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Can aspect ratio be used to categorize intra-aneurysmal hemodynamics?—A study of elastase induced aneurysms in rabbit

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Abstract

Clinical studies suggest aneurysm aspect ratio (AR) is an important indicator of rupture likelihood. The importance of AR is hypothesized to arise from its influence on intra-aneurysmal hemodynamics. It has been conjectured that the flow in the domes of high AR sacs is slower than in low AR sacs and some aspect and leads to a cascade of enzymatic activities that weaken the aneurysm wall. However, the connection between AR, hemodynamics and wall weakening has never been proven. Animal models of saccular aneurysms provide a venue for evaluating this conjecture. The focus of this work was to evaluate whether a commonly used elastase induced aneurysm model in rabbits is suitable for a study of this kind from a hemodynamic perspective. In particular, to assess whether hemodynamic factors in low and high AR sacs are statistically different. To achieve this objective, saccular aneurysms were created in 51 rabbits and pulsatile computational fluid dynamics (CFD) studies were performed using rabbit specific inflows. Distinct hemodynamics were found in the low AR ($AR < 1.8$, $n=25$), and high AR ($AR > 2.2$, $n=18$) models. A single, stable recirculation zone was present in all low AR aneurysms, whereas a

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second, transient recirculation zone was also found in the superior aspect of the aneurysm dome for all high AR cases. Aneurysms with AR between 1.8 and 2.2 displayed transitional flow patterns. Differences in values and distributions of hemodynamic parameters were found between low and high AR cases including time averaged wall shear stress, oscillatory shear index, relative residence time and non-dimensional inflow rate. This work lays the foundation for future studies of the dependence of growth and remodeling on AR in the rabbit model and provides a motivation for further studies of the coupling between AR and hemodynamics in human aneurysms.

Keywords

Aneurysm; hemodynamics; aspect ratio; CFD; wall shear stress

1. Introduction

Intracranial aneurysms (IAs) are localized deformations of the arterial wall that frequently rupture, leading to subarachnoid hemorrhage resulting in a high risk of morbidity and mortality (Broderick *et al* 1994; Kaminogo *et al* 2003; Winn *et al* 2002). It is therefore desirable to identify and treat high risk lesions prior to rupture. However, the identification of one or more clinically measurable quantities that can be used independently or collectively to predict rupture risk remains elusive. Geometric factors such as maximum sac diameter and aspect ratio (AR = height/neck width) have been considered.

Statistically significant differences in average size of unruptured aneurysms (4–6mm) and ruptured aneurysms (5–8 mm) have consistently been found, (Lall *et al* 2009). The majority of ruptured aneurysms are less than 5mm, and therefore, this single parameter is insufficient. Ujiie *et al.* retrospectively studied 201 patients with 207 ruptured and unruptured aneurysms and found that 80% of ruptured aneurysms had an AR larger than 1.6 whereas 90% of unruptured aneurysms had an AR less than 1.6 (Ujiie *et al* 1999). Based on an investigation of 774 ruptured and unruptured aneurysms, Weir *et al.* concluded AR is a useful clinical index (Weir *et al* 2003). Nader-Sepahi retrospectively studied patients with multiple aneurysms, one of which had ruptured. In 79% of the patients, the higher AR aneurysm had bled (Nader-Sepahi *et al* 2004). Raghavan *et al.* found AR to be a better predictor of rupture than any of the aneurysm size factors (Raghavan *et al* 2005).

Ujiie *et al.* conjectured the correlation between aneurysm rupture and AR is due to differences in intra-aneurysmal flow. In an experimental study of flow in vein pouch bifurcation aneurysms in rabbits, they found a single recirculation zone in aneurysms with $AR < 1.6$ and a second slower circulation in the dome of sacs with $AR > 1.6$. Studies in human IA have identified correlations between intra-aneurysmal hemodynamics and rupture (Cebal *et al* 2005; Jou *et al* 2008; Shojima *et al* 2004; Shojima *et al* 2005). It is commonly accepted that aneurysm rupture occurs when the mechanical loading exceeds the strength of the aneurysm sac and that local wall weakening occurs in response to the local hemodynamic environment. Ujiie *et al* conjectured low wall shear stress leads to inflammation and hence to localized degeneration of the wall. However, this conjecture has never been studied, largely due to the inavailability of human aneurysm tissue. Animal models provide a mechanism for investigating this connection. The objective of the proposed work is to determine whether there are significant differences in the hemodynamics in low and high AR sacs in the elastase induced aneurysm model and if so, which hemodynamic parameter differ and where in the sac these differences are most pronounced. With this information, future studies of the effect of AR on growth, remodeling and damage in the rabbit model can be planned. Further, this information can guide investigations of the coupling between AR and hemodynamics in human IAs.

