Role of hemodynamics in the life cycle of cerebral aneurysm

PhD Thesis

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1. Introduction

Cerebral aneurysms are pathological dilatations of the brain arteries located at their bifurcations, branching points and curvatures. These regions are exposed to increased hemodynamical forces, suggestinga significant role of hemodynamics in the life cycle of aneurysms. The importance of the disease relies on the fact that aneurysms affect a significant percentage of the population, and that during their growth they may rupture and cause subarachnoid hemorrhage (SAH), a highly life threatening situation.

Approximately 2% of the adult population is harbouring an aneurysm, however only a small minority of these lesions will end up in rupture. The incidence of SAH is estimated at cca. 10 cases/100.000 population/year. Due to its high morbidity and mortality, it would be best to avoid SAH, but our efforts are still limited in this regard. Theoretically we should be able to first identify the patients at risk of developing or harboring an aneurysm, then to be able to predict and last to reduce or eliminate the risk of rupture in individual cases.

By primary prevention one could prevent the development of aneurysms, but to achieve this, besides the regular risk factors, we should identify the hemodynamical factors triggering aneurysm formation. For secondary prevention, analysis of the hemodynamical microenvironment of an existing aneurysm may help to predict its stability or instability over time. This in turn could serve as the basis of the therapeutic decision, allowing us to choose conservative therapy for stable lesions, or invasive treatment for high rupture risk lesions. ,

In the life cycle of cerebral aneurysms hemodynamic conditions and and subsequent biological processes are not well understood.

2. Objectives

The main goal of this work was to analyse the role of hemodynamic forces acting on the cerebral vasculature in the life cycle of cerebral aneurysms, with special attention to the endothelial wall shear stress (WSS), from the phase of initiation through development until stabilization or rupture. Based upon literature findings, we carried out Computer Flow Dynamic (CFD) resaearch to answer three specific questions as listed below.

1. What is the role of spatial Wall Shear Stress (WSS) distribution in the initiation process of aneurysms?
Animal studies have demontrated that the combination of extremely high endothelial WSS and its spacial gradient (SWSSG) at a constrained region of the vessel wall plays an important role in the initiation phase of brain aneurysms. This statement was so far not proven in human clinical studies. Reviewing the patient population database of our Institute, we studied the role of these factors in the development of real human aneurysms.

2. How does the localization and morphology of an aneurysm influence the intraaneurysmal heomdynamics?
Analysis was performed on patient specific aneurysm morphologies from our own population based database.

3. What is the relationship between hemodynamics and its biological and clinical effect?
Merging the literature data with our results, we tried to identify the specific cause and effect relationships between the hemodynamical factors and the biological and clinical sequelae.

3. Materials and methods

3.1. According to our objectives, the study consisted of two main parts. In the first part we studied the hemodynamics of *aneurysm initiation*. Out of 3213 patient studied for intracranial aneurysms in our Institute using 3D DSA tachnique since 2001, three cases were identified as suitable for our study. studied During the follow-up, these patients developed a saccular aneurysm at a location where, at the time of the initial angiogram including 3D-DSA, no aneurysm was present (2 patients) or only a small aneurysm-like dilation was demonstrated (1 patient). The studies were obtained due to ruptured (2 cases) and incidentally discovered aneurysms (1 case) at different locations from the studied segments. Medical history, risk factors, and the time between the initial angiogram and the follow-up studies demonstrating a fully developed aneurysm were recorded for all patients. CFD modeling was performed in all 3 patients at baseline and also in 2 patients after aneurysm development. The local flow fields were also determined on 2 models with the developed aneurysms, in which a 3D-DSA was performed after the formation of the aneurysm.

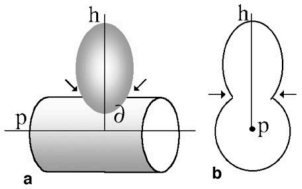
Despite the aparently low sample size, the originality of this study relies on the fact that it is seemingly difficult to catch the initiation phase of aneurysm formation, because several criteria need to be fulfilled at the same time. Due to these factors there are no clinical data pulished to date.

