Masters of research thesis: Haemodynamic Modelling of Cerebrovascular Aneurysm Risk Diagnosis using Computer Fluid Dynamic (CFD)

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Thanks

Statement of Originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

(Signed) Quincy Chan

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<u>1</u>. Abstract

A large number of different measures exist to determine the likelihood and risk of aneurysm rupture. In computational fluid dynamics (CFD). The likelihood of aneurysm rupture is predicted via physical forces enacted upon the blood vessel walls given by a set of known physiological parameters. The most common measures are wall shear stress (WSS) and energy loss (EL), though more exotic physical measurements exist and have been experimented upon (such as oscillary shear index) typically these are complex and unwieldy.

Size measures are also used, including various ratios such as height to width (aspect ratios). In a clinical setting, typically decisions to treat are based on a simple measure of aneurysm size taken by a radiologist with computer simulations being too difficult and time consuming to be used, thus size measures for the foreseeable future will be the commonplace method of clinical radiological assessment.

This study aims to perform a small number of case studies to correlate morphological characteristics with physical stresses known to predict aneurysm rupture in order to more accurately predict and quantify how these measures relate to each other and hopefully refine and improve the morphological parameters to improve clinical decision making.

2. Introduction

2. 1. Public health statistics

In a survey conducted by the World Health Organization (WHO), it was reported that vascular disease accounted for the top 2 causes of death in human mortality in 2016 accounting for 15.2 million deaths worldwide. (WHO fact sheet 2018).

These were classified into ischaemic heart disease (~9 million) and stroke (~6 million) out of the estimated 56.9 million total deaths that year, making cardiovascular research the most important area of medical research with respect to human mortality.

Figure 1 From WHO fact sheet 2018

2.2 Aneurysm risk factors

There are a myriad of risk factors associated with risk of aneurysm formation and rupture, the most immediate factors are age, gender, family history, diet and

smoking (increasing with age, positive family history). Notably females are at higher risk of cerebrovascular aneurysm, while males are at higher risk of aortic aneurysms (Broderick et al 1994, CDC 2018, Thompson 2015).

Lifestyle and acquired factors such as smoking, diet and high blood pressure, and also various infections (Juvela 2000, Alg et al 2013).

Aneurysm risk is also associated with various anatomical defects such as arteriovenous malformation (AVM), (an abnormal connection between an artery and a vein), Coarctation of the aorta. A narrowing of the aorta, Various liver enzyme deficiencies, such as Alpha-glucosidase deficiency. Alpha 1-antitrypsin deficiency which leads to various metabolic issues organ damage (the mechanisms of which are beyond the scope of this paper) Various connective tissue disorders, such as Ehlers-Danlos syndrome. Fibromuscular dysplasia, Hereditary hemorrhagic telangiectasia. Tuberous sclerosis, with poorly understood etiologies and pathophysiological mechanisms. Various systemic disorders, such as Klinefelter syndrome. Noonan's syndrome. Polycystic kidney disease (PCKD).

Sub-arachnoid haemorrhage (SAH) account for approximately 5% of strokes and occurs when there is a bleed between the Pia Mater and arachnoid mater which is a clinically significant form of aneurysm due to it's high mortality and prevalence. (Broderick et al 1994, Thompson 2015).

Interestingly however the prevalence varies greatly amongst different populations due to the variations in genetic, environmental and lifestyle factors as outlined above. According to the WHO, the prevalence varies from 2 per 100 000 (population: China) to 22.5 per 100 000 (Finland). (Ingall et al 2000, Yoon 1999).

The mortality of SAH though is high regardless of the rate with approximately 50-60% mortality within 30 days. This however is a pooled rate and mortality

varies with various risk factors, including size, morphology and location as well as the availability and timeliness of medical intervention. (Broderick et al 1994, Keedy 2006).