The geometric and hemodynamic relevance of the rabbit model to human IAs has previously been demonstrated (Zeng *et al* 2011). The similarity of the walls of elastase induced rabbit aneurysms to human IAs is less well studied. The wall structure has been considered at two and twelve week time points (Abruzzo *et al* 1998, Kadirvel *et al* 2007, Kadirvel *et al* 2010) and compared with walls of recently ruptured human aneurysms (Abruzzo *et al* 1998). As for human IAs, the rabbit aneurysms showed loss of elastic lamina, no intramural inflammation and greatly diminished cellular content. In contrast with human aneurysms the medial layer in the rabbit model was intact at two weeks. by twelve weeks, this layer was absent on the distal walls of high AR sacs (Kadirvel *et al* 2010).

In this work, flow as a function of AR was evaluated in 51 elastase induced aneurysm models in rabbits. A broad range of aspect ratios were created using previously developed techniques (Zeng *et al* 2011). The aneurysms considered here are all side wall, formed downstream from a bifurcation. This provides an opportunity to explore the effects of geometry on flow in a fairly controlled setting.

2. Materials and Methods

Aneurysm Creation and image acquisition

Elastase-induced saccular aneurysms were created in 51 New Zealand white rabbits (body weight, 3–4 kg) using a previously reported protocol (Ding *et al* 2005; Ding *et al* 2006; Ding *et al* 2007; Kadirvel *et al* 2010). Three dimensional rotational angiography (3DRA) was performed 12 weeks after creation of the aneurysms and 3D geometric models of the aneurysm and sections of local vasculature were reconstructed from the serial image data using Mimics software (Materialise Inc., Leuven, Belgium) (Fig.1). Geometric measurements were obtained from the 3D reconstructed geometries and used to obtain AR, bottle neck factor (BF)(Ebina *et al* 1990) and non-sphericity index (Raghavan *et al* 2005),

$$AR=H/N, BF=D/N, NSI=1 - (18\pi)^{1/3}(V)^{2/3}/S, \quad (1)$$

respectively, where N is the hydraulic diameter of the neck cross section, H is the maximum distance between the center of this cross section and sac wall (aneurysm height), D_{max} is the largest hydraulic diameter in the sac and P is the hydraulic diameter of the parent artery proximal to the aneurysm neck, Fig. 2A.

To obtain the rabbit specific *in vivo* blood flow information, transthoracic Duplex Doppler ultrasound imaging (ACUSON Sequoia 512 machine with a 15L8 transducer, Siemens Medical Solutions) was performed in rabbits and arterial waveforms were obtained within the left common carotid artery (LCCA) and distal parent artery (DPA) (Fig. 2C).

Computational Fluid Dynamic (CFD) Analysis

The pulsatile blood flow was modeled using computational fluid dynamic (CFD) simulations. The unsteady, incompressible Navier-Stokes equations were solved using a commercial finite element package ADINA (64 bit) (ADINA R&D, Inc. Watertown, MA). Blood was modeled as incompressible with a constant viscosity of 3.5 mPa·s and a density of 1,050 kg/m³. Following earlier work, the computational domain for each case was chosen to ensure hemodynamic results in the aneurysm would not be substantially altered with the inclusion of additional arterial structures (Zeng *et al* 2010). Briefly, the computational domain for Model 1 included the LCCA, proximal parent artery, DPA and aneurysm. For Model 2, the computational domain included these same vessels and the downstream bifurcation /quadrifurcation structure (Fig. 2B).

