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RISK STRATIFICATION OF CEREBROVASCULAR ANEURYSMS USING CFD — A REVIEW

Kaavya Karunanithi[1*], **Chang-Joon Lee**[1], **Yu Zhang**[1] **and Yi Qian**[1]

[1] Australian School of Advanced Medicine, Macquarie University, Sydney, AUSTRALIA
*Corresponding author, E-mail address: Kaavya.karunanithi@mq.edu.au

ABSTRACT

Management of cerebral aneurysms is currently done solely based on clinicians' experience and knowledge. Computational fluid dynamics (CFD), a numerical method aims to provide data that will help in clinical decision making and in the treatment of cerebral aneurysms. A review of relevant research conducted to date was incorporated in this paper to delineate the current standing in our grasp of the various hemodynamic and morphologic parameters that might play a crucial role in the initiation, growth and rupture of cerebral aneurysms. The limitations of CFD from a hemodynamic point of view are discussed in detail. This helps us to identify the areas of future research that is essential to improve the accuracy of its clinical application.

NOMENCLATURE

SR-Size Ratio
WSS-Wall shear stress
D_{max} -Clinical risk assessment metric
OSI – Oscillatory Shear Index
AR – Aspect Ratio
EL – Energy Loss
IA – Inflow angle

INTRODUCTION

Cerebral aneurysm is a localized dilation of the blood vessel. It is a cerebrovascular condition where the blood vessel becomes enlarged to form a balloon like structure due to weakness of the arterial wall. Although mostly stable, intracranial aneurysms sometimes rupture leading to a subarachnoid haemorrhage. They can be classified into various types based on the size, shape and location. Cerebral aneurysms most commonly occur in the base arteries of the brain surrounding the Circle of Willis such as internal carotid artery, external carotid artery and middle cerebral artery. Aneurysms are classified into saccular or fusiform based on their shape. (Lasheras Juan C., 2007) Congenital defects, blood pressure changes, atherosclerosis and trauma have been reported to be the cause of intracranial aneurysms. Most intracranial aneurysms are asymptomatic until they rupture. However rupture can cause various complications, the most dominant being sub arachnoid haemorrhage (SAH) (Adamson et al.1994) Haemorrhagic stroke also occurs as a result of rupture in some patients. There are a multitude of morphologic and hemodynamic factors contributing to the initiation, growth and rupture of cerebral aneurysms. Depending on these factors one can assess the risk of rupture of cerebral aneurysms. Apart from these factors smoking and hypertension are also considered to be independent risk factors that lead to sub arachnoid haemorrhage in an aneurysm. (Isaksen et al.2002) Treatment of cerebral aneurysms is strongly based on their risk stratification. Intracranial aneurysms are treated either by surgical clipping/bypass or by endovascular methods. Surgical clipping is traditional method which is proven to be effective in the treatment and control of cerebral aneurysms. However, it is a highly invasive surgery which involves risks associated with an open cranial intervention. On the other hand, endovascular methods of treatment are preferred at the moment. Various endovascular methods exist to treat intracranial aneurysms i.e. Endovascular coil embolization and placement of stents/flow diverters across the parent artery. The endovascular methods aim to reduce the flow of blood into the aneurysms thereby leading to its occlusion. However, endovascular methods are still not perfect, the mortality/morbidity and complications of endovascular were reported in an average of 2-8 % of patients (Santillan et al.2012 and Park et al.2005)

Computational fluid dynamics (CFD) is applied widely in cerebrovascular aneurysm research. Various research groups around the world are now trying to understand the underlying mechanisms leading to aneurysm initiation, development and rupture along with trying to determine the efficacy of surgical intervention. A detailed investigation of various morphological and hemodynamic parameters is necessary to understand the various factors that contribute to aneurysm rupture. In addition to this, CFD can also be used to specifically determine the efficiency of the treatment such as stenting and flow diversion. Morphological parameters such as aneurysm size, shape, aspect and size ratio and inflow angle are believed to be important factors that contribute to the development and rupture of an aneurysm. Of these, previous studies have shown that the size ratio and aneurysm inflow angle are autonomous parameters that helps in the prediction of aneurysm rupture. Various hemodynamic parameters like flow velocity, pressure, wall shear stress, oscillatory shear index and energy loss are believed to play a crucial role in the growth and rupture of cerebral aneurysms (Bisbal et al. 2011).

