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# Hemodynamics in Ruptured Intracranial Aneurysms

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## Abstract

Incidental detection of unruptured intracranial aneurysms (UIA) has increased in the recent years. There is a need in the clinical community to identify those that are prone to rupture and would require preventive treatment. Hemodynamics in cerebral blood vessels plays a key role in the lifetime cycle of intracranial aneurysms (IA). Understanding their initiation, growth, and rupture or stabilization may identify those hemodynamic features that lead to aneurysm instability and rupture. Modeling hemodynamics using computational fluid dynamics (CFD) could aid in understanding the processes in the development of IA. The neurosurgical approach during operation of IA allows direct visualization of the aneurysm sac and its sampling in many cases. Detailed analysis of the quality of the aneurysm wall under the microscope, together with histological assessment of the aneurysm wall and CFD modeling, can help in building complex knowledge on the relationship between the biology of the wall and hemodynamics. Detailed CFD analysis of the rupture point can further strengthen the association between hemodynamics and rupture. In this chapter we summarize current knowledge on CFD and intracranial aneurysms.

**Keywords:** intracranial aneurysm, hemodynamics, rupture, cerebral blood flow, computational fluid dynamics

## 1. Introduction

Intracranial aneurysm (IA), a pathological dilation of the vessel wall, is the result of hemodynamic forces on the wall of the intracranial artery. It is characterized by mild to moderate structural changes of the vessel wall, which may result in aneurysm rupture, leading to a severe form of hemorrhagic stroke [1].

In the last 15 years, there has been increasing incidental detection of unruptured intracranial aneurysms (UIA) due to an increasing use of noninvasive radiological examinations, such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA) [2]. The increasing use of these noninvasive techniques for various non-specific complaints results in higher detection and increasing treatment of UIA. While 20% of individuals operated on for an IA in 1998 were carrying a UIA, in more recent years, the number has increased to more than 50% of all patients operated on for IA in the Department of Neurosurgery of

the Jan Evangelista Purkyně, Masaryk Hospital in Ústí nad Labem, Czech Republic. Concurrently, there have been an increasing number of patients that we monitor for UIA who do not receive treatment. Should the aneurysm not rupture, which occurs in the majority of IA cases, very few become symptomatic in other ways. If it does rupture, it results in severe consequences including death, various levels of neurological disabilities, and cognitive or social difficulties.

The decision on whether to treat an individual with a UIA is based on the balance between the risk of treatment and the risk of the natural history of the aneurysm. If the aneurysm does not rupture, the risk of other clinical symptoms is quite low. These symptoms may appear as compression of the nervous structures (the optic nerve may be compressed by an ophthalmic aneurysm, the oculomotor nerve by a posterior communicating artery aneurysm, or the brain stem may be compressed by a large basilar aneurysm). Other symptoms may result from embolization of thrombi from the sac of an aneurysm; this is, however, very rare [3]. The worst outcome is that patients may experience aneurysm rupture. Overall, this risk is low in most patients and therefore does not occur in the vast majority of them in their lifetime [4]. The risk of rupture is associated with many factors; some of them are inherent (higher risk of rupture in females, some nations, such as Japanese); other factors are modifiable (higher risks are associated with hypertension or smoking). The rupture leads to a severe form of hemorrhagic stroke or even death. The risk of death after rupture is somewhere between 26 and 36% of patients [5]. The improved care of patients with SAH in specialized neurovascular centers improves survival rates [6]. Alternatively, about 15% of patients die immediately after rupture or before they are transported to hospital. Approximately 20% of those that survive develop a global cognitive deficit [7].

Contrarily the treatment, even in selected UIA, may carry the risk of severe complications may be as high as 16% of patients; the risk of mortality being 0–3.2% and the chance of not being discharged home almost 20% [8]. All the scoring systems used for analyzing the risk of rupture are based on data from large population studies. These factors include the size of the aneurysm, its location within the circle of Willis, its shape, etc. However, the size or the shape of the aneurysm is a result of forces that themselves lead to aneurysm initiation, its growth, and eventual rupture (or stability with no rupture). This is the result of the balance between hemodynamic forces and the quality of the blood vessel wall at the site of the aneurysm. Immediately when the hemodynamic forces overcome the strength of the aneurysm wall, it will rupture. Consequently an understanding of the hemodynamics within the cerebral blood vessels and the aneurysm itself may help with understanding its initiation, growth, and eventual rupture. The ability to model the hemodynamics within the aneurysm could also possibly assist with predicting their risk element and the direction to preventive treatment. It may also be possible to securely monitor aneurysms with a non-risky hemodynamic profile.

In this chapter we aim to provide current information on aneurysm hemodynamic modeling, using CFD. We will focus on ruptured and unruptured aneurysms, the hemodynamic characteristics at the point of rupture and the difference between ruptured and unruptured IA. We will discuss the issue from the perspective of neurosurgery and its possible contribution to clinical practice. We will summarize our 8 years of experience with CFD modeling in intracranial aneurysms, as well as the current literature.

