IN VITRO AND IN SILICO STUDY OF INTRACRANIAL STENT TREATMENTS FOR CEREBRAL ANEURYSMS: EFFECTS ON PERFORATING VESSEL FLOWS

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ABSTRACT

Background: Many cerebral aneurysms can be treated effectively with intracranial stents. Unfortunately, stents can occlude perforating vessels near the treatment site, which can decrease cerebral perfusion and increase risk of stroke.

Methods: In this study, we use particle image velocimetry to investigate the effects that intracranial stents have on flows in perforators near a treated aneurysm. In Phase 1 of the study, different stent configurations were deployed into an idealized physical model of a sidewall aneurysm with perforating vessels. The configurations investigated were the Pipeline embolization device (PED) and one, two, and three telescoping Neuroform stents. In Phase 2 of the study, a single Neuroform stent was deployed such that stent struts directly occluded the perforating vessel.

Results: In Phase 1 of the study it was found that even three telescoping stents affected perforating vessel flow less (32.7% reduction average) than a single PED (46.5% reduction average) under pulsatile conditions. Results from Phase 2 indicated that the location of the occluding strut across the perforating vessel orifice had a greater impact on perforating vessel flow than the percentage occlusion.

Conclusion: The findings of this study show that the use, configuration, and positioning of intracranial stents can all have considerable influence on flow in affected perforating vessels near treated cerebral aneurysms.
INTRODUCTION

Cerebral aneurysms occur in an estimated 6% of the world’s population[1]. When they rupture, cerebral aneurysms are lethal nearly 50% of the time[2]. Accordingly, treatments that prevent rupture, by eliminating flow into and out of the aneurysmal sac, are critically important to global health. Endovascular treatments such as coil embolization have been used more frequently in recent years, not only because they are less invasive than surgical techniques, but also because they are more effective[3-5]. Unfortunately, recurrence rates for large aneurysms can be as high as 50% after embolic coling[6]. Such frequent recurrence demonstrates a clear need for improved coil embolization techniques and/or for other endovascular approaches to cerebral aneurysm treatment.

One way to improve coil embolization is to use a stent as a support structure for deployed coils. In fact, expanded clinical use of stent-assisted coiling has led to markedly decreased aneurysmal recurrence over the past decade, especially for wide-neck aneurysms[7]. As new and improved designs are being developed, one characteristic that is critically important in most, if not all, applications of stents is porosity (defined as the fraction of metal free area per total surface area covered by a stent). The porosity of a stent directly affects the amount of flow that enters an aneurysm or perforating vessel covered by the stent. Studies have found that lower-porosity stents lead to greater flow reductions within aneurysms[8,9]. To reduce stent porosity across the aneurysm (using high-porosity flexible stents), many clinicians use a stent-within-a-stent technique or “telescoping.” Telescoping comprises the sequential deployment of additional high-porosity stents inside of an initial high-porosity stent in order to increase metal coverage at the aneurysm and thereby reduce effective porosity. Low-porosity stents have been found safe for
clinical use[10]; however, understanding of the specific hemodynamics they affect is limited[11]. Further, there is well-justified clinical concern that low-porosity stents may decrease cerebral perfusion and increase risk of stroke when they are deployed across perforating vessels in the brain[12]. An image showing the deployment of a stent across an aneurysm is presented in Figure 1.

Since FDA approval in 2010, the low-porosity Pipeline embolization device (PED) has been used regularly to treat cerebral aneurysms, which has stimulated considerable interest in the clinical community[13]. Interest in the device stems from its potential to regulate aneurysmal fluid dynamics, thereby facilitating thrombus formation, vascular remodeling, and aneurysmal elimination. An important related question is, can similar treatment effects be achieved by telescoping-higher porosity stents until a lower effective porosity is achieved? Further, what levels of decreased perfusions can result, in either case, when low-porosity perforating vessel coverage results near the treatment site? This study presents experimental and simulated data that address both questions.

Experimentation and simulation have both been used before to examine fluid dynamics in cerebral aneurysm models treated with intracranial stents. However, previous studies dealing with multiple stent deployments have focused almost exclusively on flow within aneurysms[14-16]. In contrast, the primary focus of this study is flow in perforating vessels. Stereo particle image velocimetry (PIV) is used to quantify flows in an idealized perforating vessel (and aneurysm) before and after different intracranial stent treatments. In Phase 1 of the study, global effects of the PED and one, two, and three telescoping Neuroform stents are examined
experimentally and compared. In Phase 2 of the study, more detailed, local flow effects of stent strut placement at the perforating vessel orifice are analyzed both experimentally and with computational fluid dynamics (CFD).

