◆ EXPERIMENTAL INVESTIGATION ◆

In Vitro Performance Assessment of Distal Protection Devices for Carotid Artery Stenting: Effect of Physiological Anatomy on Vascular Resistance

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Purpose: To assess in vitro the performance of 5 distal protection devices (DPDs) by evaluating the capture efficiency, pressure gradient, volume flow rate, and vascular resistance in the internal carotid artery (ICA).

Methods: The time-averaged mean peak velocity in the common carotid artery and a blood-mimicking solution were used to simulate physiological conditions in a silicone carotid phantom representing average human carotid artery geometry with a 70% symmetrical ICA stenosis. Five milligrams of dyed 200-μm nominal diameter polymer microspheres (larger than the pore size of the devices, except Spider RX, which was tested with 300-μm-diameter particles) were injected into the ICA. The percentages of particles missed after injection and lost during device retrieval were measured for the 5 devices (Spider RX, FilterWire EZ, RX Accunet, Angioguard XP, and Emboshield). The normalized pressure gradient, fraction of the volume flow rate, and vascular resistance in the ICA were calculated.

Results: Spider RX captured the most particles (missing 0.06%, $p<0.05$) and yielded the smallest normalized pressure gradient increase (4.2%), the largest volume flow rate fraction (0.40), and the smallest vascular resistance in the ICA (272 mmHg/L·min^{-1}, a 5.4% increase with respect to initial conditions). Angioguard XP captured the fewest particles (missing 36.3%, $p<0.05$ except Emboshield) and resulted in the largest normalized pressure gradient increase (37%) in the ICA. RX Accunet produced the smallest volume flow rate fraction in the ICA (0.30) and the largest vascular resistance in the ICA (470 mmHg/ L·min^{-1}, an 82.2% increase). Emboshield migrated ~6 cm distal to the original position after particle injection. FilterWire EZ lost the fewest particles during retrieval (0.45%, $p<0.05$ except Accunet RX and Spider RX) and had the best overall performance with 200-μm emboli ($p<0.05$ except Accunet RX).

Conclusion: None of the devices tested completely prevented embolization. Overall, Spider RX had the best performance and is conjectured to have the best wall apposition of the devices tested. Vascular resistance should be considered a key filter design parameter for performance testing since it represents a quantitative estimation of the ''slow-flow phenomenon.'' Our findings should be extrapolated cautiously to help interventionists choose the best device.

J Endovasc Ther 2007;14:712–724

This work was supported in part by Carnegie Mellon's Biomedical Engineering Department and grants from the Pennsylvania Infrastructure Technology Alliance (PITA) and the Samuel and Emma Winters Foundation.

Gail M. Siewiorek has no financial interests to disclose. Mark H. Wholey has disclosed that he is a consultant to Cordis, Abbott (Guidant), Medrad, Boston Scientific, Edwards Life Sciences, and Mallinckrodt. Ender A. Finol has disclosed that for this study he received grant/research funding from Guidant Endovascular Solutions (Abbott), the Pennsylvania Infrastructure Technology Alliance, and the Samuel and Emma Winters Foundation.

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Key words: carotid artery, stent, cerebral protection, embolic protection filter, stenosis, pressure gradient, distal protection device

Carotid artery stenting (CAS) is a relatively new alternative treatment for severe carotid artery disease. The widespread acceptance of CAS is dependent on the equivalent effectiveness of this procedure compared with its surgical counterpart, carotid endarterectomy (CEA), in preventing periprocedural stroke. The first major multicenter trial, CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study), reported no statistical difference between the 2 treatments after a total of 504 patients were recruited to receive either CAS or CEA.[1] The rate of disabling stroke or death was 6% in both groups within 30 days of the procedure. This outcome indicates that there is still concern about the risk of periprocedural complications due to distal embolization. Therefore, the use of distal protection devices (DPDs) during CAS for cerebral protection has been a widely accepted adjunct to the procedure.

There are 2 types of DPDs used for CAS: distal balloon occlusion and distal filters. Distal balloon occlusion devices usually consist of a 0.014-inch hollow nitinol wire with a compliant elastomeric polyurethane occlusion balloon that can be inflated to a diameter of 3 to 6 mm.[2] The column of trapped blood is aspirated before retrieval of the device. Advantages of distal balloon occlusion devices include a lower crossing profile and the ability to capture particles of all sizes. Disadvantages include possible embolization into the external carotid artery (ECA) during lesion crossing, inability to perform angiograms during CAS, possible injury to the internal carotid artery (ICA), and the potential for patient intolerance to complete occlusion.

Filters usually consist of a 0.014-inch wire with a basket frame made of nitinol and a polyurethane membrane over the frame, a delivery sheath, and a retrieval sheath. Pore sizes typically vary between 70 to 200 μm. Filters were selected for the present investigation since they allow distal perfusion (and thus the ability to perform angiograms) during CAS. Disadvantages of filters include a larger crossing profile, possible filter thrombosis, embolization of particles smaller than the pore size of the device, possible embolization during lesion crossing or device retrieval, difficulty in navigating severely stenosed or tortuous vessels, potential for spasm or dissection of the ICA, filter basket detachment, and possible incorrect wall apposition of the filter against the vessel wall.[2,3]

The SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial was a large multicenter randomized study that compared the effectiveness of CAS with distal protection (using the Angioguard filter) to CEA. This study included 747 patients, of which 334 were randomly assigned either to CAS with the use of distal protection or to CEA, while the remaining 413 patients were non-randomly assigned to either of the 2 procedures.[1] The study reported that CAS with distal protection was not inferior to CEA. Wholey et al.[4] found in the Global Carotid Artery Stent Registry that patients undergoing unprotected CAS had a complication rate of 5.9% versus 2.8% for patients with distal protection.

