HEMODYNAMIC EVALUATION OF NOVEL ENDOVASCULAR TREATMENT TECHNIQUES FOR CEREBRAL ANEURYSMS

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ABSTRACT

The presence of cerebral aneurysms and its growth lead to the enhancement of the secondary motions induced in bifurcating and curved vessels, due to the measured strong, three-dimensional vortex created in the aneurysmal sac. In addition, the inertia imparted to the vortex during systole sustains the rotational motion throughout the whole cardiac cycle. This persistent flow inside the aneurysmal sac prevents the formation of a thrombus that could potentially fill the sac, reducing the mechanical stresses on the arterial wall and, thus, stopping the growth. Aneurysmal treatment techniques aim to prevent aneurysmal growth and rupture by reducing or eliminating the rotational motion measured in the aneurysmal sac. Two different aneurysmal treatment approaches are considered here: filling the aneurysmal sac with an embolic agent (Guglielmi Detachable Coils, hydrogel-coated coils, and a polymer), and placing stents across the aneurysmal neck. All the endovascular treatment techniques analyzed in this study have shown to effectively reduce or eliminate the rotational motion in the aneurysmal sac, thereby reducing the wall shear stresses acting on the neck of the aneurysm which are believed to be responsible for the aneurysmal growth.

INTRODUCTION

Until the early 1990's, patients harboring cerebral aneurysms were treated medically with drugs to lower intracranial pressure, or, if the aneurysm could be reached safely using open surgery, the aneurysm was treated by closing its neck with a metallic clip such that normal blood flow through the parent vessel was restored. Endovascular techniques have been developed to overcome the limitations of clipping. New development in the design of thin, flexible arterial catheters has opened a new, less invasive venue for the endovascular treatment of cerebral aneurysms. This microcatheter is introduced into the arterial system through the femoral artery and it is then navigated to the aneurysmal location. Once the tip of the catheter is properly positioned, an embolic agent or device is inserted and placed in the desired location.

In this in-vitro study, the hemodynamic changes in the aneurysmal and parent vessel flow resulting from using various endovascular treatment techniques are measured. The measurements presented here will provide for quantitative assessment of the potential benefits and drawback that each one of the techniques represents from a purely mechanical point of view.

Two different aneurysmal treatment approaches are considered: filling the aneurysmal sac with an embolic agent (Guglielmi Detachable Coils, hydrogel-coated coils, and a polymer), and placing stents across the aneurysmal neck.

Guglielmi Detachable Coil

This system consists of a soft platinum coil soldered to a stainless steel delivery wire. When the coil is positioned within the aneurysmal sac, an electrical current is applied to the delivery wire detaching the coil by means of electrolysis. The delivery wire is then removed, leaving the coil in place. The process of inserting coils continues until the aneurysmal sac is densely packed with them.

Hydrocoils

The Hydro*Coil* Embolic System (HES; MicroVention, Aliso Viejo, CA) consists of platinum coils coated with an expansible hydrophilic polymer.

Onyx Liquid Embolic System (OnyxLES)

It is a biocompatible liquid embolic agent consisting of ethylene vinyl alcohol copolymer (EVOH) dissolved in the solvent DMSO (Micro Therapeutics, Inc., Irvine, CA). Once this solution is injected inside the aneurysm the polymer solidifies through a process of precipitation when Onyx comes into contact with an aqueous solution (e.g., blood). The solvent DMSO rapidly diffuses out of the polymer mass and is washed

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away by the blood flow. The resulting precipitation of the polymer forms a spongy mass which fills the aneurysmal sac.

Stents

The Neuroform stents (Boston Scientific/Neurovascular, Fremont, CA) used in this study are flexible, self-expanding, microcatheter-delivered nitinol stents specially designed for the treatment of cerebral aneurysms (Howington *et al.*, 2004).

EXPERIMENTAL FACILITY

The different aneurysm models used in this study were made out of silicone, as an attempt to achieve the compliance of the arterial wall (Kerber *et al.*, 1989). They were built from cadaver casts taking into consideration that most cerebral aneurysms arise at either bifurcating or curved vessels. The chosen aneurysmal locations were the anterior communicating and the basilar arteries (Figure 1).

The aneurysm models are placed in the test section perfused with a mixture of de-ionized water and ethylene-glycol (with a density of 1.045 g/ml and a viscosity of 2.5 cp, at room temperature), that is seeded by lycopodium powder (Carolina Biological Supply Company, Burlington, NC) with a mean diameter ranging between 1 and 10 μm. In order to avoid distortion of the visualized flow by refraction, the model is placed in a transparent box filled with the same perfusion fluid.