## **2. The pathophysiology of the life cycle of intracranial aneurysms**

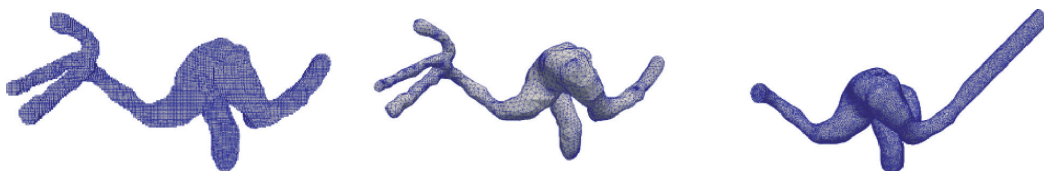
During physiological conditions, the cerebral blood vessels consist of three layers: (1) tunica intima with a basal membrane, endothelial cells, and the internal

elastic lamina; (2) tunica media, which consists of circumferentially oriented smooth muscle cells inside a dense network of collagen and elastin fibers; and (3) tunica adventitia, which consists mostly of collagen providing strength for the vessel wall. Tunica intima and tunica media are separated by a layer of lamina elastica interna, which is the key structure and has to degrade for the intracranial aneurysm to develop [9]. Cerebral blood vessels differ from extracranial blood vessels in that they have a thicker internal elastic lamina, less elastin, and smooth muscle cells in the media; in addition, they have no lamina elastica externa and a thinner layer of adventitia. There is minimum perivascular tissue in the subarachnoid space. The bifurcations of cerebral blood vessels contain irregularities in the vessel wall. The bifurcations are the typical areas of aneurysm development [10, 11]. Due to the small diameter of intracranial blood vessels, the wall shear stress plays a significant role in the degeneration of blood vessels and development of IA. The small diameter of cerebral blood vessels is also influenced by pathological forces induced, for example, by hypertension, and these lead to the development of IA. On the other hand, it is not quite clear what is the character of hemodynamic forces that lead to the development and rupture of IA. Some hypotheses describe the pathological influence of low wall shear stress leading to blood flow stagnation and the accumulation of blood elements (erythrocytes, leukocytes, thrombocytes), causing degeneration of the vessel wall together with inflammatory changes [12]. Another theory is based on high wall shear stress (WSS) causing damage of the endothelium, remodeling of the blood vessel wall, and its eventual degradation. It seems that possibly both scenarios could play a role [13].

### 3. Computational fluid dynamics (CFD) of intracranial aneurysms

The actual process of modeling hemodynamic parameters consists of several steps. Creating a 3D model is done by manual or semiautomatic segmentation (**Figure 1**). Angiographic examinations (3D angiography, CT angiography, or MR angiography) are used as the source data. Each radiological method has its own limitations (calcifications, flow artifacts, etc.). Several studies have tried to assess the relationship between different imaging examinations [14, 15]. In one such study, the authors compared the results of CFD obtained from CTA or DSA [14]. In conclusion, the authors state that, despite the quantitative differences in the individual hemodynamic parameters between the CTA and the DSA segmented group, the basic flow characteristics of both groups were identical.

In the next step, a calculation is performed using the Navier-Stokes equations, which describe the flow of incompressible fluid with constant viscosity. The use of the numerical solution of the Navier-Stokes equations calculates with assumption of blood having laminar flow. Possible influences of phenomena not captured by this model are further investigated, such as the influence of turbulent flow or viscosity change depending on the shear stress [16–19].



**Figure 1.** *The process of obtaining patient-specific geometry from the CT or MR scan with high resolution includes accurate voxel segmentation of the vessel, generating surface mesh, and finally smoothing, generating volumetric mesh, and prescribing inlets and outlets with possible shortening and elongating of the outputs.*

These calculations characterize the flow, i.e., they provide information about fluid velocity and pressure on the vessel wall and the quantities derived there from such a stress tensor. Due to the uncertainty in the description of the area, as well as the specified boundary conditions, the inconsistency of these variables may be significant, but certain global-derived quantities—wall shear stress and oscillatory shear index (OSI)—are identical for a certain variation in the accuracy of numerical solutions [20]. WSS is defined as the pressure that acts in parallel with the blood vessel lumen. The OSI then describes the difference between the WSS vector and the blood flow during the cardiac cycle. When interpreting the data, we always need to bear in mind the approximations and assumptions during the process of CFD modeling.

The development of intracranial aneurysm can be divided into three phases: initiation, growth, and stabilization. Only a small percentage of aneurysms are unstable, progressing, and eventually resulting in rupture. The growth, shape change, and rupture of the aneurysm are the situations that we try to understand by mathematical modeling and to estimate the risk of these critical phases of development.

