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Initial Experience with Collagen-Filled Guglielmi Detachable Coils for Endovascular Treatment of Experimental Aneurysms

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PURPOSE: To evaluate the effectiveness of Guglielmi detachable coils (GDCs) filled with collagen threads in the permanent treatment of experimental aneurysms. **METHODS:** Seventeen side-wall aneurysms were surgically constructed in the canine common carotid artery; six were treated with conventional GDCs and 11 with collagen-filled GDCs. One aneurysm was removed at 1 week, the others were studied by digital subtraction angiography for a period of 8 to 12 weeks. Longitudinal sections of all aneurysms were examined by light microscopy. **RESULTS:** Angiograms obtained throughout the follow-up period showed no significant difference between aneurysms treated with conventional GDCs and those treated with collagen-filled GDCs. Light microscopy revealed a dense meshwork of newly formed collagen and fibroblasts near the collagen-filled GDCs, whereas a loose cellular meshwork surrounded the conventional GDCs at 8 and 12 weeks after treatment. **CONCLUSION:** Collagen threads within GDCs do not noticeably improve angiographic treatment of experimental aneurysms; however, these threads did induce local proliferation of fibroblasts and production of collagen within the aneurysmal cavities.

Index terms: Aneurysm, embolization; Interventional instruments, coils; Animal studies

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The Guglielmi detachable coil (GDC) system (Target Therapeutics, Fremont, Calif) has been proved effective in treating both experimental and human aneurysms of the cerebral circulation (1, 2); however, this system has certain limitations. Complete occlusion of the aneurysm requires tight packing with GDCs, which is difficult to achieve in wide-orifice aneurysms because of the risk of coil herniation and subsequent thrombosis of the parent artery (3). Fewer coils or looser packing would be required if the coils were more thrombogenic or capable of generating tissue proliferation within the aneurysmal cavity. Collagen is a biologically active material that plays an important role in healing wounds and forming connective tissue (4, 5). The addition of collagen to detachable coils reportedly improved treatment results in previous studies of experimental aneurysms (6, 7).

In this study, we used a modified GDC system that had cross-linked collagen threads incorporated within the primary structure of the coils. Our purpose was to evaluate the propensity of these modified coils to enhance occlusion within experimentally created aneurysmal cavities and to prevent recanalization without inducing thrombosis of the parent artery. We compared the effects of loose and tight packing of both conventional and collagen-filled GDCs.

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Materials and Methods

Thirteen mongrel dogs were used in the study. All procedures were performed with the dogs under general an-

Fig 1. Photomicrograph shows two loops of collagen-filled Guglielmi detachable coils. *Arrow* indicates collagen thread within the primary structure of the coil (original magnification ×40).

esthesia, following a protocol approved by our institution's Animal Care Committee.

Construction of the Aneurysms

Bilateral side-wall vein-pouch aneurysms with 5-mm orifices were surgically constructed on the common carotid artery by grafting a 7-mm section of the external jugular vein to a 5-mm arteriectomy created with a vascular punch (8). A total of 26 aneurysms were constructed. Aneurysmal patency was confirmed by digital subtraction angiography (DSA) 1 and 4 weeks after surgery.

In an attempt to provide comparable packing densities in different aneurysms, aneurysmal volumes were estimated from magnified DSA images obtained before treatment. Aneurysmal volumes were calculated either as prolate spheroids ($V = 4/3\pi \times a \times b \times c$, where a, b, and c are half the greatest diameter of the aneurysm in three perpendicular directions) or as cylinders ($V = r^2 \times \pi \times l$, where r is the radius and l is the height of the cylinder), depending on the aneurysm's geometry. The magnification factor was determined by using the distance between the proximal and distal markers of a double-marker Tracker-18 microcatheter (Target Therapeutics) as a reference. The microcatheter was placed in a straight position within the carotid artery, adjacent to the aneurysm's orifice.

Aneurysms were treated at least 4 weeks after surgery.

Coil System

Modified, experimental GDCs were fabricated by incorporating collagen threads with a diameter of 0.18 to 0.23 mm into the primary structure of the coils (collagen-filled GDCs; Target Therapeutics) (Fig 1). Bovine collagen cross-linked with polyethylene glycol (PEG) (W. Rhee, US patent 5 162 430 issued November 10, 1992) was used (T. D. Estridge, J. Tefft, E. Lowings, K. Jones, "The Effect of Crosslinked Collagen on the Proliferation of Human Cell Lines in Vitro," presented at the annual meeting of the Society for Biomaterials, Boston, Mass, April 1994). Four different sizes of collagen-filled and conventional GDCs were used: 8-mm diameter with 30-cm length, 8-mm diameter with 15-cm length, 5-mm diameter with 15-cm length, and 4-mm diameter with 10-cm length. The coils were considered cylinders for volumetric calculations.

