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CFD for Evaluation and Treatment Planning of Aneurysms: Review of Proposed Clinical Uses and Their Challenges

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Abstract—Computational fluid dynamics (CFD) has been used for several years to identify mechanical risk factors associated with aneurysmal evolution and rupture as well as to understand flow characteristics before and after surgical treatments in order to help the clinical decision making process. We used the keywords, "CFD" and "aneurysms" to search recent publications since about 2000, and categorized them into (i) studies of rupture risk factors and (ii) investigations of pre- and post-evaluations of surgical treatment with devices like coils and flow diverters (FD). This search enables us to examine the current status of CFD as a clinical tool and to determine if CFD can potentially become an important part of the routine clinical practice for the evaluation and treatment of aneurysms in near future. According to previous reports, it has been argued that CFD has become a quite robust non-invasive tool for the evaluation of surgical devices, especially in the early stages of device design and it has also been applied successfully to the study of rupture risk assessment. However, we find that due to the large number of pre-processing inputs further efforts of validation and reproducibility of CFD with larger clinical datasets are still essential to identify standardized mechanical risk factors. As a result, we identify the following needs to have a robust CFD tool for clinical use: (i) more reliability tests through validation studies, (ii) analyses of larger generalized clinical datasets to find converging universal risk parameters, (iii) fluid structure interaction (FSI) analyses to better understand the detailed vascular remodeling processes associated with aneurysm growth, evolution and rupture, and (iv) better coordinated and organized communications and collaborations between engineers and clinicians.

Keywords—CFD, Aneurysms, Rupture risk factors, Endovascular devices.

INTRODUCTION

It is widely known that the rupture of aneurysms has devastating consequences with large morbidity and mortality rates.[96] Early treatment of aneurysms used open surgery (clip or hunterian ligation)[80,108] however, recent clinical reports[52,62,119,127] show that minimally-invasive endovascular devices such as coils, stent graft and flow diverters (FD) have largely replaced open surgical treatments. The etiology of aneurysms has been discussed earlier by many scientists and clinicians. It is now well accepted that hemodynamic environments in aneurysms play a key role on initiation, growth and rupture processes in combination with biochemical and physical interactions.[40,106] With the rapid development of computer and imaging technologies, computational studies on unsolved mechanisms responsible for aneurysm evolution and rupture have been performed. After the first attempt of applying CFD to the field of aneurysms by Gonzalez *et al.*,[35] there have been numerous reports by CFD researchers using this approach to the study of aneurysms.

Previous authors were already aware of the value of CFD as a practical diagnostic tool for the prediction of cerebral aneurysms[75] since biophysical factors are believed to play a significant role in the development, diagnosis, and therapy of stroke,[40] as also shown in the literature by Liou *et al.*,[63] which demonstrated the importance of morphological and hemodynamical factors in their study of aneurysm risk factors. A recent review by Wong *et al.*[121] confirmed that CFD can play a critical role for routine clinical practice in the near future with further improvement of computational power, from their literature search in PubMed using the keywords "CFD" and "cerebral aneurysm".

Several attempts have been made to identify CFD-based hemodynamic risk factors for initiation (see for

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example, Mantha *et al.*[66]; Shimogonya *et al.*[100]), growth and rupture. In addition, CFD has been suggested as a valuable tool for treatment planning and evaluation of surgical devices. The use of patient-specific simulation technology seems to be obviously necessary because of the limitations of current imaging modalities to provide reliable *in vivo* hemodynamic information and to evaluate the pre-, post and follow-up conditions following surgical interventions. These latter evaluations are problematic or sometimes impossible due to the limitations and difficulties of access of an invasive measurement tool to *in vivo* geometries. The goal of this review is to describe the proposed clinical uses of CFD, in particular in the field of aneurysms, and how it could alter the clinical decision making in the near future. For this purpose, we searched the literature using the keywords, "CFD" and "aneurysms" in PubMed and collected studies of aneurysms using CFD. We searched the studies based on patient specific intracranial aneurysms for the most part. The search enables us to understand the current status of CFD in the diagnosis and evaluation of aneurysm treatments and to discuss what challenges we still face to incorporate CFD in the routine clinical practice.

A number of authors have reported hemodynamical and morphological risk factors associated with rupture of aneurysms. Other CFD studies using patient specific models have aimed at recreating the altered flow fields after treatment, and evaluating endovascular procedures and devices such as coils and stents. Such patient-specific CFD "design optimization" studies could help to evaluate the effectiveness of different procedures and devices prior to intervention. Hence, we will discuss how CFD has contributed to the study of aneurysms (i) by proposing or introducing mechanical risk variables for the rupture risk assessment and (ii) by providing understanding of the effects of devices and procedures, proposing new or improved devices and suggesting interventional plans to clinicians. Different researchers seem to have successfully implemented CFD techniques suitable for clinical use and therefore, demonstrated it as a very promising tool (see for example,[21]).

Despite all these advances and valuable contributions, it has been pointed out by many authors that there still remain several issues related to the consistency and reliability of computational results and the mechanical variables used to characterize the hemodynamic environment, as well as to the analysis of relatively small clinical datasets. Therefore challenges such as reproducibility and sensitivities of flow parameters due to diverse preprocessing inputs like geometries, grid resolution, inflow and outflow boundary conditions, blood rheology, wall compliance, and solution methods that need to be addressed in order to enhance the reliability of CFD simulation outputs will be also discussed, and it will be followed by discussion of future directions and conclusion.

DIAGNOSIS AND CLINICAL TREATMENT USING CFD

Image-based patient-specific CFD models have received substantial attention since Steinman *et al.*[110] used a patient specific CFD model from high resolution, clinical 3D angiographic data for the study of aneurysms in 2003, with the hope that they can be used to improve the clinical practice. These models have been used with two main objectives: (a) identify hemodynamic factors that can be used to discriminate between low and high risk aneurysms, and thus develop systems for aneurysm evaluation, and (b) understand the effects of different devices and procedures to improve the device designs and select the most appropriate intervention for a particular patient. Therefore, this section is divided into two parts discussing the proposed clinical uses of CFD for aneurysm risk evaluation, and for treatment and device selection.

