $\beta$  (TGF- $\beta$ ) and VEGF. For example, de Gast and colleagues,<sup>24</sup> using elastase-induced saccular aneurysms in New Zealand white rabbits, found that the thickness of tissue overlying TGF- $\beta$ -coated coils was  $36 \mu\text{m}$  2 weeks after implantation and  $86 \pm 74 \mu\text{m}$  6 weeks after implantation. With control coils, tissue thickness was  $3 \mu\text{m}$  and  $37 \pm 6 \mu\text{m}$  at the same time points.

VEGF is a heparin-binding glycoprotein that is also known as vascular permeability factor. We<sup>25</sup> hypothesized that it is difficult for GDCs alone to occlude larger aneurysms completely because the coils do not provide enough mechanical or biologic support to promote neck closure. Instead, we postulated that GDCs modified with an angiogenesis-promoting factor, such as VEGF, may promote fibrosis and subsequent aneurysm obliteration in a low-flow hemodynamic environment. To study vessel wall responses under conditions of stasis and arterial pressure analogous to cerebral aneurysm, we inserted GDC coil segments into surgically created, blind-ended CCAs of adult male rats for 14 days (Fig. 63-1). The GDC coil segments (0.4 cm) were either unmodified, modified with type I collagen (2.1 mg/mL), or modified





**Figure 63-1.** Illustration of a rat carotid artery model for rapid screening of coil modifications. *A*, Exposure of the common carotid artery showing the temporary proximal and permanent distal ligatures. *B*, The coil has been inserted into the common carotid artery, a permanent ligature has been placed proximal to the arteriotomy, and the temporary ligature has been released.

with type I collagen and recombinant human VEGF-125 (rhVEGF; 500  $\mu\text{g}/\text{mL}$ ).

The coils were examined using scanning electron microscopy. The coils coated with rhVEGF-collagen were completely encapsulated in fibrotic tissue. By contrast, there was minimal cellular accumulation on the surface of unmodified coils (Fig. 63-2A). There was greater cellular proliferation on the coil plus collagen segment (Fig. 63-2B). The coil plus collagen plus VEGF segment showed the greatest cellular accumulation with large cellular structures accumulating on the coil surface (Fig. 63-2C). A total of 26 procedures were performed and 32 arterial segments were harvested and grouped into normal ( $n = 6$ ), coil ( $n = 9$ ), coil plus collagen ( $n = 5$ ), and coil plus collagen-rhVEGF ( $n = 12$ ). The normal group ( $n = 6$ ) consisted of normal vessels taken from the contralateral CCA; no coil placement or surgical disruption was performed in these vessels. In Figure 63-3, representative histologic sections from each group are shown. Massive intimal hyperplasia and clot organization absent of red blood cells were the dominant characteristic of the CCA implanted for 2 weeks with coils coated with collagen-rhVEGF.