Treatment of the Aneurysms

In an attempt to evaluate the impact of collagen on aneurysmal occlusion, we compared aneurysms that were packed to the same density with either conventional or collagen-filled GDCs. The packing density was the ratio of the volume of the coils used for packing to the volume of the aneurysm. Ten aneurysms were packed loosely (packing density, 10%; range, 9% to 12%), four with conventional GDCs and six with collagen-filled GDCs. Six aneurysms were packed as tightly as possible (packing density, 25%; range, 23% to 26%), two with conventional GDCs and four with collagen-filled GDCs. One additional aneurysm was packed with collagen-filled GDCs, and this animal was sacrificed 1 week later to provide information on early histologic changes.

The coils were delivered through a double-marker Tracker-18 Unibody microcatheter (Target Therapeutics). No systemic anticoagulation was used during the procedures, but the guiding catheters were flushed with heparinized saline (500 U per 1000 mL).

Of the 26 constructed aneurysms, 17 coil-treated aneurysms were included in the analysis of results. Two other aneurysms thrombosed spontaneously during the 4-week maturation period. Five more aneurysms were used as internal controls and remained patent during the follow-up period. The two remaining aneurysms served to determine the appropriate volumetric ratio of coils to aneurysm for loose and tight packing.

Angiographic Follow-up

All animals were studied with DSA immediately after coil packing, 5 to 10 days later, and 4 and 8 weeks after that. Six animals that had both collagen-filled GDC-treated aneurysms and untreated aneurysms also had DSA 12 weeks after treatment.

Histology

All aneurysms were removed and fixed in a 10% formaldehyde solution under a pressure of 100 mm Hg. Specimens were embedded in methylmethacrylate. For the light microscopic study, longitudinal sections 0.5-mm thick were obtained by means of a circular diamond saw, hand-polished to a thickness of 30 to 40 μm, and then stained with mineralized bone stain (9).