Hemodynamical and Morphological Variables for Rupture of Aneurysm and Risk Assessment

With the aid of 3D imaging technology, CFD researchers have used patient specific geometries mostly from 3DRA (3-dimensional rotational angiography) and CTA (Computed tomography angiography) for their analyses of both ruptured and unruptured aneurysms. Many researchers have identified different variables related to flow characteristics in aneurysms and proposed a number of critical hemodynamic and morphologic parameters as potential rupture risk factors. Such variables include mean wall shear stress (WSS), maximum wall shear stress (MWSS), oscillatory shear index (OSI), pressure, flow structure, as well as aspect ratio (AR) defined as the ratio of the maximum perpendicular height to the average neck diameter, size ratio (SR) as maximum aneurysm height divided by average vessel diameter, *etc*. See for example Dhar *et al.*[26] for detailed definitions of morphological variables, and Mut *et al.*[71] for detailed definitions of hemodynamic variables. In order to examine whether CFD could become a useful risk-analysis tool, we searched various CFD studies in PubMed using the keywords such as "CFD" and "aneurysms" and found that many authors have investigated flow characteristics in human intracranial aneurysms. Many of these studies claim to have identified critical flow or morphological variables associated to aneurysm rupture. Here, we review these studies including their diagnostic and clinical suggestions.

Pressure, OSI, AR, SR, and Flow Structure

Pressure has been proposed as a risk factor. In an early study in 2004, Hassan *et al.*[39] suggested that high systolic pressure on the aneurysm dome may trigger the growth of the aneurysm. This was observed in a model of a giant vertebrobasilar aneurysm constructed from 3D digital subtraction angiography which was subsequently followed up at 6 months. Baek *et al.*[7] also found higher pressure surrounded by a band of a high instantaneous WSS on a region of infundibulum, which seems to coincide with the locations of the rupture of infundibulae or progression to aneurysms based on earlier reports. They employed seven patient-specific ICA with PcomA infundibulum or aneurysm from four patients and performed high-resolution CFD simulations. OSI has also been investigated, and a high level of OSI has been identified as a potential rupture risk factor by Lu *et al.* and Xiang *et al.*[64,123] Lu *et al.*[64] used rotation digital subtraction angiography (RDSA) to model nine pairs (ruptured and unruptured groups) of intracranial MANs (mirror aneurysms) and found much higher mean OSI in the ruptured group. The relationships between morphologic and hemodynamic characteristics were studied by Zeng *et al.*[125] This group used 51 rabbits to investigate the effect of aneurysm aspect ratio (AR) on time averaged wall shear stress, oscillatory shear index, relative residence time and non-dimensional inflow rate and suggested AR as an important indicator of rupture likelihood. Interestingly, the study by Xiang *et al.*[123] using one hundred nineteen intracranial aneurysms (38 ruptured, 81 unruptured) from 3DRA, however found that AR was not statistically significant but higher SR was associated to the rupture. Other studies have proposed the energy loss (EL) due to aneurysm as a useful parameter for the quantitative estimation of the rupture risk for intracranial aneurysms (IAs).[81] They used four incidentally found ICA-PcomA aneurysms ruptured during observation and compared the differences in hemodynamic factors, such as EL and WSS from 26 unruptured aneurysms (stable-IAs) with similar location, size, and morphology.

The complexity and stability of intra-aneurysmal flow structures have also been suggested as hemodynamic factors for rupture risk assessment. Cebral *et al.*[17] in 2005 analyzed 61 aneurysms and proposed that inflow concentration as well as intra-aneurysmal flow complexity and instability could be markers of increased aneurysm risk. Subsequently, Sforza *et al.*[98] in 2010 found that an aneurysm imaged just hours before it ruptured had a concentrated inflow stream, small impingement region, complex intra-aneurysmal flow structure, asymmetric flow split from the parent vessel to the aneurysm and daughter branches, confirming the previous suggestion. The recent article by Hodis[41] in 2014 also supported these earlier results, showing that the concentrated jet that impinged directly at the site of rupture in an anterior communicating artery that spontaneously ruptured immediately following three-dimensional rotational angiography. Cebral *et al.*[22] in a 2011 study confirmed these trends with a larger study based on 210 consecutive aneurysms which showed that concentrated inflow jets, small impingement regions, complex flow patterns, and unstable flow patterns were statistically associated with a clinical history of prior aneurysm rupture. The result that more complex flow patterns with multiple vortices are more commonly found in ruptured aneurysms compared to unruptured aneurysms was also confirmed by Xiang *et al.*[123] in 2011.

Because of known effects on the endothelial function and integrity, WSS has been suggested as the most critical factor related to the evolution and rupture of aneurysms by several researchers. However, it has been the most controversial variable as well. The level of WSS in ruptured and unruptured aneurysms has been compared and both, high or low levels of WSS have been proposed as important indicators for the prediction of aneurysm rupture.

Low WSS

A previous study in 2004 investigated the WSS effect on cerebral aneurysms using twenty MCA aneurysm models built from 3D CTA. They identified low average WSS as a predictor for the rupture of a cerebral aneurysm.[101] Later studies agree with this result.[64,73] Lu *et al.*[64] reported that lower WSS was found in ruptured aneurysms compared with their parent arteries and the ruptured aneurysms had a wider range of the low WSS area compared with the unruptured aneurysms by modeling nine pairs of intracranial MANs (ruptured and unruptured groups). Omodaka *et al.*[73] modeled six ruptured middle cerebral artery aneurysms with intraoperative confirmation of rupture point from three-dimensional rotational angiography images and showed that low WSS was associated with the site of rupture. The recent study in 2013 by Fukazawa *et al.*[34] supported these earlier results. They found markedly low WSS at the rupture point compared with aneurysm dome, and parent artery using twelve ruptured middle cerebral artery bifurcation aneurysms. Lower WSS was also identified as a risk factor in the study of Xiang *et al.*[123] using one 119 intracranial aneurysms. They claimed that ruptured IAs showed lower WSS and MWSS than their parent vessels, whereas comparable WSS and MWSS were found in unruptured IAs. A recent study by Lauric *et al.*[60] evaluated WSS on nine ruptured and nine unruptured volume matched ICA aneurysms at similar locations in order to avoid biased evaluation of WSS for rupture assessment because larger aneurysms are associated with lower WSS regardless of rupture status. They reported that low range WSS values were significantly lower for ruptured aneurysms, regardless of WSS evaluation (time averaged, mean peak systole, mean end diastole).