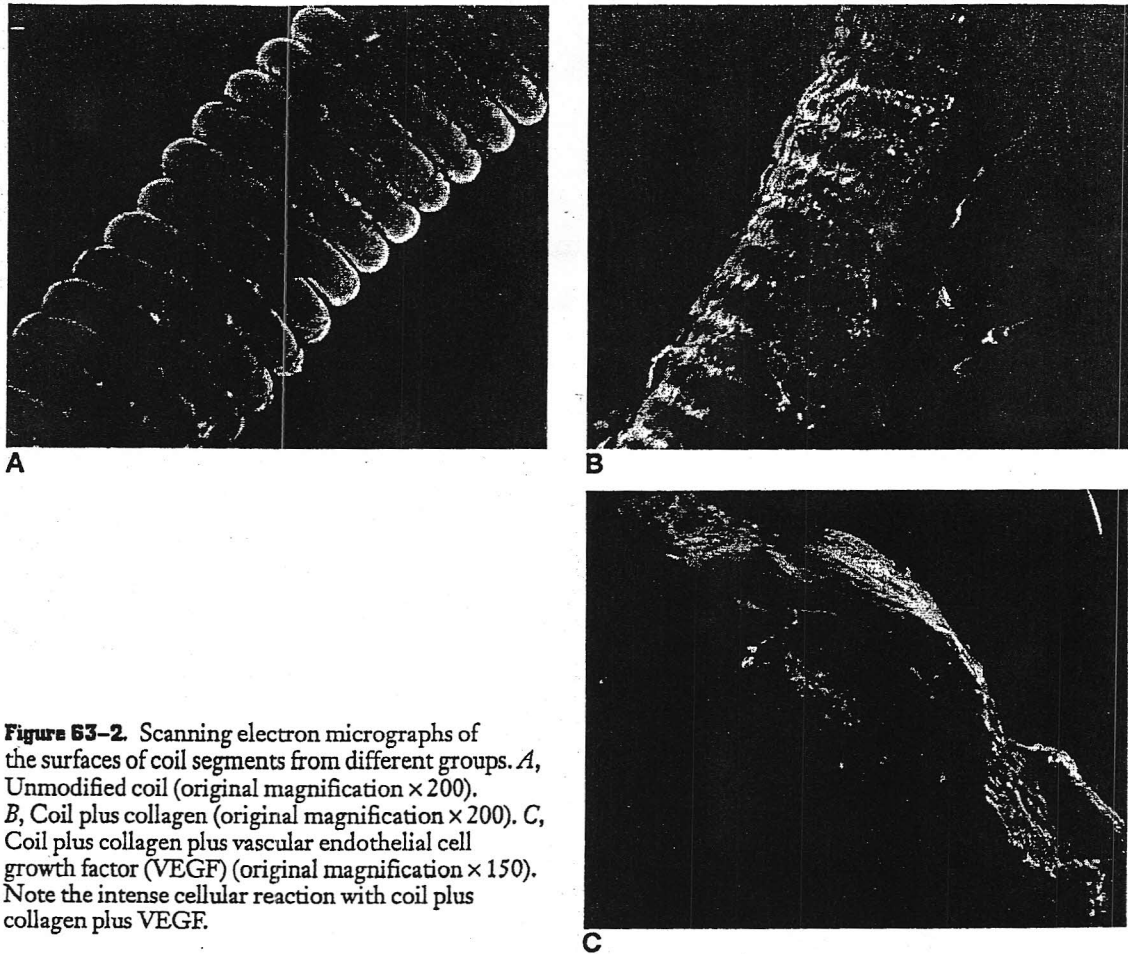
A slight vessel dilatation was seen after coil placement. This was accompanied by an increase in lumen diameter and area and a twofold increase in wall thickness. Collagen-coated coils resulted in a threefold increase in wall thickness (0.15 mm vs. 0.05 mm), whereas a fivefold increase in wall thickness was observed in the CCA treated with collagen-rhVEGF-modified coils (Table 63-3). These findings suggest that rhVEGF added onto the surface of a GDC may promote endothelialization, clot organization, and tissue integration of the coils. Consequently, use of rhVEGF as a surface modification to GDCs may enhance their therapeutic effects in the treatment of cerebral aneurysms.

### Biodegradable Implantable Devices

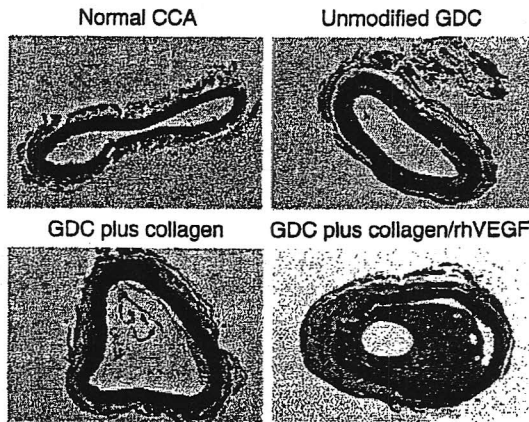
Considerable experimental work has been performed to improve coronary artery stents, including the use of biodegradable materials. The goals of coronary artery stenting and aneurysm coiling are different, however. We postulated that biodegradable coils, particularly when modified with matrix components or growth factors, may provide benefits to aneurysm stasis and thrombosis. Consequently, we designed biodegradable polyglycolide coils (BPCs) and compared the histopathologic response with that of platinum GDCs after insertion into ligated CCA of adult rats.<sup>26</sup> BPCs were also tested for use in local drug and gene delivery; segments (4 mm) of unmodified BPC, unmodified GDC, or BPC coated with type I bovine collagen and rhVEGF-165 (500  $\mu\text{g}/\text{mL}$ ) were inserted into blind-ended CCAs of adult rats for 14 days and compared with contralateral control CCAs.