The boundary conditions for the models follow those in (Zeng *et al* 2010). Briefly, the vessel wall was idealized as rigid and the no-slip boundary condition was applied. Animal specific *in vivo* doppler measurements in the DPA and LCCA provided estimates of the time averaged flow rate at these locations (denoted Q_{DPA} and Q_{LCCA} , respectively, Fig. 2C). These values were used to define the magnitude of the flow rates Q_i at the outlets (Γ_i) of the computational domain (Fig. 2B).

A structured hexahedral mesh was used with element numbers ranged from 40,000 to 60,000 depending on the geometric complexity. The mesh density was chosen to give less than 3% change in maximum WSS compared with results with double the axial mesh density. CFD analyses were performed for each model for two cardiac cycles using 100 time steps per cycle. Simulations were done using a work station with 3-GHz dual Xeon processor and 8-GB of memory. The computational time for each model ranged from 16 to 20 hours depending on model size.

A non-dimensional flow rate, Q_{ND} was defined as the percentage of PPA flow entering the aneurysm sac at peak systole, (Fig. 2D). Hemodynamic features including flow streamlines, velocity magnitude and flow impingement regions were analyzed. Several scalar measures of the wall shear stress vector $\underline{\tau}_w$ were considered including its magnitude (WSS), the time averaged WSS (TAWSS), the oscillatory shear index (OSI) (He and Ku 1996) and relative residence time (RRT),

$$TAWSS = \frac{1}{T} \int_0^T |\underline{\tau}_w| dt \quad (2)$$

$$OSI = \frac{1}{2} \left(1 - \frac{\left| \int_0^T \underline{\tau}_w dt \right|}{\int_0^T |\underline{\tau}_w| dt} \right) \quad (3)$$

$$RRT = \frac{1}{(1 - 2 \times OSI) \times TAWSS} = \frac{1}{\left| \int_0^T \underline{\tau}_w dt \right|} \quad (4)$$

where T is the duration of one cardiac cycle. The inverse of RRT is an indicator of the distance traveled by a particle close to the wall during time T (Himburg *et al* 2004). The time averaged Reynolds and Womersley numbers

$$Re = \frac{\rho V D_{PPA}}{\mu}, \quad (5)$$

$$\alpha = \frac{D_{PPA}}{2} \sqrt{\frac{2\pi\rho f}{\mu}} \quad (6)$$

were calculated one diameter upstream of the aneurysm neck. Here V is the cross sectional average velocity, further averaged over one period.

2. Results

In the 51 models, Re ranged from 200 to 400 and α ranged from 2.5 to 5.0.

Flow structures

The intra-aneurysmal flow could be categorized as three types with type I having a single circulation, type II flows having a single circulation with an inflection in the streamlines and type III flows displaying two circulations, (Figs. 3 and 4). Of the 51 aneurysms studied, 28 were of type I, 5 of type II and 18 of type III, (Fig. 3). In all cases, flow entered the distal sac and exited the proximal sac. In type II flows, an inflection point appeared during diastole and the relative position of inflow and outflow streamlines shifted. In type III flows, a second transient recirculation appeared in the upper sac during diastole causing a reversal in flow direction at the top of the sac and a separation point to appear at the proximal wall, (Fig. 4C). The projected streamlines traced a figure eight rather than appearing as two distinct vortices of the type found in driven cavity flows. In comparing streamlines for late diastole in Figs. 4B and C, it appears the increasing AR caused the inflected streamlines of type II flows to undergo an out of plane rotation to form the secondary recirculation of type III flows.

Correlation of AR and other geometric indices with flow types

There are many geometric parameters considered in the aneurysm literature and it is therefore important to assess the independence of these variables in correlating with hemodynamics of interest. For example, in this case, whether AR and other geometric parameters are in some sense redundant. Scatter plots of H , Q_{ppa} , BF , D_{max}/H , and H/P for the three AR categories did not demonstrate a strong correlation between these parameters and AR categories (Fig. 5). For example, while the average value of BF is larger for the high AR aneurysms, the range of BF in the high AR group spans BF from 1 to approximately 3.7.

