A Novel Endovascular Device for Emboli Rerouting
Part I: Evaluation in a Swine Model

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Background and Purpose—The feasibility and safety of a novel endovascularly delivered tubular mesh designed to reroute emboli away from a critical artery as a means of ischemic stroke prevention was tested in vitro and in vivo.

Methods—Emboli rerouting efficacy was assessed in vitro. Perfusion through the external femoral artery that was jailed by the device, cellular proliferation rate over the jailing mesh, and the resulting tissue coverage of the orifice were assessed in the swine iliofemoral bifurcation. Device-induced embolization was assessed in a swine kidney model.

Results—In vitro experiments demonstrated that particles as small as 60% of the pore dimension can be rerouted by the device, although at low efficacy, and rerouting efficacy approached 100% as the particle size approached the pore dimension. Repeat assessment of flow preimplantation and at various follow-up times by Doppler ultrasound showed no significant changes in the perfusion ratio of the jailed branch to the parent artery or the jailed branch to the naive contralateral artery either as a result of device implantation or at the follow-up times. Tissue coverage over the jailed ostium was limited to approximately 12% after stabilization. Cellular proliferation rate gradually decreased to diminishing level approximately 22 weeks postimplantation. The devices implanted across the renal arteries did not demonstrate any device-induced embolization after 1 month.

Conclusions—It is proposed that this device could be used to reroute emboli away from important intracranial vessels as a means of stroke prevention. (Stroke. 2008;39:2860-2866.)

Key Words: carotid arteries ■ embolism ■ hemodynamics ■ prevention ■ stroke

This is the first part of a 2-part article. Part I of the study presents animal model results of a novel endovascular approach to prevention of embolic stroke. Based on these data, a human study was initiated and its results will be presented in Part II.

An innovative endovascular tubular mesh device was designed to reroute proximally originating emboli, regardless of their type and origin, away from a critical artery into a non- or less harmful territory while maintaining uncompromised blood flow.

There is a growing body of evidence that coronary1 and peripheral2 side branches unintentionally crossed by stents remain patent to flow, in particular when their diameter is over 1 mm, and they are not heavily burdened by atherosclerotic plaque. We hypothesized that a novel delicate “stent-like” tubular mesh specifically designed to cross the internal carotid artery orifice would follow the same rule. The device is designed to be implanted from the human distal common carotid artery and into the external carotid artery crossing the bifurcation and “mesh-guarding” the internal carotid artery orifice, thus potentially preventing anterior circulation territorial brain infarcts. To further reduce the thrombogenic potential, preliminary simulations of the blood flow through meshes were performed in vitro using a particle image velocimetry technique in a model of carotid bifurcation.3 In brief, mesh was found to be hemodynamically optimal when having high porosity (ratio between pores and filaments) by using very fine filaments. Furthermore, thin filaments impose flow streamlines that closely follow its round profile without flow disturbances, thus minimizing shear stress-induced platelet activation.4,5 In this study, we assessed in vivo the safety in swine and in vitro the emboli-rerouting efficacy of a novel delicate “stent-like” tubular mesh device designed based on these hemodynamic considerations.

Methods

Materials (the device)
The device is a delicate self-expandable, “stent-like” tubular mesh. It is composed of approximately 50-μm round uniformly braided...
filaments (cobalt-based alloy, ASTM F1058 Grade 2) with pores size of approximately 500 μm (Figure 1). The device wires, crossing a side branch ostium (human internal carotid artery orifice), function as a protecting filter mesh, whereas the remaining portions adhere the device to the vessel wall.

**Implantation Site in Swine**

The swine iliofemoral bifurcation model was chosen, because it resembles the anatomic and hemodynamic parameters of the human carotid bifurcation (Figure 1A).6–10 The swine common carotid bifurcation was not suitable because of its particularly narrow diameter (<3 mm) and distal intracranial location, precluding noninvasive assessment of flow.