2.3 Cerebral vascular structure and anatomy

Arteries and veins, while varying significantly in thickness are anatomically similar throughout in that they broadly consist of 3 layers, the fibrous outer layer, *Tunica Adventitia*, largely made from collagenous fascia material, the muscular *Tunica Media* which allows for contractility and elasticity and the smooth lining of the *Tunica intima* which prevent blood turbulence and clotting. This is anatomically separated by a layer of elastic fibrous tissue. (Keedy 2006, Narayanan 2017, Saladin 2005).
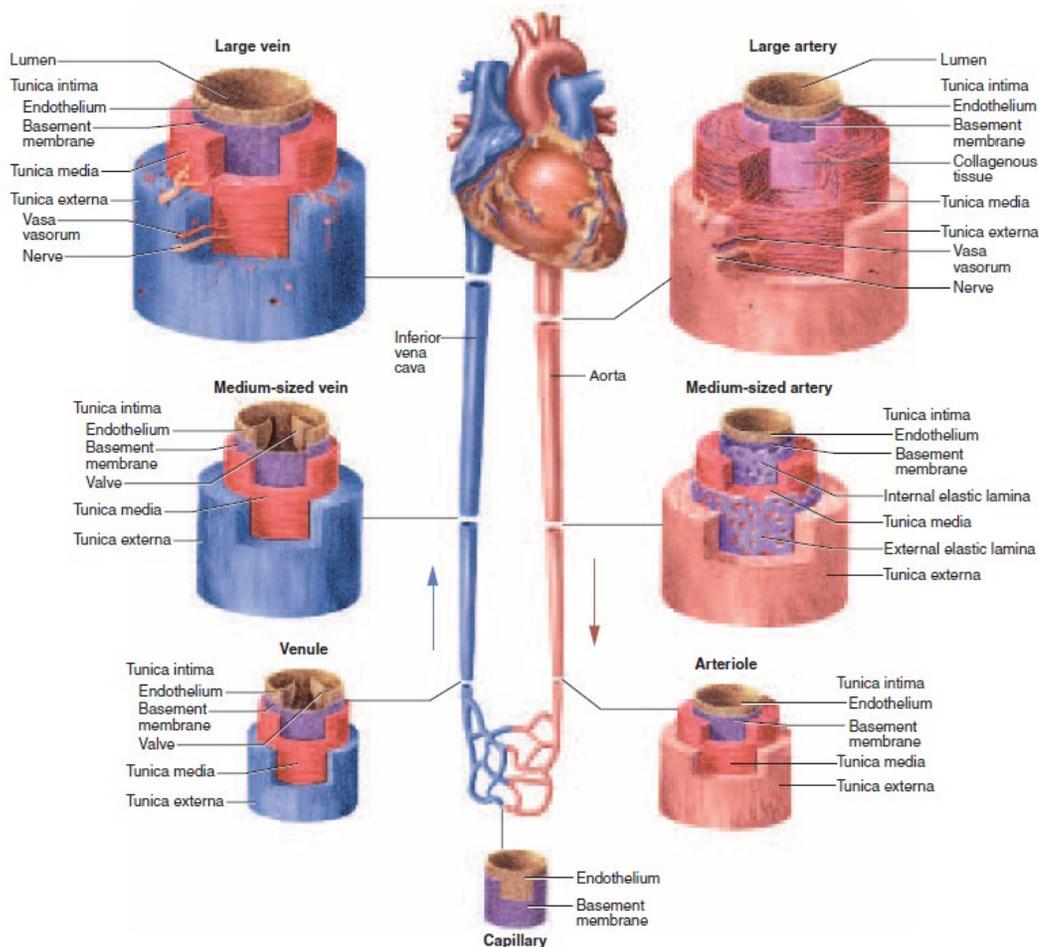
Figure 2, Basic blood vessel anatomy (From Saladin 2005)

2.4 Morbidity and Mortality from aneurysms

Overall intra-cranial aneurysms impact approximately 2-5% of the population (Dhar et al 2008).While much research and modelling has been done to refine the treatment and surgical techniques used to reduce mortality form aneurysm and sub arachnoid haemorrhage, the decline in mortality due to such improvements have been modest. (ACROSS study 2000, Dhar et al 2008).

While the majority of detected aneurysms will not rupture during the course of a person's lifetime, estimates vary from 50-80%, (Brisman et al 2006) to as low as ~1% (Dhar et al 2008), Making the majority of treatment unnecessary, and even likely to cause harm (as this may cause an otherwise stable aneurysm to rupture, and put at risk the patient to various other surgical risks such as infection scarring, damage to other organs due to surgical error etc), treatment of aneurysms is also imperative due to the high rate of mortality and disability with aneurysms that do rupture, with 50-60% mortality, from initial rupture and 20-25% having subsequent and serious complications (Dhar et al 2008).

