◆ EXPERIMENTAL INVESTIGATION ◆

In Vitro Performance Assessment of Distal Protection Filters: Pulsatile Flow Conditions

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Purpose: To evaluate in vitro the capture efficiency of a distal protection filter (DPF) used during carotid artery stenting and examine the longitudinal vascular impedance in the presence of a DPF.

Methods: Four approved DPFs (Spider RX, FilterWire EZ, RX Accunet, and FiberNet) were evaluated in a physiologically realistic in vitro setup. A pulsatile programmable piston pump circulated a blood analog at a time-varying flow rate representative of the human common carotid artery. A silicone carotid bifurcation having average human dimensions was used for the carotid flow model. Microspheres ranging from 40 to 900 μm were injected to simulate embolization. The longitudinal vascular impedance was calculated as the ratio of the time-varying pressure gradient across the DPF to the time-varying flow rate in the internal carotid artery.

Results: RX Accunet had the highest capture efficiency (99.4%) and Spider RX the lowest (78.1%). Spider RX increased the longitudinal vascular impedance the least after deployment (+23%), while FilterWire EZ increased the longitudinal vascular impedance the least after particles were injected (+29%). FiberNet increased longitudinal vascular impedance the most (+84%).

Conclusion: This investigation, unique for examining the effects of physiologically realistic pulsatile flow on DPF performance, can aid in the development of future generations of novel DPFs.

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Key words: in vitro study, carotid artery stenting, distal protection, embolic protection device, filter, pulsatile flow, vascular impedance
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Carotid artery stenting (CAS) is an endovascular treatment for occlusive carotid artery disease for high-surgical-risk candidates with symptomatic stenosis $>70\%$.¹ The surgical

counterpart, carotid endarterectomy (CEA), has proved to be an effective treatment in the same clinical setting.² The incidence of occlusive carotid artery disease has not been

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	Spider RX	FilterWire EZ	RX Accunet	FiberNet
Picture
Material	Nitinol mesh	Nitinol frame / polyurethane membrane	Nitinol frame / polyurethane membrane	Polymer fibers
Pore size, μm	70–200	110	up to 150	down to 40

Figure 1 ♦ Four DPFs tested in vitro: Spider RX, FilterWire EZ, RX Accunet, FiberNet.

reported, but ~50% of strokes occur due to embolization that originated at the carotid bifurcation.¹ Approximately 1 million stroke-related deaths occur each year, making it the third leading cause of death in the United States.¹

Controversy remains regarding the safety and efficacy of CAS due to the risk of generating embolic debris. Cerebral protection devices, such as distal protection filters (DPFs), were developed to protect distal vascular beds from being occluded by plaque particulate. Evidence supporting the safety and efficacy of CAS with DPFs is still ambiguous due to conflicting results from prospective clinical trials and retrospective record reviews. Several studies have found that protected CAS improved patient outcome.^{3–5} In the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial, the unprotected CAS leg of the trial was ended prematurely due to a 30-day stroke rate nearly 4 times that of protected CAS, suggesting that protected CAS yields favorable outcomes compared to unprotected CAS.⁶ Other studies have shown no reduction in embolic lesions with the use of protection,⁷ while others have shown an increase in embolic showers.⁸

Numerous *ex vivo*^{9,10} and *in vitro*^{11–18} studies have investigated the effects of DPFs on pressure and flow rate or evaluated the efficacy of DPFs under steady flow conditions. It is likely that pulsatile flow will alter the performance of DPFs. In particular, we expect that, *in vivo*, flow pulsatility will give plaque emboli the potential to enter and exit the basket during the cardiac cycle and/or yield

local expansions and contractions of the ICA, adversely affecting device apposition and capture efficiency. The objective of this investigation was to evaluate the effect of pulsatile flow on the capture efficiency, pressure, and flow rate in the carotid artery with four DPFs approved by the Food and Drug Administration. The integration of pulsatile flow into the experimental setup yields more physiologically realistic testing conditions. To the best of our knowledge, no other study has examined the effects of pulsatile flow on DPF performance in bench-top experiments.