**Experimental Design**

Seventy-seven devices at oversizing >1.5 mm were deployed and successfully implanted in the iliofemoral bifurcations (56 devices bilaterally in 28 swine and 21 unilaterally). Animals were followed-up and implanted bifurcations were harvested at 1 to 2 (n=14), 3 to 5 (n=19), 6 to 8 (n=8), 9 to 14 (n=27), and 20 to 23 (n=9) weeks postimplantation. Investigations were set up to: (1) determine whether there is evidence of flow compromise in the “mesh-guarded” branch; and (2) study tissue growth on the mesh filaments and assess whether it reaches a steady state. Further experiments were designed to assess in a swine kidney model whether there is evidence of device-induced embolization (2 swine, 4 “mesh-guarded” kidneys) and, in a compliant in vitro model of the human carotid bifurcation, the emboli rerouting efficacy of the device.

**Deployment Procedures**

The experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC, 1996). Domestic crossbred female pigs were studied. The animals were pretreated with 325 mg aspirin and 75 mg clopidogrel (Plavix CTS) starting 3 days preprocedure, clopidogrel for 1 month postimplantation and aspirin for the entire follow-up period. Implantations were done according to standard percutaneous stenting procedures. The devices were implanted from the external iliac artery (parent artery) into the internal femoral artery, thus “mesh-guarding” the external femoral artery ostium (Figure 1A).

**Flow Evaluation**

The patency of the guarded ostium was evaluated by angiography and Doppler ultrasound (Ultramark 9; ATL, Bothell, Wash) postimplantation and before euthanasia. In addition, blood flow was measured by Doppler ultrasound during follow-up.11 To minimize inaccuracies due to anesthesia-induced hemodynamic parameters, we calculated ratios of blood flow volume comparing the flow in the “mesh-guarded” artery with the more proximal parent artery or, alternatively, with the contralateral-naive artery in cases of unilateral implantation.

**Histological and Cell Proliferation Evaluation**

Immediately after euthanasia, Ringer’s lactate solution was infused into the treated bifurcation area at a pressure of 100 mm Hg for 15 minutes followed by installation of a fixation solution of 10% formalin. The entire arterial bifurcation was then removed en bloc, and specimens were soaked in a fresh fixative for 24 hours. Specimens were excised parallel to the longitudinal axis of the artery. For quantitative analysis of the neointimal growth at the “mesh-guarded” ostium filaments, all (n=77) specimens were examined by light microscopy and digital pictures were taken. Morphometric software (Image Pro; Media Cybernetics, Silver Spring, Md) was used to delineate the tissue coverage beyond the filaments throughout the filtering area and to calculate the percentage of neointima out of the total orifice-free area (Figure 2). Cell proliferation rate was assessed by the bromodeoxy uridine immunolabeling technique.12 Briefly, 4 randomly selected slices of each specimen were hematoxylin and eosin-stained and immunolabeled by bromodeoxy uridine and were scanned under light microscope to identify mitotic versus resting cells. The proliferation rate was expressed as percentage of cells in mitosis. Histological analyses (characterization of tissue matrix and cells) were done concomitantly. To further characterize the cells adhered to the wire’s surface and the coverage extension, random samples were scanned by electron microscopy after fixation performed according to standard procedures.13

**Assessment of Device-Induced Embolization**

The swine kidney was used as an end organ to assess the risk of device-induced emboli. The devices were implanted within the aorta across the renal ostia in 2 animals “mesh-guarding” 4 kidneys. In 1-month follow-up, the harvested kidneys were assessed for infarcts by gross inspection and histology. To verify that we visualized kidney infarcts, kidney infarcts were deliberately induced in an additional 2 animals (positive control) by injecting 100-μm (N=50) or 500-μm (N=70) -sized particles to the renal artery at one side,
bifurcation branches relative to the total injected weight. The diversion efficacy was determined comparatively (Figure 3A), and their distribution with and without the device was viscidous fluid that was analogous to blood. Particles were collected by through a computer-controlled pump into a circuit of circulating olis, Minn) were injected over 1 minute toward the bifurcation bifurcation. Naturally buoyant polyethylene spherical particles (8

Angiographic and Doppler Ultrasound

Emboli rerouting efficacy of the device. A, The device emboli-rerouting model. Efficacy calculation, in which Qcca and Qica are the averaged flow rates in the common and internal carotid arteries, respectively; Wica and Weca are the weight of the particles rerouted into the internal and external carotid arter-
ries, respectively. B, Emboli rerouting capacity of the device by particle diameter.