High WSS

In contrast with the above results, high WSS was found in ruptured aneurysms from several other CFD studies. For instance, in 2008, Chien *et al.*[25] compared the hemodynamic characteristics of ruptured and unruptured small aneurysms at the same anatomical location using six internal carotid artery-ophthalmic artery aneurysms smaller than 10 mm. They found that WSS was higher in ruptured aneurysms. A later study showed WSS distributions with elevated levels of MWSS statistically associated with a clinical history of prior aneurysm rupture in a cohort of 210 cerebral aneurysms.[23] Zhang *et al.*[128] also suggested high magnitude of wall shear stress (|WSS|) and wall shear stress divergence (WSSD) as important risk factors for rupture by testing on 19 patients. Another recent study supported these earlier results by finding maximal WSS near the rupture location by CFD analysis of the hemodynamic environment of an anterior communicating artery that spontaneously ruptured immediately following three-dimensional rotational angiography.[41] Another recent study by Russell *et al.*[89] supported the earlier result by showing that maximal WSS was statistically associated with aneurysm bleb location or adjacent to the location where an increased risk of rupture has been reported. In this study, they simulated computational anatomic models from 3DRA data in 27 patients with cerebral aneurysms harboring a single bleb to identify flow feature at the location of bleb formation using the models of aneurysms before bleb formation by digitally removing the bleb.

Risk Assessment

As summarized above, several CFD studies have identified candidate hemodynamic and geometric factors that could potentially be used to evaluate the rupture risk of aneurysms. Image-based CFD technology has become quite accessible, affordable and easy to use to allow for its clinical use. There are other risk parameters suggested as well. For instance, Cebral *et al.*[23] in their study using over two hundred aneurysms found that low aneurysmal viscous dissipation ratio (VDR) was correlated to the rupture of aneurysm. The study by Xiang group using also a large group of aneurysms (more than one hundred aneurysms)[123] considered other risk factors such as higher RRT (relative residence time) and LSA (low shear area), which were shown to be statistically associated with rupture.

The definitions of risk parameters may vary by different authors. WSS may represent for time averaged wall shear stress magnitude normalized by WSS found in parent vessel to be more reliable than absolute WSS. Some authors use WSS further spatially averaged or others employ MWSS (spatial maximum time averaged wall shear stress magnitude normalized by parent vessel WSS). Current debate on WSS risk factor shows the four different findings correlated with rupture: (1) high MWSS,[23] (2) low MWSS,[123] (3) the maximum intra-aneurysmal WSS magnitude at the systolic peak,[14] and (4) WSS is not correlated with rupture.[36,81] Note that the two largest studies by Cebral *et al.*[23] and Xiang *et al.*[123] showed opposite trends in the association of MWSS (same definition by both groups) and rupture risk as shown above.

Regardless of these efforts by CFD engineers and scientist to identify several important risk factors, the recent editorial by Kallmes[46] in 2012 clearly showed the perception of the clinical community about the current status of CFD for clinical use. He pointed out that a large number of un-standardized risk parameters from CFD simulations under several modeling assumptions by diverse CFD groups may be confounding factors, and suggested that CFD researchers need a lot more work to close gaps in information and address the conflicting information to find well defined and clinically relevant parameters. However, as argued by Cebral and Meng[19] the large number of risk variables proposed may originate from the complexity of the disease and the largely unknown mechanisms of initiation, progression and rupture. Strother and Jiang[111] further suggested that aneurysms may not be a single disease but a spectrum of diseases or multiple diseases. According to the hypothesis by Xiang *et al.*[124] in 2013, both low and high levels of WSS may be associated with rupture processes because of the complexity of IAs. High WSS may trigger a mural cell-mediated destructive remodeling pathway, akin to the process of IA genesis (small IAs with thin walls, Type I) whereas low WSS may trigger an inflammatory cell-mediated destructive remodeling pathway, akin to atherosclerotic (aortic aneurysm) development (large IAs with thick walls, Type II), and a combination of Type I and Type II aneurysms may contain both low and high WSS.[124] This seems consistent with the review of Cebral and Raschi[18] which suggests that all of the risk variables may not play as single independent factors but depend on each other because aneurysm progression should be considered as a complex mechanobiological process. It was also discussed that current controversies may also be caused by the small data bases used in the CFD analyses. Cebral and Meng[19] also indicated that there should be more attempts to standardize hemodynamic variables, as well as closer collaborations among engineers to use larger unified and standardized clinical series to objectively test a number of candidate risk factors and, thus obtain converging universal parameters.

There seems to be consensus among clinicians that in order for CFD to be used as a clinical tool for evaluation of IA it is necessary to demonstrate a strong statistical association between well defined, robust and reliable hemodynamic factors and rupture in large clinical series. Additionally, assumptions made in CFD simulations should be validated against experiments and *in vivo* data, and by reproducibility or sensitivity studies which will be further discussed in "Evaluation of CFD" section.

The Role of CFD in the Clinical Treatment of Aneurysms

From the beginning of 2000s, there have been numerous CFD studies of the hemodynamic effects of endovascular devices such as coils and stents, and less frequently surgical procedures such as clipping by clamp. The efforts seem to have produced useful outputs for the evaluation of such devices and treatments. We reviewed the literature to explore how CFD could be used as a tool in the clinical decision making process prior to intervention, namely selecting devices and courses of action. There are a number of studies related to this subject. The studies are categorized by the different treatment of human intracranial aneurysms (IAs).

Intracranial Aneurysms (IAs) Treated by Clipping and Hunterian Ligation

A recent publication describes the numerical investigation of the blood flow in 3D models of cerebral aneurysm treated with clips. The feasibility of the surgical procedure was evaluated with calculated hemodynamics parameters, which showed significantly increased blood velocity and WSS and decreased pressure postoperatively.[82] Another CFD simulation analyzed the treatment of a giant basilar tip aneurysm which eventually ruptured 6 months following hunterian ligation.[102] They argued that hunterian ligation switched the parent artery from the basilar artery to the left posterior communicating artery, changing the direction and the diameter of the parent arteries, resulting in higher shear magnitude and gradient on the posterior wall of the aneurysm. Thus, they suggested that the ligation may negatively affect the flows and possibly cause rupture in specific cases.