### **3.1 CFD in ruptured vs. unruptured intracranial aneurysms**

One way to determine the risk of intracranial aneurysms is to compare the hemodynamic characteristics between ruptured and unruptured aneurysms. We can either compare non-specific aneurysms based on the status of rupture or only compare ruptured and unruptured aneurysms either at specific locations (MCA, PCom, etc.) or the so-called “mirror” aneurysms (right and left PCom or MCA aneurysms) [21, 22].

To date, several studies have been conducted to compare ruptured and unruptured aneurysms [22, 23]. Some of them were performed on a large number of aneurysms; others were focused on a small number of aneurysms at a specific location [22, 24–26]. The aim of these studies was to find differences between morphological and hemodynamic parameters, which would distinguish both groups. The characteristics of ruptured aneurysms could then help to identify the risky ones.

In one of the largest studies on 119 aneurysms, the authors found differences in 4 morphological and 6 hemodynamic parameters between ruptured and unruptured intracranial aneurysms [27]. The multivariate logistic regression analysis revealed that the morphological factor of size ratio and two hemodynamic factors, WSS and OSI, were independent factors of rupture risk. In 2017, a meta-analysis was published which, based on 1257 aneurysms from 22 studies, evaluated differences in hemodynamic parameters between ruptured and unruptured aneurysms. It showed that in ruptured aneurysms, WSS is significantly lower than in unruptured ones [28]. The same result was shown on 106 ACM aneurysms [22]. Alternatively, the largest ever study comparing ruptured and unruptured aneurysms has shown that wall shear stress is higher than those in unruptured aneurysms [29].

Previous results must therefore be given careful consideration as many factors have a significant influence on WSS. The meta-analysis itself shows, for example, the difference in WSS in aneurysms at different locations (the lowest is in the aneurysms of the apex of the basilar artery). One way to eliminate the influence of different localizations is to compare either the so-called mirror aneurysms (right and left IA MCA or PCom) or aneurysms of one localization in general (ACom, ICA, MCA, PCom, etc.).

Another important factor affecting IA hemodynamics is their size [13, 30]. We compared hemodynamic factors in small and large aneurysms based on the largest diameter of 10 mm (small <10 mm, large >10 mm) as this is commonly used to

differentiate between small and large aneurysms in clinical practice (publication in preparation). We have found that size significantly influences the WSS within the aneurysm, independent of its rupture status. WSS in small aneurysms was significantly smaller. The only similar study used a volume of the sac to differentiate small and large aneurysms [30]. However, in clinical practice, the volume of the sac is not assessed on a regular basis, and its use is less practical in clinics. Nonetheless the results of both studies emphasize the importance of aneurysm size assessment with respect to evaluation of hemodynamic factors; generally it is necessary to compare hemodynamic parameters in equally sized aneurysms. One possible way to circumvent this effect is to use the so-called WSS statistical maps to convert the results to the surface of the aneurysm sac [31].

Specific limitations of studies comparing ruptured and unruptured aneurysms result from the fact that we already assess the condition given by rupture, not the aneurysm at risk, before rupture. Therefore, altered morphology of the aneurysm after rupture can lead to erroneous results or misinterpretations [32]. Another limitation in these studies is that we usually do not possess the individual boundary conditions for each aneurysm and need to use literature-based information.

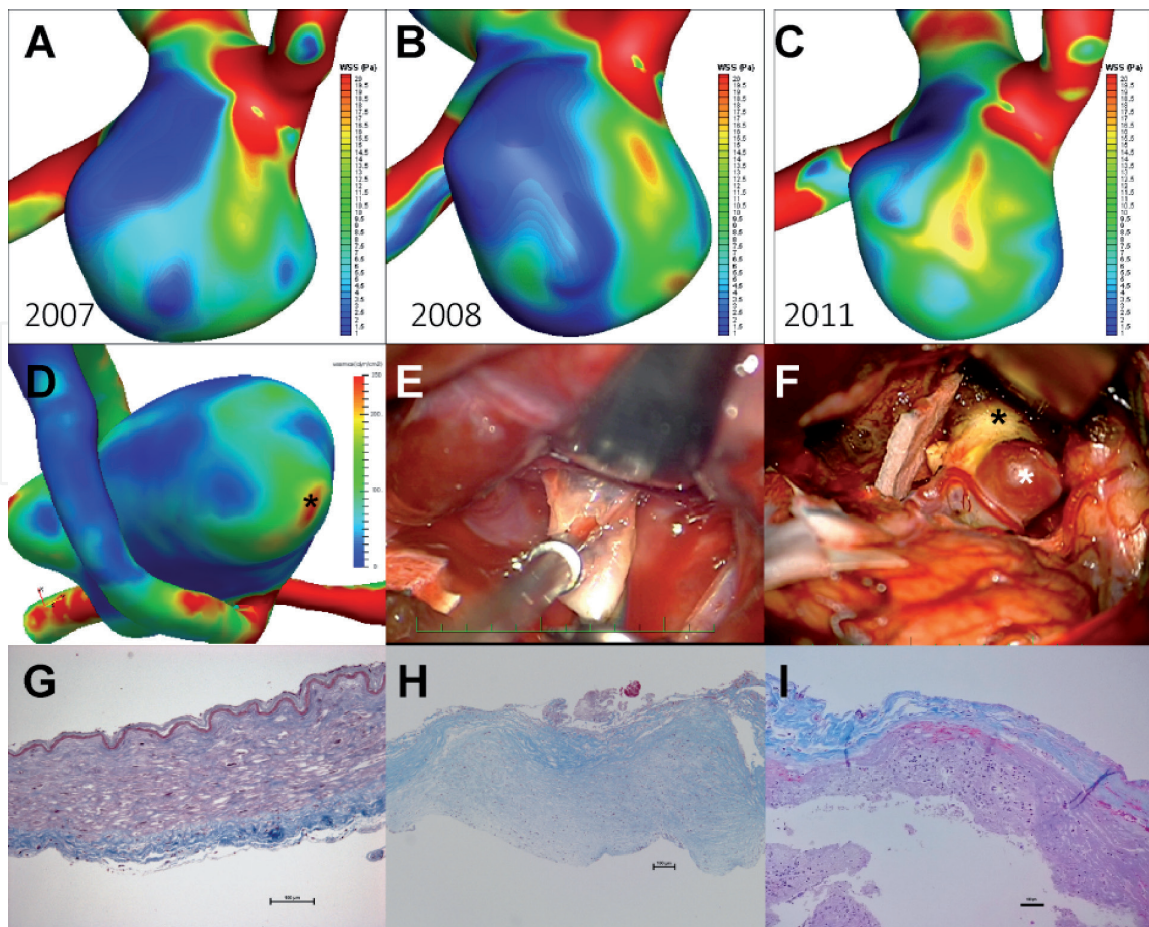
### 3.2 CFD in ruptured intracranial aneurysms