The ability of these other geometric parameters to correlate with types was assessed using receiver operating characteristic (ROC) curves, (Fig. 6). BF , D_{max}/H and H/P had AUC values over 0.90, whereas NSI and N/P had lower AUC values. Compared to other aneurysm size or shape ratios, AR has the best performance in categorizing the flow types.

Correlation between AR and hemodynamics

The speed of flow in high AR sacs was diminished relative to low AR sacs with speeds less than 20 mm/s throughout most of the sac, (Fig. 4).

For both low and high AR aneurysms, the spatial average of TAWSS ($\overline{TAWSS}$) was substantially lower (< 0.3 Pa) than in the neighboring parent artery, where it ranged from 1.0 to 2.0 Pa, (Table 1, Fig. 7). The average $\overline{TAWSS}$ was 0.051 ± 0.047 Pa for high AR sacs and increased to 0.20 ± 0.22 Pa for low AR sacs ($P=0.02$). More generally, a negative correlation between $\overline{TAWSS}$ and AR was found.

Jou *et al.* identified 0.1 Pa as a critical WSS value for local aneurysm growth, with largest growth occurring in regions with WSS below this threshold (Jou *et al* 2005). On average, TAWSS was less than this threshold on 82% of the sac surface in high AR aneurysms as opposed to 42% for low AR aneurysms, (Table 1). In fact, in 94% of the high AR cases, more than 50% of the sac had TAWSS below 0.1 Pa. A positive correlation was found between AR and percent surface area with TAWSS below 0.1 Pa ($R=0.69$) (Table 1).

$\overline{WSS}$ at peak systole was also significantly different between these groups ($P = 0.03$) with $\overline{WSS}$ averaging 0.68 ± 0.78 Pa and 0.28 ± 0.29 Pa for low and high AR groups, respectively (Table 1). A negative correlation was found between $\overline{WSS}$ and AR (Fig.8). The WSS was elevated at the distal neck and wall of the low AR sacs, but only at the distal neck of high AR sacs, (Fig. 7).

A significant difference ($P=0.01$) was found between Q_{ND} for the low and high AR groups (Table 1). Only three of the fifty-one aneurysms received 20% or more of the parent flow rate. All high AR sacs received less than 10% of the parent flow (Table 1). The OSI was elevated at the neck regions of all sacs (Fig. 9). An additional region of elevated OSI was observed at the apex of all high AR cases that was absent in all low AR cases (Fig. 9, Table 1). The maximum value of RRT is over 2000 for most high AR sacs (73%) and located at the apex of the sac, the location of the transient secondary circulation, (Fig. 3, Fig. 9). In contrast, the RRT is below 2000 throughout the sacs of 96% of low AR models. A positive correlation was found between AR and percentage area above a RRT cutoff value. For example, $R=0.74$ for a cutoff value 50 and $R=0.82$ for cutoff value of 2000, (Fig.10).

4. Discussion

In 1999, Ujiie *et al.* conjectured AR may be a better index than aneurysm size for planning treatment of unruptured aneurysms due to the role of AR in determining intra-aneurysmal flow (Ujiie *et al.* 1999). This long standing conjecture has never been proven, despite its clinical significance. It is based on two premises. The first is that hemodynamics in high and low AR aneurysms are different. The second is that high AR flow conditions lead to detrimental changes in the aneurysm wall.

In a previous work, hemodynamics features in the elastase induced aneurysm model in rabbits were shown to be similar to the hemodynamics in a large percentage of human IAs including both bifurcation and sidewall aneurysms (Zeng *et al.* 2011). In the present work, we demonstrated the first premise behind Ujiie *et al.*'s conjecture is valid in this aneurysm model. Namely, flow in the low and high AR models are significantly different. Low, transitional and high AR categories could be defined such that for all low AR aneurysms, only a single circulation was observed, whereas in all the high AR aneurysms, a transient, slower secondary circulation was also found with an associated separation point. The distinctness of these groups could not be explained by differences in animal specific flow rates between the groups, nor to differences in height.