As of yet, the clinical significance of distal embolization during CAS is unclear. Crawley et al.[5] did not find a correlation between the number of microembolic signals generated during either angioplasty or CEA and the periprocedural stroke rate. They postulated that it is possible that the microembolic signals detected during angioplasty are microscopic air bubbles generated during injection of contrast for angiography.

Others have observed the effects of DPDs on fluid flow properties, such as pressure and flow rate. Hendricks et al.[6] found a correlation between the pressure gradient and flow rate reduction of a blood-mimicking solution through 4 DPDs (Spider RX, RX Accunet, FilterWire EZ, and Angioguard) in a single tube setup. Casserly et al.[7] observed via angiograms a significant reduction in antegrade flow in the ICA proximal to the DPD, which they referred to as a ''slow-flow

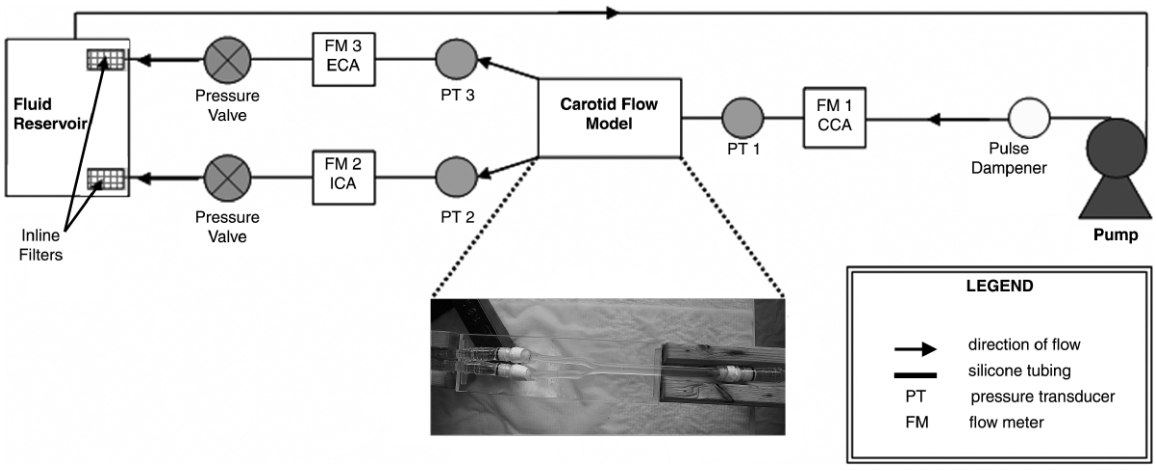


Figure 1 ◆ Schematic of flow loop system with inset of carotid artery model.[11] CCA: common carotid artery, ICA: internal carotid artery, ECA: external carotid artery.

phenomenon.'' Currently, the causes of this event are unknown, but Casserly's working hypothesis is that antegrade flow is impeded by plaque particles clogging the filter's pores. Patients with a slow-flow condition had a higher incidence of stroke or death within 30 days of the procedure than patients with normal blood flow (9.5% versus 2.9%). Casserly et al.[7] found recent (<6 months) history of stroke or transient ischemic attack, increased stent diameter, and increased patient age as possible predictors of slow flow.

We have previously conducted experimental and computational studies on DPDs used during CAS. Finol et al.[8] investigated in vitro the performance of 3 DPDs (Angioguard XP, RX Accunet, and FilterWire EZ) in 3 vessel sizes (5.0-, 5.5-, 6.0-mm internal diameter). The devices performed best in the smallest tested vessel diameter. Computationally, under peak systolic conditions of a Newtonian fluid through a filter, vortices formed at the proximal and distal ends of the device.[9] The RX Accunet was modeled with a gap in between the filter basket and the vessel wall; the vortices and gap may both contribute to decreased capture efficiency of this device.

In the present investigation, we evaluated in vitro the performance of 5 DPDs in an anatomical model of a human carotid artery with an ICA stenosis. The objectives of this study were to (1) assess the capture efficiency of the devices based on the percentage of particles missed after particle injection and lost during device retrieval and (2) determine quantitatively the effect that this efficiency has on pressure gradients, flow rate decrease, and vascular resistance in the ICA. The novelty of our protocol is based on incorporating physiologically realistic features for testing DPDs, which include navigation of the device through a stenosis, pressure measurements proximal and distal to the device, quantitative assessment of the ''slow-flow'' phenomenon in the ICA, use of a blood-mimicking fluid in the flow model, and indirect assessment of device-wall apposition.

METHODS

Experimental Setup

The in vitro flow loop (Fig. 1) consists of 0.25-inch ID Tygon tubing and a silicone carotid artery bifurcation model, which is an average representation of a typical human carotid artery with a 70% symmetrical ICA stenosis (Fig. 2).[10] A peristaltic pump (Ismatec SA, Wertheim-Mondfeld, Germany) and pulse dampener maintain a constant flow of a 36%/64% glycerol/deionized water blood-mimicking solution having a viscosity of 3.5 cP. The flow rate of 737 mL/min represents the mean peak velocity averaged over 1 cardiac cycle for the human common carotid artery

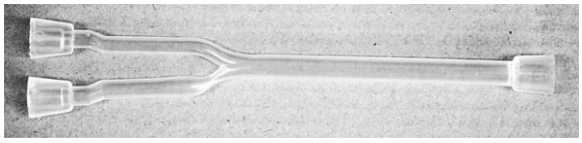


Figure 2 ◆ Photograph of the symmetric 70% stenosed carotid bifurcation phantom.