MATERIALS AND METHODS

Modeling:

An idealized model of a sidewall aneurysm and perforator vessels was designed based on in vivo angiographic images. A computational model of the geometry was developed in SolidWorks (SolidWorks, Concord, MA, USA), with a parent vessel diameter of 3.0 mm and an upstream perforating vessel diameter of 1.2 mm (to simulate the ophthalmic choroidal artery), as shown in Figure 2. The computational model was used to create a physical core model of pot metal utilizing computer numerical controlled cutting. Sylgard 184® silicon elastomere (Dow Corning, Midland, MI, USA) was molded around the metal core model, which was then melted out, leaving an optically clear model to be used for experiments.

Device Deployment:

This study was performed in two phases. Phase 1 examined four different stent treatments: sequential telescoping of low-porosity Neuroform stents (Stryker, Freemont, CA) across the aneurysm (one, two, and three high-porosity stents) and deployment of a single PED (Chestnut Medical, Menlo Park, CA). An untreated case was also run for comparison. Each stent was placed across the aneurysm and perforator vessel, as shown in Figure 2. Phase 2 of the study examined four different deployments across the perforator vessel. Photos taken looking up the perforator vessel (down-the-barrel view) from the parent vessel of the model were used to
quantitatively assess stent strut placements as shown in Figure 2. For each deployment, the location of the center of mass of the stent strut was calculated as a percentage from the upstream edge of the vessel, where 100% corresponded to the downstream edge. MATLAB was used to determine the percent coverage of each placement by calculating the percentage of pixels at the orifice of the perforator that were covered by the strut. The percent coverage was then determined by dividing the number of pixels of the strut by the total number pixels of the perforator vessel. The stent deployments investigated were: (A) untreated, (B) a stent located 100% downstream with an occlusion of 0%, (C) a stent located 50% downstream with an occlusion of 26%, and (D) a stent located 25% downstream with an occlusion of 7%. Deployment parameters and images for Phase 2 of the study are presented in Table 1.

**Particle Image Velocimetry:**

During experiments the model was attached to flexible polyvinyl chloride tubing and connected to a Compuflow 1000 piston pump (Shelley Medical, Toronto, ON, Canada). Pulsatile flow conditions, employing a vertebral flow waveform, were examined at four flow rates (3, 4, 5, and 6 m1/s), to simulate a physiologic range of normal and diseased conditions[17]. The blood analog solution was comprised of water, aqueous sodium iodide, and glycerol and maintained a refractive index of 1.43, the same as that of Sylgard 184®, and a viscosity of 3.16 cP.

PIV was performed using a Flowmaster 3D stereo PIV system (LaVision, Ypsilanti, MI, USA), which included a Solo PIV III dual cavity pulsed YAG laser with a 532 nm wavelength (New Wave Research, Fremont, CA, USA) and two Imager Intense cross-correlation CCD cameras. The working fluid was seeded with 8 µm fluorescent particles (Thermo Scientific, Waltham,
MA, USA), which were illuminated with a 0.5 mm thick laser sheet. Low-pass optical filters with a 572 nm cutoff (Omega Optical, Brattle Bro, VT, USA) were installed on the cameras to allow the particles to be imaged despite laser reflections from the stent.

Two hundred image pairs were acquired across a single plane taken at the center of the aneurysm and perforator. From the acquired images, velocity vectors were calculated using a cross-correlation algorithm within DaVis software (Lavision, Ypsilanti, MI, USA). The velocity vectors were averaged over the 200 image pairs to form a single velocity flow field for each flow rate. The root-mean-squared velocity magnitude \( (V_{RMS}) \) was then calculated within the aneurysm and within the perforator. The equation used was as follows:

\[
V_{rms} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} |V_i|^2}
\]

where \( n \) is the number of data points within the aneurysm or perforator vessel and \( V_i \) is the flow velocity magnitude at point \( i \). The use of this equation for PIV is explained fully in Babiker et al.[18]. For the aneurysm, \( V_{RMS} \) represents the overall velocity magnitude within the aneurysmal volume, where a reduction in velocity magnitude is analogous to a reduction in overall fluid dynamic activity within the aneurysm. For the perforator vessel, \( V_{RMS} \) is proportional to velocity magnitude along the vessel axis (which is proportional to volume flow rate). This means that a reduction in \( V_{RMS} \) across the perforator domain corresponds to a reduction in flow through the perforator vessel.