The study of hemodynamics in ruptured aneurysms provides a chance to link the hemodynamic parameters with rupture (**Figure 2A–D**). Most studies have focused on the aneurysm sac as a whole. However, the aneurysm sac in ruptured aneurysms may be divided into the site of the rupture and the surrounding part of the sac. In these rare cases when we are able to differentiate those two parts of the aneurysm sac, we can combine our knowledge with local hemodynamic parameters. There are two types of studies in which the authors were able to identify the point of rupture. Firstly, there are surgical series when the neurosurgeon perioperatively identifies the site of rupture (perioperative rupture, apparent wall rupture during inspection of the sac usually before clip deployment, etc.) [33, 34]. Secondly, there are mostly case reports when the rupture in the angiographic room occurs, and the leakage of blood from the sac is thus identifiable during the interventional procedure [35, 36].

The site of rupture may show specific hemodynamic features (**Figure 2D**). So far there have been few studies with altogether a low number of patients (around 40 in total). The results are rather contradictory as it is apparent from the table; thus, it is difficult to make any straightforward general conclusions (**Table 1**).

It seems that the site of rupture is associated either with concentrated jet flow and high WSS (**Figure 2D**) or, on the other hand, a slow flow and low WSS. Both types of flow can lead to degeneration of the blood vessel wall but via a different mechanism [13]. Whereas low WSS and high OSI may lead to the activation of inflammatory cells and impairment of vessel wall structure, high WSS leads to the activation of cells in the vessel wall, leading to the growth of aneurysm sacs and rupture in small sacs or blebs. Reaching a certain size of the aneurysm sac during its growth leads to slowing the flow and recirculations, resulting in WSS decrease. In the IA itself, the highest WSS is usually around the neck and it decreases toward the apex. The low WSS can lead to degradation of the internal structure of the vessel wall and a further increase in the size of the sac. Most ruptures take place just in the apex of the aneurysm sac.

The disadvantage of all studies evaluating local hemodynamic parameters relative to the rupture site is the same as in all studies evaluating ruptured aneurysms. As mentioned above ruptured aneurysms may have a different shape after rupture, which can influence the results of hemodynamic modeling parameters as compared to the pre-rupture situation [32, 37]. Studies in which a hemodynamic analysis was



**Figure 2.**

(A–C) Development of WSS over time in an IA that eventually ruptured. The WSS gradually decreased between the years 2007 and 2011. (D) A ruptured ACom aneurysm. The point of rupture (\*) was confirmed during surgery. It was associated with increased WSS. (E) A perioperative image showing a ruptured MCA aneurysm. The point of rupture is in the weak part of the aneurysm wall. (F) A perioperative image showing an unruptured MCA aneurysm with heterogenous wall, an atherosclerotic part with a thrombus inside (black asterisk) and a red thin wall (white asterisk). (G) A histological image showing in detail the vessel wall of the Willis's circle without an aneurysm: the structure consists of the tunica intima with endothelial cells, which is separated from the tunica media by the internal elastic lamina (IEL), the tunica media with linear layer of smooth muscle cells, and the tunica adventitia, the outermost layer, which comprise mainly of collagen. (H) An UIA: moderate structural changes of the vessel wall, mainly fibrosis across the vessel wall without layers and the internal elastic lamina. (I) A ruptured IA: severe structural changes of the vessel wall. The wall is thinner, without tunica intima, and linear layer of smooth muscle cells, with the presence of organized thrombus (Masson trichrome staining in all three histological images).