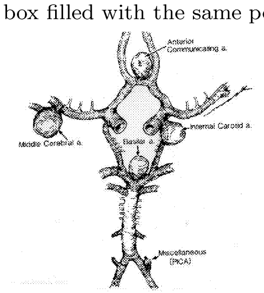

Figure 1: Circle of Willis

A pulsatile flow corresponding to the flow through the carotid artery (Figure 2) was supplied to the model by means of a pulsatile pump (UHDC flow system, Sidac Engineering, Ontario, Canada). The peak volume rate selected for this study was 360 cc/min. The period of the pulsatile flow was 0.83 s, corresponding to a cardiac rate of 72 ppm.

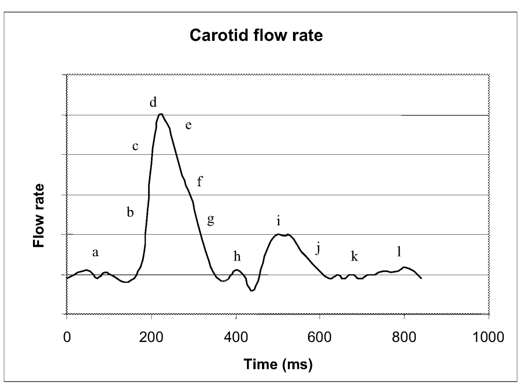

Figure 2: Waveform corresponding to the flow in the carotid artery, supplied to our sidewall aneurysm model.

A Digital Particle Image Velocimetry (TSI Inc., St Paul, MN) is used to quantify the instantaneous two-dimensional velocity field inside the aneurysm model and the parent vessel. For each cardiac cycle, twelve to thirteen pair of images at the times indicated in Figure 2 (a to l on the flow waveform) were obtained (measuring rate of 15 pairs of images per second). The velocity field is then computed by the appropriate software ($Insight^{TM}$, TSI Inc., St Paul, MN) cross-correlating the two images and measuring the particle displacements from statistical correlations of each pair of images. Measurements of the velocity field were taken before and after placing the embolic agent.

To measure the intra-aneurysmal pressure a Camino Parenchymal Intracranial Pressure Catheter (Integra Neurosciences, Neurosurgery Division of Integra LifeSciences, Corporation, Plainsboro, NJ) was used. This pressure monitoring system has a miniature transducer at the distal tip that allows to take the measurements. The accuracy of the measurements is ± 2 mmHg. The analog signal was acquired with an A/D converter and processed using LabVIEW^{TM} (National Instruments Co., Austin, TX) software.

RESULTS

In order to evaluate the performance of the above described treatment techniques, measurements of the velocity field were taken in the aneurysmal sac before and after placing the embolic device.

The hemodynamic changes due to embolization with the GDCs and Onyx were analyzed using sidewall aneurysm, whereas the bifurcating aneurysm was used for the hydrocoil embolization and for the stenting procedure.

Reference case

Sidewall aneurysm. The anterior communicating artery (ACommA) is a recognized site of predilection for development of saccular cerebral aneurysms. For this reason, a model of an aneurysm arising at this location was built to study the hemodynamics of sidewall or curved vessels.

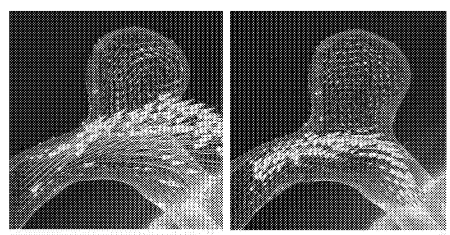

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Figure 3: Velocity field in a sidewall aneurysm. Flow in the parent vessel is from left to right. Labels correspond to the ones in Figure 2.

Although the flow in the aneurysmal sac is three-dimensional and not confined to any particular plane, the velocity field was measured in an axial plane running along the centerline of the aneurysm and dissecting the aneurysmal sac at a midpoint. The flow field in both the parent vessel and the aneurysm at peak systole and at diastole is shown in Figure 3. The arrows indicate both the magnitude and direction of the measured velocities. The curvature of the parent vessel generates a secondary flow, making the flow in the parent artery already three-dimensional. This three-dimensional flow creates a region of flow separation at the inner wall of the curve and at the outer wall bifurcates upon impingement on the distal neck of the aneurysm, generating a stagnation point at this location.