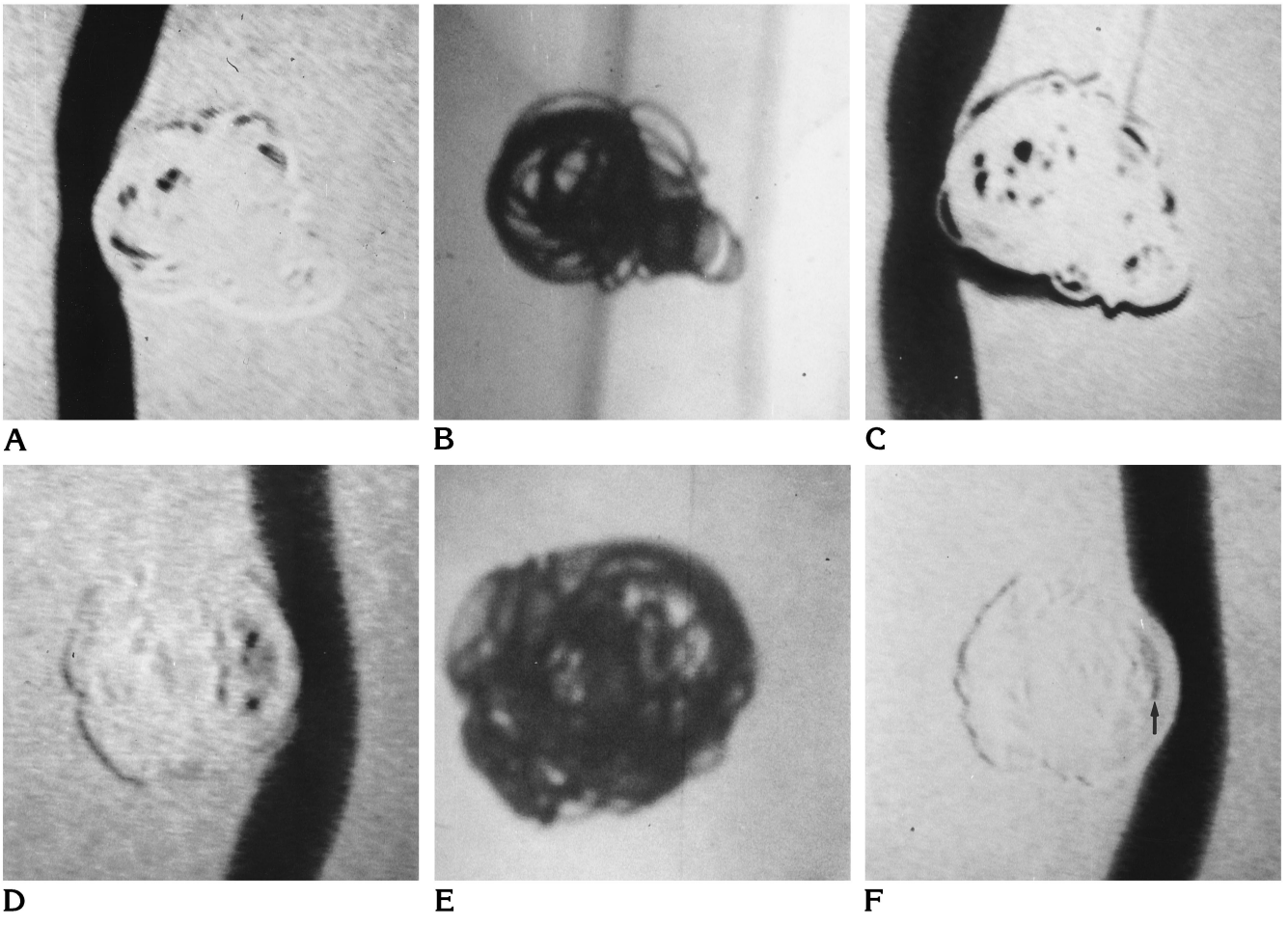


Fig 2. Imaging findings in aneurysms that were loosely packed (up to 10% density) with conventional or collagen-filled GDCs.
A, DSA, lateral view, displays partial occlusion of the side-wall aneurysm immediately after treatment with conventional GDCs.
B, Plain radiograph, same view, shows conventional GDCs occupying 9% of the calculated volume of the aneurysm.
C, DSA, same view 8 weeks after treatment, shows aneurysmal recanalization and remodeling of the coil mass (notice a single loop of the coils within the aneurysm's orifice).
D, DSA, lateral view, displays partial occlusion of the contralateral aneurysm in the same animal immediately after treatment with collagen-filled GDCs.
E, Plain radiograph, same view, shows collagen-filled GDCs occupying 9% of the calculated volume of the aneurysm.
F, DSA, same view 8 weeks after treatment, shows small neck remnant (*arrow*).

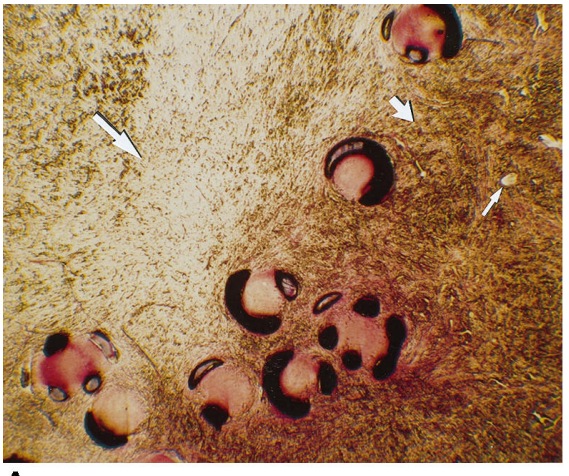
Results

Angiographic Follow-up

Current imaging techniques do not permit precise quantification of aneurysmal occlusion. Treatment results were assessed on magnified DSA images, each obtained with an identical view, and findings were rated as partial occlusion (multiple areas of contrast filling present throughout the aneurysmal cavity), nearly complete occlusion (small neck remnants and/or small areas of contrast filling present in the vicinity of the aneurysmal orifice), or complete occlusion (no contrast filling visible within the aneurysm).

Loose packing (10% density) initially resulted in partial occlusion of all 10 aneurysms (six treated with collagen-filled GDCs and four with conventional GDCs). Eight weeks after treatment, two aneurysms treated with collagen-filled GDCs and none of the aneurysms treated with conventional GDCs were occluded completely. In two aneurysms treated with conventional GDCs, angiographic evidence of recanalization was seen at 8 weeks, because of coil mass remodeling (Fig 2).