The surgical cost of treatment is also potentially very high with each surgical intervention potentially costing approximately $50,000- $100,000 (Brinjikji 2012) not including subsequent hospitalization costs.
It should be noted however that both the cost structures, and standards of medical treatment, vary significantly between countries.

Thus this illustrates the potential benefits both in cost, and quality of patient care an accurate and predictive model could potentially provide.

2.5 Computer fluid dynamics (CFD) overview

Computer Fluid Dynamics (CFD) is a method of modelling fluid flows in order to analyse the physical forces which act upon blood vessels in order to predict the behaviour of blood vessels, especially in pathophysiological sequelae such as in

aneurysms. An aneurysm is a bulge in any blood vessel and can vary in anatomical location, from the large artery that carries blood from the heart through the chest and torso to the fine arteries located in the brain (Keedy 2006).

These can either be relatively benign to constituting a major medical emergency depending on the site of the aneurysm. The two major aneurysm types which constitute major medical emergencies are Abdominal Aortic Aneurysms (AAA) and Cerebrovascular Aneurysms (Humphrey et al 2008).

Aortic aneurysms are potentially deadly due to the large volume of blood loss, the aorta being the largest vessel carrying oxygenated blood throughout the entire body, the rupture of which would cause hypo-volemic shock (Bown 2002). Cerebrovascular aneurysms while smaller are also potentially deadly and well as more likely to be debilitating due to the higher sensitivity of neural tissue to hypoxaemia, with brain damage (due to tissue necrosis by hypoxia) typically occurring within minutes of oxygen deprivation (Erecińska 2001).

Aneurysms rupture via in two main mechanisms:
Dissection: The shear force exerted by the pumping blood can split the layers of the arterial wall, allowing blood to leak in between them.
Rupture: When the "balloon" of the aneurysm bursts.
According to the CDC (centre for disease control in the United States),
"Aortic aneurysms were the primary cause of 9,863 deaths in 2014 and a contributing cause in more than 17,215 deaths in the United States in 2009" (CDC fact sheet 2018).

While in our current project are mainly interested in intra cranial aneurysms, the CFD techniques used to study intra-cranial aneurysms can be used to model either type. It should be noted though that while many of the parameters and measures could potentially be very similar, measures such as wall shear stress, energy loss, dome aspect ratio etc could be similar and even comparable between

cerebrovascular and aortic abdominal aneurysms, they differ significantly in size, with aortic aneurysms typically in the scale of centimetres (typically 5.5cm, before treatment is requires) whereas cerebrovascular aneurysms are typically measured in millimetres (5mm-10mm before treament is required) as well as typically having different thickness in the vessel walls. (Beck et al, 2003, Forget et al 2001, Raghaven et al 2005, Rinkel et al 1998, Uijiie et al 1999, Uijiie 2001 et al, Weir et al 2002).

Thus while the modelling could potentially be similar and use similar methodologies, there could be significant variations due to scale mechanics, and anatomical/histological differences between the two aneurysm mains types of clinical significance. (Humphrey 2008).

2.6 Computer fluid dynamics (CFD) Modelling
One potential method of modelling is known as CFD.
CFD is a method of modelling fluids in engineering which simulates fluid flow, heat transfer, and other physical processes in an engineering model.
This is a well established engineering domain to predict the behavior of materials under fluid stress. While traditionally this has been used in applications such as hydraulics, aerospace engineering and wind shear stress in large mechanical structures (and is the industry standard in most architectural and engineering fields. (Nore, Blocken & Thule 2010, Stewart 2012, Majumdar 2011, Sayma 2009, Tu, Yeoh & Liu 2018).

More recently with the increasing computing power and technological refinement, it has been possible to model more complex biological and medical applications such as the modelling of air flow, blood flow, the design of inhalers and drug delivery system, etc. (Lee & Smith 2012, Behbahani et al 2009, Ou & Chubin 2016, Sayma 2009, Stewart 2012, Tu Yeoh & Liu 2018).