METHODS

Four DPFs were evaluated (Fig. 1): Spider RX (ev3, Plymouth, MN, USA), FilterWire EZ (Boston Scientific, Natick, MA, USA), RX Accunet (Abbott Vascular, Abbott Park, IL, USA), and FiberNet (Lumen Biomedical, Plymouth, MN, USA). Spider RX, FilterWire EZ, and RX Accunet have been described previously.^{17,18} FiberNet is composed of polymer fibers arranged such that it can filter emboli in 3 dimensions; the density of the fibers allows for filtration of particulate as small as 40 μm .

The *in vitro* bench-top flow apparatus described previously^{11,17,18} was updated for pulsatile flow (Fig. 2A). The CompuFlow 1000 (Shelley Medical Imaging Technologies, London, Ontario, Canada), a programmable piston pump,¹⁹ was used to output a pulsatile flow rate typical of the human common carotid artery (CCA).²⁰ The waveform had a period of 0.92 seconds and an average flow rate of 360 mL/min. The carotid flow model

Figure 2 ♦ (A) Schematic diagram of the experimental flow apparatus, (B) carotid flow model, and (C) flow rate in the common carotid artery (CCA).²⁰

had average human dimensions and a 70% asymmetrical stenosis (Fig. 2B) at the inlet of the internal carotid artery (ICA).²¹ A blood analog consisting of 60% glycerol and 40% deionized water ($\mu=4.1$ cP) was circulated. Electromagnetic flow meters (Seametrics Inc., Kent, WA, USA) and pressure transducers (Honeywell Sensotec, Columbus, OH, USA) were located proximal and distal to the flow model to measure flow rate and pressure at the CCA, ICA, and external carotid artery (ECA). Pressure valves (Omega Engineering, Stamford, CT, USA) located distal to the flow model maintained an average CCA pressure of 59 mmHg. The reservoir was open to the atmosphere and elevated 22 cm to prevent the reservoir inside the CompuFlow 1000

from emptying. Although rigid polyvinyl chloride (PVC) braided tubing was used, damping created a discrepancy between the programmed waveform and the flow rate measured by the CCA flow meter. A trial and error process was used to alter the programmed waveform to obtain the desired output measured at the CCA flow meter. Short sections of more compliant Tygon tubing were used to bridge the compliant silicone carotid model and the rigid PVC tubing to reduce wave reflections due to impedance mismatches.

The particulate generated during CAS²² and in saphenous vein grafts²³ using distal balloon occlusion were used as the clinical reference for determining the number and

TABLE 1

Particle Distributions of Previous Clinical Studies Compared to the Current Investigation

Carotid Artery Stenting ²²		Saphenous Vein Grafts ²³		Current Study	
Particle Size Range, μm	Number of Particles	Particle Size Range, μm	Number of Particles	Particle Size Range, μm	Number of Particles
≤ 50	33	40–120	58	40–120	58
100–300	45	100–300	10		
300–500	9	300–500	2	300–500	9
500–700	5	500–700	2		
700–900	5	700–900	4	700–900	5
900–1100	4				
≥ 1100	3				
Totals	104		76		72

size of microspheres injected in the CCA to simulate embolization (Table 1). Polyvinyl alcohol microspheres were used (Biosphere Medical, Rockland, MA, USA), ranging from 40 to 900 μm in diameter; the 72 microspheres were divided into 3 non-overlapping size ranges (small: 40–120 μm , medium: 300–500 μm , and large: 700–900 μm). The microspheres were suspended in 15 mL of 0.9% saline. Inline polyurethane mesh filters (Qosina, Edgewood, NY, USA) were used to capture microspheres distal to the carotid flow model missed by the DPF in the ICA and microspheres that traveled through the ECA.

The waveform period resulted in a cardiac cycle rate of 65 bpm. A data acquisition card and custom LabVIEW program (National Instruments Co., Austin, TX, USA) recorded data at a rate of 100 Hz for 92 seconds, yielding ~ 100 cardiac cycles of data. Data acquisition was gated with a transistor-transistor logic pulse output from the CompuFlow 1000 at the beginning of each cardiac cycle. Pressure and flow rates were measured before DPF deployment [initial condition (IC)], after DPF deployment [empty filter condition (EF)], and after particle injection [full filter condition (FF)]. Ten trials of the experiment were repeated for each DPF.