Promising results have already been obtained demonstrating differences in wall structure and function in low and high AR sacs (Kadirvel *et al* 2010). The structure of the proximal and distal walls were seen to differ in high AR sacs whereas no such differences were identified in the low AR sacs. In the proximal walls of high AR sacs, three mural layers were found while these layers were absent in the thinner distal wall which was composed of collagenized tissue. In our work, we found an additional region of elevated OSI on the distal wall of high AR sacs compared. Regions of elevated OSI have been tied to local wall remodeling (Kaazempur-Mofrad *et al.* 2004; Ku *et al.* 1985). Elevated OSI and RRT values in arteries are associated with altered endothelial permeability and lesion formation (Himburg *et al* 2004; Ku *et al* 1985). The distal aneurysm wall was also a region of greatly diminished TAWSS in the high AR sacs. The wall thinning and remodeling in this region may be associated with the drop of TAWSS below a critical value, though animal specific comparison of histology and hemodynamics are needed since the TAWSS is generally low in the sac. Regions of pathologically low WSS have been positively correlated with increase in aneurysm size in humans (Jou *et al* 2008; Shojima *et al* 2004). Guided by the current

work, the relationship between *local* histology and *local* hemodynamics are currently under investigation in our group to further explore the role of AR.

We have also previously identified functional differences in the walls of high and low AR sacs (Kadirvel *et al* 2010). Differential gene expression of 14 genes (4.8 %) was seen for high and low AR aneurysms from eleven animals included in the present study. In the high AR sacs, up regulation was seen in 11 genes including inflammatory /immunomodulatory genes, structural genes, extracellular matrix related genes. These studies were performed on the entire aneurysm sac. The current work provides guidance on how to divide the tissue for future gene expression and proteomics studies, so as to diminish dilution of the data.

Another interesting finding was the existence of transitional flow type in the intermediate AR group, supporting the use of categories of low, high and transitional AR when assessing rupture risk. While most clinical studies identified a statistically significant difference between AR in ruptured and unruptured aneurysms, there is some disagreement about whether a threshold exists and if so, where it lies. As noted by Lall *et al.*, aspect ratios between 1.6 and 2.2 are consistently considered borderline in risk (Lall *et al* 2009). This range is close to that identified here as transitional. The rabbit model has been used to evaluate novel flow altering treatment strategies such as flow diversion and coiling. Based on the current work, it would seem advisable to interpret results from such studies in the context of low, transitional and high AR groups.

The elastase induced aneurysm model in rabbits is not intended to be used for studies of aneurysm initiation since the sac is constructed using elastase. It is also unlikely that it will be practical to study the rupture process until we know more about growth and remodeling. The rupture rate of human saccular aneurysms is quite low-much less than one percent per year. If a similar rupture rate is reproduced in the animal model, we would need to study more than 500 animals for a year to obtain five ruptured aneurysms. This is clearly impractical, both for the duration and quantity of the study. However, once we better understand the growth and remodeling process using this model, we may be able to design long term studies that are more likely to be unstable.

Several idealizations have been included in the model. Motivated by the lack of elastin in the arterial wall, the aneurysm wall has been modeled as rigid. Further, the blood has been idealized as Newtonian.

It will be valuable to determine whether the distinct flow categories identified in this work, carry over to a wider range of vascular geometries such as bifurcation aneurysms. Ujiie *et al.* identified these similar flow categories in low AR (<1.6) and high AR (> 1.6) in surgically created bifurcation aneurysms in rabbits (Ujiie *et al* 1999). Based on their study of flow and rupture in 68 human saccular aneurysms, Hassan *et al.* concluded that AR may be a useful index for predicting rupture in side wall aneurysms with and without branches, while other geometric factors likely play an important role in end wall aneurysms (Hassan *et al* 2005).

3. Conclusion

Low AR ($AR < 1.8$) and high AR ($AR > 2.2$) categories with distinct intra-aneurysmal flow were identified in 51 elastase-induced rabbit aneurysms. A third transitional flow type was identified in the intermediate range. Flow in high AR aneurysms appears to be more deleterious to the wall, displaying larger regions of pathologically low WSS, elevated OSI and elevated RTT. Future studies will be directed at evaluating differences in wall remodeling in these distinct flow environments.

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Figure 1.

A: 2D angiography of elastase-induced rabbit aneurysms, left: low AR case; right: high AR case; B: 3D reconstructed geometric models of the aneurysm and peripheral vasculature.

