Endovascular treatment of arteriovenous malformations with selective intranidal occlusion by detachable platinum electrodes: technical feasibility in a swine model.

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Endovascular Treatment of Arteriovenous Malformations with Selective Intranidal Occlusion by Detachable Platinum Electrodes: Technical Feasibility in a Swine Model

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Summary: The technical feasibility of selective intranidal endovascular occlusion of experimental arteriovenous malformations with detachable superfine platinum electrodes was assessed in a swine model. The delivery and release of electrodes were performed within normal carotid retia mirabilia, the faster-flowing nidus (bilateral retia) of a carotid-jugular fistula-type model of an arteriovenous malformation, and a small-caliber H-type direct arteriovenous fistula. Controllable atraumatic placement of the electrodes was possible deep within each rete and in the middle of the fistula. The devices were soft and flexible, allowing them to conform to the tight turns and branches of rete vessels. Marked diminution of flow was achieved by release of multiple devices within each rete. Migration of the electrode occurred when detached within the larger-caliber arteriovenous fistula. The main advantages of this technique appear to be the controlled delivery and assured release of an occlusive radiopaque embolic agent within the nidus.

Index terms: Animal studies; Arteriovenous malformations, embolization; Interventional instruments, embolizing systems

Arteriovenous malformations (AVMs) are vascular hamartomas consisting of a conglom- erate of abnormal low-resistance vessels (the nidus) of variable diameter and wall thickness situated between feeding arteries and draining veins. They represent the most commonly encountered symptomatic vascular malformation of the central nervous system (CNS), and are second in importance to saccular aneurysms as a cause of spontaneous subarachnoid hemorrhage (1). These lesions are considered dangerous and usually require an aggressive therapeutic approach, because hemorrhage can be severely incapacitating or fatal (2).

The basic methods of treating AVMs include surgery, radiosurgery, and endovascular embolization alone or in combination. Endovascular embolotherapeutic techniques continue to evolve. In particular, advances in catheter technology, embolic materials, and greater experience by interventional neuroradiologists have decreased the risks of endovascular treatment and increased the number of patients in whom it can be used. Nevertheless, as currently practiced, embolization of brain AVMs carries an intrinsic risk of transient or permanent neurologic deficit or death. Endovascular embolo- therapeutic procedures have overall morbidity rates of 12.8% and mortality rates of 0.9% (3). Complications of using currently available embolic materials (the most widely used being N-butyl cyanoacrylate glue or polyvinyl alcohol particles) can be divided into two main categories: those due to technical mishaps, such as gluing of the microcatheter in an AVM feeder, vasospasm, dissection, rupture, and emboli from coaxial catheters; and those consequent to the embolization process itself, namely, postembolization cerebral ischemia, intracranial hemorrhage, and vasogenic edema (3, 4). In this experimental study, we attempted to address some of the shortfalls of current embolic agents by investigating the technical feasibility of a method for treating AVMs in which detachable platinum electrodes are used to occlude intranidal microvessels in an appropriate laboratory swine model.
Materials and Methods

All animal experimentation was conducted in accordance with policies set by the local University Chancellor's Animal Research Committee and by guidelines established by the National Institutes of Health. Six swine were used in this preliminary study. The animals were 3 to 4 months old, weighed 30 to 40 kg, were of mixed sex, and were maintained on a standard laboratory diet. After an overnight fast, each swine was premedicated with intramuscular 20 mg/kg ketamine and 2 mg/kg xylazine. General anesthesia was maintained with mechanical ventilation and inhalation of 1% to 2% halothane after endotracheal intubation.

Animal Models

The carotid rete mirabile of the swine is a fine network of microvessels, with connections across the midline, situated at the termination of both ascending pharyngeal arteries as they perforate the skull (Fig 1). It has some morphologic and angiographic similarities with a plexiform nidus of an AVM, and therefore was used in this study to simulate treatment of such a structure in humans. Angiographic access to the rete was via superselective catheterization of the ascending pharyngeal artery.