Power spectrum analysis and the root mean square error were calculated to compare the desired waveform from Holdsworth et al.²⁰ (Fig. 2C) and the measured flow rate at the CCA. The root mean square error was 158 mL/min, representing 11% averaged over the cardiac cycle. The average measured CCA flow rate in IC was 400 mL/min. Although the

accuracy in reproducing the waveform could have been improved by using a “closed” flow loop, i.e., removing the external reservoir open to the atmosphere, this would have altered the particle filtration method and increased the pressure in the system unrealistically. Thus, a reservoir open to the atmosphere was used.

Efficiency Measures, Vascular Impedance, and Statistical Analyses

The number and size of particles were determined among those missed by the DPFs, embolized in the ECA, and remaining in the syringe. Capture efficiency was calculated based on the injected particle suspension and the number of particles missed by the DPF, as shown in Equation 1.

Capture efficiency =

$$100 - \left[\frac{\text{Particles Missed by DPF}}{\text{Total Particles} - \text{Particles in ECA} - \text{Particles Left in Syringe}} \right] \cdot 100 \quad (1)$$

Thus, the most desirable capture efficiency was 100%. Longitudinal vascular impedance was calculated as the ratio of the time-varying pressure gradient to the time-varying flow rate in the ICA:

$$Z_L(t) = \frac{P_{CCA}(t) - P_{ICA}(t)}{Q_{ICA}(t)}, \quad (2)$$

where $Z_L(t)$ is the longitudinal vascular impedance, $P(t)$ is the time-varying pressure, and $Q(t)$ is the time-varying flow rate.²⁴ Longitudinal

TABLE 2
Mean Missed Particles by Size* and Capture Efficiency of 4 Distal Protection Filters in 10 Tests

	Small	Medium	Large	Capture Efficiency
Spider RX	14.6±3.7	0.2±0.4	0.0±0.0	78.1%†
FilterWire EZ	1.3±1.8	0.1±0.3	0.0±0.0	98.1%
RX Accunet	0.2±0.6	0.2±0.6	0.0±0.0	99.4%
FiberNet	3.6±4.6	0.4±1.0	0.0±0.0	94.2%

Continuous data are presented as means ± standard deviation.

* Small: 40–120 µm, medium: 300–500 µm, and large: 700–900 µm.

† P<0.0005 by ANOVA.

vascular impedance was chosen to have a single measure of pressure and a flow rate representing the resistance to blood flow along an arterial segment under pulsatile flow conditions. The longitudinal vascular impedance was calculated for all 4 DPFs at the 3 aforementioned conditions (IC, EF, and FF). The mean EF and FF values for each DPF were compared to the mean IC rate and expressed as a percentage increase (+) or decrease (–).

Data are presented as the mean ± standard deviation. A 1-way analysis of variance (ANOVA) was used to compare the mean capture efficiencies among the DPFs; Tukey's pairwise comparison was applied with a family confidence interval of 95% to identify any specific differences. Statistical analyses were performed using Minitab (version 15; Minitab Inc., State College, PA, USA). P<0.05 was considered significant.

RESULTS

RX Accunet had the highest capture efficiency (99.4%) and Spider RX had the lowest (78.1%; Table 2). Spider RX missed the largest average number of small particles (14.6) and RX Accunet missed the fewest small particles (0.2). All 4 DPFs missed a similar average number of medium sized particles (range 0.1–0.4). All DPFs captured all large particles. ANOVA indicated a significant difference in the mean capture efficiency rates among the DPFs ($p<0.0005$, $F_3=40.55$); Tukey's pairwise comparison identified the Spider RX as statistically different from the other DPFs at the 0.05 level. The capture efficiencies of the remaining 3 DPF were not statistically different from each other.