3.2. In the second part of the study we analyzed the influence of *aneurysm geometry* on the intraaneurysmal hemodynamics. A total of 21 aneurysms were retrospectively selected making sure that different morphological types (such as side wall or bifurcation aneurysms) were equally represented in the entire group. During the selection process, the clinical history of the patients

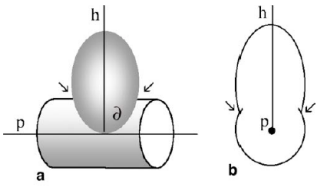
and anatomical locations of the aneurysms were not taken into consideration. In order to achieve good flow visualization, very small aneurysms (<6 mm) were not included in this study.

All aneurysms were then analyzed using 2-D angiograms in two standard planes, the 3-D reconstruction model and the simulated flow pattern. Patient history, lesion location, aneurysm diameters in two planes, aspect ratio, morphological type, aneurysm to parent vessel angle, flow pattern, pressure and shear stress distribution over the aneurysm wall were recorded for each aneurysm. The two largest diameters of each aneurysm were measured in two perpendicular planes selected on 3-D reconstructed images. The aspect ratio was defined as the height of the aneurysm divided by the width of the neck.

Aneurysms were categorized as side-wall or bifurcation type on the basis of their morphology. Based on our previous observations using flow studies, we further classified side-wall aneurysms as side-wall type with either a limited focal involvement of one side of the parent artery wall (*single-sided*) or circumferential involvement of the parent vessel (*circumferential*).



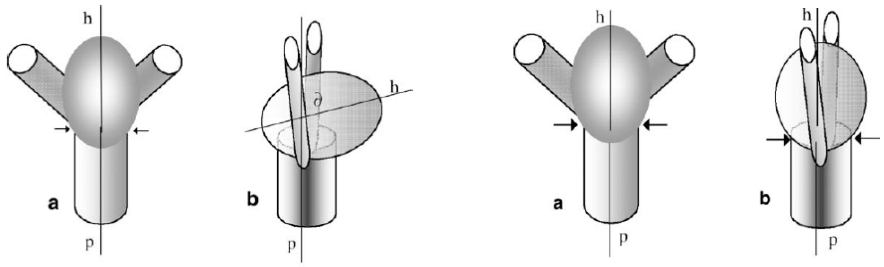
Single-sided



Circumferential

On 3-D reconstructed images, the main axis of the last straight segment of the parent artery immediately proximal to the aneurysm and the two main axes of the aneurysm (considered as the two largest diameters) were obtained in two perpendicular planes. The angles between the parent

artery axis and the two axes of the aneurysm were measured. Aneurysms with axial angles less than 45° in both planes were considered as *parallel type* and those with an angle of more than 45° in one plane were classified as *perpendicular type.*



Perpendicular type **Parallel type**

Intraaneurysmal flow patterns were characterized as *regular vortex flow* with inflow at the distal and outflow at the proximal edge of the neck and a single vortex within the sac; *irregular vortex flow* with reversed inflow/outflow zones and/or multiple vortices; or *jet type flow* with a straight inflow zone hitting the aneurysm dome that behaved as a flow divider, and outflow either at one or both edges of the neck. Pressure and WSS was recorded on flow simulations and classified as either evenly distributed over the aneurysm surface or having a peak at a small area over the neck or dome.

3.3. Flow dynamic simulations

Conventional 2-D and 3-D rotational angiography studies were obtained in all aneurysms using a GE LCV+ digital subtraction angiography unit. CFD modeling was performed in all patients. The initial 3D rotational angiography was reconstructed by using an Advantage Windows workstation with ADW 4.2 reconstruction software (GE Healthcare, Milwaukee, Wisconsin). The 3D image data base was then converted to a 3D surface. The commercially