The flow enters the aneurysm along the distal wall creating a counter-clockwise vortex, whose core position and strength vary along the cardiac cycle. At the beginning of the cycle, the vortex core is located near the distal neck, and it progressively moves along the distal wall following a counter-rotating trajectory. Image e shows the peak systole. During the deceleration of the systole the vortex core moves towards the neck, where it stays through diastole (image i). Note that the vortical motion remains until the end of the cardiac cycle.

Bifurcating aneurysm. The measurements of the velocity field at two representative stages of the cardiac cycle are shown in Figure 4, where the labels correspond to the ones in Figure 2.

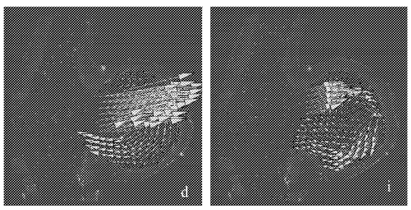

Figure 4: Velocity field measured inside the aneurysmal sac of a bifurcating aneurysm model at four stages, the labels correspond to the ones in Figure 2. The flow is from left to right.

At peak systole (Figure 4d) a very strong jet is seen entering the aneurysmal sac. This jet is then projected onto the aneurysmal fundus. Upon impingement on the aneurysmal fundus, the jet bifurcates into a very strong clockwise rotating vortical flow engulfing most of the central and lower portion of the sac, and a much weaker counter-clockwise rotating vortical motion confined to the upper section of the sac. During diastole, these two vortical motions are shown to persist. In particular, the stronger vortex, although decaying in strength due to viscous dissipation, retains its coherency and the clockwise rotation of the flow persists until the end of the cardiac cycle (Figure 4i). The persistence of the rotational motion is a direct consequence of the large rotational inertia generated by the splitting jet upon impacting on the fundus, a condition typical of basilar tip aneurysms where the incoming blood flow is directed straight into the aneurysmal sac. The non-symmetric form of the flow in the sac is simply a consequence of the small geometrical asymmetries which are also typical of this arterial configuration. In fact, the non-symmetric nature of the flow is a characteristic to be expected as the norm rather than as an exception (Foutrakis *et al.*, 1999).

Treatment techniques

GDC embolization. The anterior communicating artery aneurysm model was filled with three coils (Boston Scientific, Fremont, California): GDC-10 8mmx30cm, GDC-18 9mmx30cm, GDC-10 7mmx25cm (diameter x length). The flow velocity field resulting from the coil embolization is shown in Figure 5 for two stages of the cardiac cycle. Image e correspond to the peak systole, whereas image i corresponds to the peak diastole. The flow separation region observed in the parent vessel before the occlusion (see Figure 3) remains after the embolization, although it is located in a downstream location with respect to the control case. Regions of flow stasis appear now in the aneurysmal neck due to an incomplete blockage at this region.

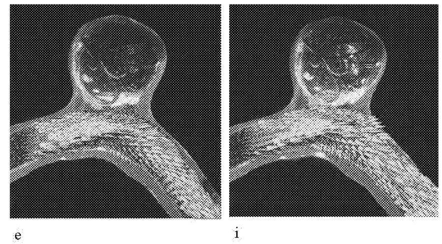

Figure 5: Velocity field in a GDC-10 coil embolized sidewall aneurysm.

Hydrocoils. In order to analyze the possibility that the expansible hydrogel might increase the intra-aneurysmal fluid pressure when fully expanded, pressure measurements were taken using a probe by placing the catheter tip at the fundus of the sac. Measurements were taken for the control case and subsequently after placing each coil, including the non-coated platinum coils used as a support structure. Figure 6 summarizes the measurements, showing only the results for the control, after placing the two structural coils (denoted as 2nd coil in the figure), after placing six hydrogel-coated coils, and after complete filling (12 Hydro*Coils*). These results indicate that there is not a significant change in the intra-aneurysmal fluid pressure with the expansion of the polymer coating the platinum coils, not even after placing twelve Hydro*Coils* and achieving a filling capacity to 93%.