The gated pressure and flow rate data were filtered and averaged to derive representative

waveforms (Fig. 3). The average pressure gradient ($P_{CCA}-P_{ICA}$) was 16.5 mmHg and the average flow rate in the ICA was 157 mL/min in IC. The longitudinal vascular impedance was calculated by using the average pressure and flow rate for all DPFs at IC, EF, and FF. Although the peak EF longitudinal vascular impedance of RX Accunet appeared to be greater than the peak FF, the time-average impedance indicated the opposite was true (Table 3). All values of longitudinal vascular impedance increased for each successive phase: FF was greater than EF, which in turn was greater than IC. An increase in longitudinal vascular impedance indicated an increase in pressure gradient and decrease in flow rate. Spider RX had the smallest increase in longitudinal vascular impedance in EF (7.77 mmHg/mL/s, +23% increase from IC), closely followed by FilterWire EZ (7.94 mmHg/mL/s, +26% increase). The longitudinal vascular impedances of Spider RX and FilterWire EZ in FF were very similar (8.26 mmHg/mL/s, +31%; 8.17 mmHg/mL/s, +29%, respectively). FiberNet had the largest increase in longitudinal vascular impedance for both EF and FF [10.5 (+66% increase) and 11.6 (+84% increase) mmHg/mL/s, respectively]. RX Accunet, which had the highest capture efficiency, yielded the second highest increase in longitudinal vascular impedance for both EF and FF [9.29 (+47% increase) and 9.82 (+56% increase) mmHg/mL/s, respectively].

DISCUSSION

The current in vitro study evaluates the capture efficiency and longitudinal vascular impedance of 4 DPFs in current clinical use. Previous in vitro investigations conducted in

Figure 3 ♦ Longitudinal vascular impedance of DPFs in initial condition (IC), empty filter (EF), and full filter (FF): (A) Spider RX, (B) FilterWire EZ, (C) RX Accunet, and (D) FiberNet.

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TABLE 3

ICA Longitudinal Vascular Impedance in Empty Filter and Full Filter Conditions

	ICA Longitudinal Vascular Impedance, mmHg/mL/s	
	Empty Filter	Full Filter
Spider RX	7.77 (+23%)	8.26 (+31%)
FilterWire EZ	7.94 (+26%)	8.17 (+29%)
RX Accunet	9.29 (+47%)	9.82 (+56%)
FiberNet	10.5 (+66%)	11.6 (+84%)

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Data are presented as the mean and in parenthesis the percentage increase relative to the initial condition (IC) mean of 6.31 mmHg/mL/s.

our laboratory^{11,17,18} found that DPFs have a remarkable ability to capture particles larger than the basket pore size. Results from the present work corroborate these findings. In a study using microspheres ranging from 297 to 1000 μm , FilterWire EZ obtained a capture efficiency of 99.4% and 99.8% for RX Accunet in a 5.5-mm inner diameter tube.¹¹ The capture efficiency rates of FilterWire EZ and RX Accunet were 96.1% and 95.1%, respectively, in a study using 200- μm particles, while Spider RX had a capture efficiency of 99.9% using 300- μm microspheres.¹⁷ Intuitively, as the mass of particulate injected increased, the capture efficiency decreased.¹⁸ One study conducted in our laboratory investigated the

capture efficiency of RX Accunet in a patient-specific carotid model with microspheres $>200\text{ }\mu\text{m}$, approximately equal to ($116\text{ }\mu\text{m}$) and smaller than (combination of 49, 116, and $200\text{ }\mu\text{m}$) the pore size of the device.^{25,26} The capture efficiency of RX Accunet diminished for each successive category of microspheres: 98.9% for $200\text{ }\mu\text{m}$, 98.1% for $116\text{ }\mu\text{m}$, and 97.7% for 49/116/200 μm .

Müller-Hülsbeck et al.^{13–16} conducted in vitro studies on the ability of DPFs to capture both microspheres and human plaque.^{13–16} All particulates were larger than the pore size of the DPF, and the capture efficiencies obtained were similar to our previous investigations using steady flow conditions.