In Vitro Emboli Rerouting Efficacy

The device emboli rerouting efficacy was assessed in vitro under physiological waveforms and internal/external carotid artery flow ratio6,14 using a compliant silicone model of a human carotid artery bifurcation. Naturally buoyant polyethylene spherical particles (8 size groups in the range of 150 to >500 μm; Aveka Inc, Minneapolis, Minn) were injected over 1 minute toward the bifurcation through a computer-controlled pump into a circuit of circulating viscous fluid that was analogous to blood. Particles were collected by microporous filters located distally in both bifurcation branches (Figure 3A), and their distribution with and without the device was determined. The diversion efficacy was determined comparatively for each particle size group according to the distribution ratios in the bifurcation branches relative to the total injected weight.

Results

Angiographic and Doppler Ultrasound Flow Assessment

The average diameters of the external iliac, external femoral, and internal femoral arteries were 6.5±0.9, 5.8±1.0, and 4.4±0.6 mm, respectively. The mean velocity (and peak systolic velocity) were 18±9 (92±24) in the external iliac, 11±5 (63±16) in the internal femoral, and 14±7 (80±25) cm/s in the external femoral artery.

Presacrifice angiograms revealed rapid runoff of the contrast media in all bifurcations implanted with a device (Figure 4A). In all implanted arteries, Doppler ultrasound measure-
ments taken over time proximally and distally to the “mesh-guarded” ostium demonstrated no alteration in blood flow volume ratios between the parent and guarded arteries with flow ratios of (mean±SE) 0.56±0.03, 0.56±0.03, and 0.55±0.04 at preimplantation, 1 to 5 weeks, and at 7 to 14 weeks, respectively (n=33, P=0.97 in repeated measurement analysis; Figure 5A). In addition, there was no linear relationship found between changes in the flow ratio during follow-up and the time of measurement (r=0.033, P=0.84). Furthermore, no significant alterations of blood flow volume ratios were observed in unilateral implantations comparing flow in the “mesh-guarded” artery and the naive contralateral artery (0.97±0.21, 1.06±0.33, and 1.04±0.23, respectively; n=12, P=0.30; Figure 4B). Flow ratios at 20 to 23 weeks postimplantations (n=3) were 1.01, 0.98, and 1.35 versus 0.94, 0.99, and 1.51, respectively, before device implantation.

Morphometric and Cell Proliferation Analysis

Quantitative analysis of the “mesh-guarded” ostium by computerized morphometry, performed in all devices, demonstrated that the average percentage of tissue coverage (mean±SD) after 1 to 2 (n=14), 3 to 5 (n=19), 6 to 8 (n=8), 9 to 14 (n=27), and 20 to 23 weeks (n=9) was 3%±3%, 3%±5%, 9%±7%, 12%±12% and 12%±14%, respectively. The cellular proliferation rate, assessed by bromodeoxy uridine, at the “guarding-mesh” portion of the devices decreased from 19%±7% and 13%±5% after 1 to 2 (n=4) and 3 to 5 weeks (n=4) to 3%±3% and 0.7%±0.5% at 9 to 14 (n=8) and 20 to 23 weeks (n=9), respectively (Figure 6).

Histological and Scanning Electron Microscope Analysis

Light microscopy evaluations were done for all samples. The supporting parts of the implant were fully incorporated into the vessel wall by 4 weeks (Figure 4D) covered by a thin uniform neointima (Figure 4D–H). The “guarding-mesh” was nonhomogeneously covered by neointima predominantly at the orifice rim. Random histological analyses done concomitantly with bromodeoxy uridine sample evaluations (n=25 devices) showed that the neointima is composed of a delicate extracellular matrix embedded with smooth muscle cells and fibroblasts and covered by endothelial monolayer. Scanning electron microscopy analyses done 2 (n=1), 5 (n=2), and 22 (n=2) weeks postimplantation revealed a thin endothelial monolayer over the “mesh-guarding” filaments (Figure 4F–I) with filaments not fully covered in the 2 samples at 22 weeks.