Intracranial Aneurysms (IAs) Treated by Coil

We found numerous papers related to CFD analysis of the flow characteristics in intracranial aneurysms after endovascular treatment with coils, beginning from 2004 to 2013. These studies used either a mesoscopic approach where the geometry of the coils is taken into account, or a macroscopic approach where the coils mass is represented with a porous media and the geometric details of the individual coils are neglected. While a macroscopic approach seems adequate to derive global hemodynamic quantities such as mean aneurysm velocity or inflow rate, the main limitation is the choice of the right porous media parameters and the lack of validation or comparison to more precise approaches.

The earlier study in 2004 by Byun *et al.*[11] analyzed the blood flow fields in two idealized lateral intracranial aneurysm models using a sphere representing coils and pointed to coil locations with small inflow and low wall shear stress as effective for aneurysm embolization. Fukasaku *et al.*[33] simulated the fluid dynamics with the virtual models of therapeutic devices like coils and stents to study their influences to blood flow and demonstrated the suitability of these devices for the treatment of intracranial aneurysms. The first attempt at using a porous medium-based method for coiling simulations was performed by Mitsos *et al.*[68] They built a CFD model of a ruptured anterior communicating aneurysm from a rotational 3D digital subtraction angiogram which demonstrated less vortical blood flow patterns in the aneurysm sac and the reduced wall pressure at the fundus after coiling. A later CFD study used an isotropic porous medium to model a vertebro-basilar junction giant aneurysm filled with platinum coils.[120] Morales *et al.*[69] in 2013 utilized CFD to successfully obtain the reduced wall shear stress and intra-aneurysmal velocities after coiling using image-based aneurysm models with a virtual coiling technique validated using clinical information of real coiled aneurysms. A treated vertebrobasilar giant aneurysm by partial coil or Onyx embolization was studied by Graziano *et al.*[37] They concluded that the intra-aneurysmal environment induced by partial coil or Onyx embolization may lead to hemodynamic stress at the neck region, potentially favoring recanalization of the aneurysm, by modeling the coiled region as a porous medium material. Two other recent studies using CFD for coiling treatment were performed by Morales *et al.*[70] and Babiker *et al.*[4] Morales *et al.*[70] investigated the sensitivity of CFD for a Newtonian and non-Newtonian model of blood in the simulation of the flow in coiled aneurysms. In this study, they used three aneurysm models virtually coiled with a packing density of around 30% and three untreated aneurysms, and successfully compared the results between a Newtonian and non-Newtonian viscosity models. They claimed that the assumption of a Newtonian fluid can be made in CFD study of coiled aneurysms. The most recent study based on CFD simulation for coiled aneurysms illustrates the feasibility of using CFD for the optimal design of coils.[4] They performed eighty CFD simulations of post-treatment flows in idealized basilar tip aneurysm models with virtually modeled coils to investigate the effects of packing density, coil shape, aneurysmal neck size, and parent vessel flow rate on aneurysmal hemodynamics.

Intracranial Aneurysms (IAs) Treated by Flow Diverters

Flow diverter or multilayer stents have been used as promising endovascular devices for clinical treatment of aneurysms.[52,62,119,127] Many CFD authors demonstrated that these devices reduce the inflow through aneurysms inducing endovascular embolization and aneurysm thrombotic occlusion. An earlier study in 2004 by Fukasaku *et al.*[33] reported that CFD can be used to study the effect of therapeutic devices like stents on aneurysmal flows and to design devices. In 2006, Kim *et al.*[51] compared the hemodynamics of untreated and stented anterior cerebral aneurysms (ACA) by performing CFD analysis. This study showed that the stent effectively blocked the strong inflow jet into the stented aneurysm. There have been many recent CFD studies on the efficiency of stent devices for the prevention of aneurysm rupture. Tremmel *et al.* quantified the effect of single and multiple self-expanding Enterprise stents alone or in combination with balloon-mounted stents on a wide-necked, saccular, basilar trunk aneurysm. They found lowered average flow velocity and decreased WSS with increasing number of deployed stents in the aneurysms and recommended multiple stents for the treatment of aneurysms.[115] A comparison of the flow characteristics between pre- and post treatments of three giant aneurysms that ruptured after treatment and four successfully treated aneurysms was made by Cebral *et al.*[20] They found the reductions in velocity and WSS in successfully treated aneurysms. In this study, they suggested careful consideration for stenting, arguing that increased pressure in the aneurysm after treatment can potentially lead to rupture, especially for giant aneurysms with proximal stenosis. Another CFD study also demonstrated reduced vortex and decreased wall shear stress on stented wide-necked intracranial aneurysms which may facilitate thrombus formation and decrease the chance of recanalization.[129]

Larrabide *et al.*[59] introduced a new method for the deployment of stent models, the Fast Virtual Stenting (FVS) method to provide additional information to clinicians before treatment in order to choose the therapy that best fits individual patients. Another group also developed finite element analysis (FEA) based workflow for simulating mechanical deployment of flow diverter (FD) in patient-specific aneurysms.[65] An optimal stent design for an idealized wide-neck basilar tip aneurysm was proposed by Babiker *et al.*[5] in 2012. Computational models with three different stent configurations (half-Y, Y and, cross-bar) were studied and validated using particle image velocimetry. They found the most significantly reduced velocity magnitudes within the aneurysmal sac in a model with the cross-bar stent. Kulcsár *et al.*[56] compared the flow characteristics in untreated and treated aneurysms at the para-ophthalmic segment of the internal carotid artery in eight patients with the results of the clinical follow-up ranged between 6 days and 12 months. In this CFD work, significantly reduced mean intra-aneurysmal flow velocities and WSS were obtained in the seven of eight aneurysms, showing complete occlusion during the follow-up. More recent CFD works are in good agreement with these earlier studies. All of the results showed lower WSS with slower flow in aneurysms treated by stents (see[53,54,58,72,114]).