BPCs were constructed from Biosyn Glycomer 631 monofilament synthetic absorbable suture (United States Surgical, Norwalk, CT). The actual polymer blend consisted of polyglycolide (60%), dioxanone (14%), and trimethylene carbonate (26%). A size 5-0 suture (diameter 180  $\mu\text{m}$ ) was used as a central core and another 5-0 suture was tightly wound around this core to a length of 4.0 cm (2.13 turns/cm) and an outer diameter of 540  $\mu\text{m}$ , thus forming the primary coil. The primary coil was further coiled around a 3-mm shaping cylinder forming a secondary coil. The secondary coil was heated to 160°C for 20 minutes and allowed to cool over 20 minutes before being removed from the shaping cylinder. This heat-treated BPC displayed mechanical flexibility amenable for catheter-based delivery.

Fourteen days after coil insertion, the coils and CCAs were examined using histopathologic techniques. Arterial segments with BPC had greater



**Figure 63-2.** Scanning electron micrographs of the surfaces of coil segments from different groups. *A*, Unmodified coil (original magnification  $\times 200$ ). *B*, Coil plus collagen (original magnification  $\times 200$ ). *C*, Coil plus collagen plus vascular endothelial cell growth factor (VEGF) (original magnification  $\times 150$ ). Note the intense cellular reaction with coil plus collagen plus VEGF.



**Figure 63-3.** Histopathologic findings in the rat common carotid artery (CCA) segments. Sections on the left are trichrome stained and those on the right are H & E stained (original magnification  $\times 20$ ). *A*, No coil. *B*, Coil. *C*, Coil plus collagen. *D*, Coil plus collagen plus vascular endothelial cell growth factor (VEGF). There is significant intimal hyperplasia in the CCA segment treated with a collagen/VEGF-modified coil. GDC, Guglielmi detachable coil; rhVEGF, recombinant human VEGF.

wall thickening than GDC-treated vessels that had a luminal diameter reduced by 40% relative to untreated contralateral controls (Table 63-4). Arterial segments treated with BPC also displayed a reduction in luminal area with marked cellular proliferation within the coil diameter, indicative of coil integration (see Table 63-4). Arterial segments with collagen-rhVEGF-coated BPC displayed a 2.9-fold increase in wall thickness and a 34% reduction in luminal diameter compared with contralateral control vessels but similar to non-modified BPC coils (see Table 63-4). There was marked proliferation of cells within the coil lumen of vessels treated with BPC with collagen-rhVEGF.

These results suggest that BPCs enhance the vascular response of CCA segments compared with GDCs. In addition, modified BPCs appear suitable for local protein delivery to the vessel lumen. There are, however, limitations to this feasibility study. First, the coils were placed directly into the CCA using the microscope rather than a catheter delivery system, and second, the model does not fully

TABLE 63-3

| Modified Guglielmi Detachable Coils Increase Vessel Wall Thickness |                               |                     |                     |
|--|-------------------------------|---------------------|---------------------|
| Group  | Lumen Area (mm <sup>2</sup> ) | Lumen Diameter (mm) | Wall Thickness (mm) |
| Normal (n = 6)   | 1.01 ± 0.49*                  | 0.35 ± 0.09         | 0.05 ± 0.01         |
| Coil (n = 9)   | 1.99 ± 0.99                   | 0.49 ± 0.14         | 0.10 ± 0.02         |
| Coil + collagen (n = 5)  | 1.34 ± 0.84                   | 0.40 ± 0.12         | 0.15 ± 0.05         |
| Coil + collagen + rhVEGF (n = 12)                                  | 0.62 ± 0.74                   | 0.21 ± 0.20         | 0.26 ± 0.18         |

\*Measurements are mean ± standard deviation.

RhVEGF, recombinant human vascular endothelial cell growth factor.

Modified from Abrahams JM, Forman MS, Grady MS, Diamond SL: Delivery of human vascular endothelial growth factor with platinum coils enhances wall thickening and coil impregnation in a rat aneurysm model. *AJNR* 22:1410-1417, 2001.