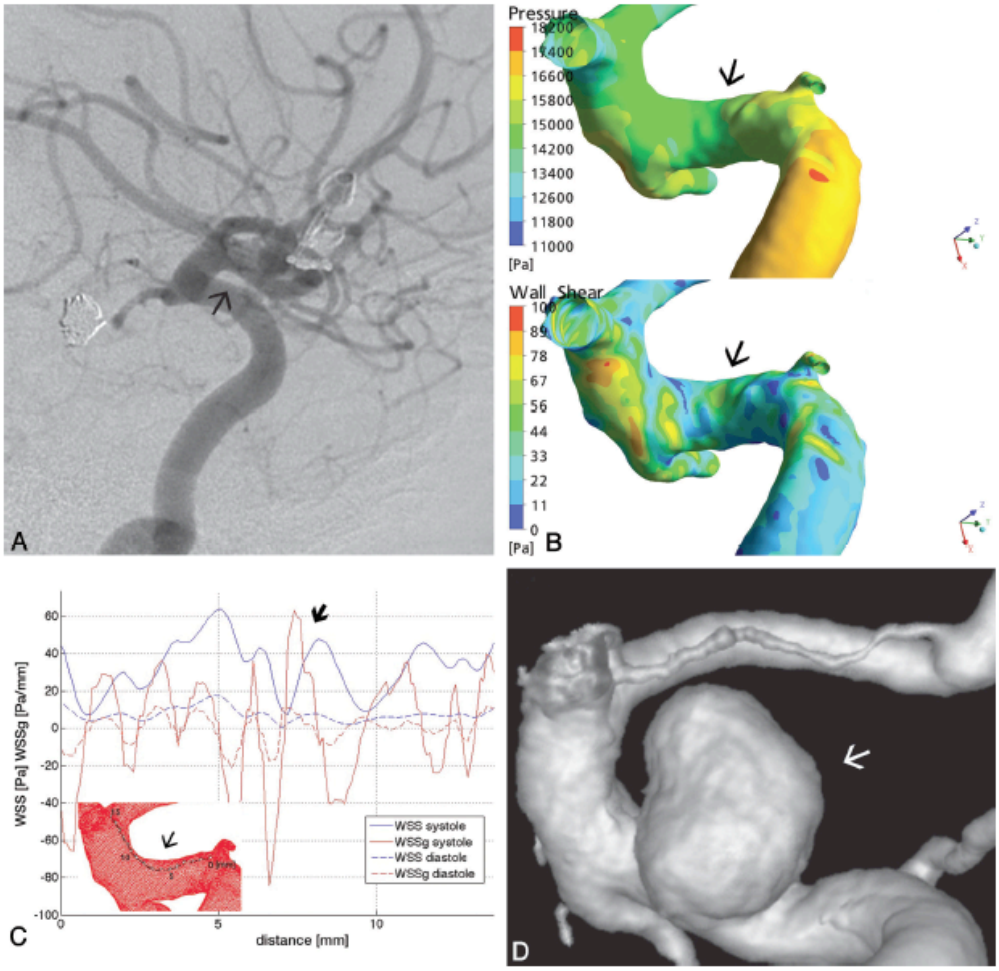
available ICEM CFD 10.0 (ANSYS, Canonsburg, Pennsylvania) was used to generate an advanced tetrahedral mesh inside the extracted surface. To have a good numeric resolution near the vessel wall, we used 5 layers of prismatic cells in all cases. The mesh sizes were ap-proximately 300,000 to 800,000 elements. Flow was then simulated in the resulting finite-volume model assuming the circulating fluid to be Newtonian and incompressible with an attenuation of 1050 kg/m3 and a viscosity of 0.003 kg/m/s. Vessels were considered to be rigid tubes. Flow was simulated by using the CFX 11.0 commercial software (ANSYS). The analytic cardiac cycle was 0.8 seconds with a time-step of 0.01 or 0.2 seconds, so that 1 cycle comprised 80 or 40 time-steps. A total of three cycles were simulated making sure that the initial transients disappeared. Flow was considered pulsatile with a synthetic inlet velocity function reproducing a realistic shape of the cardiac function. Constant pressure was used as the outlet boundary condition considering the constant nature of the peripheral resistance. The parameters were chosen so that the fluctuation of the average pressure level in the region under investigation remained between 80 and 120 mm Hg. This method leads to a velocity and pressure field inside the studied vessel segments fluctuating in the same phase.

4. Results

4.1. Hemodynamic microenvironment of aneurysm initiation

By observing the natural history of aneurysm formation from its preaneurysm state and by using 3D reconstructions of the vascular segments not yet harboring a true aneurysm, we have performed CFD analysis at both sidewall and bifurcation arterial segments where aneurysms later developed.

Increased WSS accompanied by high positive SWSSG was found at the sites of future aneurysms, leading to the idea that these factors could potentially be involved in aneurysm initiation.