Karmonik *et al.*[47] in 2013 reported the comparison results between the velocities, pressures and wall shear stresses (WSS) of eight ICA pre-treatment and post flow diverter treatment aneurysms from 3D digital angiography subtraction (3D-DSA) image data. They modeled the virtual flow diverter as a porous interface in their CFD fluid domain and the study showed reduced velocities and WSS in all the cases of post flow diverter treatment. Larrabide *et al.*[58] compared hemodynamic variables for conditions before and after virtual FD implantation in aneurysms of different sizes and shapes, all located at the supraclinoid segment of the ICA from 23 patients. The study showed significant changes in WSS and velocity. Similarly, Tanemura *et al.*[114] found that stent placement induced stagnant and disturbed blood flow in a study analyzing both patient specific saccular aneurysm and blister-like aneurysm models. A study comparing a no-stent model and 8 stent models from patient-specific asymmetric bifurcation aneurysms treated by Enterprise closed-cell stents showed a strong reduction in flow velocity in the aneurysm and redirection of impingement flow.[53] Another study by Kono *et al.*[54] in 2014 analyzed an anterior communicating artery aneurysm after carotid artery stenting (CAS), which remained unruptured for 14 months after the CAS. They argued that low WSS is correlated with the prevention of rupture. Another recent report by Mut *et al.*[72] in 2014 using 23 aneurysms presented the results of a comparison of hemodynamic conditions between aneurysms occluded at 3 months (fast occlusion) and occluded at 6 months (slow occlusion) after FD treatment. They suggested that CFD can predict occlusion time after treatment because aneurysms in the fast occlusion group had significantly lower post-treatment mean velocity, inflow rate and shear rate than aneurysms in the slow occlusion group. This study demonstrated that CFD may be a valuable tool to examine the performance of devices, as well as for prognosticating the long term outcome of endovascular procedures.

Lower flow impingement and WSS in aneurysms treated by flow diverter were consistently identified by many authors. A previous report on the Virtual Intracranial Stenting Challenge 2007 showed the development of a multicentre-controlled benchmark to investigate differences arising by CFD methods and diverse grid generation techniques and mesh resolution in the computational analysis of stented aneurysms. The report demonstrated the suitability of CFD in consistently quantifying the performance of three commercial intracranial stents.[83] However, as indicated above, more efforts to enhance the reliability of CFD are still needed, which will be discussed in the following section.

EVALUATION OF CFD

Several authors have investigated the reproducibility and sensitivity of CFD for accurate flow analysis of patient specific aneurysm models. Many of them compared their computational results with image data or *in vitro* experiments for a reproducibility test or validation. Computational results may vary with computational inputs such as inflow and outflow boundary conditions, mesh resolution and its type, model geometry, blood model (Newtonian or non-Newtonian fluid) and solution algorithms. Hence a number of authors have also studied the effect of diverse input values on computational results.

Evaluation of CFD with Physical Phantom Models

Ford *et al.*[31] used clear silicone elastomer phantom models of a giant internal carotid artery (ICA) aneurysm and a basilar artery (BA) tip aneurysm to compare the velocity fields of CFD calculations against those measured using particle imaging velocimetry (PIV). The study found that the vector fields showed good overall agreement. Other authors also employed physical models to validate their computational results. For instance, a comparison was made between the flow field measured *in vitro* within a patient specific model of a mature abdominal aortic aneurysm and predicted from CFD, showing good agreement throughout the aneurysm.[88] Sun *et al.*[112] used a silicon phantom cerebral aneurysm model to qualitatively and quantitatively compare the simulated flow features using CFD with the measured flows by electromagnetic flow meters (EMFs), demonstrating good agreement between the results. A phantom model of a cerebral aneurysm was successfully used for comparison of velocity magnitude profiles by in situ, laser-Doppler velocimetry (LDV) measurements and by CFD simulation.[10] A physical silicone model was employed to qualitatively and quantitatively compare the flow field in a growing anterior communicating artery (AcomA) with CFD.[84] This study showed the flow pattern from CFD was consistent with the flow structure measured by PIV.

Evaluation of CFD with Imaging Data

Steinman *et al.*[110] qualitatively compared the hemodynamic patterns in a patient specific giant ICA-PcomA aneurysm model from 3D angiographic data with the patterns of contrast agent wash-in during cine angiography and showed that they are in good agreement. Ford *et al.*[32] proposed cine X-ray angiograms for the purpose of indirectly validating patient-specific CFD models of a giant internal carotid-posterior communicating artery aneurysm from computed rotational angiography (CRA). They found virtual angiographic images and residence time maps derived from the image-based CFD in excellent agreement with the X-ray angiograms. Other groups also used imaging data to validate their computational results. Karmonik *et al.*[48] quantified flow patterns in an aneurysm of the anterior commuting artery *in vivo* using 2D phase contrast MRI (pcMRI) to compare the data with CFD. A qualitative flow structure comparison of dynamic DSA (Digital subtraction angiography) images and virtual angiograms from CFD simulations using patient specific IAs was made by Cebral *et al.*[24] showing good agreement. Rayz *et al.*[85] in 2008 made successful application of *in vivo* magnetic resonance (MR) for velocimetry measurements and comparison to CFD models. They found good agreement between the flow fields measured *in vivo* and those from CFD simulations. A comparison between 3D cine PCMR imaging (4D-Flow) and CFD data was made by Isoda *et al.*,[45] demonstrating comparable 3D velocity vector fields, 3D streamlines, shearing velocity, WSS, and OSI in five intracranial aneurysms. Berg *et al.*[9] recently validated their computational results using two intracranial aneurysm models by quantitatively and qualitatively comparing the results with 4D velocity fields from time-dependent PC-MRI. They claimed that realistic geometries and boundary conditions are necessary to reproduce *in vivo* hemodynamic conditions.