(CCA).[11] Three low-flow magnetic flow meters (SeaMetrics Inc., Kent, WA, USA) and 3 pressure transducers (Honeywell Sensotec, Columbus, OH, USA) are placed at the CCA, ICA, and ECA, respectively. Pressure valves maintained physiological CCA pressure in the 80- to 100-mmHg range.

The DPDs tested have been described previously (Fig. 3).[2,3] The Spider RX (ev3, Plymouth, MN, USA) consists of a nitinol wire filter basket having a pore size ranging from 70 to 200 μm, with the largest and smallest pores located at the proximal and distal ends of the basket, respectively. It comes in sizes of 3 to 7 mm in 1-mm increments. The FilterWire EZ (Boston Scientific, Natick, MA, USA) has a nitinol wire frame and a polyurethane membrane having a pore size of 110 μm; it is a one-size-fits-all device designed for vessels from 3.5 to 5.5 mm in diameter. The RX Accunet (Guidant Corporation [Abbott], St. Paul, MN, USA) also has a nitinol wire frame and polyurethane membrane having a pore size of 115 μm; it comes in sizes 4.5 to 7.5 mm in 1-mm increments. The Emboshield (Abbott Vascular, Santa Clara, CA, USA) has a pore size of 140 μm in the polyurethane membrane and comes in 3- to 6-mm diameters in 1-mm increments. The Angioguard XP (Cordis Endovascular, Miami Lakes, FL, USA) has 100-μm pores and ranges in size from 4 to 8 mm in 1-mm increments.

Protocol

Each device was inserted in the flow loop by means of its deployment catheter and delivery sheath following the manufacturer's instructions. After flow stabilization, pressure and flow rate were recorded using a data acquisition system (DAQ 6224 and LabVIEW 7.1; National Instruments Co., Austin, TX, USA) to establish the initial condition (IC).

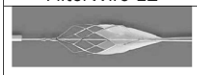
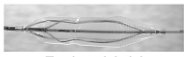
DPD	Pore Size, μm	Device Size, mm
 Spider RX	70–200	3, 4, 5, 6, 7
 FilterWire EZ	110	3.5–5.5 (one size fits all)
 RX Accunet	115	4.5, 5.5, 6.5, 7.5
 Emboshield	140	3, 4, 5, 6
 Angioguard XP	100	4, 5, 6, 7, 8

Figure 3 ◆ Distal protection devices (DPD) tested in vitro.

The device was deployed and pressure and flow rate measured after flow stabilization for the empty filter (EF) condition. All devices were deployed 5 cm distal to the stenosis. A syringe filled with 5 mg of dyed polymer microspheres (Duke Scientific, Palo Alto, CA, USA), 5 mL of deionized water, and 1 mL of Tween-20 (Fisher Scientific, Fair Lawn, NJ, USA) was inserted into the system for delivery of the embolized solution into the ICA. The 200-μm nominal diameter microspheres selected for testing were larger than the pore size of any of the devices except the Spider RX; for testing that device, microspheres measuring 300 μm in nominal diameter were used. The density and actual diameter of the microspheres were provided by the manufacturer. Due to a slight variation in the particle size (4.7% coefficient of variation, as reported by the manufacturer), some of the microspheres have a diameter slightly smaller than 200 μm, the largest pore size in Spider RX. Thus, it is not possible to make a statement about wall apposition if some of the microspheres injected have the potential to pass through the pores of the device. Instead, Spider RX was tested with microspheres having a nominal diameter of 300 microns to ensure that all of the microspheres would be larger than the largest pore size (200 μm).

Particles that were not captured in the basket of a device were collected distal to

the ICA and ECA pressure transducers and flow meters in 2 polyurethane mesh filters having a pore size of 40 μm. These were labeled as the particles missed by the device after injection. Pressure and flow rate were measured for the full filter (FF) condition. The polyurethane mesh filters were replaced with 2 new filters of the same kind, and the device was retrieved, such that any particles released during device retrieval were collected distal to the ICA and ECA. The protocol was repeated 10 times per device.

Definitions and Calculations

The particles collected in the mesh filters were counted for each trial. The mass was calculated based on the number of particles, diameter of the spherical particles, and the density of the particles. The *percentage of particles missed after injection* was estimated by calculating the ratio of the mass of particles missed by the device (found in the ICA inline filter after injection) to the mass of particles that traveled through the ICA (mass of particles found in the ECA inline filter after injection subtracted from the total mass of particles injected). The *percentage of particles lost during device retrieval* was estimated by calculating the ratio of the mass of particles that escaped the device basket during retrieval (found in the ICA inline filter after removal of the device from the system) to the mass of particles captured in the basket of the device after injection [mass of particles found in the ICA inline filters after injection subtracted from the mass of particles that traveled through the ICA (calculated previously as the percentage of particles missed after injection)].