CFD IN DIAGNOSIS AND MANAGEMENT OF CEREBRAL ANEURYSMS

It is necessary to understand the mechanisms responsible for aneurysm growth and rupture for accurate risk stratification and management of intracranial aneurysms. In order to understand them, we need to look into numerous morphological and hemodynamic parameters and their role in the growth and rupture. Research is being conducted to assess the effect of specific morphologic and hemodynamic parameters on intracranial aneurysm.

Morphological parameters and risk of rupture

Cerebral aneurysms are mostly asymptomatic until they rupture which makes diagnosis and treatment of cerebral aneurysms harder. When an un-ruptured aneurysm is diagnosed in a patient, image-based morphological analysis of the aneurysm is still the most widely followed method for its treatment and management. Initial factors that are used by clinicians for assessment of rupture include the size, shape and location of the aneurysm (Nikolic et al.2012) For instance; larger or wide-necked fusiform aneurysms are believed to hold a higher risk of rupture than smaller aneurysms. The location of aneurysm occurrence, i.e. the artery in which the aneurysm occurs is also said to play a crucial role in increasing the risk of rupture. Conventionally, aneurysms occurring at a bifurcation site and sidewall aneurysms with curved parent artery were believed to be in a higher risk of rupture.

Aside from the image-based indicators several other morphological parameters are believed to contribute significantly. A wide range of parameters such as aspect ratio, size ratio, inflow angle, nonsphericity index, ellipticity index, ostium ratio and undulation index was defined by earlier research publications as important in determining the risk of rupture of an aneurysm (Nikolic et al. 2012, Raghavan et al.2005 and Dhar et al.2008) Aspect ratio has achieved statistical significance as an important risk factor for rupture. (Ujiie et al.1999) Aspect ratio is defined by the following equation

$$\text{Aspect Ratio (AR)} = \frac{Depth}{Neck\ width} \qquad (1)$$

Increasing values of aspect ratio is agreed upon to increase the risk of rupture of an intracranial aneurysm. However, there have been discrepancies in determining the absolute threshold value of aspect ratio beyond which aneurysms are deemed to have a high risk of rupture.

Nader et al. in 2004 reported a mean aspect ratio of 2.7 for ruptured aneurysms. Weir et al.(2003) reported rupture for 7 per cent of aneurysms having an aspect ratio as small as 1.38. Dhar et al.(2008) reported an average value of 1.18 for ruptured aneurysms using images that were obtained using a 3D rotational angiography. In general, a value of 1.6 is predicted to be the lower threshold value of aspect ratio for ruptured aneurysms. Hence aspect ratio, though believed to be an important risk factor for aneurysm rupture, cannot be taken as a standalone method for risk stratification. Other parameters such as undulation index and ellipticity index though statistically significant, are inter-dependent in serving as rupture risk indicators

Prediction of risk of rupture for intracranial aneurysm based on morphological parameters involves analysis of the properties of parent artery. As a result, inflow angle was looked into to serve as an indicator of rupture risk. Aneurysm inflow angle or vessel angle (IA) is defined as the angle of blood flowing from the parent artery into the daughter aneurysm. Baharoglu et al. (2012) demonstrated that apart from clinical risk assessment metric, $D_{max,}$ Size and Aspect ratio, the Inflow angle is the only independent morphological feature that can be used to differentiate the rupture status of intracranial aneurysms. Aneurysms with higher inflow angle have a greater tendency to have complex flow patterns which might lead to the development of blebs that act as rupture sites. Dhar et al.(2008) and Wong et al. (2012) have reported higher risk of rupture for vessel angles greater than 112 degrees and 180 degrees respectively. Thus the risk of rupture is proved to increase with increasing inflow angle.

Size ratio is defined as SR = (maximum aneurysm height)/ (average vessel diameter). (2)

Tremmel at al.,(2009) found that size ratio can serve as an independent contributor to analyse the risk of rupture in cerebral aneurysms. They reported a threshold value of 2.0, beyond which it was proposed that aneurysms hold a higher risk of rupture. However, a more recent study done by Rahman et al.(2010) reported a size ratio value of 2.76 for ruptured aneurysms from logistic regression method. A multi-centre study using larger cohorts is proposed to determine the size ratio value that can serve as an effectual risk index (Lauric et al.2012)

Currently, size ratio and aneurysm inflow angle are proven to be independent morphological risk assessment factors for aneurysm rupture. Further large scale studies are in order to further investigate the magnitude of these risk factors in rupture prediction.