***A*, Right ICA lateral view DSA of patient 2 shows no aneurysm at the upper wall of the C2 ICA segment (*arrow*). *B*, Surface pressure (upper) and WSS distribution map (lower) demonstrate increased forces at the site of future aneurysm. *C*, Along the arbitrarily defined line, the diagram shows a major peak in SWSSG approximately at point 3 (*thin arrow*), followed immediately by a WSS peak at point 5 (*thick arrow*). *D*, The first combined peak is followed by a second at approximately points 7– 8, which fell later into the neck area of the developed aneurysm, as seen on the 3D reconstructed angiogram.**

Our results are in consistence with animal studies showing that the excessive endothelial WSS and the spatial gradient of the WSS (the SWSSG) may play a role in the initiation phase of aneurysm formation. The affected vessel segments, where later on an aneurysm had developed, was exposed to higher surface pressure as suggested by the simulations. The relative surface pressure at the affected segments was increased in all patients. The high peak in WSS and the SWSSG peak presented exactly at the site of the proximal edge of the neck of the aneurysm that developed later. The WSS values at these points were at least 5 times higher than the temporal average values of the parent vessel. One can assume that the initial destructive changes in the vessel wall, like rupture of the *internal elastic lamina* and weakening of the muscular layer, take place at the site of the highest hemodynamic stress. With these effects concentrating at a relative small segment of the vessel wall, like in the cases studied, the biological consequences may present in an exponential way, not allowing the vessel wall for reconstructive remodeling.

4.2. Impact of aneurysm geometry on intraaneurysmal flow

In the second part of the study we assessed the effect of aneurysm geometry on parameters that may have an impact on the natural history of intracranial aneurysms, such as intraaneurysmal flow pressure and shear stress.

Four of five *single-sided* aneurysms had regular vortex flow and four of five *circumferential* aneurysms had irregular vortex flow with the inflow/outflow zones being reversed or complex.

The current observations suggest that the size of the neck in a plane perpendicular to the parent vessel axis also plays a role by changing the flow pattern of the aneurysm. With circumferential involvement, the aneurysm sac is not necessarily positioned symmetrically on top of the parent artery. If the

sac is arranged in an asymmetric fashion, the shear-driven vortex flow may develop in a plane perpendicular to the parent artery axis rather than in the parallel plane as generally thought. This may explain the reversal of the locations of the inflow/ outflow zones, since proximal or distal positions cannot be interpreted in a plane perpendicular to the main stream of flow within the parent vessel.

Similar to the above, bifurcation aneurysms were classified based on the angle between the height of the aneurysm and the main axis of the parent artery. As expected, all side-wall aneurysms were perpendicular, but not all bifurcation aneurysms were parallel to the parent artery. The axis of 4 of 11 bifurcation aneurysms diverged significantly from the axis of the parent artery. All perpendicular aneurysms had vortex flow (either regular or irregular), including four bifurcation aneurysms. On the other hand, all seven parallel aneurysms had jet flow, and were bifurcation aneurysms. These results, however, suggest that the shear-driven versus jet type nature of the flow pattern is primarily determined by the aneurysm/ parent vessel angle rather than by the side-wall or bifurcation configuration of the lesion.

We found a strong correlation between flow type and unsteady pressure distribution: all seven aneurysms with jet flow had an uneven distribution with a peak at the dome, while 11 of 14 with vortex flow had an even distribution of pressure along the wall of the aneurysm sac. The significance of this finding is debatable. The magnitude of pressure inhomogeneity was very low, with intraaneurysmal peaks not exceeding the maximum pressure within the parent artery. However, even at low magnitudes, coupled spatial and temporal inhomogeneity may play a role in aneurysm wall fatigue and eventual rupture. Clinically, four of five ruptured aneurysms in the study group had a parallel axis, jet flow and peak pressure at the dome.

5. Conclusions

5.1. By observing the natural history of aneurysm formation from its preaneurysm state, in correspondence with previous animal experimental data, the current CFD study with clinical follow-up suggests that the combined presence of increased WSS and high positive SWSSG focused at a small arterial segment may have a role in the initiation process of an aneurysm. This is the first such study showing the role of hemodynamics in aneurysm initiation in real human cases, with true clinical follow up. Because both of these parameters are relatively easily deducible by CFD simulations, they may be considered for further analysis in this disease process. The exact pathomechanism of how this complex hemodynamic setting will translate to a biologic response also needs further study.