Robertson and Watton (2012), outlines the history of CFD use in medical

research, with limited uses in decade of the early 2000s to many hundreds of results today, indicating a general acceptance of use of CFD as a technique for medical modelling for aneurysms, with various review papers citing their model validity usefulness in the medical field (Cerbral and Meng 2012, Lee and Smith 2012, Robertson and Watton 2012).

While CFD is primarily used because of various advantages such as replicability, cost effectiveness, measurement error, scale mechanics, etc, other models are also used in the field of aneurysm research such as silicone models.

Silicone models of cerebral aneurysm and stroke pathology are typically produced by reproducing the images of clinical cases to evaluate the simulation of endovascular procedures. Conventional silicone models, are made typically constructed from separate aneurysm sac and parent artery sutured together.

The conventional silicone models provide very close reproduction of the aneurysm and vessels, even the fine branches. However, it is reported that there is greater physical resistance, when passing the device through curved vessels, and also more difficult to dilate using stents and other such devices. (Suzuki et al 2005).

2.7 Alternative modelling types
Other types of physical modelling exists such as collagen based physical models which involves suspending a reconstituted collagen scaffold in a solution of embedded vascular cells. While superficially this appears to be a good alternative to silicone modelling due to the similarity in material to blood vessels as opposed to silicone, and is a technique used by a number of researchers, for modelling, this technique suffers from inconsistent construction making experiments more difficult to repeat, and histologically the tissue is fairly different to a real blood vessels raising doubts as to whether the alterations in the micro structure would affect it's macro physical properties.(Seliktar et al 2000).

2.8 Forces and stresses modelled using CFD to predict anuerysm behavior

Ultimately Aneurysms are a physical phenomenon. While pathophysiological processes at the biochemical and cellular level can be responsible for altering the strength and integrity of the cell wall. The measurable phenomena which predict the pathophysiology sequelae of the aneurysms are ultimately determined by, and thus can be modelled by the net physical forces acting upon the structures and the physical integrity of those structures, and their ability to resist breakage in the presence of those forces (Frosen et al 2012).

Haemodynamics have been shown to play an important role in intra-cranial aneurysm development and rupture. Using CFD Hassan et al. 2005 suggested that high wall shear stress (WSS) may be responsible for IA growth and rupture in high-flow aneurysms, low-flow aneurysms are more affected by high intra-aneurysmal pressure and flow stasis.

The literature presents a number of different physical parameters which are associated with greater likelihood of aneurysms as well as the measurable physical forces and stresses which exacerbate aneurysms rupture which will be discussed in the next sections.

2.8.1 Wall shear stress (WSS)

Wall Shear stress is given mathematically as

$$\frac{1}{T}\int_0^T |WSS_i|\, dt$$

Equation 1

Where T is the length of the cycle) and WSS_i is the instantaneous shear stress vector averaged over the course of the cardiac cycle (Taken from Takeo et al 2012) Wall shear stress is of course the shear stress upon the wall, or the component of the stress vector that is acted upon perpendicular to the wall of the blood vessel. This is the direct force acting upon the vessel wall. This is considered to be one of

the main contributors to the formation, and rupture of aneurysm.

It should be noted however while it may appear to follow logically that high shear stress is associated with wall rupture, there is conflicting evidence with some studies showing that low shear stress is associated with aneurysm rupture (Boussel et al 2008, Meng 2014).

2.8.2 Oscillary Shear Index (OSI)

OSI is the absolute of WSS integral over time divided by integral of absolute wall shear stress over time, as given by the equation.

$$\frac{1}{2}\left(1-\frac{|_0^T\int WSS_i dt\,|}{\int_0^T |\,WSS_i dt\,|}\right)$$

Equation 2 (From Xiang et al 2011)

This is a more complicated measure of WSS, as it is effectively a measure of not only the force upon the blood vessel wall, but also a measure of changes of direction of that force over time rather than simply a measure of net force over time. Where T is defined as the time of the oscillary cycle and WSS_i is the instantaneous shear stress (that is the vector of the stress at that moment) This is an important consideration in terms of modelling real blood flow, as blood naturally flows in a pulsatile fashion due to the presence of a heartbeat, although the evidence is mixed as to whether adding the measure of blood pulsation increases the predictiveness and utility of the model.

