Endovascular coiling for intracranial aneurysms has evolved rapidly, which allows for the successful treatments of most aneurysms. However, endovascular treatment for some complex aneurysms remains a technical challenge. Moreover, the long-term stability of coil-occluded aneurysms, especially in wide-necked aneurysms, is rather poor. Use of a stent serves as a mechanical scaffold in the course of aneurysm coil placement by preventing coil protrusion into the parent vessel. This technique enables safer and denser coil packing and may help to prevent aneurysm recanalization and facilitate further thrombosis by means of redirecting flow and facilitating endothelialization at the aneurysm neck. A series of in vivo and in vitro studies have demonstrated that stent deployment across the aneurysm neck causes significant hemodynamic changes. A new generation of endovascular devices, known as flow diverters (FDs), has been developed to treat aneurysms. These stent-like devices are designed to divert blood flow along the normal anatomic course of the vessel and away from the aneurysm dome. The FD has achieved promising clinical results in treating large or giant aneurysms.

Computational fluid dynamic (CFD) simulations have been used to predict the flow disruption effects induced by flow-diverting stents. Some techniques for simulation of stent deployment were used for CFD calculation. In most previous studies on the hemodynamics of flow-diverting stent, a computer aided design drawing of the stent pattern with homogeneous porosity was virtually implanted into either idealized aneurysm models or patient-specific aneurysm models. Cebral and Löhner proposed an adaptive grid embedding technique for modeling the stent deployment, which was successfully applied to several realistic cases. This study provided the real structural configurations of fully deployed FDs in vivo. We demonstrated the decrease of wall shear stress, inflow volume, increase of relative residence time, and change of inflow stream induced by FD implantation. The more prevalent near the central part of the neck may be closely related to healing.

Key Words: aneurysm ■ computational fluid dynamics ■ flow diverter ■ hemodynamics

Hemodynamic Changes by Flow Diverters in Rabbit Aneurysm Models
A Computational Fluid Dynamic Study Based on Micro–Computed Tomography Reconstruction
Qinghai Huang, MD*; Jinyu Xu, MD*; Jiyong Cheng, MD; Shengzhang Wang, PhD; Kuizhong Wang, MD; Jian-Min Liu, MD

Background and Purpose—The effect of flow diverter (FD) on hemodynamic changes observed in aneurysms is inevitably affected by the actual structural configuration of deployed FD. We studied the resultant hemodynamic changes after implantation of FDs using computational fluid dynamic simulations based on micro–computed tomography reconstructions in rabbit aneurysm model.

Methods—The FDs by micro–computed tomography images and vascular model based on rabbit-specific angiograms in 14 rabbits were reconstructed for computational fluid dynamic studies, and rabbit-specific inlet flow waveforms were used as boundary conditions. The occluded group (n=10) and unoccluded group (n=4) were divided according to the follow-up angiography. Hemodynamic parameters were separately evaluated for significance with respect to FD implantation and healing.

Results—The normalized mean wall shear stress of the aneurysm sac and inflow volume were significantly reduced after FD deployment, and the relative residence time was significantly increased after treatment, without significant differences in mean pressure of aneurysm sac. When compared with the unoccluded group, the average relative residence time increment and percentage of inflow volume reduction in occluded group were higher. Additionally, the inlet of stream after FD deployment in the occluded group was more prevalent near the central region of the neck, whereas in the unoccluded group, it was more likely to occur near the proximal part of the neck.

Conclusions—This study provided the real structural configurations of fully deployed FDs in vivo. We demonstrated the decrease of wall shear stress, inflow volume, increase of relative residence time, and change of inflow stream induced by FD implantation. The higher relative residence time increment, percentage of inflow volume reduction, and location of stream inlet near the central part of the neck may be closely related to healing. (Stroke. 2013;44:1936-1941.)