Increased blood flow through the rete mirabile was experimentally induced by creation of an AVM model following carotid-jugular fistula formation. The relevant vascular anatomy of the swine head and neck and the details concerning construction of this model have been described previously (5). Briefly, preoperative endovascular occlusion of the right occipital artery, the muscular branch of the right ascending pharyngeal artery, and the right external carotid artery was performed to maximize postoperative blood channeling from both retia to the fistula. This step was followed by surgical construction of a side-to-side arteriovenous fistula between the right common carotid artery and the external jugular vein. This model resulted in rapid blood diversion from the left side of the neck via the left ascending pharyngeal artery (terminal feeder), across both retia (nidus), to the contralateral right ascending pharyngeal artery (draining vein) toward the fistula (Fig 2). Minor left external carotid arterial branches (ramus anastomoticus and arteria anastomotica) also supplied the nidus, thus simulating en passage feeders.

A fistulous component of an AVM nidus was also simulated by surgical construction of an H-type arteriovenous fistula in the neck of the swine, using a segment of the ascending cervical artery (diameter, about 2 mm) as a horizontal limb grafted between the right common carotid artery and the right external jugular vein.

Device Characteristics and Endovascular Techniques

The device used is a modified version of the Guglielmi electrolytically detachable coil (GDC) (Target Therapeutics, Fremont, Calif), here called superfine straight GDC (SS-GDC). The main components include a 175-cm stainless steel core delivery wire soldered to a very soft platinum coil/electrode of varying length. The lengths used in this study were 0.5 cm, 1.0 cm, and 2.0 cm. This platinum coil is straight (ie, has no circular memory, unlike the conventional GDC), and is of superfine thinness (ie, 0.005-inch or 0.008-inch thickness compared with 0.010-inch or 0.015-inch thickness for conventional GDCs). A 1.0 to 1.5 mA/2.0 to 3.1 V positive electric current is applied to the proximal end of the stainless steel delivery wire. The negative ground pole is connected to a skin surface electrode. In 2 to 6 minutes, the current dissolves the stainless steel immediately proximal to the platinum SS-GDC by electrolysis, allowing it to detach. The delivery wire is then withdrawn. More platinum electrodes can be introduced and detached via the same microcatheter (a Tracker 10 for GDC use, manufactured by Target Therapeutics), according to the desired degree of vascular occlusion.

Under general anesthesia, the swine had a 6F angiographic sheath placed in the femoral artery after standard Seldinger puncture and catheterization. Via this transfemoral route, a selective common carotid arteriogram was obtained by using a 6F Royal Flush guiding catheter (Cook, Bloomington, Ind) to outline the normal rete mira-
bile (in four swine), or the nidos of the AVM model (in one swine), or the horizontal limb of the arteriovenous fistula (in one swine). The guiding catheter was connected to a Touhy-Borst Y-connector to allow coaxial insertion of a Tracker 10 microcatheter/Dasher microguidewire combination (both manufactured by Target Therapeutics). Superselective angiograms were then obtained after microcatheterization of the relevant ascending pharyngeal artery or arteriovenous fistula. A bolus intraarterial dose of 3000 U of heparin was given. With fluoroscopic and road-mapping guidance, an SS-GDC was advanced via the microcatheter, the tip of which was situated proximal to the entrance of the rete or within the arteriovenous fistula. The SS-GDC was then carefully advanced beyond the microcatheter tip to achieve either proximal or distal positioning within the confines of the rete, or in the middle of the arteriovenous fistula. After repeat angiography, the SS-GDC was electrically detached. Single or multiple SS-GDCs were detached in the rete by means of the above procedure. In one swine, the rete was also approached from an ipsilateral minor arterial branch (the ramus anastomoticus branch of the middle meningeal artery), and an SS-GDC was detached in the rete to simulate endovascular treatment of an AVM nidus via multiple feeders. Following detachment of each SS-GDC, whether in the rete or the arteriovenous fistula, postembolization angiography was performed to monitor stability of the device at the site of detachment, the degree of vascular occlusion, and any untoward complications. No long-term assessment was performed in this preliminary feasibility study.