Effect of Different Inflow and Outflow Boundary Conditions on Flow Characteristics

Several studies have identified the inflow boundary condition as an important input to obtain comparable hemodynamic conditions in aneurysms. For example, in 2010, Karmonik *et al.*[49] examined the effect of two inflow conditions on flow characteristics in six unruptured ICA aneurysms: (1) idealized averaged waveform from Ford *et al.*[29] and (2) patient-specific waveform measured with 2D phase contrast magnetic resonance imaging. They compared mean WSS, temporal WSS magnitude variation, and OSI on the aneurysmal wall for both conditions. They suggested that patient-specific information on physiological flow may be necessary for inflow condition. However, a later study by Marzo *et al.*[67] argued that 1D-model data by Reymond *et al.*[86] or a physiologically coherent method based on local WSS at inlets can be used as an inflow condition in absence of patient-specific Bcs (boundary conditions), since they found strong similarities in WSS, OSI and other hemodynamic indices between patient-specific phase-contrast-MR measurements and modeled data. Nevertheless many authors pointed out the significance of accurate patient specific inflow conditions for the reproducibility of CFD outputs. The requirement of relevant patient specific inflow conditions for CFD study was well discussed by Schneiders *et al.*[93] They compared flow velocities measured with PCMR imaging with that obtained by using intra-arterial Doppler sonography in unruptured intracranial aneurysms of ten patients. The study revealed large differences in flow velocities between the patients, highlighting the importance of patient specific inflow boundary condition for CFD study. Other researchers used transcranial color coded Doppler (TCCD) measurements to impose CFD BCs.[113] Onishi *et al.*[74] also proposed a novel correction method to determine inflow BCs accurately using a 3D cine phase-contrast MRI (4D Flow) velocimetry. Evju *et al.*[28] studied the sensitivity of inflow boundary condition using two different average flow velocities at the inlet and outflow boundary condition using a flow rate resistance and traction free conditions at the outlet of twelve middle cerebral aneurysm geometries. They argued for the need of accurate inflow and outflow conditions since they observed significant differences in WSS for the different conditions. The effect of outflow boundary conditions was discussed by Baek *et al.*[7] in their study of rupture assessment for PComA infundibulum. They imposed constant pressure and two reduced volume flow rates at PcomA outlet boundary. The volume flow rates at MCA and ACA outlets as well as WSS and pressure distributions and their fluctuation in neighboring aneurysm did not show dramatic change. However WSS on infundibulum at PComA was extremely high which seems to be physiologically unreasonable at constant pressure condition. Further efforts to obtain realistic inflow and outflow boundary conditions may be necessary to better understand hemodynamic environments in patient specific aneurysms.

Effect of Different Viscosity Models on Flow Characteristics

The effect of non-Newtonian viscosity for blood modeling in aneurysmal geometries has been discussed by a number of authors. A study by Cavazzuti *et al.*[15,16] used three stented cerebral aneurysms from the Virtual Intracranial Stenting Challenge'07[83] to show that a Newtonian model can underestimate WSS. A later study by Xiang *et al.*[122] however, argued that a Newtonian model can overestimate WSS in regions of stasis or slowly recirculating secondary vortices, typically found at the dome in elongated or complex-shaped saccular aneurysms as well as in aneurysms following endovascular treatment. In this study, they used a Newtonian viscosity model and two non-Newtonian models (Casson and Herschel-Bulkley) for their comparison. However, these results are difficult to interpret since they considered a single case and the overestimation of WSS they observed seems to occur in regions where the WSS is already close to zero. Evju *et al.*[28] used twelve middle cerebral aneurysms to compare WSS in the aneurysms using four different viscosity models (Newtonian, Modified Cross and two Casson models). The low sensitivity of the average WSS over the aneurysm sac with respect to the viscosity model was observed in this work. Interestingly, Morales *et al.*[69] suggested that a Newtonian model can be used for CFD studies of hemodynamics in coiled aneurysms. They found that the main flow pattern and velocity magnitudes were not significantly altered due to the viscosity modeling, even though they showed slight overestimation of the intra-aneurysmal velocity inside the aneurysm before and after coiling.

Effect of Different Mesh Resolutions and Types on Flow Characteristics

Spiegel *et al.*[104,105] have studied the importance of mesh resolution and element type to obtain accurate and fast convergent solutions. They pointed to polyhedral meshes for better accuracy and convergence in cerebral hemodynamic simulation. Hodis *et al.*[42] employed five patient-specific brain aneurysm models with different dome morphologies and estimated grid convergence errors for each model using five levels of refinements. They reported that velocity, pressure, and wall shear stress for four of the five models at six different spatial locations converged monotonically except the fifth model due to geometric complexity. They suggested that each patient specific model requires its own grid convergence study for CFD accuracy. The significance of turbulence in blood flow has been discussed by Antiga and Steinman.[3] These authors argued that cell to cell interactions between RBC (red blood cells) may cause high frequency fluctuations in blood flow and suggested that blood flow may be considered to be turbulent. *In vivo*[57] and *in vitro*[107] studies showed high-frequency flow fluctuations in certain aneurysms. Baek *et al.*[7] found WSS temporal fluctuations inside the aneurysm in their CFD study of rupture assessment for ICA aneurysms and PComA infundibulum. Their later study[8] also reported a high-frequency oscillation of WSS vectors in the range of 20–50 Hz. Their simulation showed such hydrodynamic instability not in a narrower-necked saccular, but in one or two adjacent wide-necked saccular aneurysms using high resolution numerical simulations. Valen-Sendstad *et al.*[116] investigated the effects of turbulence on blood flow in a patient specific middle cerebral artery (MCA) bifurcation aneurysm using a high resolution Direct Numerical Simulation (DNS). They found that the frequencies of change of wall shear stress (WSS) direction and WSS magnitude were predominantly (higher turbulent kinetic energy) in the range of 1–500 Hz. Their recent report[117] also suggested that adequate temporal and spatial mesh resolutions are required in order not to overlook such fluctuations, which may affect the estimation of WSS in rupture risk assessment. They detected high-frequency velocity fluctuations in MCA bifurcation, but not sidewall, aneurysms by employing high temporal and spatial mesh resolutions.