**Computational Fluid Dynamics:**
CFD simulations were also conducted to investigate the effects of strut placement on perforator flow (by varying the placement of a Neuroform stent strut across the perforator orifice). The Neuroform strut was approximated as 40 µm thick bar. The strut was created in ANSYS ICEM 12.1 software (ANSYS, Inc., Canonsburg, PA, USA). The strut was placed across the perforator orifice (perpendicular to the flow direction) in the computational model, at 20, 40, 60, and 80% downstream from the upstream edge. The computational geometries of the strut and perforator vessel were meshed using ANSYS ICEM 12.1 software. A mesh density function was prescribed near the volume around the stent struts. The OCTREE method was then used to generate approximately 3,300,000 tetrahedral mesh elements (corresponding to 560,000 nodes) for the vessel lumen and strut volume in each stent placement case. CFD simulations were conducted in ANSYS Fluent 12.1 software (ANSYS Fluent, Inc., Lebanon, NH, USA). The vessel walls and strut volume were assumed to be rigid, and a no-slip boundary condition was imposed at the boundaries of the vessel and strut walls. The fluid volume was approximated as an incompressible fluid with the same viscosity and density as the blood analog solution used in in vitro experiments. Steady laminar flow profiles with 3 ml/s flow rates were prescribed at the inlets and zero pressure boundary conditions were prescribed at the outlets. Fluid dynamic simulations were conducted using a second-order upwind scheme for momentum and the SIMPLE algorithm was used to define the pressure-velocity coupling.

RESULTS

Effects of Stents on Aneurysmal Flows:
Results are presented in this section in Figure 3 as line graphs comparing the percentage reduction in $V_{RMS}$ within the aneurysm, or within the perforator, to the untreated case. With high-
porosity stents, fluid dynamic activity within the aneurysm was reduced after each sequential stent deployment. The greatest percentage reductions were observed after the first and third stent deployments, with an average of 24% reduction after the 1st deployment and an additional 36% reduction after the 3rd deployment. Reductions between the first and second stent placement were lower, with an average 7% reduction. The PED led to reductions comparable to those for two and three sequentially placed stents: an average of 54% total reduction was observed for the PED.

**Effects of Stents on Perforator Flows:**

$V_{RMS}$ in the perforator vessels followed similar trends in comparison to aneurysmal $V_{RMS}$ after telescoping stent treatment. As shown in Figure 3, the placement of each stent across the upstream vessel led to greater $V_{RMS}$ reductions in each case. In contrast to the aneurysmal data, perforator $V_{RMS}$ reductions were more consistent with each stent placement, ranging between 10 and 20% for most cases. The PED led to the greatest $V_{RMS}$ reductions of any treatment, with an average of 47%.

**Effects of Stent Strut Placement on Perforator Flows:**

Figure 4 illustrates the $V_{RMS}$ through the perforator vessel for each case investigated, as well as percentage changes from the untreated case. Occlusion by the stent (deployments C and D) led to a reduction in perforator $V_{RMS}$. Deployment B (100% downstream, 0% occlusion), led to an increase in perforator $V_{RMS}$ as compared to the untreated case. With one exception at the 3 ml/s parent vessel flow rate, results showed that deployment D (25% downstream, 7% occlusion) led to greater perforator $V_{RMS}$ reductions as compared to deployment C (50% downstream, 26% occlusion).
DISCUSSION

Intracranial stents have been proven to help reduce flow into cerebral aneurysms and successfully occlude them from circulation[7]. However, an unfortunate consequence of treatment with stents is decreased perforating vessel flow. The results presented in this study show that stent placement reduces flow through perforator vessels. Further, the porosity of the stent configuration, the type of stent used, and the placement of the stent struts all affect flow through the perforator.