Results

All swine tolerated the general anesthesia and the surgical and endovascular procedures with no ill effects. As with conventional GDC coils, it was easy to navigate the new device through the microcatheters. Despite its thinness, the SS-GDC was seen clearly on fluoroscopic images and plain radiographs owing to the high radiopacity of its platinum component (Fig 3A). Furthermore, despite the small caliber of the swine rete microvessels, it was possible to penetrate deep into each rete without difficulty by careful manipulation of the device (Fig 3B). Each device was of sufficient softness and flexibility to allow it to conform to tight turns and branching angles of rete vessels. In one swine it was possible for a 2.0-cm SS-GDC to be navigated through the rete and into the contralateral rete (through the midline interretial microvessels) (Fig 4). Care was necessary to advance the stainless steel delivery wire proximal to the platinum SS-GDC. Usually, the delivery wire only just entered the rete microvessels or was positioned just proximal to the rete. No vascular perforation of rete vessels was observed consequent to advancement of the soft and flexible platinum SS-GDC or as a result of inadvertent advancement of the distal stainless steel delivery wire or after electrolytic detachment; nor were there any complications due to manipulation of the stainless steel delivery wire when it exited beyond the tip of the microcatheter within the ascending pharyngeal artery or the fistula. It was possible to achieve a small degree of control over the site of SS-GDC detachment by repeated easy retrieval and redelivery of the same SS-GDC within the rete. It was also possible to release multiple devices within the same rete (Fig 5), achieving a greater amount of intranidal packing and vascular occlusion of this simulated plexiform nidos. There was no angiographic evidence of thrombus propagation or obvious embolization beyond the retia mirabilia into the circle of Willis or its major branches, as seen by opacification via the basilar artery (in
the swine, the occipital artery, distal branches of the vertebral arteries, and the basilar artery can be opacified by common carotid arteriography, especially when there is reduced flow through the more anteriorly situated ascending pharyngeal artery and the rete). Marked diminution of flow within the nidus was also achieved in the carotid-jugular fistula model of an AVM (Fig 6). Total obliteration of the simulated nidus was not observed in this preliminary study. All devices detached within the normal or faster-flowing rete microvessels maintained their position after release. However, when the device was detached in the larger-caliber arteriovenous fistula, it immediately migrated into the venous circulation and to the right lung (Fig 7).

Discussion

Current Embolic Agents

The ideal embolic material for embolization of an AVM should flow freely through the entire length of available delivery microcatheters; lodge controllably and safely within the nidus, not passing through to the venous drainage or

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**Fig 4.** Left common carotid arteriogram shows tip of SS-GDC (short arrows) in the left rete after being navigated through contralateral ascending pharyngeal artery and right rete. Long arrow indicates delivery wire.

**Fig 5.** Left external carotid arteriogram shows filling of the left rete via the ramus anastomoticus (curved arrow). Multiple SS-GDCs have been detached within the left rete (straight arrows).

**Fig 6.** Left common carotid arteriogram after detachment of multiple SS-GDCs within the left rete (nidus) of the AVM model. Arrow shows direction of reduced flow in the draining vein.

**Fig 7.** Testing of SS-GDC detachment within an H-type carotid-jugular fistula.

A, Carotid angiogram shows device (thin arrow) in center of fistula before detachment. Thick arrows show direction of flow.

B, Immediately after detachment of the SS-GDC within the fistula, the platinum device (long arrow) has migrated to the jugular vein, which is faintly opacified (short arrows). Delivery wire (curved arrow) is seen in the carotid artery and proximal fistula.

C, Within a few seconds the SS-GDC (arrows) has embolized to the right lung.
to the lungs; cause complete and permanent occlusion of the nidus; and not induce a necrotizing vasculitis or a significant inflammatory reaction in the adjacent normal brain (6, 7). Additional desirable features should include its ready availability and a resultant treated AVM that is easy to manipulate during surgery and to section at histopathologic examination. In addition to use of liquid sclerosants (eg, alcohol and estrogen), several solid embolic agents have been used for AVM treatment in an effort to improve on the previously mentioned disadvantages of injecting glue or particles. These techniques include the injection of surgical silk suture (7), polyethylene suture (8, 9), or platinum microcoils (10, 11). Therefore, consideration of the true merits of the SS-GDC device for intranidal occlusion of AVMs requires critical comparison with these solid embolic agents and the assessment of how closely the SS-GDC approaches the above ideal properties.