The pressure gradient across the ICA was calculated as the difference between the measured pressure (P) at the CCA inlet and the ICA outlet. The pressure gradient in the ICA was normalized by the average pressure gradient at initial conditions, as defined by Eq. (1). The normalized pressure gradient in the ICA was calculated for all 3 phases of the experiment: IC, EF, and FF. The normalized pressure gradient will be partly dependent upon the mass of particles captured by the device (particles occluding pores in the filter basket) and the pore size of the device.

$$\Delta P^* = \frac{P_{CCA} - P_{ICA}}{(P_{CCA} - P_{ICA})|_{I.C.}} \quad (1)$$

The volume flow rate decrease in the ICA was evaluated by comparing the fractional volume flow rate at IC, EF, and FF conditions. The fractional volume flow rate through the ICA was defined as the ratio of the flow rate (Q) measured at the ICA outlet to the flow rate measured at the CCA inlet, as defined by Eq. (2). As with the pressure gradient, the fractional volume flow rate will be partly dependent upon the mass of particles captured by the device (particles occluding pores in the filter basket) and the pore size of the device.

$$Q^* = \frac{Q_{ICA}}{Q_{CCA}} \quad (2)$$

Vascular resistance is the flow impedance when the frequency of oscillatory motion is zero (fluid is moving steadily).[12] The resistance to flow in the ICA was calculated for the 3 testing conditions using Eq. (3).

$$R = \frac{P_{CCA} - P_{ICA}}{Q_{ICA}} \quad (3)$$

Statistical Analysis

A 2-sample Student 2-tailed *t* test was used to compare the percentage of particles missed after injection and lost during retrieval for the 5 devices to one another at a significance level of $\alpha = 0.05$. This represents the probability of making a type I error or concluding that the null hypothesis (i.e., there is a difference in the ability of each device to capture particles) is false when it is actually true.

RESULTS

Capture Efficiency After Particle Injection

The average mass of particles that traveled through the ICA for all trials conducted (4.99 ± 0.01 mg) was nearly identical to the measured 5 mg of particles, indicating negligible embolization into the ECA during the experimental protocol. None of the devices

TABLE 1
Mean Mass (M) of Particles and Percentages ($\bar{R}$) Missed After Injection and Lost During Device Retrieval

	Spider	FilterWire	Accunet	Emboshield	Angioguard
After Particle Injection					
$M_{injected}$, mg	5.00±0.01	4.99±0.01	4.99±0.02	5.00±0.00	4.99±0.01
M_{missed}, mg	0.01±0.01	0.20±0.13	0.24±0.20	1.77±0.45	1.81±0.72
$\bar{R}_{missed}$, %	0.06	3.9	4.9	35.4	36.3
During Device Retrieval					
$M_{in,retrieve}$, mg	4.99±0.01	4.80±0.13	4.75±0.21	3.23±0.45	3.18±0.72
$M_{lost,retrieve}$, mg	0.03±0.02	0.02±0.02	0.13±0.19	0.09±0.04	1.90±0.58
$\bar{R}_{retrieve}$, %	0.55	0.45	2.9	2.8	59.5

Continuous data are presented as means ± standard deviation.
$M_{injected}$ is the mass of particles injected that traveled through the ICA. M_{missed} is the mass of particles missed by the device after particle injection. $\bar{R}_{missed}$ is the percentage of missed particles after particle injection (average of 10 trials). $M_{in,retrieve}$ is the mass of particles in the device basket prior to retrieval. $M_{lost,retrieve}$ is the mass of particles lost by the device during retrieval. $\bar{R}_{retrieve}$ is the percentage of lost particles during device retrieval (average of 10 trials).

tested was able to completely prevent embolization in the ICA (Table 1). Spider RX had the lowest percentage of particles missed of the 5 devices tested ($\bar{R}_{missed}$=0.06%), while Angioguard XP had the highest percentage of particles missed (36.3%). It should be noted that in preliminary experiments (results not reported here) testing the Spider RX device with particles having a nominal diameter of 200 μm, which approximates the largest ''pores'' of the Spider RX nitinol basket (200 μm at its proximal end), the percentage of particles missed was significantly higher (on average 48.3%, $p<0.05$). In these preliminary experiments, 95% of the particles injected ranged in size from 183 to 221 μm (a 4.7% coefficient of variation, mean diameter 202 microns, as reported by the manufacturer). The efficacy of Spider RX decreased dramatically when capturing particles <200 μm, which is problematic if embolized plaque <200 μm is clinically significant.

Capture Efficiency During Device Retrieval

None of the devices tested was able to completely contain all the particles in the filter basket during the retrieval operation, which consisted of collapsing the basket into the recovery sheath and extracting the sheath from the flow model (Table 1). Notice that $M_{in,retrieve}$ is a function of the mass of particles missed by the device after injection. Spider RX and FilterWire EZ performed equally well during device retrieval ($\bar{R}_{retrieve}$ 0.55% and 0.45%, respectively). RX Accunet and Emboshield had similar percentages of particles lost (2.9% and 2.8%, respectively). Angioguard XP had the highest percentage of particles lost during retrieval (59.5%).

Pressure Gradient in the ICA

All devices tested experienced an increase in normalized pressure gradient in the ICA (Fig. 4). Angioguard XP had the largest normalized pressure gradient of the devices tested in the full filter condition compared to initial conditions (increasing 37% with respect to IC) compared to Spider RX, which had the smallest (increasing 4.2%).

Volume Flow Rate in the ICA

The fractional volume flow rate in the ICA decreased from initial to full filter conditions for all devices tested (Fig. 5). Spider RX had the largest fractional volume flow rate in the ICA in the full filter condition (0.40), while RX Accunet had the smallest (0.30).

Vascular Resistance in the ICA

The vascular resistance increased in the full filter condition (Table 2). Spider RX had the lowest resistance increase at EF (3.5%) and FF

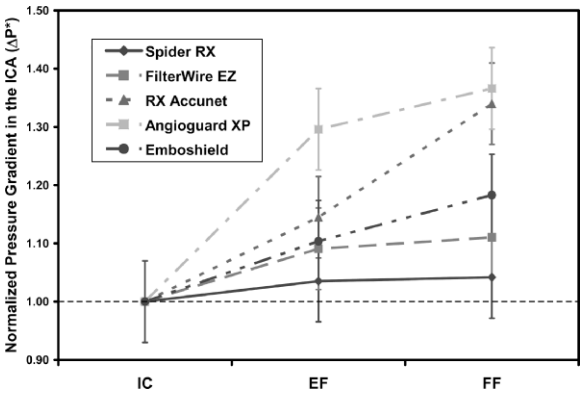


Figure 4 ◆ Normalized pressure gradient with y error bars in the ICA. IC: initial condition (prior to device deployment), EF: empty filter condition (device deployed), FF: full filter condition (device filled with particles).