Key Words: aneurysm ■ computational fluid dynamics ■ flow diverter ■ hemodynamics
used to model different stents. Ma et al.10 developed a finite element analysis based on workflow for simulating mechanical deployment of FD in patient-specific aneurysms. However, all of the abovementioned approaches have a major limitation: they are restricted to stents deployed ideally that have a high degree of symmetry and uniformity. However, the porosity of stent changes with the curvature and diameter of the parent vessel. Determining how to represent the true situation of the implanted FD in vivo is the key technical and clinical question to address to predict the treatment outcome. Micro–computed tomography (CT) can be used to reconstruct the true deployed states of the stent, but it is difficult to reconstruct stent with micro-CT in vivo. In addition, there is no previous report on the study of hemodynamics and prognosis of FD-implanted aneurysms based on micro-CT reconstruction.

The aim of this study is to develop a model that combines data from in vivo experiments, 3-dimensional (3D) imaging techniques, and CFD simulations to investigate hemodynamic changes in realistically stented vessels and aneurysms and subsequently to analyze the relationship between the hemodynamics and aneurysm occlusion on follow-up.

Methods

Animal Experiments

We established histologically simulated human aneurysms by using elastase to digest the right common carotid artery of healthy adult New Zealand white rabbits as previously described.13 Fourteen wide-necked aneurysm models of both sexes (body weight, 3–4 kg) were developed and treated by FDs. The FD (first-generation TUBRIDGE embolization device; MicroPort Medical [Shanghai] Co Ltd, China) in this experiment is composed of 32 nickel–titanium alloy strands, including 2 parallel radiopaque struts containing platinum; the diameter of each strut is 0.05 mm. The FD was placed in the innominate artery covering the neck of aneurysm. We chose the diameter of FD according to the size of proximal reference vessels.

All animals underwent both intravenous digital subtraction angiography (DSA) at 4 weeks after the procedure and DSA at 3 months. After DSA, the rabbits were euthanized by intravenous injection of sodium pentobarbital (100 mg/kg). The entire segment of parent vessel, including FD, was marked with steel-wire needles to confirm the exact position of aneurysm neck and was then dissected. The tissue, including FD, was pressure fixed with 10% formalin under 100 cm of water pressure for about 4 hours and then stored in the same solution for minimum of 24 hours.

The pulsatile velocity waveform was obtained by transthoracic duplex Doppler in the innominate artery of 1 healthy rabbit. We then digitized the Doppler spectrum envelope to obtain blood flow velocity waveform in a whole cardiac cycle by using Matlab version 7.0 software (MathWorks, Natick, MA).

Vascular Modeling and 3D Stent Micro-CT Reconstruction

The images of 14 rabbit-specific aneurysm models were obtained from Integris Allura Flat DSA (Phillips Healthcare, Best, The Netherlands). All of the acquired rotational digital subtraction angiography images were transferred to the Philips Allura FD20 workstation (Phillips Healthcare) for reconstruction and produced a virtual reality modeling language format. This virtual reality modeling language was then converted into a stereolithography format by using 3DMax8.0 (Autodesk). The stereolithography version was subsequently segmented and surface smoothed by Geomagic Studio version 9.0 software (Geomagic. Research Triangle Park, NC).

All embedded samples, whose aneurysm necks were marked by steel-wire needles, were scanned using micro-CT (GE eXplore Locus SP) with a 17-μm pixel size. The scanned CT data of FDs were processed with Mimics (version 10.01, Materialise, Leuven, Belgium) to reconstruct 3D FD geometries, as observed in Figure 1. The diameter of the strut was modified to 0.05 mm by adjusting the threshold of image.

Meshing and Flow Modeling

To deploy the FD in the aneurysm models, the reconstructed FDs were fitted into the parent vessel lumen across the aneurysm neck according to the steel-wire marker with the help of Geomagic Studio software. The separately reconstructed aneurysms and FDs were merged in ICEM CFD version 11.0 (ANSYS, Lebanon, New Hampshire) to create volume grids for fluid dynamics computation. Each model was meshed to create 2.3 to 3.8 million finite volume tetrahedral elements and wall prism elements (for accurate boundary layer resolution). The elements per cubic millimeter were $4.74 \times 10^5$ to $1.44 \times 10^6$. Previous studies have shown that this mesh resolution is sufficient for hemodynamic simulations.