performed shortly before rupture avoid this limitation and may be helpful [35, 38]. These studies are rare, but their results are important, as they provide a hemodynamic characteristic within an extremely vulnerable aneurysm (which will soon rupture). Zhang et al. described three cases of large carotid aneurysms just before their rupture (2–5 days before SAK from aneurysm) and compared them with the same large eight unruptured ones [35]. They found that all ruptured aneurysms had an irregular shape and a higher aspect ratio (AR), and the WSS was lower than in the parent artery, as opposed to ruptured aneurysms. Additionally, in another study where the hemodynamic study of the basilar artery apex was performed 2 hours before the aneurysm rupture, the authors also found that in this aneurysm, WSS was lower than the parent artery [38]. However, the actual rupture site was associated with high WSS at the point of the blood jet into the sac. We found a similar flow characteristic in our case report where the site of rupture correlated with concentrated jet flow accompanied with high WSS and high normal pressure [39].

Understanding the changes in hemodynamics in ruptured aneurysms over time before the moment of rupture is of great importance; such studies are obviously quite

Author, year	No. of cases	Identification of rupture	Hemodynamics at the site of rupture
Kono et al., 2012 [33]	1	3DRA	Low WSS at diastole and high pressure at systole
Omodaka et al., 2012 [56]	6	Periop finding	Low WSS and high OSI
Hodis et al., 2013 [36]	1	2DA	Jet flow, elevated WSS, and pressure at systole
Fukazawa et al., 2015 [34]	12	Periop finding	Low WSS and slow flow
Cebral et al., 2015 [57]	9	3DRA and CT	High WSS
Hejčl et al., 2017 [39]	1	Periop finding	Jet flow and high WSS
Wang et al., 2018 [58]	1	Periop finding	Low WSS and high OSI
Suzuki et al. 2019 [59]	7	Periop finding	Max pressure areas, then decreased WSS

**Table 1.**  
*CFD studies evaluating hemodynamic parameters at the known site of rupture.*

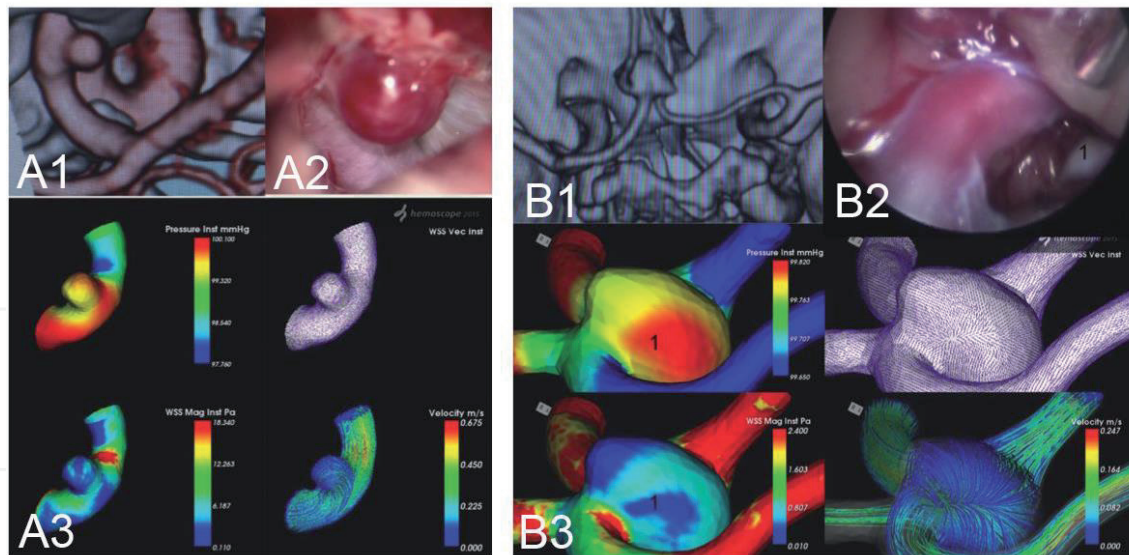
rare [32, 40]. Our own study showed that a secondary aneurysm, a frequent rupture site, was observed in the aneurysm that subsequently ruptured (**Figure 2A-C**) [40]. WSS was reduced and the flow was slow at the rupture point. Over time, the area of low WSS increases in aneurysms that rupture (Sejkorová et al., in preparation). Such studies are vital for identifying the hemodynamic factors associated with the increased risk of rupture and may possibly be used in the future as an indicator for the active treatment of monitored UIA.