All embolic agents share one or more of the following characteristics that predispose to immediate and/or delayed postembolization AVM hemorrhage (7): high injection pressures required for their delivery into the nidus; possible uncontrollable deposition in the feeding artery or, if an intranidal fistula is present or fragmentation occurs, in the draining veins or lungs; an induced vessel wall inflammatory response; and thrombus formation around the embolic agent, with subsequent natural thrombolysis and restoration of flow to a possibly weakened necrotic vessel. Other mechanisms for postembolization hemorrhage have been suggested: venous stasis and thrombosis with delayed AVM rupture (12), and preferential obliteration of intranidal fistulas causing immediate flow redistribution into more delicate plexiform nidus portions, with consequent rupture (3). Injectable silk possesses many of the unfavorable features mentioned above, not least of which is its radiolucency, allowing its disadvantages to outweigh its advantages when used for treatment of brain AVMs (7). Injectable polyethylene sutures appear to share the same drawbacks, except that they produce a milder inflammatory response. Their use in brain AVMs, however, is associated with an unacceptable overall complication rate close to 20% (9). Platinum wires or microcoils offer the advantage of being commonly available, highly radiopaque, and biocompatible (10). However, when used with a coil pusher there is the risk of arterial perforation because the coil pusher may be stiff and frequently difficult to distinguish from the coil when the latter is pushed out of the catheter (11). Equally, when platinum microcoils are injected, they share many of the handicaps of silk and polyethylene, especially uncontrollable deposition in the draining vein (13) and the arterial feeder (11). Upon injection, retrograde propulsion of previously deposited microcoils may even occur into normal non-AVM arteries (11). Stability of a coil at the deposition site depends on several factors (14); namely, relative size of the coil and the surrounding vessel, shape of the coil, ability of a coil to produce a compact mass configuration (ie, a tight packing), blood flow velocity, compliance of the vascular wall, and coil thrombogenicity. Although platinum is regarded as a thrombogenic metal, bare noncoated coils may be ineffective for reliable vascular occlusion owing to their small surface area of contact with blood (11, 14). Such coils also show a high rate of recanalization at 4 weeks’ follow-up because too little thrombus forms initially (14). Coil thrombogenicity may be enhanced by increasing the surface area with fabric strands, such as Dacron, and by placing such coils into a thrombin solution before deployment (15). Such coils still suffer the disadvantage of being injectable or requiring a coil pusher. Another possible method to augment thrombus formation is to use an electric current to achieve electrothrombosis.

Cerebrovascular Electrothrombosis

The electrochemical basis and historical background of techniques that use intravascular electrothrombosis have been reviewed previously by Guglielmi et al (16). The use of electrothrombosis for occlusion of human cerebrovascular lesions was attempted by Mullan (17), who electrothrombosed saccular aneurysms through stereotactically inserted fine needles. Yoneda et al (18) treated two patients with large deep-seated AVMs by a combination of conventional craniotomy and stereotactic electrothrombosis. This entailed insertion of copper wire needles into the feeders and nidus, as demonstrated by biplane intraoperative angiography, and with the help of a stereotactic grid apparatus and electrode holder. As many as 30 to 60 electrodes were needed for large AVMs. A cathode electrode was placed under the galea, and progression of thrombosis was
monitored angiographically. Following electrothrombosis of the lesion, the inserted needles were cut off and a radical extirpation of the thrombosed solid AVM was carried out easily with no troublesome bleeding. However, this technique has not become popular because the AVM has to be punctured, extensive equipment is required, it is necessary to penetrate cerebral tissue with the electrodes in order to reach the AVM, and it is unsuitable for a wide spectrum of AVMs. More recently, Guglielmi et al (16) have developed an endovascular technique for occlusion of intracranial saccular aneurysm by using GDC electrolytically detachable coils and electrothrombosis. In vitro investigations of this technique have shown that the weight of the electrothrombus formed on an anodic GDC is proportional to the current and its time of application (19). A more recent study in laboratory monkeys has shown that thrombosis does not occur in vivo until after 2 days of GDC detachment; in the early stages (within a few hours of detachment), only leucocytes and blood proteins are attached to the surface of GDCs (H. Tenjin, S. Fushiki, Y. Nakahara, et al, “Remodeling of Vessel Induced by Guglielmi Detachable Coil in Primate’s Experimental Aneurysm,” presented at the International Joint Conference on Stroke and Cerebral Circulation, Charleston, SC, February 1995). The new SS-GDC device used in this study is a modification of these conventional GDC coils, developed for the purpose of selective occlusion of small-caliber vessels, including intranidal AVM microvessels. On the basis of the above-mentioned experimental observations, we speculate that the vascular occlusion that results with use of the SS-GDC is likely to be due to mechanical interruption of flow more than from electrothrombosis around tiny electrodes, at least in the short term after detachment.