Hemodynamic parameters

In addition to morphologic parameters, hemodynamic parameters play an important role in the rupture process of an aneurysm. Several hemodynamic factors have been studied in the past to identify their contribution to aneurysm rupture. Although extensive research is being done in this field, no conclusive pattern pertaining to aneurysm rupture has been established till now.

Pressure is an imperative hemodynamic factor that influences aneurysm rupture. Cebral et al.(2011) discussed the impact of intra aneurysmal pressure on rupture of an aneurysm. His paper discussed the effects of placement of flow diversion device on intra aneurysmal pressure. They reported a drastic increase in the intra-aneurysmal pressure following flow-diverter placement. There was a difference of about 25 mm Hg between ruptured and un-ruptured aneurysm. This high difference is cited to be due to the increase in the complexity of flow pattern in the aneurysm and presence of jet flow impingements. Although this statement appears cogent, clinically such difference in pressure is quite large in magnitude and hence considered implausible. A standard reference point for pressure needs to be specified where necessary to avoid such large pressure differences. (Shojima et al.2011) Furthermore, CFD is capable of measuring only the pressure difference at specific points and not the absolute pressure at any given point in the aneurysm. This is noteworthy in order to derive a realistic inference that would help us understand the relationship between pressure and aneurysm rupture. There exists a moderate elevation in intra-aneurysmal pressure due to flow impingement which is discussed by Shojima et al. (2005) and Burleson et al. (1995). This leads to substantial changes in the wall shear stress distribution pattern thereby resulting in loss of aneurysmal wall integrity. (Torii et al.2011)

Wall shear stress (WSS) is another important indicator of aneurysm rupture. Wall shear stress also has a significant role in aneurysm initiation and growth. (Crompton et al.1966 and Nakatani et al.1991) and research is being done to understand how wall shear stress contributes to aneurysm rupture. Wall shear stress in an aneurysm is calculated by the following equation

$$\text{wss} = \mu\omega_{|\text{wall}}, \quad (3)$$

where μ is the dynamic viscosity of blood and ω is the velocity gradient at the aneurysm wall (Sheard 2009)

An increase in the complex flow patterns and a flow impingement on the aneurysm wall is reported to cause wall shear stress which is due to the frictional force of the blood against the wall (Jou et al.2003) Wall shear stress patterns have been analysed for various aneurysms such as saccular and fusiform aneurysms at various locations. There is varied opinion of the way that wall shear stress influences the rupture process. Cebral et al. (2011) and Hashimoto et al. (1980) observed high values of wall shear stress inside the aneurysm that was almost twice the normal value. Cebral et al. (2011) also showed that high WSS with a small impingement region possessed statistical significance between the rupture and un-ruptured group for about 210 cerebral aneurysms in different locations. Shojima et al. (2011) however, argues that a low WSS pattern compared to that of the parent artery was found in the bleb region. Thus they contribute low WSS to increasing the risk of rupture of aneurysm. Xiang et al. (2011) stated that low wall shear stress triggers an inflammatory response in the aneurysm wall which leads to its heterogeneous remodelling.