2.8.3 Energy loss

Energy loss is mathematically defined as

$$\frac{v_{in} \bullet A\left(\left(\frac{1}{2}pv_{in}^2 + P_{in}\right) - \left(\frac{1}{2}pv_{out}^2 + P_{out}\right)\right)}{Vm}$$

Equation 3

where V_{in} and V_{out} is the mean flow velocity in and out of the system, and P_{in} and P_{out} represents the static pressure at the inlet and outlet (From Xiang et al 2011).

This is generally a different approach to using WSS, but fundamentally the same idea, as while WSS measures the direct force exerted upon the vessel, energy loss indirectly measure this as the total loss of energy from the flow of blood (composed of the velocity, momentum and pressure due to friction and turbulence.)
This (assuming conservation of energy) assumes that any loss of such momentum and pressure would naturally be enacted upon the vessel wall, causing it stress and damage upon the wall. More formally, this is defined by the Bernoulli equation that the total energy of any fluid (the blood in this case though this applies to fluid in any system) remains constant along a streamline or laminar (smooth) flow of fluid assuming no work is done on or by the fluid and there is no transfer of heat.

2.8.4 Pressure loss
Pressure loss is defined as

$$\text{Ploss} = \frac{\Delta P}{\frac{1}{2} p v_{in}^2}$$

Equation 4

Where the denominator is the the kinetic energy or "dynamic pressure.

$$\text{dP} = \left(\frac{1}{2} p v^2{}_{in} + p_{in} \right) - \left(\frac{1}{2} p v^2{}_{out} + p_{out} \right)$$

Equation 5

This is a comparable measure to energy loss, but accounts for only pressure. While this may appear to be a simpler, less exhaustive model of measurement, it may be clinically a better proxy given that blood pressure is a commonly

measured parameter in a day to day clinical setting as opposed to blood velocity, wall shear etc.

2.9 Morphology Measures of Aneurysms

Cebral et al. (2005) demonstrated that ruptured Aneurysms have turbulent flow patterns, and smaller impinging jet diameters, and impingement zones, which would naturally create areas of high blood velocity and pressure due to the conservation of energy.

Shojima et al. (2004) found that ruptured Aneurysms have a higher average WSS in the aneurysm sac and re-circulation/blood stasis at the apex of aneurysms that rupture, thus the haemodynamics associated with aneurysm rupture is strongly dependent on the geometry of the aneurysm itself (Hassan et al 2005, Hoi et al 2004, Uije et al 1999).

Cebral et al. (2005) showed that haemodynamic physiological variations such as flow rate, blood pressure, and waveform have only small effects upon the likelihood of aneurysm rupture making the modelling of such factors relatively low priority as compared the need for accurate modelling of geometry.

2.9.1 Size

The most obvious measure of an aneurysm's physical parameter is size, and this is reflected in the literature (Dhar et al 2008). This is comparatively easy to measure in a clinical sample to investigate as well as to develop a clinical guideline for.

There is some variance clinically as to the limits of what intra-cranial aneurysm size warrants treatment. In the real world most hospitals would typically begin treatment at around 5 to 10mm. It is uncertain however how evidence based this is, and may really amount to little more a rule of thumb than anything else, To illustrate this, aneurysms 10 mm or larger would be considered dangerous and

warranting operation several studies have shown that a large percentage of ruptured aneurysms are, in fact, smaller than 10 mm, and that there is in fact a good amount of variation for any given size of aneurysm(Beck et al, 2003, Forget et al 2001, Raghaven et al, 2005, Rinkel et al 1998, Uijiieet al 1999, Uijiie 2001 et al, Weir et al 2002).

This shows that while size may be an important variable predicting aneurysm rupture, it may be in fact a very course grain picture of an aneurysm, which can be improved by measuring other geometric parameters.