Effect of Geometric Variation on Flow Characteristics

In an early study, Hoi *et al.*[43] investigated hemodynamic parameters such as vorticity, positive circulation, and WSS using idealized oblate phantom aneurysm models to compare PIV measurements with CFD results of a spherical and two oblate numerical aneurysms. They found that small geometric variations on an aneurysm model can significantly alter the flowfield, arguing that accurate geometrical representation of aneurysm for CFD computation is necessary. Castro *et al.*[13] also discussed the necessity of accurate geometric representation to obtain realistic flows in subject-specific cerebral aneurysms by using a novel combination of image co-registration and surface merging techniques. They showed that a CFD geometry for aneurysm of anterior communicating artery requires both the left and right anterior cerebral arteries (ACA) for inflow conditions. In another study Castro *et al.*[12] also showed the influence of early truncation of the parent artery in patient-specific models of intracranial aneurysms. They suggested incorporating long segments of the parent artery into the CFD models. Zeng *et al.*[126] supported the earlier report, arguing for the requirement of sufficient vasculature to impose correct inflow and outflow boundary conditions. In this work, CFD studies were performed on five models with varying extents of neighboring vasculature representing saccular aneurysms in rabbits with two aspect ratios (AR) to compare flow properties. A later report by Pereira *et al.*[77] agreed with these previous findings. This work showed that mean flow velocities, WSS and OSI were all significantly different in (1) Model A: maximum inlet vessel including the petrous part of the right internal carotid artery. (2) Model B: Model A truncated to a shorter inlet length (3) Model C: model B with flow extension. It showed that CFD outcomes of Model A matched well with high frame rate Digital Subtraction Angiography (DSA) sequences. Kono *et al.*[55] also showed that changes in aneurysm shape after rupture may cause 20–30% changes in WSS. Accordingly, they argued that aneurysm geometries should be carefully considered in rupture risk assessment studies. A recent study by Schneiders *et al.*[95] measured the changes in volume, displacement and shape of nine aneurysms before and after rupture from nine patients. The study showed an average increase of 137% in volume after rupture and the changes in displacement and shape due to perianeurysmal hematoma. They argued that geometric and hemodynamic comparison of unruptured and ruptured aneurysms to find rupture risk factors should be interpreted with caution because a key risk factor such as WSS inversely relates aneurysm volume.

Effect of Motion of Walls on Flow Characteristics

The effect of aneurysmal wall compliance on flow properties was studied by Dempere-Marco *et al.*[27] in 2006. In this study, unlike the previous ad hoc models accounting for flexible wall motion, image-based wall motion estimation obtained through non-rigid registration was introduced. It showed a small systematic overestimation of WSS by rigid models but a negligible change in the overall characteristics of the wall shear stress distribution for the model considering wall pulsation. Sforza *et al.*[97] also demonstrated small effects of parent artery motion on the hemodynamics of two basilar tip saccular aneurysms. Two CFD calculations were performed for each patient, corresponding to static and moving models and they noticed that the motion observed in pulsating intracranial vasculature does not have a major impact on intra-aneurysmal hemodynamic variables such as WSS, velocity profiles, and streamlines.

FUTURE DIRECTIONS

Importance of Reproducibility of CFD

Reproducibility and consistency of CFD computations are indispensable if they are to be incorporated into the clinical workflow. A few previous studies have focused on the variability and reproducibility of hemodynamic simulations of intracranial aneurysms through CFD challenges. The Virtual Intracranial Stenting Challenge (VISC), carried out in 2007, engaged in the development of a multicentre-controlled benchmark to analyze differences by diverse grid generation and CFD technologies by international teams from both academic and industrial institutions and demonstrated consistent quantification of the performance of three commercial intracranial stents.[83] The ASME 2012 Summer Bioengineering Conference CFD Challenge showed that pressure drop in a giant cerebral aneurysms with a proximal stenosis was predicted with consistency by CFD across a wide range of solvers and solution strategies from diverse research groups.[109] In this latter work, the authors suggested that future challenges may be necessary to assess the consistency of flow patterns by different solution methods, and produce reliable CFD results. Similarly, it seems that further investigations are necessary to enhance the reliability of hemodynamical simulations with respect to the variability and sensitivity of CFD results due to various pre-processing steps and assumptions. In this context, U.S. Food & Drug Administration started a Critical Path Initiative program (http://www.fda.gov/scienceresearch/specialtopics/criticalpathinitiative/spotlightoncpiprojects/ucm149414.htm) to standardize CFD techniques for evaluation of performance and blood damage safety in medical devices. Participating the program may help provide benchmarks for comparison of CFD results based on diverse computational methods.

Importance of Fluid Structure Interaction (FSI) Simulation

It is well known that an aneurysm ruptures as wall tension exceeds wall strength. Recent authors pointed out the significance of fluid structure interaction (FSI) simulations in rupture risk assessment. Complex biomechanical processes involved in growth, stabilization and rupture of aneurysms must be explored by the combination of fluid and solid mechanics analyses to provide a more general framework in rupture risk assessment.[87] A previous report introduced an advanced isogeometric fluid–structure analysis model incorporating flexible aneurysm wall based on patient specific computed tomography angiogram images.[44] They used the flow and material properties for isotropic nonlinear hyperelastic solid wall from a literature review and claimed that aneurysm rupture may be associated with the exposed areas of high wall tension and wall displacement. A recent CFD study with a wall stress analysis by computational structure dynamics (CSD) in patient specific aneurysm models identified local rupture stability. Valencia *et al.*[118] successfully performed the simulations in an anatomically realistic model of a saccular cerebral aneurysm using FSI, by considering the wall mechanical properties and wall thickness of the aneurysm. Another group also performed FSI simulations in five patient-specific aneurysm geometries using different blood pressure conditions and elastic properties of walls to investigate the difference between ruptured and unruptured aneurysms.[61] A new cyber-physical system composed of *in vitro* dynamic strain experimental measurements and CFD simulation for cerebral aneurysms was introduced for the diagnosis of cerebral aneurysms by Shi *et al.*[99] WSS can damage endothelium (EC) which typically initiates a thrombus (blood clot) formation process by platelets. The process may be associated with growth or rupture of aneurysm. Grinberg *et al.*[38] successfully simulated platelet depositions on the wall of a brain aneurysm using multi-scale modeling of blood flow using coupled continuum-atomistic models with platelet aggregation model.