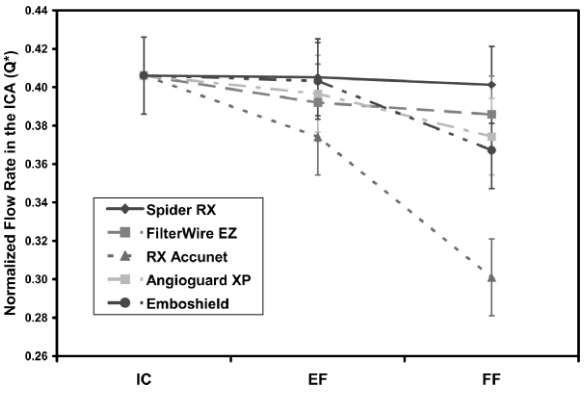


Figure 5 ◆ Normalized volume flow rate with y error bars in the ICA. IC: initial condition (prior to device deployment), EF: empty filter condition (device deployed), FF: full filter condition (device filled with particles)

(5.4%) conditions compared to the IC baseline. This is a further indication of the device's ability to allow continuous flow through its basket with minimal drop in ICA pressure. Angioguard XP presented the greatest resistance at EF (30.6% with respect to IC), while RX Accunet greatly obstructed the flow at FF conditions (82.2% increase in vascular resistance with respect to IC).

Special Case: Emboshield

During testing of the Emboshield device, the filter and guidewire migrated ~6 cm distal to the initial position of deployment after particle injection (Fig. 6). Since this migration has not been documented in the literature, a second set of experiments was conducted with the guidewire of the device secured to the frame of the bench-top system with a clamp preventing the filter from moving downstream. In clinical practice, the position of the filter is fixed by controlling the guidewire. We have observed in vivo that the filter can migrate along the guidewire in the retrograde direction during hypotension or transient ischemic arrest. Clamping had a significant effect on the performance assessment variables of the device, namely, capture efficiency, pressure gradient, and flow rate decrease in the ICA. Emboshield captured more particles while clamped (Table 3) compared with unclamped (28.3% versus 35.4%, $p=0.055$). When clamped, the normalized pressure gradient (Fig. 7) in the ICA was greater (68% versus 18%) than when unclamped. The fractional volume flow rate in the ICA further decreased when clamped than when unclamped (0.20 versus 0.37).

Device Comparisons

Pairwise comparison of DPDs relative to either percentage of particles missed after injection or percentage of particles lost during retrieval found several significant differences (Table 4). Spider RX, which had the smallest percentage of particles missed after injection,

TABLE 2
Vascular Resistance in the ICA at Empty Filter and Full Filter Conditions for a Variety of Protection Devices

	Vascular Resistance,* mmHg/L·min^{-1}	
	Empty Filter	Full Filter
Spider RX	267 (+3.5%)	272 (+5.4%)
FilterWire EZ	291 (+12.8%)	301 (+16.7%)
RX Accunet	322 (+24.8%)	470 (+82.2%)
Angioguard XP	337 (+30.6%)	375 (+45.4%)
Emboshield	296 (+14.7%)	347 (+34.5%)

* Vascular resistance at the initial conditions is 258 mmHg/L·min^{-1}. Parentheses show the percent increase in vascular resistance of the device with the filters empty and full with respect to the initial conditions.

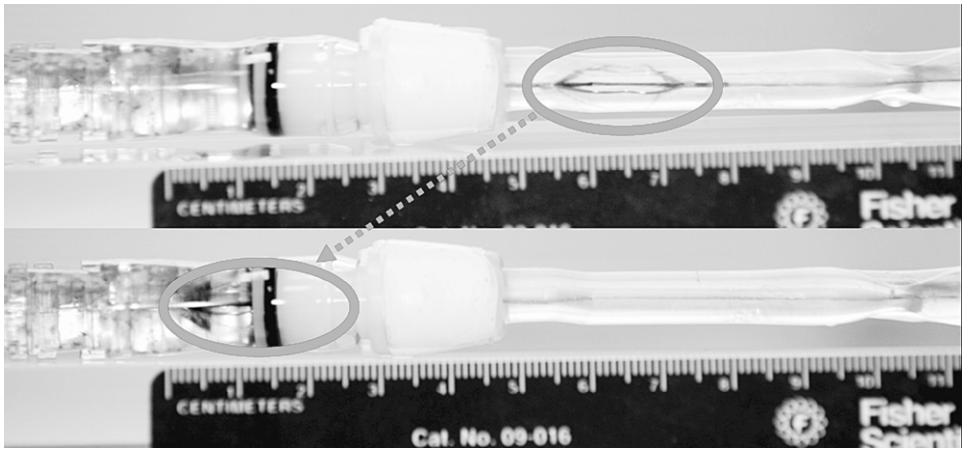


Figure 6 ◆ Distal migration of unclamped Emboshield device.

had a significantly different performance from all the other devices tested ($p<0.05$). Emboshield and Angioguard XP, which captured the fewest particles after injection, were also significantly different from all other devices ($p<0.05$) tested except each other ($p>0.05$). FilterWire EZ and RX Accunet performed equally well after particle injection and were not significantly different from each other ($p>0.05$). During device retrieval, Angioguard XP exhibited a significantly higher percentage of particles lost compared to the other devices tested ($p<0.05$).