The governing equations underlying the calculation were the Navier–Stokes formulation, with an assumption of laminar and incompressible blood flow. We treated blood as a Newtonian fluid. The density and dynamic viscosity of blood were specified as $\rho = 1050$ kg/m$^3$ and $\mu = 0.0035$ Pa·s, respectively. The inlet was imposed by pulsatile velocity profile measured from ultrasound Doppler as described above. The outlet was modeled as opening boundary condition with zero static pressure. The vessel was assumed to be rigid with no-slip boundary conditions. The simulation was performed by CFX version 11.0 (ANSYS, Lebanon, NH). We discretized the entire cardiac cycle of 0.48 seconds by a time-step of 0.001 seconds for numeric simulation. Three cardiac cycles were simulated to ensure that full periodicity had been reached, and the last cycle was taken as output. The aneurysm geometries were isolated from their parent arteries for subsequent data analysis. We then postprocessed and visualized the results of these simulations with CFX.

Hemodynamic Parameter Calculation

We calculated the following hemodynamic parameters: wall shear stress (WSS), pressure, relative residence time (RRT), and inflow volume. WSS (already time-averaged, as in Equation 1) was averaged over the sac area (the entire luminal surface of the aneurysm sac). In this study, WSS distributions were normalized by the average parent vessel WSS in the same rabbit to allow comparison among different models. RRT, a combination of WSS and oscillatory shear index (OSI), reflects the residence time of blood near the wall. Thus, a new metric termed RRT was defined to quantify the state of disturbed flow:

$$WSS = \frac{1}{T} \int_0^T |wss| dt$$

$$OSI = 2 \left[ 1 - \frac{\int_0^T wss dt}{\int_0^T |wss| dt} \right]$$

$$RRT = \frac{1}{(1 - 2 \times OSI) \times WSS} \frac{1}{T} \int_0^T wss dt$$

where $wss$ is the instantaneous WSS vector and $T$ is the duration of the cycle.

The percentage of inflow volume reduction was the difference of inflow volume before and after FD implantation at aneurysm neck at peak systole ($t=0.06$ s), and this value was then normalized by the inflow volume before FD implantation. We also observed the inflow stream of aneurysm sac by velocity magnitudes on a cut plane and streamlines before and after the FD implantation.
Statistical Analysis

The means and SDs of all hemodynamic parameters were calculated for pretreated/poststented and occluded/unoccluded groups. Data are expressed as mean±SD. The differences between the pretreated and poststented groups were analyzed by a paired nonparametric Wilcoxon test. A P value <0.05 was regarded as statistically significant, and all tests were 2-sided. Statistical analyses were performed using Microsoft Excel 2003 (Microsoft, Redmond, WA), Matlab.

Results

The angiographic follow-up showed that 10 out of 14 aneurysms were completely occluded, whereas the other 4 were unoccluded (smaller than 95% occlusion; Figure 2). Accordingly, the occluded (n=10) and the unoccluded aneurysms (n=4) were divided into 2 groups. Overall, 14 rabbit-specific aneurysm models were constructed. The values for mean and SDs of each parameter are displayed in the Table.

Distributions of WSS for rabbit-specific aneurysm models before and after FD deployment are shown in Figure 3. WSS values in the poststented group were lower within the aneurysm than in the parent vessels and were especially lower at the domes of the aneurysms (Figure 3). Poststented aneurysms had lower WSS magnitudes than pretreated aneurysms.

The mean WSS of the aneurysm sac in poststented group, normalized by the average parent vessel WSS in the same model, was significantly lower than that in pretreated group (0.16±0.12 versus 0.27±0.12; P=0.011).

The mean pressure of the aneurysm sac was 107.92±67.86 Pa in poststented group and 109.69±70.56 Pa in pretreated group. However, there was no significant difference in this parameter between the poststented and the pretreated groups (P=0.331).

Figure 3 also exemplifies the distribution of RRT for the models before and after FD deployment, with regions of increased RRT corresponding to regions of long residence time of blood near the wall. There was a significant difference in RRT between the poststented and the pretreated groups (2437.88±5.00 versus 10.83±8.17; P=0.001). The average RRT increment in unoccluded group was lower than that seen in the occluded group (821.07±1.09 versus 3069.45±5.83), although they displayed no statistical significance.