5.2. Aneurysmal geometry has a significant impact on intraaneurysmal flow conditions. Circumferential involvement of the parent artery wall modulates the characteristic flow pattern of side-wall aneurysms and may result in reversed inflow/outflow zones. This feature should be considered in treatment planning, while blocking the inflow zones of the aneurysms is the one of the most important goals of endovascular therapy.

5.3. In this study, the aneurysm/parent vessel angle was the primary factor determining the basic flow pattern of the aneurysm. Aneurysms perpendicular to the parent artery had shear-driven, vortex flow and those parallel to the parent artery had jet flow, regardless of whether they were located on the side-wall or at a bifurcation of the parent artery. Jet flow seems to induce an uneven pressure distribution over the aneurysm wall, and might

be more frequently associated with aneurysm rupture. This may have an implication in treatment planning.

Although the significance of the study may seem to be limited by the low number of cases, the limitations are not only technical, but also due to the fact thet there's a need for a coincidence of fortuitous factors. All these results however may play an important role in the primary and secondary prevention, and in the treatment planning of aneurysm disease, in the not very distant future.

6. List of publications

6.1. Peer-reviewed publications that serve as the basis of the Ph.D. thesis:

1. **Kulcsár Zs**, Ugron A, Marosfői M, Berentei Z, Paál G, Szikora I. (2011): Hemodynamics of cerebral aneurysm initiation: the role of wall shear stress and spatial wall shear stress gradient. AJNR *Am J Neuroradiol*. **32**(3):587-94.
2. Szikora I, Paál G, Ugron Á, Nasztanovics F, Marosfői M, Berentei Zs, **Kulcsár Zs**, Lee W, Bojtár I, Nyáry I. (2008). Impact of aneurysmal geometry on intraaneurysmal flow: a computerized flow simulation study. *Neuroradiology*. **50**(5):411-21.
3. **Kulcsár Zs**, Berentei Z, Marosföi M, Vajda J, Szikora I. (2010): Thromboembolic complication induced stable occlusion of a ruptured basilar tip aneurysm. Case report and review of the literature. *Interv Neuroradiol*. **16**(1):83-8.

6.2. Other, most important publications

1. **Kulcsár Zs**, Bonvin C, Pereira VM, Altrichter S, Yilmaz H, Lovblad KO, Sztajzel R, Rüfenacht DA (2009). Penumbra^{TM} System: A Novel Mechanical Thrombectomy Device for Large Vessel Occlusions in Acute Stroke. AJNR *Am J Neuroradiol*. **31**(4):628-33
2. **Kulcsár Zs**, Bonvin C, Lovblad KO, Gory B, Yilmaz H, Sztajzel R, Rufenacht D (2010): Use of the Enterprise Intracranial Stent for Revascularization of Large Vessel Occlusions in Acute Stroke. *Klin Neuroradiol*. **20**(1): 54-60
3. **Kulcsár Zs,** Yilmaz H, Bonvin C, Lovblad KO, Rüfenacht DA (2010): Multiple Coaxial Catheter System for Reliable Access in Interventional Stroke Therapy., *Cardiovasc Intervent Radiol*. **33**(6):1205-9.
4. **Kulcsár Zs**, Wetzel S., Augsburger L., Gruber A., Wanke I., Rüfenacht D (2010): Effect of flow diversion treatment on very small ruptured aneurysms. *Neurosurgery*. **67**(3):789-93.
5. **Kulcsár Zs**, Ernemann U., Wetzel S.G., Bock A., Goericke S., Panagiotopoulos V., Forsting M., Ruefenacht D. A., Wanke I (2010): High-profile flow diverter (Silk) implantation in the basilar artery: efficacy in the treatment of aneurysms and the role of the perforators. *Stroke*.**41**(8):1690-6.
6. **Kulcsár Zs** et al (2011). Intraaneurysmal thrombosis as a possible cause of delayed aneurysm rupture after flow diversion treatment. AJNR *Am J Neuroradiol*.; **32**(1):20-5.

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