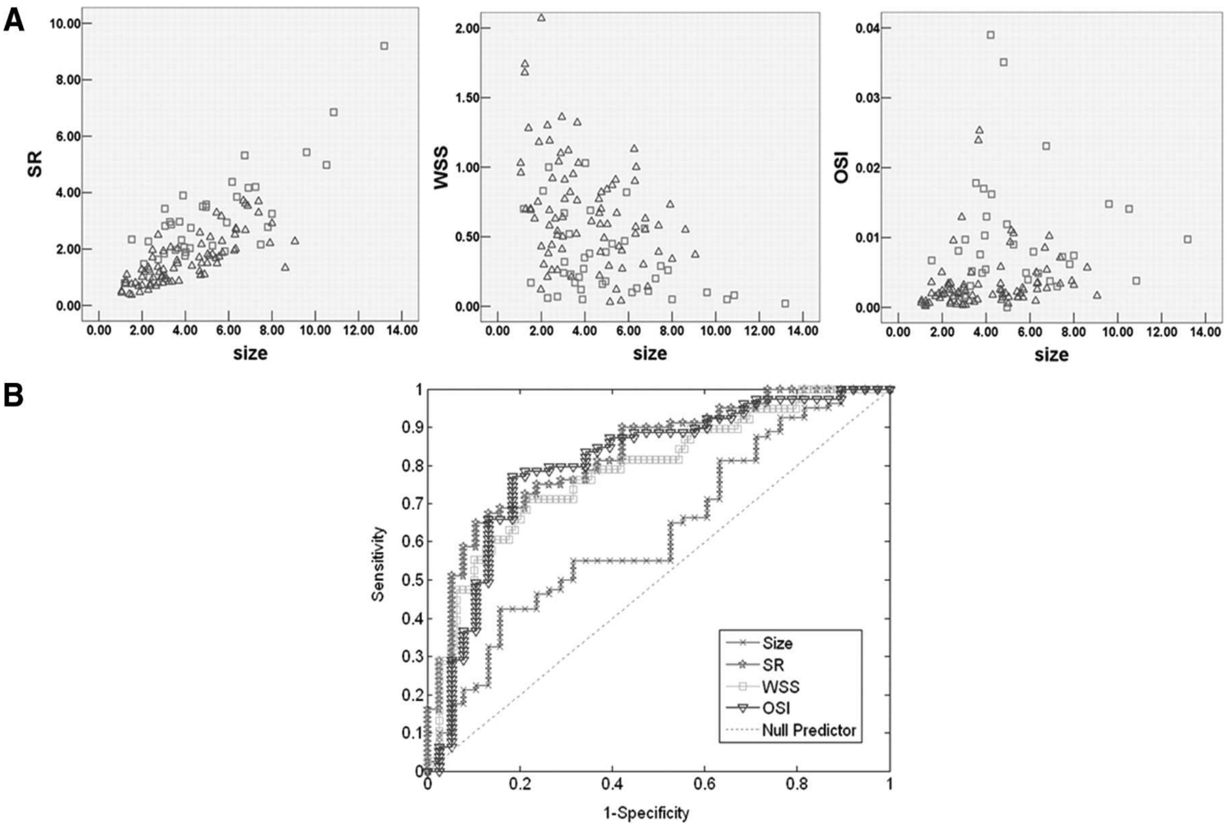

Figure 1: Scatter plots (A) showing the distribution of key parameters in unruptured and ruptured cases. The solid square represents ruptured aneurysm data and the hollow triangle represents unruptured aneurysm data and ROC curve (B) for key parameters SR, WSS, and OSI. [Reprint with permission from Wolters Kluwer Health of Figure 4 from: XIANG, J., TREMMEL, M., KOLEGA, J., LEVY, E. I., NATARAJAN, S. K., & MENG, H., (2012), “Newtonian viscosity model could overestimate wall shear stress in intracranial aneurysm domes and underestimate rupture risk”, *Stroke*, 42(1), 144-152.]

This in turn contributes to aneurysm growth that increases the size ratio thereby increasing the complexity of flow patterns which results in rupture of an aneurysm. Different derivations of wall shear stress magnitude may also serve to accurately portray the role of wall shear stress in aneurysm dynamics. Wall shear stress gradient aims to illustrate the spatial distribution of the wall shear stress in the directions normal and tangential to the wall. (Finol et al.2002). Goubergrits et al. (2012) attempted to determine the pattern of wall shear stress gradient by plotting statistical wall shear stress maps in ruptured and un-ruptured aneurysms that is believed to increase the sensitivity of rupture risk analysis. By considering wall shear stress magnitude and its directions we can better determine how wall shear stress induces aneurysm growth and rupture.

Oscillatory shear index (OSI) is another hemodynamic parameter that is speculated to influence the rupture of aneurysms. It defines the disturbance in the flow field.