2.9.2 Aspect ratio

Numerous studies have investigated the significance of shape in the likelihood of intra-cranial aneurysm rupture. A common measure taken is aspect ratio defined as the height of the aneurysm from the neck to the apex divided by neck diameter, shown as follows.
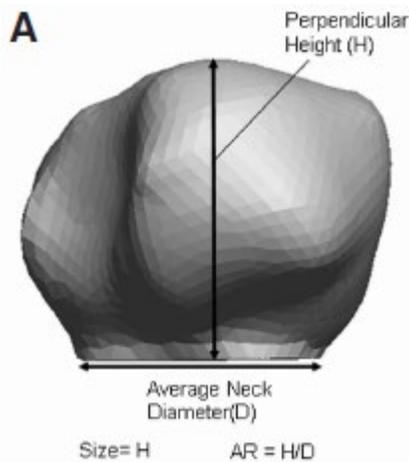
Figure 2 (From Dhar et al 2008)

While numerous studies show that aspect ratio is a predictor of aneurysm rupture, there is a wide variation as to the exact ratio that is predicted to lead to rupture (Beck et al, 2003, Raghaven et al2005, Uijiie et al 1999, Uijiie 2001 et al, Weir et al 2002), other, more complex, shape parameters such as undulation index (UI), nonsphericity index (NSI), and ellipticity index (EI) have been proposed

(Raghaven et al 2005).

2.9.3 Undulation Index (UI)

The aneurysm UI was defined as UI $= 1 - (V/Vch)$, where V is the volume of the aneurysm above the neck plane and Vch is effectively a smoothed outer imaginary surface enclosing the aneurysm, this ultimately is a measure of the smoothness or regularity of the aneurysm.

This is believed to be significant as a higher undulation index, i.e a less smooth surface is believed to weaken wall integrity as well as more likely to spawn daughter aneurysms from the main aneurysm (Raghaven 2005, Dhar 2008).
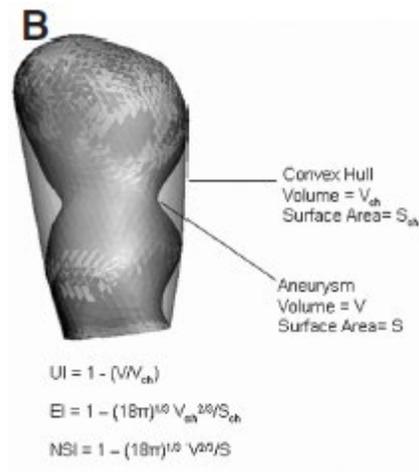
Figure 3 (From Dhar et al 2008)

2.9.4 Ellipticity Index (EI)

EI is defined as EI $= 1 - (18\pi)^{1/3} Vch^{2/3}/Sch$, where Sch is a perfect hemisphere fitted over the aneurysm and serves a similar function to the UI in measuring the smoothness of the aneurysm (Raghaven 2005, Dhar 2008).

2.9.5 Nonsphericity Index

NSI is defined as NSI $= 1 - (18\pi)^{1/3} Vch^{2/3}/S$, where S is the aneurysm surface area This is effectively mix of EI and UI where S is fitted to the surface area of the the aneurysm, (Raghaven 2005, Dhar 2008). Note the similarity to the previous

equation indicating that many of these measures are simply variations of one another and that conceptually many of them are essentially the same with minor refinements to account for theoretical and modelling requirements.

2.9.6 Size Ratio

The aneurysm-to-vessel size ratio (SR) is defined as SR = (maximum aneurysm height)/(average vessel diameter). This is a measure effectively of how much the aneurysm deviates from the size of an average blood vessel.

2.9.7 Vessel Angle & Aneurysm Inclination angle

These are measure how the degree to which the aneurysm deviates from its main branch as show in the figure below, there are a two of different variations of this measure due to the different methods of defining the neck plane as show by figure 4, A & B, known as the Vessel Angle & Aneurysm Inclination angle respectively.
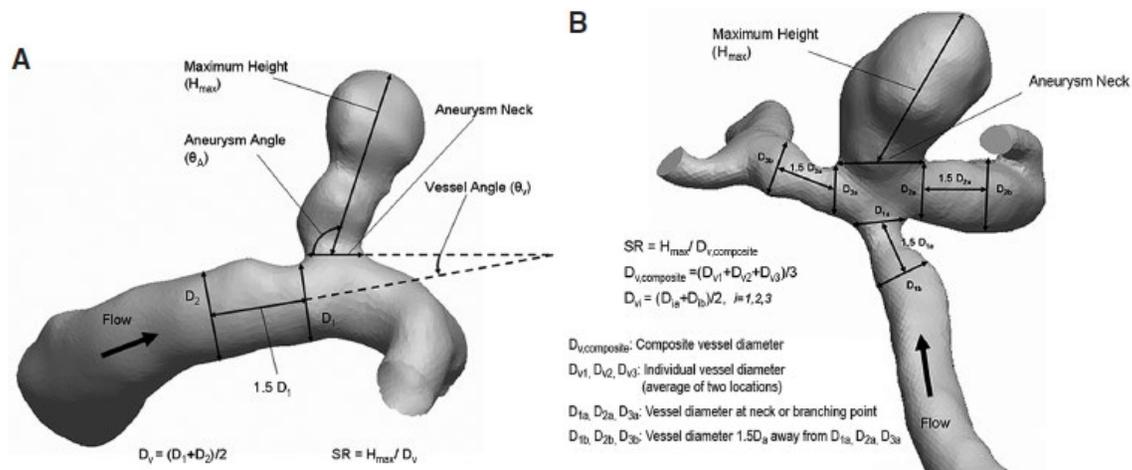
Figure 4 A diagram showing complex measures of deriving vessel angle & aneurysm nclination angle respectively(From Dhar et al 2008)