Effects of Stents on Aneurysmal Flows:

The changes in fluid dynamic activity observed within the aneurysm were in agreement with previous studies that examined multistent placements. Specifically, a PIV study by Canton et al. concluded that sequential placement of stents led to a decrease in fluid dynamic elements that may lead to rupture, including vorticity strength and wall shear stresses[14]. Our results agree, showing that there was a reduction in the $V_{RMS}$ within the aneurysm. The non-linear pattern in the flow reduction found with sequential stent placement was also consistent with previous studies[14,16]. The differences in $V_{RMS}$ reductions after each stent placement may also relate to the alignment of the respective stents’ struts. Because the alignment of the struts was not specifically regulated (except to ensure the struts were not perfectly overlapped along the long axis), the positioning of the struts within the telescoping configuration may have influenced the fluid dynamic activity within the aneurysm. Specifically, differences in relative strut position could lead to local flow effects near the aneurysmal entrance that effect changes in aneurysmal fluid dynamic activity.
The PED led to $V_{RMS}$ reductions comparable to those for multistent deployments, indicating that it reduced fluid dynamic activity within the aneurysm more effectively by itself. This finding agrees with a review of the PED wherein the device was most effective at reducing mass effect as a standalone device than high porosity flow diverters[19]. A more comprehensive study of the PED and telescoping stents is currently underway; however, observations from this study provide a useful starting point for comparison. While observing fluid dynamic activity within the aneurysm was not the main goal of this study, the agreement of our findings with previous studies indicates that our experiments represent aneurysmal fluid dynamic activity accurately, which in turn supports the results we observed in perforator vessels.

**Effects of Stents on Perforator Flows:**

$V_{RMS}$ reductions across the perforator vessel domains with sequential telescoping stent placement was consistent with observations from the aneurysm. However, while reductions in $V_{RMS}$ contribute to aneurysmal occlusion, for the perforator vessels, similar $V_{RMS}$ reductions may lead to inadequate circulation or even to occlusion of vessels. While clinical studies have shown that, in general, the use of intracranial stents is safe, these studies focused on single stent placements[10]. Our results agree with previous *in vitro* studies that found high-porosity stents to have a flow reduction at or below 15% through the perforator vessel for a single stent deployment[20]. However, we also found that the reduction in porosity that occurs when three stents are deployed telescopically can lead to reductions in $V_{RMS}$ through perforator vessels that range from 27 – 46% across parent vessel flow rates. These reductions in flow through the
perforator vessel are 20% higher than those observed with the use of a single stent. Such a
difference indicates that the use of multiple stents could increase perforator occlusion.

The PED device led to perforator $V_{RMS}$ reductions greater than those for three telescoping stents.
As discussed by Fiorella et al., flows into the aneurysm and perforator vessels are governed by
different hemodynamics, and devices such as the PED are designed to have a greater effect on
aneurysmal flow[19]. Our results agree that fluid dynamics within the aneurysm are more
affected than perforator flow by the PED, except at higher flow rates where very similar
reductions were observed. Previous in vivo studies have shown that a reduction in perforator
flow greater than 50% can result in complications including loss of patency of the perforating
side branches and increased risk of infarction or ischemia[21]. Unfortunately, for all flow rates
(except 6 ml/s) the PED led to $V_{RMS}$ reductions near or at 50% in the perforator vessel. While the
$V_{RMS}$ reductions are not the exact same as the physiological flow rate reductions that would be
observed clinically, the reduction in the $V_{RMS}$ observed implies that the superior reduction in
aneurysmal fluid dynamic activity associated with PED treatment may also lead to unwanted
complications relating to perforating vessels. The relationship between flow diverting devices
and perforator vessels they may be deployed across is important when considering the
development of new low-porosity stents, which have a higher stent strut density.

Effects of Stent Strut Placement on Perforator Flows:
A correlation between the placement of a stent strut across the perforator vessel and $V_{RMS}$ in the
vessel was observed, but results were contrary to initial expectations. As shown in Figure 4, $V_{RMS}$
decreased as predicted for the occluded cases (C and D) as compared to the untreated (A) and
0% occluded (B) cases. At 0% occlusion (B), \( V_{RMS} \) was greater than in the untreated (A) case for all but the 3 ml/s flow rate. Because the stent was specifically placed to achieve 0% occlusion, this may have lead to a hemodynamic change that actually directed flow to the perforator. Similar observations were made in a CFD study by Kim et al. which found that single stent placement across an aneurysm led to varied hemodynamic changes based on geometry, and that the change in aneurysmal inflow rate after single stent placement was unremarkable in comparison to the untreated case[16].

The intuitive hypothesis about stent strut placement is that the greatest \( V_{RMS} \) reduction would coincide with the largest degree of occlusion; however, our results show that there was a greater \( V_{RMS} \) reduction within the perforator vessel at 7% occlusion (D) than at 26% occlusion (C). Rather than varying with degree of occlusion, the \( V_{RMS} \) reduction correlated to the position of the strut’s center of mass relative to the perforator ostium. At a flow rate of 3 m1/s, greater flow was observed for 7% occlusion (D). However, we feel that this was simply an anomaly at a very low flow rate.