Figure 2.

A. Measurements of aneurysm height (H) and neck width (N), B. Boundaries of the computational Model 2, arrows denote the flow direction; C, Measured ultrasound waveform (at LCCA and DPA); D. Schematic view of flow going through the parent artery and into the aneurysm, red arrow indicates the cross section normal at aneurysm neck.

Figure 3.
Distribution of AR and flow types for rabbit aneurysm models

Figure 4. Flow streamlines at peak systole, peak diastole and end diastole as well as a schematic of streamlines during end diastole for A) type I, B) Type II and C) Type III flows. The streamline color denotes the velocity magnitude (mm/s).

Figure 5. ROC curve plots for different geometric indices, the corresponding AUC are: AR=1 NSI=0.63, BF=0.90, D_{max}/H=0.97, H/P=0.92, N/P=0.66.

Figure 6. Scatter plots of: (A). Aneurysm height; (B). Flow rate at PPA; (C). $D_{\max}/H$; (D). H/P ; and (E). BF distributions for three AR categories.

Figure 7.

A: Typical contours of TAWSS for a flow type I (left), a flow type I case (middle) and a flow type III case (right), using exponential scale; B: TAWSS profiles in the aneurysm sac (left) extracted from intersection curve (right), from proximal neck to distal neck region.

Figure 8. AR vs. percentage sac area with TAWSS below 0.1Pa for aneurysms with low AR (AR < 1.8, blue), transition AR (1.8 < AR < 2.2, yellow) and high AR (AR > 2.2, red).

Figure 9. Upper row: Contour plots of OSI for a flow type I case (left) and flow type III case (right); Lower row: Contour plots of RRT for a flow type I case (left) and flow type III case (right).

Figure 10.

AR vs. percentage sac area with RRT larger than 2000, for aneurysms with low AR (AR < 1.8, blue), transition AR (1.8 < AR < 2.2, yellow) and high AR (AR > 2.2, red).

Table 1

Hemodynamic results in low, transition and high AR models

AR and Hemodynamic features	AR<1.8 (n=25)	1.8<AR<2.2 (n=8)	AR>2.2 (n=18)	P value (between AR<1.8 and AR >2.2 Groups) (95% CI)
AR	1.40 ± 0.32 Range [0.56–1.77]	1.99 ± 0.11 Range [1.81–2.13]	2.86 ± 0.47 Range [2.23–3.98]	--
$\overline{TAWSS}$	0.20 ± 0.22 Range [0.011–1.23]	0.11 ± 0.09 Range [0.02–0.31]	0.051 ± 0.047 Range [0.002–0.18]	=0.02
$\overline{WSS}$ at peak systole	0.68 ± 0.78 Range [0.11–3.22]	0.38 ± 0.38 Range [0.12–1.37]	0.28 ± 0.29 Range [0.02–.20]	=0.03
% area with TAWSS below 0.1 Pa	42% ± 27% Range [0–77%] Above 50% n=14 (40%)	71% ± 14% Range [46%–94%] Above 50% n=7 (88%)	82% ± 12% Range [47%–97%] Above 50% n=17 (94%)	1E-5
Non-dimensional Q	10.4% ± 9.7% Range [1.5%–49.6%] Less than 10% n=13 (52%)	5.7% ± 6.3% Range [1.2%–21%] Less than 10% n=7 (88%)	4.1% ± 2.5% Range [0.8%–9%] Less than 10% n=18 (100%)	0.005
Locations of elevated OSI	At neck n=25 (100%) At sidewall n=7 (28%) At dome n=1 (4%)	At neck n=18 (100%) At sidewall n=3 (38%) At dome n=4 (50%)	At neck n=18 (100%) At sidewall n=5 (28%) At dome n=18 (100%)	--
% sac area of RRT >50	Average: 22.6% Above 30% n=10 (40%)	Average: 51% Above 30% n=7 (88%)	Average: 69% Above 30% n=18 (100%)	1E-6
% sac area of RRT >2000	Average: ~0 Above 20% n=0 (0%)	Average: 14% Above 20% n=1 (12%)	Average: 28.6% Above 20% n=12 (67%)	5E-9