### 3.3 Correlating hemodynamics with the histology of the wall of intracranial aneurysms

One of the shortcomings of mathematical modeling is that we still know little about the relationship between hemodynamics and its influence of the biology of the vessel wall [41]. Understanding the balance between the flow and the biology of the aneurysm wall is the key factor in the life cycle intracranial aneurysms. The aneurysm wall ruptures when there is an imbalance between the aneurysm wall thickness and hemodynamic forces; both reciprocities are influenced. Modeling the relationship between histological changes and hemodynamic parameters is a logical way of research development (**Figure 2E-I**). The correlation of histological changes with mathematical models can help to verify the accuracy of mathematical models of hemodynamics, to improve understanding of the acquired data, and to transfer this methodology closer to practice in clinical neurosurgery. The correlation of histological changes and hemodynamics avoids errors related to CFD parameter evaluation in relation to, for example, aneurysm rupture; while the ruptured one was not ruptured prior to the event, the unruptured one could be ruptured in a few hours.

Frösen et al. classified four types of histological wall structures of aneurysms, based on disorganization of the vessel wall structure, myointimal hyperplasia or hypocellularity of the vessel wall, smooth muscle cell (SMC) proliferation, and the presence of organized thrombus [42]. The ruptured aneurysm wall is more often characterized by being disorganized, thinner, hypocellular, with an organized thrombus present (**Figure 2I**). Different types of wall structures can be found within one aneurysm sac. One of the first studies to correlate hemodynamic parameters with the pattern of the vessel wall has recently been published [43]. Quite





**Figure 3.** (Left panel) Red, thin areas on aneurysm wall are more often associated with low WSS. (A1) Right ICA aneurysm. (A2) Intraoperative microsurgical view. (A3) CFD analysis. (Right panel) Yellow, atherosclerotic areas on aneurysm wall are more often associated with low WSS, high pressure, diverging WSS vectors, direct impact of streamlines with high-velocity flow (labeled with “1” in the figure). (B1) Anterior communicating artery aneurysm. (B2) Intraoperative endoscopic view. (B3) CFD analysis.

surprisingly, the authors found that the high WSS and high-velocity flow were associated with the appearance of inflammatory changes in the aneurysm wall, while low flow areas were associated with degenerative changes in the aneurysm wall and loss of smooth muscle and pericytes. This finding is quite different from the previous studies, which did not correlate hemodynamics and histological characteristics. The correlation of histological changes and hemodynamics avoids the risk of error in comparing ruptured and unruptured aneurysms. There will most likely be a difference between an aneurysm that never ruptures and an aneurysm whose rupture is imminent. However it is not known which aneurysms we are analyzing.

In a less elaborative way, CFD modeling can be correlated simply with the perioperative findings during surgery (**Figures 2E, F and 3**). The wall of many aneurysms can be heterogenous including thin red areas, calcifications, and the thick yellow atherosclerotic wall part. In one such study, red, thin aneurysm wall areas were more often associated with low WSS (**Figure 3A1–3**) [44]. A total of 39 areas were identified and directly visually inspected on the aneurysms walls. The study showed that red, thin aneurysm wall areas were more often associated with low WSS, high pressure, parallel WSS vectors, and curved streamlines (75%) [40]. On the other hand, the association of low WSS with high pressure, diverging WSS vectors, direct impact of streamlines, and high-velocity flow more frequently matched with yellow, atherosclerotic aneurysm walls (79%) (**Figure 3B1–3**). Although routinely used imaging techniques can provide information about morphology and anatomical relationships of the aneurysm with the surrounding structures, there is currently no way to predict the thickness of the aneurysm wall. CFD can potentially provide this kind of information, which would be valuable not only to assess rupture risk but also to improve the surgical strategy during clipping or coiling. The authors of this study hypothesize that direct, high-velocity impact of blood flow on a specific area of the aneurysm could trigger a remodeling of the wall, ultimately leading to a reactive thickening.

In our recent project, we evaluated histological changes in ruptured and unruptured intracranial aneurysms. According to our preliminary data on the first 30 samples of individuals with ruptured and unruptured IA together with some control samples from similar locations of the cadaver’s Willis’s circle, the wall was

damaged by scarring, with the disappearance of the tunica intima and the internal elastic membrane, in patients with both ruptured and unruptured aneurysms (**Figure 2G–I**). In the classification according to Frösen et al., categories A to C were demonstrated for unruptured IA, i.e., minor to moderate structural changes, such as fibrosis and disorganization of SMC (**Figure 2H**). However, the wall of ruptured aneurysms was thin, hypocellular, and fibrotized, often with the presence of an organized thrombus (**Figure 2I**). In the classification according to Frösen, it corresponded to categories C and D, i.e., a significantly damaged wall.