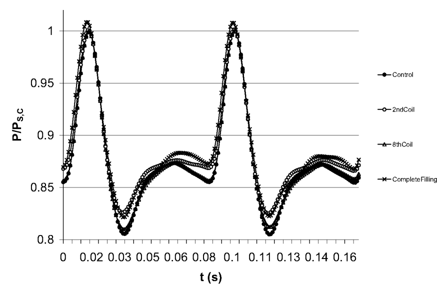

Figure 6: Intra-aneurysmal pressure measurements of the non-treated aneurysm model (control), after placing two structural coils (2nd coil), after placing 6 hydrogel-coated coils (8th coil), and for the complete filling (14th coil). Measurements were normalized with the measured pressure at peak systole for the control case, $P_{S,C}$. The slight difference between the curves remains within the measurement error ($\pm$2 mmHg).

Onyx embolization. Micro Therapeutics, Inc. has developed a new technique based on the aneurysmal embolization with a polymer called onyx. The main advantage of this embolic agent is that ensures a complete aneurysmal occlusion and reduces the risk of aneurysm regrowth. However, there is a main technical challenge related to the placement of a remodeling balloon over and beyond the aneurysmal neck to reshape the surface of the onyx while it hardens, smoothing the surface of the polymer at the neck. In order to evaluate the need of using a balloon during the procedure, from a mechanical point of view, the hemodynamics of the parent vessel of the sidewall aneurysm model were measured after onyx embolization with, and without using a balloon during the procedure.

Figure 7 shows the velocity field in the parent vessel after filling the aneurysm with and without the aid of a balloon. In both cases, the velocity field in the parent vessel is fully re-established. However, when the balloon is not used, the onyx does not uniformly fill the neck of the aneurysm, and regions of flow stasis are created at this location.

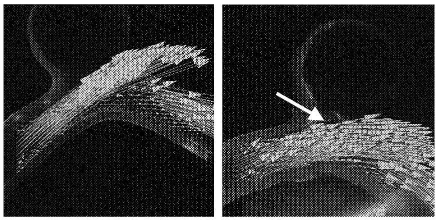

Figure 7: Velocity field measured in the parent vessel after the embolization with onyx at peak systole. The aneurysmal neck is completely filled using a balloon, eliminating the possibility of thrombus formation (left). However, without the aid of a balloon regions of flow stasis (indicated by the arrow) are formed at the neck due to the incomplete filling of the neck, they represent a potential location for thrombus formation (right).

Stenting the aneurysm. In this section the effect of placing multiple stents is quantified by accurately measuring the changes in the hemodynamic forces acting on a bifurcating aneurysm model (basilar tip aneurysm) after the deployment of two stents. Two flexible Neuroform stents (developed by Boston Scientific to facilitate their navigation through the cerebral vasculature) were placed across the aneurysmal neck in a Y-configuration.

The mean magnitude of the velocity, vorticity, and strain rate are measured before and after placing the stents for two representative stages of the cardiac cycle, the peak systole and the end of the cycle (Table 1). These mean values were calculated from the measurements over 5 cycles, and it should be emphasized here that there is a sizeable cycle to cycle variation in these measurements. At peak systole, there is a net reduction of 11% in the maximum value of the magnitude of the velocity, a 5.8% reduction in the maximum value of the vorticity, and a 9% reduction in the maximum value of the shear stress, when crossing the aneurysm neck with the two stents in a Y configuration. At the end of the cycle, although qualitatively speaking, the two flows are very similar, the remnant rotational motion is much weaker in the stented case, the vorticity is nearly depleted, having a value 58% of the control, and the corresponding maximum of the shear stress has been also drastically reduced to a value 59% of the control.

To further quantify the reduction of the vortical motion measured inside the aneurysmal sac after placing the stents, the strength of the vortex was measured computing the circulation (Γ).

The evolution with time of the circulation inside the aneurysm for the control case, as well as after placing the stents is shown in Figure 8. Apparent from these measurements is the fact that, although the circulation reaches a

		V *(m/s)*	w *(1/s)*	ε *(1/s)*
Sys	Ctrl	0.35 ± 0.18	206.68 ± 92.34	90.56 ± 43.54
	St	0.32 ± 0.07	195.25 ± 74.26	81.91 ± 34.20
Dias	Ctrl	0.04 ± 0.01	21.81 ± 6.04	10.75 ± 3.46
	St	0.02 ± 0.002	6.90 ± 1.50	3.17 ± 0.70

Table 1: Comparison of the maximum mean values of the velocity (V), vorticity (w) and strain rate (ε) fields at both peak systole and peak diastole for the control and stented cases. Sys: systolic values, Dias: diastolic values, St: stented case, Ctrl: control case.

maximum at peak systole, it never vanishes during diastole. Thus, indicating the persistency of the rotational motion inside the sac during the whole cardiac cycle. The persistence of the rotational motion inside the sac is preserved when placing the stents, but the circulation decreases dramatically.