Tight packing (25% density) resulted in nearly complete occlusion of all six aneurysms (two treated with conventional GDCs and four treated with collagen-filled GDCs). Eight weeks



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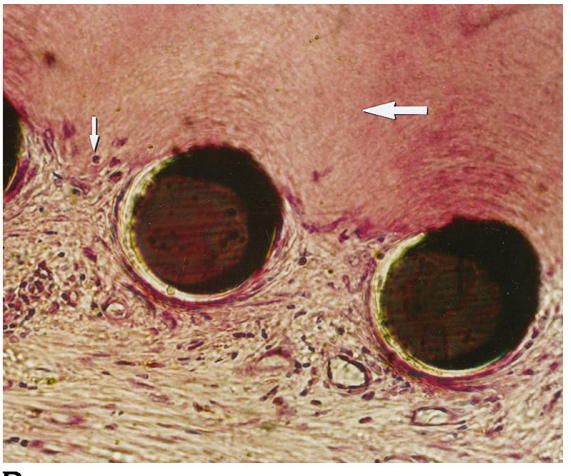

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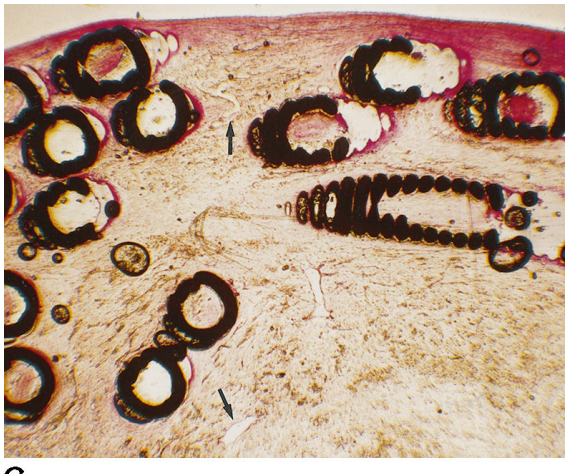

C

Fig 3. *A*, Microscopic section of an aneurysmal cavity removed 8 weeks after treatment with collagen-filled GDCs. Notice the dense meshwork of fibroblasts and newly formed collagen fibers around the coils (*short wide arrow*). *Short thin arrow* indicates neocapillary. A loose, cellular meshwork is seen about 1 mm from the coils (*long wide arrow*) (mineralized bone stain, light microscopy ×25).

B, Microscopic section of an aneurysmal cavity removed 12 weeks after treatment with collagen-filled GDCs. The collagen thread (*large arrow*) stains inhomogeneously. Leukocytes begin to infiltrate the collagen thread (*small arrow*) (mineralized bone stain, light microscopy ×40).

C, Microscopic section of an aneurysmal cavity removed 8 weeks after treatment with conventional GDCs. Notice the loose cellular structure of the organizing thrombus around and away from the coils. *Arrows* indicate neocapillaries (mineralized bone stain, ×25).

later, one of the four aneurysms treated with collagen-filled GDCs and both aneurysms treated with conventional GDCs occluded completely. All control aneurysms remained patent during the follow-up period of 12 weeks.

Parent Artery Thrombosis

In the initial phase of the experiment, two parent arteries occluded after treatment with collagen-filled GDCs (one from each of the packing groups). In both cases, the coils protruded significantly into the parent arteries through the wide aneurysmal orifices, resulting in stenoses of 75% in one case and 80% in the other (stenosis is expressed as the maximum reduction of luminal diameter of the parent artery as measured on DSA images).

Histology

The collagen threads within the GDCs that were removed 1 week after treatment remained intact and stained intensively. Around the collagen-filled GDCs, a dense meshwork of newly formed collagen and fibroblasts was found at 8 and 12 weeks (Fig 3A), and fibroblasts infiltrated the collagen threads (Fig 3B). A loose cellular meshwork containing significantly less collagen surrounded the conventional GDCs at 8 weeks (Fig 3C). Within 1 mm of the GDCs, thrombus was organized similarly in aneurysms treated with either type of coil. We found no detectable difference in the size and density of neocapillaries in relation to the type of coils used, but there were more of them in aneurysms that had thrombosed spontaneously during the maturation period.