TABLE 3
Mean Mass (M) of Particles and Percentages ($\bar{R}$) Missed After Injection and Lost During Device Retrieval for Unclamped and Clamped Emboshield Guidewire

	Unclamped	Clamped
After Particle Injection		
$M_{injected}$, mg	5.00±0.00	5.00±0.01
M_{missed}, mg	1.77±0.45	1.42±0.31
$\bar{R}_{missed}$, %	35.4	28.3
During Device Retrieval		
$M_{in,retrieve}$, mg	3.23±0.45	3.58±0.31
$M_{lost,retrieve}$, mg	0.09±0.04	0.04±0.03
$\bar{R}_{retrieve}$, %	2.8	1.1

Continuous data are presented as means ± standard deviation.
$M_{injected}$ is the mass of particles injected that traveled through the ICA. M_{missed} is the mass of particles missed by the device after particle injection. $\bar{R}_{missed}$ is the percentage of missed particles after particle injection (average of 10 trials). $M_{in,retrieve}$ is the mass of particles in the device basket prior to retrieval. $M_{lost,retrieve}$ is the mass of particles lost by the device during retrieval. $\bar{R}_{retrieve}$ is the percentage of lost particles during device retrieval (average of 10 trials).

DISCUSSION

Capture Efficiency Rates and Flow Performance Variables

One main concern of CAS is the potential for distal embolization that may be conducive to periprocedural stroke. Although it has yet to be determined that distal embolization has a direct cause and effect relationship,[5] it seems logical to reduce the number of emboli that could potentially occlude a cerebral artery. Thus, DPDs of varying nominal diameter and basket pore size have been evaluated based upon the percentage of particles missed by the device in vitro. In addition, the effect of DPDs on pressure and flow rate in the ICA can lead to a quantitative assessment of the in vivo ''slow-flow phenomenon'' described by Casserly et al.[7]

In this investigation, we found that Spider RX captured significantly more particles than all the other devices tested and had the smallest effect on normalized pressure gradient and fractional volume flow rate in the ICA at the time of deployment and after capturing emboli. The ability of Spider RX to allow few particles past the device is most likely due to adequate apposition of the basket against the

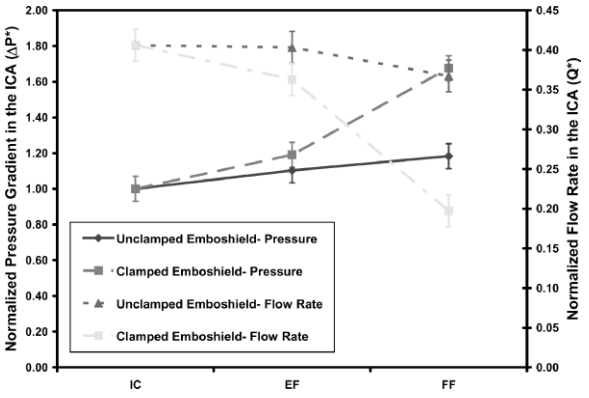


Figure 7 ◆ Normalized pressure gradient and volume flow rate with y error bars in the ICA for the unclamped and clamped Emboshield guidewire. IC: initial condition (prior to device deployment), EF: empty filter condition (device deployed), FF: full filter condition (device filled with particles)

vessel wall. The depth of the basket also allows few particles to escape during retrieval. The minimal effect on pressure gradient and flow rate reduction is due to its variable pore size (70–200 μm) and its widespread distribution of pores along the entire surface of the basket, a design feature not present in any other DPDs currently available on the market. The smallest pores are located at the distal end of the basket, where particles are first deposited, and the larger pores are located at the proximal end of the basket. FilterWire EZ, which also had a low percentage of particles lost during retrieval, has a filter basket of similar shape and dimensions as Spider RX, but the pores are limited to the distal end of the basket. Conversely, Angioguard XP has a shorter basket than either Spider RX or FilterWire EZ, leading to a significantly higher percentage of particles lost during retrieval.

The greatest normalized pressure gradient in the ICA was obtained with the Angioguard XP filter. Although it captured the fewest particles, this filter basket has pores of 100 μm in diameter, the smallest size of all the devices tested. The greatest fractional volume flow rate reduction in the ICA was obtained with the RX Accunet filter, which is likely due to the greater number of nitinol struts the device has compared to the other devices tested. The ability of DPDs to effectively navigate tortuous, stenosed vessels, also known as trackability, is a very important design parameter. All devices were able to navigate through the 70% symmetrically stenosed vessel.

Previous studies by other investigators have been conducted in order to determine the size, number, and composition of embolized plaque. Sprouse et al.[13] analyzed clinical variables to find a correlation to visible debris found in the basket of filter devices used during CAS. None of the clinical variables had a high enough negative predictive value (NPV), but hypertension, hypercholesterolemia, stent diameter >9 mm, and any neurological event had elevated NPVs. Hayashi et al.[14] retrieved a column of blood trapped by a distal balloon occlusion device during CAS. They filtered out the plaque and mounted the