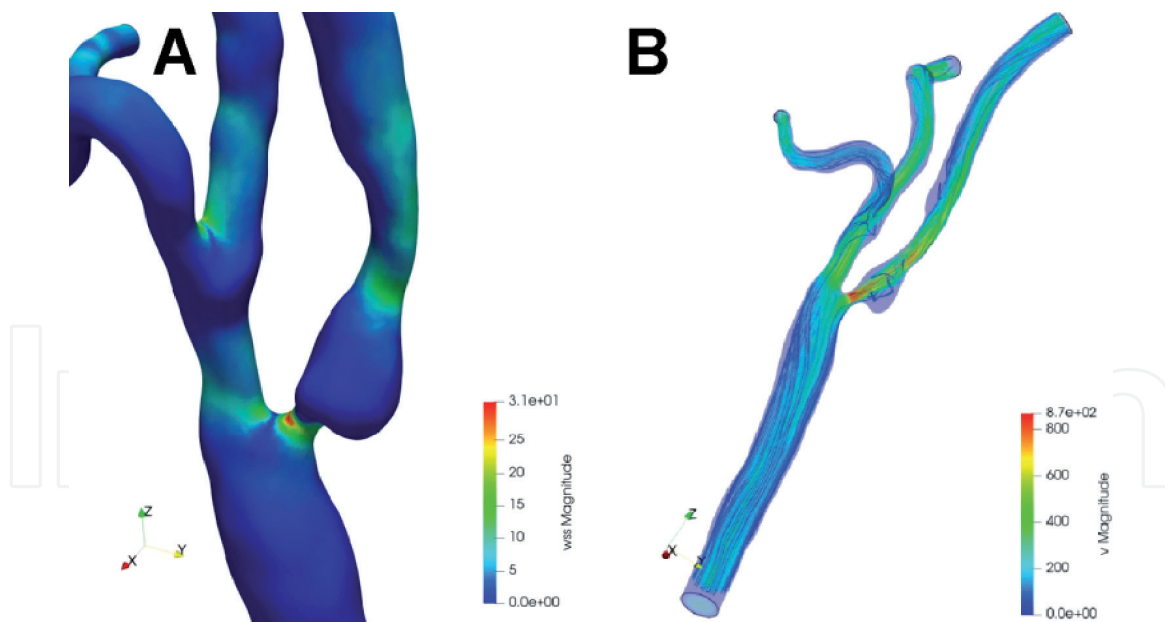
The correlation of vessel wall biology in intracranial aneurysms also has limitations:

1. Resection of only a part of the aneurysm sac. The entire aneurysm cannot be taken for histological evaluation. Due to the need to close at least the neck, but often also significant parts of the dome with an aneurysm clip, it is often possible to remove only the apex bag, even for larger aneurysms. Often small aneurysms are all hidden within a clip. On the other hand, large aneurysms often have a wall that is altered by atherosclerosis, weakened or calcified, and thus requires the application of, for example, several parallel clips and often a minimal residue of free sac to allow for sampling. A possible, at least partial, solution is the correlation of hemodynamics with the perioperative description of the aneurysm wall character (thinned wall, calcification, thickened atherosclerotic wall, etc.) by a neurosurgeon.
2. 3D orientation of the histological sample against angiographic imaging. The problem is the orientation of the cut bag in 3D space or 3D neuroradiological mapping. The hemodynamic parameters are processed in a 3D image based on CTA or 3D DSA. However, after cutting off the tip of the bag, it is necessary to orient the specimen and mark it properly so that the histology of the vessel wall with hemodynamic results can be ideally correlated. So far, a methodological study has been published to address this topic. However, it is currently quite complicated to be applied in clinical practice.

Another disease that is also used to investigate the relationship between atherosclerosis and hemodynamics is the carotid plaque in the bifurcation of the common carotid artery (**Figure 4**) [45]. This model is more advantageous for several reasons. It can be removed completely without disturbing its structure and then prepared for histological examination in one piece. Due to the size of the plaque and a simple orientation in the 3D geometry of the carotid arteries, the spatial correlation of the plaque model relative to the 3D image of hemodynamic calculations is simple. Also mathematical calculations on the carotid arteries are significantly simpler due to the relatively flat shape of the vessels and the larger cross-sectional size of the arteries, which are thus less affected by minor inequalities and errors given by the neuroradiological images. Therefore, the histological studies of carotid plaques in correlation with hemodynamic characteristics in the common carotid bifurcation can be performed with fewer approximations and thus can contribute to the understanding of atherosclerosis and degenerative changes in the vascular wall.

### **3.4 Hemodynamics and the risk of intracranial aneurysm rupture**

The degeneration of the aneurysm wall progresses from the neck toward the dome. Aneurysm rupture usually occurs at the apex, which is also often a low shear stress region. According to a large meta-analysis by Zhou et al., the low shear stress (0–1.5 Pa) in the aneurysm sac is a characteristic of ruptured aneurysms [28]. It