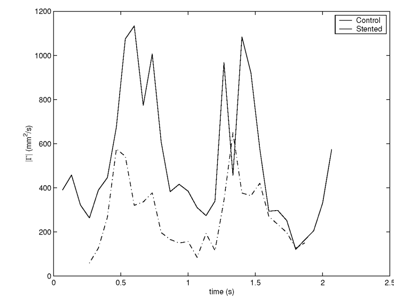

Figure 8: Comparison of the circulation measured inside the aneurysmal sac before (solid line) and after placing the stents (dashed line).

DISCUSSION

It has been shown that the strength of the vortex formed in cerebral aneurysms (both sidewall and bifurcating types) varies throughout the cardiac cycle, reaching maximum values at peak systole. Due to the inertia imparted by the vortex at systole, the rotational motion inside the sac never stops, not even during the resting period of the cardiac cycle, as it was shown by the circulation measurements. This complex three-dimensional vortex flow results in spatial and temporal gradients of wall shear stresses. The largest gradients of wall shear stresses (GWSS) are located near the distal neck and along the distal wall of the aneurysm, whereas small values are found at the dome. These are the two critical regions for aneurysm growth and rupture, respectively and, as shown here, they are associated with high wall shear stresses (neck) and low wall shear stresses (dome) (Kato *et al.*, 2001). Therefore, these measurements are consistent with the hypothesis that the mechanisms that lead to growth or rupture seem to be initiated by different degrees of wall stresses. In fact, the shear stress influences endothelial cell functions. It has been already shown that increased wall shear stresses caused by increased flow velocity stimulates the release of endothelium-derived nitric oxide, which is known as a strong vasodilator and is also a potential factor in arterial wall degeneration (Tateshima *et al.*, 2001).

In both geometries, the presence of the aneurysm cause large changes in the flow characteristics of the parent vessel. On one hand, the flow separates at various locations along the wall. On the other hand, the outflow merges with the main flow in the parent vessel, enhancing the secondary helical vortices downstream of the aneurysm.

Endovascular treatment techniques

The use, safety, efficacy and complications of the use of GDCs have been extensively reported in recent years (Bederson *et al.*, 2000; Brilstra *et al.*, 1999; Dovey *et al.*, 2001; Roy *et al.*, 2001). There are potential risks associated with this treatment such as the possible recanalization of the aneurysm with risk of rupture, or the risk of coil protrusion into the parent vessel. The circular shape of the coils represents an obvious advantage when filling the aneurysmal sac. However, this geometry does not allow to completely fill the aneurysmal neck, and regions of flow stasis are created at this location. Depending on the size of these regions and the drugs administered to the patients, thrombus may form. This thrombus has a high probability of dislodging and been shed into the main stream. In fact, it has been reported that treated aneurysms often lead to small strokes possible caused by a thrombus formed at the partially filled neck. Nevertheless, filling the aneurysmal sac with coils does indeed reduce the stresses acting on the aneurysmal walls, thus reducing the risks of growth and rupture of the aneurysm.

To achieve a complete filling of the aneurysmal sac and to minimize the number of coils needed to be deployed (known limitations of the GDCs), modifications on the coil design have been made, such as the development of three-dimensional coils, or bio-absorbable polymeric coated coils (Cloft *et al.*, 2000; Kallmes & Fujiwara, 2002; Murayama *et al.*, 1997, 2002). The case of using a hydrophilic gel (Hydrocoil Embolic System, HES) coating the coils is studied here. It has been shown that the HES significantly improves aneurysm packing, from a 20% to 30% volumetric aneurysmal occlusion with bare platinum coils to about 70% volumetric occlusion with HES coils (Cloft & Kallmes, 2004; Kallmes & Fujiwara, 2002). This higher coil packing density seems to be especially necessary to reduce the observed rates of recanalization in aneurysms that are directly affected by the arterial pressure, such as the one located at the basilar bifurcation, since coil compaction is usually observed under these conditions (Kawanabe *et al.*, 2001).

The in-vitro measurements presented here show that the intra-aneurysmal fluid pressure remains virtually unchanged, even after achieving a 93% coil filling after full hydration. It is interesting to note that these measurements are consistent with previous results using GDCs, which have shown that coiling aneurysms does not decrease the pressure transmitted from the vascular system (Boecher-Schwarz *et al.*, 2000; Sorteberg *et al.*, 2001).