TABLE 4
Pairwise Comparison of Percentages of Particles Missed After Injection and Lost During Device Retrieval

		p	
		After Particle Injection	During Device Retrieval
Spider RX	FilterWire EZ	<0.05	>0.05
Spider RX	RX Accunet	<0.05	>0.05
Spider RX	Emboshield	<0.05	<0.05
Spider RX	Angioguard XP	<0.05	<0.05
FilterWire EZ	RX Accunet	>0.05	>0.05
FilterWire EZ	Emboshield	<0.05	<0.05
FilterWire EZ	Angioguard XP	<0.05	<0.05
RX Accunet	Emboshield	<0.05	>0.05
RX Accunet	Angioguard XP	<0.05	<0.05
Emboshield	Angioguard XP	>0.05	<0.05

stained debris on a glass slide to determine the size and amount of particulates collected. In one particular case study, they found the debris ranged in size from 40 to 500 μm. Quan et al.[15] aspirated blood from 3 DPDs (GuardWire, FilterWire EX, and Interceptor) after CAS and performed morphometric and histological analysis on the debris. They found that there was no significant difference in the volume of debris captured by the 3 DPDs tested. FilterWire (pore size of 110 μm) captured fewer small particles (<96 μm) than either GuardWire (a distal balloon occlusion device) or Interceptor (a braided nitinol wire filter with 110-μm pore size). Chen et al.[16] used multifrequency transcranial Doppler to differentiate between gaseous and solid emboli during CAS. In 11 angiograms and 10 stents, they found that 39% of the emboli generated were solid. de Weert et al.[17] used multidetector computed tomography (MDCT) to assess plaque components, such as calcifications, fibrous tissue, and lipids, and compared them to plaque histology. Previous studies have suggested that rupture-prone plaques have a large lipid-rich core with a thin fibrous cap.[18] de Weert found that fibrous-rich regions could be differentiated from lipid-rich regions, but the amount of plaque was underestimated by MDCT compared with histology.

Although these initial results are promising, more testing needs to be done on DPDs used in conjunction with CAS. Ohki et al.[19] conducted ex vivo qualitative and quantitative analysis of a Neuroshield DPD during CAS using human cadaver carotid artery bifurcations and plaques. Quantitatively, the DPD captured 88% of the plaque particles. Müller-Hülsbeck et al.[20,21] have conducted in vitro studies to measure the percentage of particles missed by DPDs. A bench-top flow model was used to test the percentage of particles missed by 5 DPDs (GuardWire, Angioguard, FilterWire EX, TRAP, and Neuroshield) using polyvinyl alcohol (PVA) particles to simulate embolized plaque. The first study compared the effectiveness of 2 DPDs (GuardWire and Angioguard) with and without additional aspiration techniques in an in vitro model. Overall, a mean of 91%±6% of particles were captured. Embolization into the ECA was more frequent with the use of GuardWire compared to Angioguard. In the second study, 5 DPDs (GuardWire, Angioguard, FilterWire EX, TRAP, and Neuroshield) were tested with small (150–250 μm), medium (355–500 μm), and large (710–1000 μm) particles. The lowest weight of particles passed through Neuroshield for all 3 particle sizes. Again, GuardWire had the greatest embolization in the ECA of all devices tested. Müller-Hülsbeck et al.[22] also tested MembraX, a stent with integrated protection, in addition to the other 5 DPDs in the in vitro experimental setup. Both PVA and human plaque particles were used in the experiments. MembraX had the best performance over the DPDs tested for both types of embolic material. A second study using human plaque tested 4 DPDs (Angioguard, FilterWire EX, TRAP, and Neuroshield).[23] Neuroshield and FilterWire EX had the best performance, perhaps due to their large filter volume. Order et al.[24] assessed the influence of ICA tortuosity (normal, mildly tortuous, and severely tortuous) on the performance of 4 DPDs (Angioguard, FilterWire EX, TRAP, and Neuroshield). FilterWire EX had the best performance of all devices tested for all geometries; it was the only device whose filtration was not affected by tortuosity. In all studies, none of the DPDs tested was able to completely prevent embolization.

Three of the DPDs evaluated were also tested by Müller-Hülsbeck and associates [Angioguard, Neuroshield (predecessor to Emboshield), and FilterWire EX (predecessor to FilterWire EZ)]. Angioguard had the highest percentage of particles missed of these 3 devices for both synthetic and human plaque particles (8.03% and 4.4%, respectively),[21–23] which is in accordance with our findings. However, they found that Neuroshield had the smallest percentage of particles missed for both synthetic and human plaque particles (3.5% and 0.8%, respectively), while we have found that this device is only second to Angioguard XP in percentage of particles missed. The percentages of missed particles for the devices we have tested are also higher than those found in studies by Müller-Hülsbeck et al.[21–23] Order et al.[24] found that FilterWire EX had the smallest percentage of

particles missed for small, medium, and large particles (5.81%, 2.99%, and 1.20%) in a severely tortuous idealized ICA, while Angioguard had the largest percentage (29.71%, 19.92%, and 13.57%). These results are similar to ours. However, it should be noted that the design change made to FilterWire EX, leading to the new generation FilterWire EZ, resulted in a significant improvement in wall apposition of the basket, which likely explains the improved capture efficiency rates obtained in this investigation in comparison to previous in vitro studies.[21–24]

The outcome of our investigation with a physiologically realistic flow model correlates well with our previous work using vessels with constant cross sections. We found previously that Angioguard XP had the largest percentage of particles missed in vessels measuring 5.0, 5.5, and 6.0 mm in diameter (8.08%, 11.83%, and 16.73%, respectively),[8] while RX Accunet had the smallest (0.42%, 0.16%, and 2.13%). FilterWire EZ also performed equally well for the 5.0- and 5.5-mm sized vessels (1.07% and 1.01%, respectively).