Intranidal Occlusion with Platinum Electrodes

In this study, the carotid rete mirabile of the swine was used as a laboratory model of a plexiform AVM nidus. Rete microarteries have a mean diameter of 154 \( \mu m \) (20), which is comparable in size to microvessels of a human AVM nidus (these were an average diameter of 265 \( \mu m \) in one study [21]). However, as compared with a nidus of a human AVM, the rete possesses relatively low blood flow owing to a small drop in intravascular pressure between its afferent and efferent arteries. Therefore, in addition to use of the normal rete, an AVM model fashioned from bilateral retia after surgical formation of a carotid-jugular fistula (5) was also used in this study. This model has the experimentally induced feature of faster blood flow through both retia, caused by shunting of blood from one side of the neck to the other. Therefore, in this model one ascending pharyngeal artery resembles a terminal feeder and the other resembles a draining vein. An average drop of about 23 mm Hg between these two vessels results after carotid-jugular fistula formation (22). Although not fully representative of human AVMs, this model possesses some morphologic, angiographic, hemodynamic, and histologic similarities with human lesions (T. F. Massoud, H. V. Vinters, C. Ji, F. Viñuela, K. H. Chao, G. Guglielmi, “Histopathologic and Histometric Characterization of Nidus Microvessels in a Chronic Arteriovenous Malformation Model in Swine,” presented at the annual meeting of the American Society of Neuroradiology, Chicago, Ill, April 1995). In particular, the model appears more appropriate than the normal rete for a closer hemodynamic simulation of a plexiform AVM nidus. In this study, we also assessed the performance of the SS-GDC in an experimental model of a very fast flow arteriovenous fistula with similar dimensions and flow characteristics to large fistulous components of human AVMs.

Our results illustrate the feasibility of selective intranidal occlusion in appropriate experimental AVM models using the SS-GDC device. Although more rigorous investigations are necessary, many of the physical and performance characteristics of this device appear to approach those expected from an ideal embolic agent. In particular, the extreme thinness and softness of this SS-GDC device allows its atraumatic penetration deep into the swine rete mirabile, which is composed of microarteries similar to or smaller in size than the abnormal microvessels of a human AVM nidus. Retrievability of the device before detachment also adds an element of safety to its use, in that the operator may release the platinum electrode only when satisfied with its position within the nidus. Therefore, some of the disastrous complications associated with use of glue (such as inadvertent polymerization in the draining vein with consequent nidus rupture) may be avoided by this precise placement of SS-GDCs within the nidus. This selective intranidal occlusion is pos-
sible in experimental models with hemodynamic similarities to human plexiform AVMs. Similar safe and effective intranidal occlusion may be possible in human lesions, and would theoretically confer a greater degree of control over the entire therapeutic procedure than offered currently by injection of glue or particles. Indeed, potential application of the SS-GDC in humans may provide the only endovascular technique capable of controlled and assured deposition of an embolic agent within the nidus of an AVM. This arises by virtue of the platinum electrode’s being attached to the stainless steel delivery wire before electrolytic detachment. This also confers the properties of directionality and retrievability to the device. Directionality is achieved by gentle advancement of the delivery wire (and attached platinum electrode) beyond the microcatheter tip, within the arterial feeder, and toward the desired portion of the nidus. This maneuver would be analogous to use of a microguidewire within an arterial feeder of an AVM and, therefore, might be performed even if the tip of the microcatheter is situated considerably distant from the AVM nidus (eg, in situations in which a guidewire-directed microcatheter cannot be advanced distally into the arterial feeder). This is unlike strategies adopted with current injectable embolic agents, in which the microcatheter tip should be (but may not always be achieved in practice) as close as possible to the nidus, to avoid implication of side branches supplying normal brain (23). Therefore, the physical inability of the SS-GDC device used in this study to be delivered via flow-directed microcatheters (owing to the latter’s relatively small inner diameter) may not represent a major disadvantage in potential future applications in humans.