Assessment for Device-Induced Embolization

Renal ostia (n=4) that were “mesh-guarded” by the device for 4 weeks remained patent as demonstrated by angiography and histological evaluation. Assessment for device-induced embolization by gross inspection and histology of the “mesh-guarded” kidneys did not identify any infarcts. Histological sections of “nonguarded” kidneys (n=2) after deliberate injection of particles revealed multiple infarcts induced by both 100 and 500 μm particles.
Emboli Rerouting Efficacy

After deployment of the device (pore size 500 μm), rerouting started with particles >300 μm and reached 100% efficacy (all particles diverted) with particles >500 μm (Figure 3B). The injection of particles in the parent branch without a deployed device resulted in distribution of particles in the daughter branches that followed the flow division between the branches.

Figure 4. The “mesh-guarded” ostium and mesh filaments. A, Rapid runoff of the contrast media in the iliofemoral bifurcation angiogram at 22 weeks (the edges of the device are marked with black arrows) demonstrating patency of the “mesh-guarded” ostium (white arrow). B–C, Light microscopy of the iliofemoral bifurcation at 22 weeks, internal (B) and external (C) views. D, Histological resin cross-section view showing the parent artery lumen, the patent side branch, and the “guarding-mesh” filaments at 4 weeks. E, Histological staining after “pulling out” the “guarding-mesh” filaments at 9 weeks. A delicate extracellular matrix covered by a thin endothelial monolayer surrounds the filaments. F–I, Scanning electron microscopy views. A window of the guarding mesh (F) and a junction of 2 filaments (G) at 4 weeks covered by a thin endothelial monolayer. A general view of a guarding mesh (H) and a junction of 2 filaments in another device both after 22 weeks.
Discussion

Our study demonstrates, for the first time, the feasibility of a novel endovascular implant, which was designed to reroute emboli away from a critical artery while maintaining uncompromised blood flow. The unique hemodynamic characteristics of the device, which consists of very fine filaments and a high porosity mesh, was designed on the basis of our in vitro flow models to minimize the likelihood of platelet activation and consequent thrombosis and neointima formation.

A major finding in this study is that the “guarding-mesh” part of the device remains patent to flow and does not occlude up to a 23-week follow-up period. This observation is in accordance with that of bifurcation “jailed ostia” crossed unintentionally by stents. No flow compromise was observed after device implantations and during follow-up. This finding is not unexpected given the amount of coverage over the guarded ostium cross-sectional area. The effect of a guarding mesh on the flow dynamics distal to the mesh was extensively investigated in an in vitro model, and when high-porosity index meshes are used, the distal flow rate is uncompromised. Furthermore, the vast volume of data on focal atherosclerotic narrowing shows that critical stenosis causing flow or pressure reductions occurs only when narrowing accounts for approximately 80% to 85% diameter reduction of a major artery in the human vasculature.

Tissue coverage over the “guarding mesh” stabilized in 5 to 6 months and the cellular proliferation rate converged to negligible values, suggesting that further tissue coverage is unlikely to occur beyond 6 months. These findings might be related to shear stress induced by the flow perpendicular to the “mesh-guarding” filaments. The supporting part of the device, adhering to the vessel wall, was fully endothelialized within weeks, which is comparable to coronary artery stents.

In light of the clinical experience with long-term combined antiplatelet therapy after coronary stent implantation, the combined aspirin and clopidogrel therapy was continued for 6 months after device implantation in additional long-term substudies. To overcome the age-dependent weight gain and vessel growth of the domestic swine, additional implantations were performed in miniswine. The “guarding-mesh” part of the device remained patent to flow in subgroups followed-up to 11 months exhibiting similar results.

Figure 5. A, Repeated measurements of blood flow volume ratios (mean±SE) by Doppler ultrasonography at preimplantation, 1 to 5 weeks, and at 7 to 14 weeks. A, Between the “mesh-guarded” and parent artery (n=33, P=0.97). B, Between the “mesh-guarded” artery and the naive contralateral artery in unilateral implantations (n=12, P=0.30).

Figure 6. Cellular proliferation. A, Bar graph of cellular proliferation rate over time; B–C, bromodeoxy uridine-stained tissues (B) at 3 weeks; multiple “positive” cells (marked by arrows). C, No proliferating cells observed at 6 months.
Efficacy of Emboli Rerouting
The device was proven effective in rerouting particles larger than the mesh pore size. Moreover, rerouting started at particle size >300 μm implying a higher efficacy range in emboli rerouting. The diameter of the main cerebral arteries of the circle of Willis (ie, middle cerebral artery) is 2 to 3 mm and their main tributaries 1 to 2 mm.19 Therefore, although even smaller emboli may cause harm, we hypothesize that the device could prevent most large territorial brain infarcts in the implanted arterial distribution. Indeed, atrial fibrillation-related strokes are associated with particularly high mortality and severe disability, likely because of large emboli occluding a major cerebral vessel.20,21 The device is, however, by design not intended to prevent passage of small microemboli.