The inflow volume entering the aneurysm in poststented group was significantly lower than that in pretreated group (4.04×10⁻⁷±2.98×10⁻⁷ m³/s versus 8.45×10⁻⁷±5.83×10⁻⁷ m³/s; P=0.001). The average percentage of inflow volume reduction in the occluded group was higher than that in the unoccluded group (54.19±20.77% versus 53.70±14.76%), although there was no statistical significance.

The velocity of flow in poststented group was lower as compared with that before device placement. The inlet of
stream changed from the distal part of the neck to near the proximal part after the FD deployment. The inlet of stream after FD deployment in occluded group was more likely to be present near the central part of the neck, whereas it was more likely to be near the proximal part in unoccluded group (Figures 4 and 5).

Discussion

In this study, we tested hemodynamic parameters by using micro-CT reconstructed FDs in rabbit aneurysm models. Of these parameters, statistical significances between the poststented and pretreated groups were displayed for decreased WSS and inflow volume and increased RRT. Although there was no statistical significance between the occluded and unoccluded groups, the occluded aneurysms had a higher inflow volume reduction and average RRT increment.

An accumulating body of evidence implicates hemodynamics as a critical contributor to aneurysm pathogenesis. Of equal importance with simulating the hemodynamics in real-case cerebral aneurysms is modeling and simulating the local hemodynamic changes induced by endovascular treatment techniques. Although FD is being increasingly deployed to treat intracranial aneurysms, the clinical outcomes were highly variable and depend on the various types of aneurysms. Numeric simulation allows for assessment of the complex nature of the aneurysmal flow after stenting or FD deployment. Dorn et al18 compared the flow changes by 3 different stents (Solitaire, Silk, Phenox flow diverter) over the aneurysm neck. Their results showed that flow reduction was negligible with Solitaire stent. By contrast, FDs reduced the flow velocities by >50%, depending both on stent design and appropriate positioning. As shown by our results, the reduction of magnitude of WSS and inflow volume was significant after FD placement. A similar observation was made by Hirabayashi et al19 and Barath et al 20 with numeric and experimental results. Additionally, our results also showed significantly increased RRT caused by FD placement. This result was in agreement with animal studies21 and clinical evidence, which showed that FDs increase the contrast material washout time of the aneurysm.

The efficiency of stent is related to several parameters, including porosity, stent strut shape, cell geometry, and mesh hole shape. Kim et al22 studied the effects of stent strut shape and porosity on hemodynamic flow inside an aneurysm using numeric analysis and found that the rectangular stent was optimal. This stent decreased the magnitude of velocity by 89.2% in the aneurysm sac. Additionally, a series of in vitro23 and in vivo 24 studies have demonstrated that the porosity and pore density exert influences on intra-aneurysmal flow. Even with the same porosity, different filament sizes could cause different effects on intra-aneurysmal hemodynamics.25 The integration of stent geometry into the computational simulation may exhibit the role of stent on blood flow in/on each aneurysm. However, FDs with a rather high density increase the complexity of the meshing. Most studies have used simplified stent geometries because of the difficulty of reproduction of realistic stent geometry.10 However, these computational studies were limited to the mere demonstration of hypothetical stents in aneurysm flow alteration. In reality, the metal coverage of FD changes after

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pretreated Mean</th>
<th>Poststented Mean</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WSS (Pa)</td>
<td>0.27±0.12</td>
<td>0.16±0.12</td>
<td>0.011</td>
</tr>
<tr>
<td>Pressure (Pa)</td>
<td>109.69±70.56</td>
<td>107.92±67.86</td>
<td>0.331</td>
</tr>
<tr>
<td>RRT</td>
<td>10.83±8.17</td>
<td>2437.88±5.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Inflow volume</td>
<td>8.45×10⁻⁷±5.83×10⁻⁷</td>
<td>4.04×10⁻⁷±2.98×10⁻⁷</td>
<td>0.001</td>
</tr>
</tbody>
</table>

RRT indicates relative residence time; and WSS, wall shear stress.
elaboration or compression, and the actual changes are still unknown in vivo because the actual metal coverage rate and pore density exhibit remarkable differences once FD is implanted. We have successfully used micro-CT to reproduce the real configuration of FD in vivo and to calculate the metal coverage of FD at the neck. In our previous report,26 aneurysm occlusion was positively correlated with local metal coverage of stent at the neck. In this study, we have calculated the effect of FD on hemodynamics and achieved positive results based on the micro-CT reconstructed FD. Nonetheless, we still need to compare these results with the other techniques for virtual simulation of stent deployment.