Imaging and Computing Technologies

The success of application of CFD to the study of aneurysms strongly relies upon imaging technology and computational speed. A recent work by Schneiders *et al.*[94] showed the difference in the neck sizes of twenty aneurysms from twenty patients between images from 3DRA and 2D DSA. They claimed that the overestimation of neck size on 3DRA may have non-negligible consequences for CFD results associated with it. Computation speed, cost and accuracy are also key factors for the efficiency and feasibility of CFD for the evaluation and treatment planning of aneurysms as shown in a study by Karmonik *et al.*[50]

Significance of Larger Generalized Clinical Datasets

As discussed earlier, due to the complexity of aneurysm pathophysiology,[18,87,111,124] a large number of risk parameters have been introduced by several authors and such parameters have not been standardized. Furthermore, some parameters are still controversial in CFD community. This may stem from different datasets by diverse groups, which may be dominated by different mechanisms of IAs.[124] Thus, it seems very important to conduct studies with larger datasets, including longitudinal data of unruptured aneurysms and cross-sectional data of ruptured and unruptured aneurysms.[18,19,87,111,124] It has also been pointed out that further efforts are needed to generalize or standardize risk parameters.[18,124]

Antiga *et al.*[2] presented an image-based modeling framework for patient-specific computational hemodynamics to be performed in the context of large-scale studies. The framework takes advantage of integration of image processing, geometric analysis and mesh generation techniques and play as a tool of automatic quantification of geometrical features. Their later work applied the framework for automatic quantification of geometries to a cerebral aneurysm risk assessment project (The Aneurisk project, a joint research project in Italy).[79] The group also presented a technique of automated delineation of lateral and terminal aneurysms for the study of initiation of aneurysms.[30] They also demonstrated techniques for automatically identifying the neck plane, key aneurysm dimensions, shape factors, and orientations relative to the parent vessel in a population of 15 sidewall and 15 terminal aneurysms.[78] An automatic quantification of 3D nature of aneurysm can minimize observer variability to help find standard geometric risk factors. All of the techniques developed by the group are available as part of an open-source effort, the Vascular Modeling Toolkit (VMTK) (http://www.vmtk.org), towards the sharing of tools and data.

The development of sophisticated statistical tools to filter large data to obtain quantities associated with aneurysm rupture is also important. Sangalli *et al.*[90] introduced a novel functional data analysis to highlight the relations between the geometric features of ICA and aneurysm location using 3D angiographies of 65 patients. The group in their later studies[91,92] made an effort to resolve the issue of classification of functional data due to misalignment of the data using proposed novel algorithms: a k-mean and a k-medoid alignments for curve clustering. The procedure efficiently decouples amplitude and phase variability. Passerini *et al.*[76] combined CFD analysis and morphological characterization and statistically investigated the features of the ICA of 52 patients affected by a cerebral aneurysm using a functional principal component analysis. They found that ICA featuring a pronounced WSS peak are statistically inclined to hosting ruptured aneurysms, and that patients with a double-bend siphons (S-class) are less prone to the development of cerebral aneurysms.

We now can access and download data collected during the Aneurisk project, including DICOM images, 3D reconstructions, geometric characterizations and numerical simulations of all cases in the Aneurisk data set in AneuriskWeb (the Aneurisk dataset repository, http://ecm2.mathcs.emory.edu/aneuriskweb/index).[1] This enables us to share large data, and it will eventually help identify universal risk parameters by comparing results and performing validation. Finally, the goal may be achieved by closer collaborations and better communications among scientists, engineers and clinicians as indicated by several authors.[19,87,111,124]

Communications Between CFD Engineers and Clinicians

It seems that the use of CFD for the study of aneurysms has been limited to selected clinical personnel in collaboration with engineers or scientists (see[46]). An earlier report suggested that engineers and scientists may require more efforts to prove and validate CFD for rupture risk assessment and need more feedback from clinicians to adapt the CFD workflow for clinical use.[103] According to the report, CFD engineers trained and surveyed clinicians who participated in a workshop on CFD, conducted in Lisbon, Portugal. The clinicians were trained to perform CFD analysis for an IA, using the @neuFuse software developed within the European project @neurIST. They found that the majority of participants showed interest in CFD as a clinical decision tool, however they noticed that many clinicians could not understand the clear role of hemodynamics in the etiopathogenesis of IAs for the use of CFD in this context. Accordingly, they strongly suggested that a controlled and extensive exposure of the software and its concepts to the broader clinical community is necessary.

CONCLUSION

We searched CFD studies of aneurysms using subject specific models to understand the current role of CFD for evaluation and treatment planning for aneurysms. Many CFD researchers focused on the identification of morphological and hemodynamical risk factors responsible for aneurysm rupture. In parallel, a number of authors have applied CFD to the study of evaluation of surgical devices.

The application of CFD to device evaluation seems to have produced valuable and consistent results, especially in the early stages of device design. However, further investigations with clinical data are required to adopt CFD for treatment planning. Additional validation and sensitivity studies with devices, and further improvements in simulation speed (the whole workflow) are necessary before this technology can be used in the routine clinical practice.

Studies of rupture risk have identified several geometrical and hemodynamical variables associated with rupture. However, the underlying mechanisms are still poorly understood. Kallmes in 2012[46] argued that identifying rupture risk factors by CFD may be confounding because many not converging and un-standardized risk parameters have been introduced by several CFD authors. As discussed by other authors,[19,87,111] the confusion may originate from the complexity of the disease itself. Bacigaluppi *et al.*[6] in their recent review article underlined the value of a unifying hypothesis that merges the role of geometry, with that of hemodynamics and of genetics as concerns vessel wall structure and inflammatory pathways to better understand the physiopathology of aneurysm. Robertson and Watton[87] explained that a hemodynamical and structural modeling process to understand detailed mechanisms for vascular remodeling processes associated with evolution or rupture of aneurysms has been limited by a variety of barriers such as the absence of patient specific *in vivo* flow input conditions and wall properties, dependence on the resolution of medical scanners, and mathematical and computational modeling expenses causing from the complexity of blood properties and geometries. Therefore, it is still too early to discuss if CFD can completely predict the growth and rupture of specific aneurysms and we are still in an exploration phase.[19] Even though broader investigations using large clinical datasets are still needed to find universal mechanical risk factors, CFD seems also useful for the study of detailed mechanisms associated with rupture processes. Strother and Jiang[111] in their report in 2012, pointed out the importance of positive future role of CFD, arguing that results from CFD studies on large populations could provide great help in categorizing aneurysms according to a number of hemodynamic parameters, and these categories when correlated with other factors such as collagen mutations, smoking, family history, age, sex, and perianeurysmal environment, could give insights that might prove useful in predicting the risk of aneurysm rupture.

As a result of this review, we infer that future success of CFD as a robust clinical tool depends on: (i) further reliability tests through validation studies, (ii) analyses of larger generalized clinical datasets to find converging universal risk parameters, (iii) better understanding of the detailed vascular remodeling processes associated with aneurysm growth, evolution and rupture based on hemodynamical and structure analyses, and (iv) better coordinated and organized communications and collaborations between engineers and 3clinicians.

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