To verify whether emboli might adhere and therefore obstruct the mesh-guarded ostium of the diverter, additional substudies were performed to test the rerouting capabilities of the device using blood clots of various radii both in swine and in vitro. The diverter did not trap the clots, but acted as a diversion device. Injecting clots of various radii toward the diverter yielded no trapping of particles in any of the injections performed. The filtering windows were clean from thrombi in all filtering portions of the diverters. Diversion of the clots rather than trapping was also proven effective both in vitro and in the swine model.

Endovascular Approach for Embolic Stroke Prevention
The concept of implanting a preventive device in a healthy vessel is not new. This device is similar in concept to inferior vena cava filters, which are often implanted in a healthy vessel to prevent downstream thromboemboli to the lungs. Another endovascular approach for preventing cardioembolism in patients with atrial fibrillation is percutaneous left atrial appendage transcatheter occlusion.22 An important potential advantage of the device is its inherent capability to reroute emboli irrespective of the proximal source and type of emboli being shed (eg, thrombus or atherosclerotic plaque).

Endovascular Access to Territories Distant to the Device
Bailout procedures for catheter penetration distal to the filter and procedures for carotid revascularization are feasible, although the rerouting capability of the device is sacrificed. To address potential concerns regarding limiting the endovascular approach to the protected internal carotid artery, we successfully tested penetration and enlargement of the filtering part of the diverter using low-profile balloon angioplasty through the pores of the delicate mesh.

Protection of the Posterior Circulation
The internal carotids provide approximately 80% of the intracranial circulation7 and protection of the 20% flow through the vertebral arteries would be desired after the proof of safety of this approach in the carotids. One option could be to protect the posterior circulation by implantation of the device into a lower-level bifurcation, thus diverting proximally originating emboli into the subclavians. However, the need to do this is probably lower than believed. Emboli originating from atrial fibrillation most often cause large territorial infarcts in the anterior circulation.20 There is evidence that the rate of emboli flowing to the posterior circulation is lower even when normalized by the flow ratio. A recent study23 has shown that the tendency of large particles is to preferentially enter into the wider bifurcation branch, in a higher proportion than the flow ratio, indicating it would be better to protect the larger arteries first.

Animal Model: Pros and Cons
We have chosen the swine iliofemoral bifurcation as an experimental model, because it was found to best simulate the human carotid bifurcation in terms of hemodynamic and anatomic parameters.6–10 The findings of the current study in the swine are particularly encouraging given that the human coagulation cascade is less potent.24,25 Device-induced embolization was not demonstrated in our swine kidney model after 1 month; however, the possibility of distal microemboli requires further investigation in larger data sets with longer follow-up. Finally, the arteries in the swine model are nonatherosclerotic vessels, and our results cannot be generalized to implantation in an artery with severe atherosclerotic disease.

Implications for Clinical Research
Emboli originating from the heart and aortic arch are a major cause of ischemic stroke.26–29 Oral anticoagulants reduce stroke incidence in high-risk patients with atrial fibrillation by 60% to 70%.28,30 There is a major subset of patients in whom the perceived risk of anticoagulation outweighs the benefit, although both may be high.31,32 In this situation, a device for prevention of embolic stroke may be useful. Our work suggests the potential clinical application of such a novel catheter-based, permanent implant for prevention of embolic stroke. This approach, if found to be safe and effective in humans, could be particularly useful in elderly patients at high risk for embolic stroke who could not be safely anticoagulated. Based on the experimental results, a clinical trial has been initiated to test the feasibility and safety of this approach for embolic stroke prevention by implantation in the carotid bifurcation in high-risk patients with atrial fibrillation ineligible for anticoagulation treatment and without significant carotid atherosclerotic disease (e-DIRECT: emboli DIversion and Rerouting to the External Carotid artery Technique study).

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Disclosures
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