TABLE 63-4

| Effects of Biodegradable Polyglycolide Coils on the Rat Common Carotid Artery |                               |                     |                     |
|---|-------------------------------|---------------------|---------------------|
| Group   | Lumen Area (mm <sup>2</sup> ) | Lumen Diameter (mm) | Wall Thickness (mm) |
| Normal (n = 6)  | 1.01 ± 0.49*                  | 0.35 ± 0.09         | 0.05 ± 0.01         |
| GDC (n = 9)   | 1.99 ± 0.99                   | 0.49 ± 0.14         | 0.10 ± 0.02         |
| BPC (n = 6)   | 0.72 ± 0.93†                  | 0.21 ± 0.24†        | 0.33 ± 0.19†        |
| BPC + collagen/ rhVEGF (n = 5)  | 0.75 ± 0.84†                  | 0.23 ± 0.23†        | 0.29 ± 0.11‡        |

\*Mean ± standard deviation for area, diameter, and wall thickness.

†P value significant compared with GDC (P < .05).

‡P value significant compared with GDC (P < .005).

BPC, biodegradable polyglycolide coil; GDC, Guglielmi detachable coil; rhVEGF, recombinant human vascular endothelial cell growth factor.

Modified from Abrahams JM, Forman MS, Grady MS, Diamond SL: Biodegradable polyglycolide endovascular coils promote wall thickening and drug delivery in a rat aneurysm model. *Neurosurgery* 49:1187-1193; discussion 1193-1195, 2001.

represent an aneurysm. Nevertheless, the findings provide valuable insights into potential future aneurysm treatment. BPCs offer several possible advantages over traditional GDCs, in particular, compatibility with imaging studies; the ability to deliver bioactive drugs, proteins, or genes; and an enhanced local cellular response from the vascular endothelium.

### Coil-Based Gene Therapy

GDCs, the present "gold standard" for endovascular aneurysm occlusion, are made from platinum, which is relatively biologically inert. To improve GDC efficacy, they have been modified with a variety of extracellular matrix proteins or

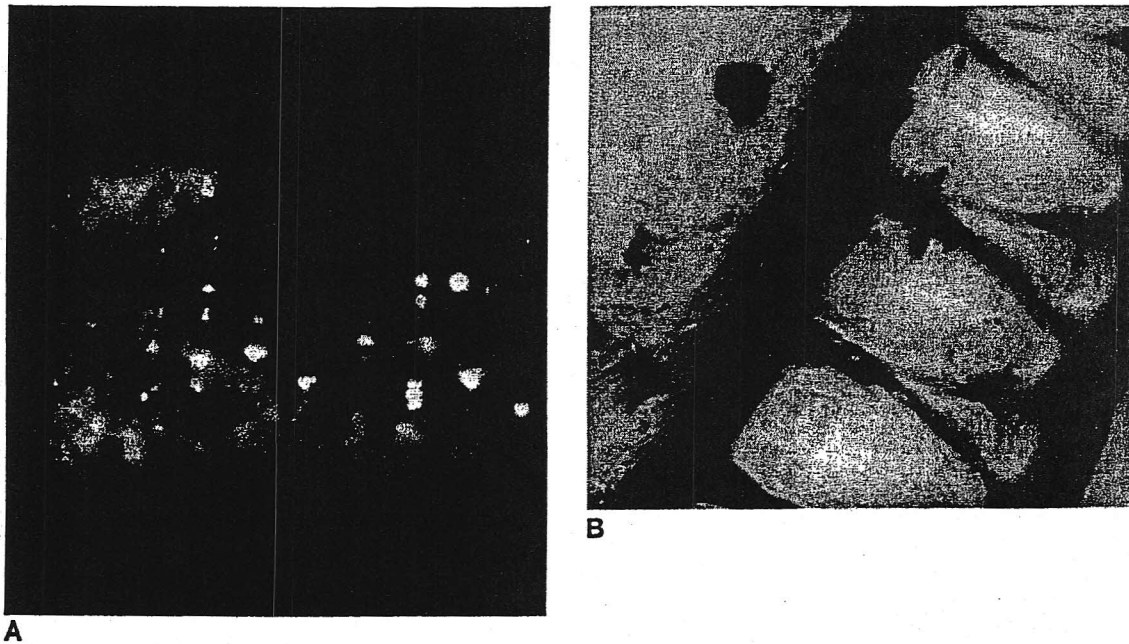
growth factors. However, there are limitations to delivery of proteins, such as protein denaturation or loading capacity. Instead, it may be feasible to use GDCs as a gene delivery system to facilitate coil-based aneurysm occlusion.