Discussion

GDCs are made of platinum, a soft material that is likely to conform to the aneurysm's shape. The configuration of the coils, however, precludes filling the aneurysm without occluding the parent artery. Thus, the unfilled portion of the aneurysmal cavity must thrombose in order to exclude the aneurysm from the circulation. Platinum has an inherently low thrombogenicity, and thrombus generated by the electrolytic detachment process may not occlude the aneurysm sufficiently unless the cavity is tightly packed with coils. Further, fresh thrombus and platinum coils create a relatively soft mass that may be incapable of resisting continuous forces of pulsatile blood flow upon the coil surface at the aneurysm's orifice, as suggested previously (10).

Collagen may increase the thrombogenicity of coils through the attraction of platelets and the absorption of factor XII (11). In addition, collagen fibers may serve as a framework to guide fibroblast invasion, supporting further production of collagen and the formation of connective tissue (4, 5). Collagen cross-linked with PEG reportedly induces significant fibroblast proliferation in cell culture (Estridge et al, "The Effect of ...") seemingly in direct proportion to the amount of cross-linker used. Fibroblast proliferation and collagen formation may increase the tensile strength of the tissue mass within the occluded aneurysmal cavity, resulting in greater resistance to recanalization. On the other hand, increased coil thrombogenicity may confer an increased risk of parent artery thrombosis.

Our study was designed to evaluate the propensity of collagen cross-linked with PEG to enhance the formation of intraaneurysmal thrombus leading to complete thrombosis without tightly packing the aneurysm. We also assessed the capability of collagen to improve the stability of aneurysmal occlusion and prevent recanalization. We tested the effect of collagen cross-linked with PEG by incorporating threads of collagen into the primary structure of the GDC. The modified coils had a looser helix than the conventional coils and approximately 50% of the surface of the collagen threads was covered by the loops of the coils, allowing sufficient exposure of collagen to blood (Figs 1 and 3). Our study was conducted with dogs. Previous experience suggests that the high frequency of spontaneous thrombosis in the pig model can lead to a misinterpretation of results (T. D. Chavis, A. K. Wakhloo, I. Szikora, S. C. Standard, L. R. Guterman, L. N. Hopkins, "Evaluation of Experimental Carotid Lateral Wall Aneurysm Model in Swine," presented at the annual meeting of the American Society of Neuroradiology, Nashville, Tenn, May 1994).

Ten aneurysms were packed loosely, four with conventional GDCs and six with collagen-filled GDCs. None of these aneurysms occluded completely immediately afterward. By the end of the follow-up period, one of the six aneurysms treated with conventional GDCs occluded completely; one aneurysm treated with collagen-filled GDCs was excluded from the analysis because of parent artery thrombosis. Some degree of recanalization occurred in two aneurysms treated with conventional GDCs; in one of them, remodeling of the coil mass was evident (Fig 2). Recanalization was not seen in any of the aneurysms treated with collagen-filled GDCs.

Six aneurysms were packed tightly, two with conventional GDCs and four with collagen-filled GDCs, resulting in nearly complete occlusion, regardless of the coil type used. By the end of the follow-up period, both aneurysms treated with conventional GDCs and only one of the four aneurysms treated with collagen-filled GDCs had occluded completely. There was no angiographic evidence of aneurysmal recanalization in this group.

The addition of collagen did not induce either immediate or delayed aneurysmal thrombosis. Packing density was the single determinant of aneurysmal occlusion. Collagen incorporated into the coils did not increase the risk of parent artery thrombosis, which may have resulted from increased coil thrombogenicity.

On microscopic sections, coils were unevenly distributed in the aneurysmal cavities in all of the treated cases. Light microscopy displayed more fibroblast proliferation and collagen fiber production around the collagen-filled GDCs than around the conventional GDCs (Fig 3). These findings indicate that collagen threads cross-linked with PEG within the GDCs have the ability to induce fibrotic transformation of the organizing thrombus inside an occluded aneurysmal cavity. The effect of this collagen preparation, however, is limited to the immediate vicinity of the coils and does not alter the morphology of the remainder of the thrombus. More

extensive fibrotic transformation of the thrombus mass is required to induce complete aneurysmal occlusion or prevent aneurysmal recanalization. Such fibrosis might be achieved by increasing the amount of cross-linker used for the collagen preparation. In this study, satisfactory results were associated with dense coil packing of the aneurysms. Further testing of occlusive materials is needed to identify a material capable of achieving extensive aneurysmal obliteration through dense, homogeneous distribution inside the cavity.

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