To our knowledge, the longitudinal vascular impedance induced by a DPF has not been quantified. Previous studies have looked at the pressure gradient¹² and vascular resistance^{17,18} in the ICA in the presence of a DPF. In a single-tube setup, Hendriks et al.¹² evaluated 4 DPFs at an input pressure of 70 mmHg and 200 mL/min. The smallest pressure gradient was caused by Spider RX (1.65 mmHg), followed by RX Accunet (3.90 mmHg) and FilterWire EZ (7.95 mmHg). Siewiorek et al.¹⁷ evaluated the increase in vascular resistance due to the injection of 5 mg of microspheres, finding percentages of +10.1% for Spider RX, +20.5% for FilterWire EZ and +40.6% for RX Accunet. Vascular resistance increased concomitantly with the mass of particulate.¹⁸ Our present findings with pulsatile flow conditions agree with these studies.

Powalowski and Pensko²⁷ used Doppler ultrasound to measure the instantaneous blood velocity and vessel wall movement and calculated the input impedance of the CCA in 10 human subjects. Input impedance is the ratio of time-varying pressure to time-varying flow rate measured at a single site, which takes into account the properties of all vessels in the distal vascular bed.²⁴ For comparison, the DC value of the fast Fourier transform of the input impedance modulus for a 25-year-old man was $16.52 \times 10^{-3}\text{ g/cm}^4 \cdot \text{s}$ (22 mmHg/mL/s), while we have calculated the longitudinal vascular impedance in the time domain as 6.31 mmHg/mL/s in IC.

Recently, Rapp et al.²⁸ described “pulsatile” flow conditions on 33 ex vivo carotid plaque specimens excised en bloc during CEA and subjected to angioplasty by 4- and 6-mm balloons. “Pulsatile” flow was simulated by 5 hand injections of 10 mL of saline. The DPFs tested (Spider RX, FilterWire EZ, RX Accunet, Emboshield, and Angioguard) captured an average of 22% of the particulates embolized. Henry et al.²⁹ reported that no stroke or death occurred 30 days after the stenting of 35 plaque lesions in 34 patients using protected CAS with the FiberNet device. The mean surface area of particulates captured by the DPF was 63.8 mm^2 compared to a mean surface area of 12.2 mm^2 for other DPFs (FilterWire EZ, RX Accunet, Emboshield, and Angioguard).

Henry et al.²⁹ described the FiberNet device as being able to filter plaque particles as small as $40\text{ }\mu\text{m}$ without compromising blood flow. However, our investigation found that the device did not capture all the small microspheres and increased the longitudinal vascular impedance the most. The experimental protocol used in the present work is a potential explanation: particle injection could have forced particles through the DPF’s fibers. Care was taken to inject the particles as slowly and smoothly as possible. In addition, the choice of a blood analog can explain the increase in longitudinal vascular impedance obtained for FiberNet in EF and FF conditions. Most blood analog solutions are composed of a viscous liquid, such as glycerol or diethyl phthalate, and a less viscous liquid, such as water or ethanol, to obtain the desired viscosity. It is possible the glycerol adhered to the polymer fibers of FiberNet, increasing the longitudinal vascular impedance in the ICA. Testing this device with a 0.9% v/v saline solution yielded smaller increases in vascular impedance, while not representative of the average viscous properties of whole blood.

Conclusion

This investigation evaluated the performance of 4 DPFs in a pulsatile flow apparatus. We conjecture that FilterWire EZ, RX Accunet, and FiberNet may provide the best in vivo

performance in capturing dislodged embolic material from the atherosclerotic carotid bifurcation based on having statistically similar capture efficiency rates. Conversely, Spider RX may be best in maintaining the local in vivo flow conditions in the cerebral vasculature due to having the smallest effect on ICA vascular impedance in EF conditions. However, it should be noted that the brain's tolerance for small plaque emboli ($<100\ \mu\text{m}$) is unknown. Thus, it is possible that the best functionality of a DPF is to capture medium- and large-sized emboli, thus preventing major stroke-related neurological events, while maintaining flow in the intracranial circulation. The results from this study can aid in the development of future generations of novel cerebral protection devices while also providing a framework for testing DPFs under physiologically realistic flow conditions.

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