Gene therapy shows promise in cerebrovascular disease. Among several factors, the efficiency of gene transfer and its subsequent therapeutic effect are central to the success of gene therapy. Adenovirus demonstrates high gene transfer efficiency compared with other vectors. There are several methods for delivering adenovirus, including direct intravenous or intra-arterial injection or delivery on the surface of an endovascular device. Abrahams and colleagues<sup>27</sup> demonstrated that an endovascular coil could function as a local adenovirus delivery system. In these experiments, adenovirus was attached to collagen that coated either platinum or biodegradable coils. Anti-adenoviral monoclonal antibodies were covalently attached to the collagen-coated surface of either platinum or polyglycolic acid microcoils. These antibodies were used to tether replication-deficient adenovirus (Ad-GFP or Ad-LacZ). Transduction on or near the coil was assessed in cell culture using rat arterial smooth muscle cells (A10 SMCs). In cell culture studies, green fluorescent protein (GFP)-positive SMCs were detected only on the platinum coil sur-

face, and LacZ-positive cells were detected only on the polyglycolic acid coil surface, demonstrating localized gene delivery. When Ad-LacZ, collagen-coated polyglycolide coils were cultured with A10 cells, transduction of cells was observed on all four polyglycolide coils tested. This was indicated by the blue cell-localized staining on the coil surface. In addition, there was evidence of a positive transduction on the BPC surface and within the collagen coating (Fig. 63-4).

Whether endovascular coils can act as a gene delivery system in vivo was tested by implanting platinum coils coated with Ad-GFP into the ligated CCA of adult rats in a model of arterial stasis and pressurization. Seven days later, CCA segments were harvested and coils removed for histopathology and GFP expression studies. Other organs

were evaluated by polymerase chain reaction (PCR) to assess viral biodistribution. GDC plus collagen/Ad-GFP were implanted for only 1 week to obtain GFP expression at its peak because cytomegalovirus promoter is known to provide highly transient expression. The coil segments removed from the CCA were evaluated for transduction activity on their surface; the CCA segments were sectioned and evaluated with green fluorescence for GFP transduction and DAPI



**Figure 63-4.** Microcoils from a common carotid artery segment showing positive transduction with Ad-GFP onto the coil surface 1 week after implantation (original magnification  $\times 200$ ) (A). Positive transduction of Ad-LacZ onto the surface of the biodegradable polyglycolide coil (BPC) (blue bromochloroindolyl-galactoside (XGAL) staining) on the BPC surface (B).



staining for cell nuclei. Positive transduction was observed on the coil surface (see Fig. 63-4). GFP was detected on the harvested platinum coil and in the organizing thrombus within the CCA. Morphometric analyses demonstrated that  $13.3 \pm 2.0\%$  of cells within the organized thrombus were transduced with Ad-GFP by the gene delivery system. Vector biodistribution was checked using PCR studies of distal organs; Ad-GFP was not detectable in lung, liver, or kidney. These studies suggest that virus biodistribution was localized to the site of endovascular coil deployment for gene delivery. Vessels were analyzed quantitatively using immunohistochemical techniques in terms of lumen area, lumen diameter, and wall thickness. Lumen area and wall thickness for GDC plus collagen/AdCMV-GFP versus GDC, GDC plus collagen, or control were all similar. This indicates that replication-deficient adenovirus used at the doses used in this study (less than  $10^7$  plaque-forming units) does not cause vascular structural changes (diameter or wall thickness) that are distinguished from those with coil or coil plus collagen. Furthermore, no endothelialization of fibroblast invasion was observed using immunohistochemical techniques.

Together, these findings demonstrate that an endovascular microcoil may also function as a gene delivery system. Catheter deployment of platinum or biodegradable gene delivery endovascular microcoils represents an interventional device-based gene delivery system that can serve as a suitable platform for either single or multiple gene therapy vectors. This approach has potential applications for improved treatment of intracranial aneurysms. In addition, the ability to modify coils and deliver genes may provide insights into aneurysm formation and rupture and endogenous reparative mechanisms.

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