**Figure 4.** CFD in a model of carotid stenosis. WSS (A) and streamlines (B).

is assumed that wall shear stress of approximately  $2.0 \text{ N/m}^2$  (Pa) is most suitable for maintaining the integrity of the vessel wall. A shear stress of less than  $1.5 \text{ N/m}^2$  results in endothelial cell apoptosis [46]. Takao et al. found that the minimum WSS value for ruptured aneurysms was half that of unruptured aneurysms [26]. Thus, low WSS may be an indicator of an increased risk of intracranial aneurysm rupture. Furthermore, several authors have demonstrated that in ruptured aneurysms, the low WSS region is greater than in unruptured aneurysms [21, 25, 47]. Similar results were found in our study (Sejkorová et al., in preparation), in which we have shown that the area of low wall shear stress (LSA) grows over time in those aneurysms that eventually ruptured. The nature of the flow and its properties are influenced by the shape of the sac. Inside the narrow neck aneurysms, there may be a slow flow with recirculations, resulting in low shear stress leading to increased vascular degeneration. Hemodynamic changes within the aneurysm lead to the production of biological signals in endothelial cells and may result in microscopic changes in the vessel wall [48]. Nitric oxide is a key mediator of low WSS and shear stress oscillation. The low shear stress further promotes the expression of adhesion molecules such as VCAM-1 and ICAM-1. These promote adhesion of leukocytes leading to inflammation and vascular changes. Therefore low WSS seems to be associated with degeneration of cerebral aneurysm vessel wall resulting in rupture. But the situation is probably more complex as in another study in a large number of aneurysms, the authors found that ruptured aneurysms were characterized by concentrated blood stream and a higher shear stress compared to unruptured ones [29].

### 3.5 Limitations of mathematical modeling of IA

Mathematical modeling performed in IA extends our knowledge on the pathophysiology of their initiation, growth, development, and rupture [13, 49]. At the same time, it is necessary to note that CFD modeling is usually based on many approximations and carries several limitations. In most studies, individual patient data are not available. This is particularly difficult to obtain in patients with ruptured aneurysms that require acute treatment, and there is usually no time for additional diagnostic examinations (TCD or PC-MR). The method that can partially reduce the disadvantage of missing individual data is to relate values

in the aneurysm to the parent artery. Such value normalization reduces the impact of missing input data. Another limitation is that CFD represents mathematical models that are currently not able to describe all aspects of the biology of the cerebral aneurysms and cerebral blood vessels, their histology, atherosclerotic changes, pulsations, etc. Also during modeling, blood vessels are simplified as rigid tubes. The rheological properties of blood are simplified as incompressible Newtonian fluid.

Another aspect associated with limitations in CFD modeling is the use of different mathematical modeling algorithms among various groups working on CFD. This has been clearly shown in the CFD rupture challenge—phase I and phase II [50, 51]. In the rupture challenge, two MCA aneurysms, one ruptured and one unruptured IA, were evaluated using CFD analysis, and the status of the aneurysm was supposed to be identified by the research groups. In the second phase, several research groups were supposed to describe the hemodynamic parameters in one IA. The vast differences among the research groups confirmed the fact that various algorithms may lead to significant differences in the hemodynamic analysis [52]. In future it will be necessary to somehow unify the methodology in order to get more universally applicable results.

Another disadvantage of CFD modeling is the relatively complicated protocol with the need to include sophisticated and laborious calculations requiring super-computers. Nonetheless, technological advances in imaging may provide hemodynamic modeling during regular MRI examinations [53]. If MRI allows precise evaluation of hemodynamic parameters in the future, it can be used even during initial MRI evaluation and during follow-ups without radiation burden.

#### **4. Final remarks and future directions**

The rationale for studying hemodynamics of IA is the increasing detection of UIA with the need to decide whether to treat or watch the aneurysm. Studying and modeling hemodynamics within an aneurysm provides more information on the pathophysiology of IA. We can evaluate the hemodynamic parameter at one time point or follow the aneurysm with CFD assessments over time [40, 54]. The method has been mostly developed by endovascular surgeons with the goal to assess the effect of various treatment modalities, such as flow diverters, stents, scarification of the parent vessel, etc. The neurosurgeons would mostly need information on aneurysm hemodynamics with respect to the rupture risk in the assessment of UIA [40]. The neurosurgeons themselves may provide unique information on aneurysm wall quality: direction visualization of the aneurysm sac under the operating microscope (calcifications, wall weakening, atherosclerotic changes, thrombosis), identification of the site of rupture, aneurysm sac harvesting after clipping, etc. The aneurysm sac wall may then be assessed histologically. Some pilot studies have already been published [43]. Despite an increasing number of CFD studies, there are, to date, still no conclusions with respect to hemodynamics and growth or rupture that would be universally accepted.

From a clinical point of view, the CFD data need to be clinically useful and relevant, such as in a study that points out the relationship between the hemodynamic factors and the risk of endovascular treatment failure in patients treated for a basilar apex aneurysm [55]. The CFD parameters more often mentioned with respect to clinical use are WSS and character of flow. Many studies show that aneurysms with low WSS and complex flow tend to be associated with a higher risk of rupture [27, 28]. Further developments are still required in CFD research before it may be considered clinically relevant in providing useful information on UIA and its assessment, with respect to the risk of rupture.

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