Previously, it has been shown that local flow disturbances caused by stent struts result in low wall shear stress and re-circulating flows[22-24]. Local flow disturbances induced by stents eventually return to normal flows with large stent strut spacing corresponding to more rapid flow restoration[23]. Since flow eventually recovers downstream of stent struts, it can be inferred that the position of the strut relative to the perforator (along the axis of fluid flow) may have a significant effect on percentage reductions in perforator \( V_{RMS} \). This effect was observed in the results from the CFD simulations, where the position of the Neuroform strut had a large effect on
perforator flow. The placement of the Neuroform strut closer to the upstream tip of the perforator orifice induced flow disturbances that led to the largest reduction in perforator flow as shown in Figure 5. Placing the strut further downstream from the tip of the orifice reduced flow disturbances and their effects on perforator flow. As shown in Figure 6, where a velocity field from the PIV data is shown, the inlet jet to the perforator enters from the upstream side of the vessel, indicating that placement of the strut in this location would lead to greater disturbances, which also agrees with the CFD simulations presented in Figure 5. Our collective results support that strut placement may be as important as porosity when considering effects on the perforator vessel flows. It is understandable that, although the placement of struts may play an important role in local hemodynamic effects, their exact placement in a desirable position may not be possible in practice. However, as placement capabilities improve, the effects we have documented could become useful for optimizing device deployments.

Limitations to this study stem from assumptions made during experimentation, including the use of an idealized model and limited flow conditions and stent deployment geometries. Because the purpose was to observe general trends between stent deployments (rather than patient-specific conditions), an idealized model obtains this goal because it is based on averaged anatomical geometries. While these types of studies can lead to an unlimited number of conditions, the ones selected represent a good range of the conditions seen in these types of aneurysms, and allow for an accurate assessment of trends.

**CONCLUSION**
As presented, the deployment of both high- and low-porosity stents to treat cerebral aneurysms had a significant effect on flow through nearby perforating vessels. Sequential telescoping deployments (which led to decreased effective porosity) significantly reduced perforator $V_{RMS}$ (which may increase risk of stroke). The placement of a low-porosity stent, the PED, led to even greater $V_{RMS}$ reductions across the perforator. Further, the location of stent struts affected local hemodynamics at the vessel orifice, leading to changes in flow through the perforator. Because these studies were the first to experimentally evaluate effects of multiple stent deployments and strut placement on perforator vessel flows, there is a great deal of room for further exploration. Future research goals include evaluating different flow diverters and their effects on perforator vessels, observing the effects of relative stent strut alignments between telescoping placements, and focusing more on local stent strut effects since those proved important in this study.
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All six authors listed contributed to the development, data collection and/or data analysis of the study. All authors have contributed to the final written product by either writing or editing.
References:


Figure Legends:

Figure 1: Rendering of a low-porosity stent deployed into a computational anatomical model. As shown in the image, the stent placement is across the perforator ostia, which could lead to possible flow interference through the vessel.

Figure 2: Computational idealized sidewall aneurysm model including perforating vessel (top). Physical model with the PED deployed across the aneurysm and the perforator (bottom).

Figure 3: Post-treatment reductions in aneurysmal (top) and perforator (bottom) $V_{RMS}$. Note that in most cases, three telescoping Neuroform stents reduced aneurysmal $V_{RMS}$ most and the PED reduced perforator $V_{RMS}$ most.

Figure 4: Post-treatment reductions in perforating vessel $V_{RMS}$ for the different stent strut placements described in Table 1. Note that $V_{RMS}$ varies consistently with respect to strut location rather than degree of perforating vessel orifice occlusion.

Figure 5: Simulated flows through the perforating vessel with a stent strut at 20% (I), 40% (II), 60% (III), and 80% (IV) from the upstream edge of the vessel. Note that the further upstream the strut is, the more it disturbs perforating vessel flow.

Figure 6: PIV-measured flow through the untreated perforating vessel for a 6 ml/s steady parent vessel flow rate. Note the high-velocity jet within the perforating vessel that originates from the upstream edge of the vessel orifice. PIV resolution was actually twice that shown (a vector skip...
was needed to make the flow map more clearly visible). The circled area highlights the vectors at
the perforator entrance, where local flow effects were affected by stent placement.