The platinum electrodes used in this study were up to 2 cm in length. Longer SS-GDCs may also be useful in achieving a greater compacted mass of embolic agent within an AVM nidus because the soft and flexible device is able to conform to tight turns within nidus vessels. Owing to its softness and pliability, a longer SS-GDC may also confer flow-directionality to the device, similar to that observed when a conventional GDC is placed in a fast-flowing AVM feeder (13). This would allow flow-assisted advancement of the SS-GDC toward the AVM nidus. Whether flow-assisted or reliant entirely on pushing the delivery wire, advancement of the SS-GDC must be done as gently as possible, not only to avoid vessel trauma but also damage to the delicate platinum-stainless steel solder and consequent premature detachment of the electrode. Our preliminary experimental observations indicate that the platinum-stainless steel solder of the SS-GDC device appears similar to that of the conventional GDC in its ability to withstand normal/gentle endovascular maneuvers without premature detachment.

As seen in this study, only one intranidal microvascular channel (and possibly other originating intranidal side channels) can be occluded at a time. This may represent a limitation for future use in large AVMs. In these lesions, the release of longer and multiple SS-GDCs may therefore be necessary to achieve an adequate degree of intranidal occlusion, or more likely, this may be performed as an adjunct to embolization with other embolic agents or surgery or radiosurgery. The usefulness of embolizing such large AVMs with injectable 2- to 5-mm straight platinum microcoils has been demonstrated recently by Henkes et al (24). For reasons outlined above, controlled delivery of longer SS-GDCs may theoretically increase the safety and efficacy of this form of therapy. Compared with large AVMs, acceptable results in small- and medium-sized AVMs may be achievable after release of only a few SS-GDCs (ie, without extensive SS-GDC nidus packing) owing to the resultant reduction of blood flow causing progression of thrombosis within the lesion (25). Our results indicate, however, that the SS-GDC is relatively unstable in large fast-flowing vessels, as may be encountered in large fistulous components of an AVM. Detailed orthogonal plane superselective angiographic assessment of human AVMs would therefore be mandatory to obtain the necessary anatomic and hemodynamic information (23) before detaching intranidal SS-GDCs. Whether SS-GDC stability sufficient to offset hemodynamic forces could be achieved with longer electrodes—producing greater compactness within an intranidal fistula and, therefore, potentially more stabilizing electrothrombus formation or simple mechanical obstruction—remains to be established in further laboratory investigations. Long-term permanence of thrombus formed initially in such fast-flowing vascular channels will also require experimental study, as previous experience with simple coils indicates that vascular recanalization occurs in high-flow states (26). Although it is generally considered useful to
reduce flow endovascularly through intranidal fistulas, the gathering of more anatomic and hemodynamic data from human AVMs may help to select those lesions with an increased likelihood of consequent dangerous rerouting of blood into plexiform portions of the nidus and to determine when SS-GDC detachment within intranidal fistulas should be avoided.

In conclusion, we have demonstrated the technical feasibility of endovascular treatment of experimental AVMs by selective intranidal occlusion with electrolytically detachable superfine platinum electrodes. The main advantages of this technique appear to be the controlled delivery and assured deposition of a highly radiopaque embolic agent within the nidus, aided by the possible production of intranidal electrothrombosis. The device is unstable once released in large fast-flowing fistulas. Therefore, the size and flow characteristics of vessels undergoing treatment, as well as long-term stability within vessels, persistence of thrombosis, and histopathologic tissue reactions, are all important factors to be considered in further experimental studies prior to human application of this new endovascular therapeutic technique. This preliminary feasibility study indicates a potential role for this device in future management of cerebral AVMs.

References