Oscillatory shear index averaged over dome area is calculated by the following equation

$$OSI=\frac{1}{2}\left\{1-\frac{\left|\int_0^T wss_i dt\right|}{\int_0^T |wss_i| dt}\right\}, \tag{4}$$

This area has also been reported to be a region of low wall shear stress. (Xiang et al.2011 and Kawaguchi et al.2012). Although the correlation between high OSI and low WSS is not reported in previous publications we believe that there exists an essential inter-dependence between the two parameters which could be investigated further. Fainod et al. (2012) have reported that a high OSI indicated the initiation of thrombus in an aneurysm that was earlier treated with a flow diverter. Supplementary studies investigating the effect of oscillatory shear index is needed to understand the method of influence of this hemodynamic parameter

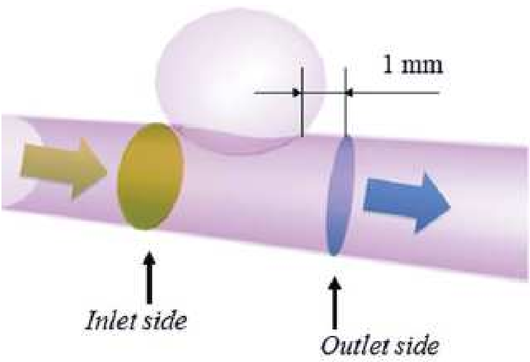

Figure 2: CFD Model of physical variable extraction site for defining energy loss

We defined Energy Loss (EL) as a parameter that measures the loss of energy by the aneurysm without the influence of the parent artery in our earlier publications. Energy loss is mathematically expressed as

$$\mathrm{EL}=\frac{v_{in}A\cdot\left\{\left(\frac{1}{2}\rho v_{in}^2+P_{in}\right)-\left(\frac{1}{2}\rho v_{out}^2+P_{out}\right)\right\}}{V_m} \tag{5}$$

where ρ is the fluid density V_m is the volume of the measurement section and A_{in} is the area of the test plane at the inlet of the measurement region. v_{in} and P_{in} represent the mean flow velocity and static pressure of the test plane at the inlet side, respectively, and v_{out} and P_{out} represent those at the outlet side, respectively.

A study of 30 intracranial aneurysms consisting of 26 stable (mean aneurysm diameter 7.07mm) and 4 ruptured aneurysms (mean aneurysm diameter 6.05mm) for calculating energy loss were performed. The results of the study showed us that the energy loss for ruptured aneurysms were 5.02 times higher than that of energy loss of stable intracranial aneurysms. This proves that energy loss is a key hemodynamic parameter of statistical significance ($P<0.001$). The results of the study are shown in the Figure 3

The discussed morphological and hemodynamic parameters are proven to influence the aneurysm growth and rupture although the statistical significance of each of them may be debated. Nevertheless, all these factors are believed to be interwoven and they collectively influence the rupture of an aneurysm. For instance, the low WSS which results in remodelling of the vessel wall results in aneurysm growth which in turn leads to complex flow patterns and impingement regions that lowers the WSS of the aneurysm wall. A collaborative study of morphological and hemodynamic factors of aneurysms would help us assess the inherent risk of rupture.

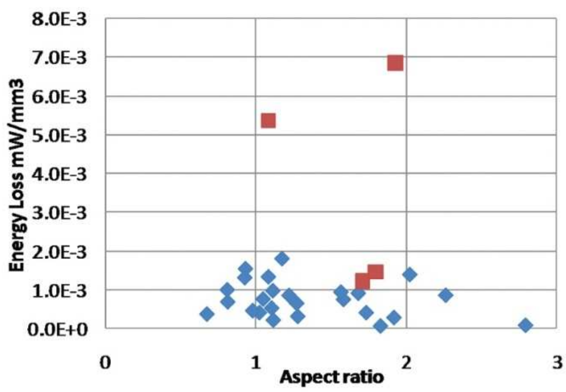

Figure 3: (a) Scatter plot of Energy loss against aspect ratios (red-ruptured IA and blue-unruptured IA)