Embolization of aneurysms with onyx has undergone extensive preclinical testing for embolization in the brain and, over the past 5 years, has been adopted in clinical use in Europe. From the hemodynamical point of view, it has a great advantage over the coils for its potential of completely filling the aneurysmal neck, reducing then the forces acting on the aneurysmal walls and, thus, the risks of growth and subsequent rupture, or re-growth from the neck; also, it diminishes the presence of flow stasis regions that may induce the formation of thrombus. Still, the benefits of using onyx during the embolization can only be achieved if using a balloon during the procedure, since it allows to fill the aneurysmal sac while shaping the polymer to conform with the parent vessel wall, avoiding the formation of pockets at the neck that would lead to thrombus formation.

Stent technology was originally developed to be used in the coronary circulation (Sigwart *et al.*, 1987) to prevent occlusion and restenosis after transluminal angioplasty. Due to its success in that field, tremendous progress has been made to modify the design of those stents so they can be navigated through tortuous vascular segments of the intracranial system. However, it has been argued that the high porosity of intravascular stents may limit aneurysm thrombosis following primary stenting (Lanzino *et al.*, 1998). There is some experience placing more than one stent (Benndorf *et al.*, 2001; Doerfler *et al.*, 2004), but there is not any evidence about the optimum number of stents needed to avoid aneurysmal growth or rupture.

In this study two flexible stents were placed across the neck of a bifurcating aneurysm and the effect on the rotational motion measured in the aneurysmal sac was evaluated. After stenting the aneurysm model, a much weaker rotational motion is measured inside the aneurysmal sac. This reduction is more noticeable at the end of the cycle, where the vorticity is nearly depleted, having a value 58% of the control, and the corresponding maximum of the shear stress has been also drastically reduced to 59% of the control value. This marked reduction in the residual rotational motion inside the sac, with the associated large reduction in the vorticity and shear stress inside the sac, begs the question if the simple use of the stents, without coil packing of the sac, could provide a viable therapy for the treatment of some aneurysms.

CONCLUSION

An evaluation on how endovascular techniques could provide the necessary changes in the flow needed to prevent the further growth of the aneurysm and/or its rupture is presented here. Their common goal is to lower the magnitude of the hemodynamic forces (lowering the strength of, or suppressing the vortical motion in the sac), and suppress the biochemical processes triggered by those stresses. The efficiency is evaluated taking into consideration that the presence of the aneurysm and its growth enhances the secondary motions measured in curved and bifurcating vessels, leading to an unstable response. Furthermore, the inertia imparted by the strong vortex measured at systole sustains the rotational motion inside the sac throughout diastole, preventing thrombus formation.

Two different approaches have been followed in the design of these techniques. In the case of using coils (either platinum coils, or hydrogel coated coils) and a polymer (like the one analyzed here, onyx), the objective is to occlude the aneurysmal sac with the embolic agent, suppressing the rotational motion; whereas, in the case of placing a stent, the device is deployed across the aneurysmal neck to reduce the vortex strength. In this study, it has been shown that the main disadvantage of the former approach is the risk of not completely filling the neck, leaving regions of flow stasis, where thrombus may form. If a thrombus indeed is formed in these regions, the shear stresses acting on it may be large enough to potentially break up the clot and shed it downstream of the aneurysm. This clot could blockage the downstream smaller arteries leading to a stroke. In fact, the measured velocities showed that pockets were left at the neck and flow stasis was indeed achieved in those regions. The use of a hydrogel coating the coils or a balloon during the polymer embolization has been shown to reduce the risk of thrombus formation since the filling of the neck is achieved. However, filling the sac with an embolic agent, although it re-establishes the flow in the parent vessel, has been shown to create new regions of flow separation that, in turn, lead to changes in the wall stresses acting on the arterial wall. The effects of these changes should be studied. In the case of placing stents across the aneurysmal neck, it has been demonstrated that the use of multiple, flexible intravascular stents reduces the strength of the vortex forming in the aneurysmal sac with subsequent decrease in the magnitude of the stresses acting on the aneurysmal wall. More importantly, this reduction is especially evident during the diastole, which represents 2/3 of the cardiac cycle. Therefore, by placing multiple stents, thrombosis may be accelerated and the risks of aneurysmal growth and/or rupture may decrease. Studies should be done to ascertain the thrombus formation with the vortical strength reduction achieved after placing these stents.

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