Hendricks et al.[6] found a significant correlation between pressure gradient and flow reduction. Of the DPDs they tested (Angioguard, FilterWire EZ, RX Accunet, and Spider RX), Angioguard had the greatest pressure gradient and Spider RX the smallest, which is in agreement with our findings. However, we have also found that FilterWire EZ (and not RX Accunet) had the smallest normalized pressure gradient of all of the polyurethane membrane filters tested. This discrepancy is likely due to the different behavior exhibited by the devices in a patient-based carotid phantom model with a 70% stenosis in comparison to a single straight silicone tube with constant cross section. The bifurcation and change in cross section due to a stenosis both affect how the flow diverts, altering the pressure and flow rate in the ICA.

In this investigation, we propose the use of vascular resistance as a filter performance assessment variable and key engineering design parameter for DPDs. Its usefulness is intrinsic in the simultaneous estimation of pressure gradient and flow rate in the ICA, which are fluid flow parameters affected by the deployment of DPDs and the capture of emboli. The computation of vascular resistance shows the benefits of designing filters with deep baskets and interstitial spaces distributed along the entire surface of the basket. Filters with small baskets (e.g., Angioguard XP), small pores (e.g., Angioguard XP), and cage-like structures preceding the porous membrane (e.g., RX Accunet and Emboshield) lead to high flow resistance and ''slow-flow'' conditions distal to the filter, which may compromise distal perfusion to the cerebrovascular vessels in vivo and increase the likelihood of stroke during CAS.

DPD Performance in Clinical Trials

The SAPPHIRE trial found that the rate of death, stroke, and myocardial infarction was 7.9% lower in patients who underwent CAS with distal protection (Angioguard or Angioguard XP) than in patients who underwent CEA.[25] The ARCHeR (Acculink for Revascularization of Carotids in High-Risk patients) trial was based on 3 sequential nonrandomized multicenter studies that enrolled 534 patients.[26] The hypothesis tested was the noninferiority of the composite endpoint events (death, stroke, and myocardial infarction within 30 days of the intervention and ipsilateral strokes between days 31 and 365). The final 2 studies, which used the RX Accunet embolic protection system in conjunction with the Acculink carotid stent, enrolled a total of 422 patients. The ARCHeR trial found that the use of RX Accunet decreased the rate of adverse events from 10.2% to 8.3% compared to stenting without distal protection.

The EVA-3S (Endarterectomy Versus Angioplasty in Severe carotid Stenosis Study) trial evaluated whether CAS with or without protection is as safe and effective as CEA.[27] The primary endpoints were the death and stroke rate within 30 days of the procedure and long-term ipsilateral stroke risk. The distal protection devices used in the study were GuardWire, Emboshield, FilterWire EX, and Angioguard XP. The EVA-3S investigators ended the part of the study evaluating protected and unprotected CAS since patients who underwent unprotected CAS had a 3.9 times higher stroke rate within 30 days of the

intervention than patients who underwent protected CAS.

All 3 studies indicate that the use of DPDs during CAS is beneficial to patient outcome. The inclusion of myocardial infarction in SAPPHIRE and ARCHeR can make comparison with these studies difficult. However, SAPPHIRE shows that Angioguard and Angioguard XP improved the outcome of CAS more than RX Accunet did in the ARCHeR trial, while we have found that Angioguard XP missed more emboli than RX Accunet. Both devices also had large effects on the pressure gradient and volume flow rate fraction in the ICA.

Limitations

The use of a constant flow rate instead of pulsatile flow limits the performance of the DPDs under physiologically realistic conditions. Pulsatile flow causes particles to enter and exit the basket periodically, possibly affecting performance of the device over time.

A silicone carotid bifurcation model does not exhibit the same soft tissue mechanics as a human carotid artery, including the coefficient of friction between the vessel wall and the basket of the device, which in addition to the use of glycerol in a blood-mimicking solution may explain the observed distal migration of Emboshield. Moreover, endothelial damage and spasm due to device deployment cannot be observed in synthetic flow models.

Vascular resistance in the ICA was calculated with pressure gradient and flow rate as dependent variables. The deployment of the device and the filter basket filling with particles affected both the pressure gradient and flow rate in the ICA. Setting either the pressure gradient or flow rate as an independent variable would be a more accurate measure of vascular resistance. The data obtained in this investigation should be extrapolated to clinical situations with great caution.

Conclusion

In addition to capture efficiency, other important design considerations relative to distal protection devices are the effects on flow variables, such as pressure and volume flow rate. One concern about the efficacy of DPDs is the potential for incomplete wall apposition of the filter basket against the vessel wall. By injecting particles having a diameter larger than the pore size of the devices, we have conjectured that the only means by which distal embolization can occur is by particles passing between the filter basket and the vessel wall. Spider RX, missing 0.06% of particles after injection, is inferred to have the best wall apposition of the 5 devices tested. Spider RX disrupted the flow in the ICA the least, having the smallest vascular resistance, pressure gradient, and decrease in flow rate. Spider RX yielded the best overall performance when tested with 300-μm particles. However, when tested with the same sized particles as the other devices (200 μm), Spider RX had a significantly less desirable capture efficiency ($p>0.05$). For 200-μm particles, FilterWire EZ had the best capture efficiency, missing the fewest particles after injection and losing the fewest particles during retrieval. Emboshield and Angioguard XP both had high percentages of particles missed after injection, greatly increasing the pressure gradient and decreasing flow rate in the ICA. RX Accunet increased the vascular resistance and decreased the flow rate in the ICA the most in the full filter condition. Our findings could be extrapolated to the clinical setting to help vascular interventionists better assess the device they are using. Future generations of embolic protection filters will likely benefit from having deep baskets with variable sized pores distributed along the entire filtering surface. Engineering design characteristics with a negative impact on filter performance include shallow baskets and cage-like structures preceding and obstructing entry to the filtering membrane.

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