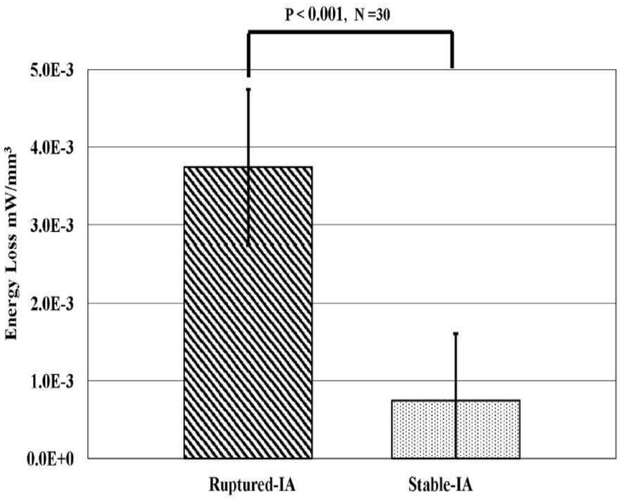

Figure 3 (b): Energy loss difference between ruptured and unruptured aneurysms

LIMITATIONS

Computational fluid dynamics has proved itself indispensable in understanding hemodynamics and the mechanism of cerebral aneurysms. There have been ground-breaking revelations in our understanding of the initiation, growth and rupture of cerebral aneurysms with the use of CFD tools. Nevertheless, the results produced by computational tools have to be validated by means of experimental methods to determine whether they are clinically relevant. Validation is made essential as CFD has indeed limitations in simulating the intracranial milieu. The difficulty stems from the method itself that is used for computation. The boundary conditions specified for simulating the blood flow through an artery will realistically never be the same as one another, as the pressure and flow conditions differ for each patient. In order for precisely calculating wall shear stress and other risk factors, patient specific physiological flow conditions should be incorporated (Karmonik et al.2012) It is practically not feasible to measure in-vivo flow rates for each patient. Apart from this, we also consider the arterial wall to be rigid which is not the case in the real world. Arterial wall possesses elastic properties with a Young's' module gradient that varies over the surface of the arterial and aneurysmal wall. So at any given point in the arterial wall the Young's modulus is unique as compared to the rest of the arterial wall surface. Hence assuming the arterial wall to be a rigid body might affect the accuracy of the simulated results. CFD has the capability to measure the pressure difference with reference to a standard and the pressure at any point inside the aneurysm is dependent on the pressure variation that is measured.

Another major limitation that we face is modeling blood flow. Blood is currently simulated as a simplified Newtonian model. This assumption is stated to cause a vast exaggeration in the wall shear stress in aneurysm domes. (Xiang J et al.2012). This in turn leads to an under estimation of risk of rupture as the wall shear stress in the aneurysm dome is considered to be an important parameter for assessing risk of rupture. Blood flow could be modelled as a non-Newtonian fluid but it does involve developing customized CFD software as commercially available software fall short of it, not to mention the long computing time involved. Although only a negligible difference in the flow pattern exists between Newtonian and non-Newtonian conditions, this could impact the risk stratification to a greater magnitude. (Perktold et al.1989)

Medical image segmentation methods also contribute to a certain degree of inaccuracy in CFD results as the image captured using various modalities possess sizeable artefact. Removal of artefact is a critical factor that improves the accuracy of results. In addition to removal of artefacts, smoothing procedures found in most commercial software leads to loss of data (Pham et al. 2000). It has been proven that the image segmentation method affects the clarity of CFD results obtained to a large extent (Fenster et al.2005). In addition to measuring the intra aneurysmal pressure, ambient pressure surrounding the aneurysm sac is speculated to play a far greater role in its rupture process. This hypothesis needs to be investigated further to shed light in our understanding of instigation of rupture. Currently, there are no in-vivo non-invasive measures that calculate the ambient pressure surrounding the aneurysm. Thus the lack of established experimental procedures leaves us in dark about various important parameters such as ambient pressure, patient specific flow rates etc.

FUTURE DIRECTIONS

Computational fluid dynamic tools are subjected to continuous evaluation by clinicians and other researchers and it undergoes constant evolution to make the results physiologically significant. Fluid structure interaction is now being delved to solve the problem of rigid wall assumption. This will enable us to understand the impact of wall structure properties on flow velocity, wall shear stress and aneurysm rupture. Various elastic and hyper-elastic models are currently under use to investigate the aneurysm fluid structure interaction (Torii et al.2008). Preservation of images during medical image segmentation is an important issue that is being addressed effectively. There have been commendable advances in the development of advanced algorithms like averaging curves, automated and semi-automated deformable models, incorporation of fuzzy logic, neural networks and pattern recognition methods that are precise, accurate and efficient. This will enable to preserve the integrity of the medical image thereby improving the accuracy of CFD post-processing results (Udupa et al.2006 and Chalana et al.1997)

In future CFD researchers will strive to reduce the difference between in-vitro and in-vivo results so that it could be translated successfully to a clinical setting to enable accurate risk stratification which will help clinical decision making and it will also play a huge role in virtual treatment planning and simulation of flow diverters, stents and bypass. This will help greatly reduce treatment associated morbidity and mortality.

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