The effect of flow-diverting stent on pressure within an aneurysm is an important issue that should be considered for clinical use. Cebral et al26 analyzed the hemodynamic changes after treatment with flow diversion and found an increase in pressure within the aneurysm after treatment, which can potentially lead to rupture, especially for giant aneurysms. Schneiders et al27 measured intra-aneurysmal pressure before, during, and after placement of a flow-diverting stent using a dual-sensor guide wire. The pressure inside the aneurysm momentarily decreased during placement, but was restored to baseline values within minutes. Our results showed a slight difference with the results of Cebral et al.26 Based on the model using micro-CT, the mean pressure of the aneurysm sac had no significant difference after the treatment of FD.

The outcomes of FD treatment were variable, and the risk of delayed rupture of intracranial aneurysm after FD treatment was estimated to be up to 1.75%.28 The prognosis of FD-treated aneurysms can be affected by many factors, such as changes in hemodynamics, function of platelets, etc. The hemodynamic-change–induced thrombosis and thrombus organization in an aneurysm sac are the key processes after the intravascular treatment for healing. These factors were supported by the findings that relative flow velocity and WSS reduction caused by FD implantation results in aneurysm thrombosis in the majority of cases.3 Our results showed differences in the average RRT increment, percentage of inflow volume reduction, and location of inlet of stream, after comparing the occluded with unoccluded aneurysms. These results may also imply the importance of hemodynamic changes for patient prognosis. Although the differences here have no statistical significance, this may be attributable to the small sample size. Similar results have been found in the study by Zhang et al27 that showed that the reduction of blood flow into the aneurysm and flow velocity magnitude at neck in a successful case were higher than that in an unsuccessful one. Because a large volume of blood flowed in/out of the aneurysm domain, the aneurysm was not fully occluded.

Limitations

The insight derived from computational simulation methodologies, such as the one described in this article, provides us with an improved understanding of this field. However, there were some limitations in this study. First, although this study confirmed the relationship between aneurysm occlusion and hemodynamic changes by FDs, the sample in the unoccluded group was small. Second, only a single flow waveform obtained from a healthy animal subject was used in all CFD calculations. Thus, this limitation might affect the validity of our results. Rabbit-specific conditions should be used in the future to obtain more accurate results. Finally, although we used micro-CT to reproduce the real configuration of FDs in parent vessels, the deformation of vessels or FDs during specimen harvesting and the resolution ratio limitation of the micro-CT might cause deviation and inaccuracy from the actual condition. Larger-scale studies are required to validate such methods further, which are expected to become a useful tool in the future decision-making process. These studies will likely lead to the development of new techniques and devices.

Conclusion

This is the first study analyzing hemodynamic modifications associated with placement of a real flow-diverting stent with the help of micro-CT. Based on our method, we demonstrated that the hemodynamic parameters of the aneurysm were significantly modified by placement of FD stents, including decreased WSS, inflow volume, and increased RRT. The significance of using micro-CT reconstructed FD in our study was to confirm the results of numeric simulation further. Compared with unoccluded aneurysms, the hemodynamic changes by FD deployment showed higher RRT increment, percentage of inflow volume reduction and showed that the location of inlet of stream was near the central region in occluded aneurysms. Our research also indicated that the difference in the clinical outcomes of FD treatment might be closely related to the diversity of hemodynamics. Reproducing the real state of deployed FD in each patient and analyzing their individualized hemodynamic changes may be a key factor for individualized therapeutic decision-making.

Acknowledgments

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Disclosures

None.

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