2.9.8 Comparison of size and shape measures

While the studies do show that all of these measures are associated with aneurysm rupture risk, it is important to note that few of these measures are sufficiently quantified, or have enough evidence to be used in a clinical setting, and the decision to treat the aneurysm is typically based on size alone.

While adding in a number of extra metrics may seem impressive, and with extra information could potentially create better models and improve accuracy in predicting aneurysm rupture, the number of different metrics is also currently quite complex and unwieldy making implementation of the data into a clinical setting impractical at this time.

It may also be the case that some of these measures may be redundant, as it may simply be that one measure directly leads to another, that is changes in geometry lead to higher stresses due to their alteration of blood flow streamlines for example Hassan et al 2005. observed that a vessel angle and aneurysm inclination was simply correlated with high WSS area near the apex of the aneurysm aneurysm dome, where rupture prone blebs (a type of lesion, discussed later) often are present.

Hoi et al. (2004) noted that the geometry of parent vessels leading to the aneurysms were associated with higher haemodynamic stresses at the inflow zone and in turn lead to aneurysm development, growth and rupture,.Other studies have also found a connection between aneurysm rupture risk and vessel location (Carter 2006, Castro, 2006, Forget 2001, Orz 1997, Ujiie 1999, Wier 2002). So it may be necessary to extend modelling and size consideration beyond simply the confines of the aneurysm and into the parent arteries.

3.Method and materials

3.1 Measurement variables

The dependent variable parameters to be measured in this study will be wall shear stress, energy loss and aspect ratio would be used as defined by the studies Takao et al 2012, Xiang et al 2011, and Dhar et al 2008 as discussed previously Note that these studies are merely representative and that these measures are used widely throughout the field.

3.2 Experimental Study

This study is comprised of 11 separate studies comprised of:

2 initial low resolution trail studies, followed by 8 regular studies (all matched compared to models with the aneurysm deleted to obtain a measure of energy loss) and 1 more atypical fusiform model in order to contrast and compare the differing measures predictive of aneurysm rupture as determined by literature review.

3.2.1 Primary investigation with lower resolution figures in two subjects,

While initially the methodology was defined for these models, the models proved to be too different in scale after rendering to provide comparable results, thus mentioned only for the sake of completeness and to illustrate the importance of consistent scale in comparison. These models did not contribute to the final result

3.2.2 Comparative cohort examination to evaluate aneurysm
risks in eight subjects,

These were the models (8 pairs, 16 models) from which the main results were derived, ideally a larger sample would yield more comprehensive results given more time and resources in the future

3.2.3 An atypical exemptive case study

This was an attempt to simulate a fusiform aneurysm however as the case could not be matched with a comparative case of have the aneurysm removed (due to the shape of the aneurysm). this attempt was reserved for future study of any fusiform type aneurysm and mentioned only for the sake of completeness and to give an idea of possible future directions).

3.2.4 Analysis technique

All of the models mentioned were analysed along the following guidelines.
The models were obtained from patient data at Macquarie university hospital and analysed at the Macquarie University Computer Fluid Dynamic (CFD) facility running the windows version of ICEM ANSYS 15.0 proprietary software. This is an industry standard software suite used to analyse and simulate various engineering systems, in particular involving fluid dynamics, structural mechanics, electromagnetics and systems of multiphysics (These being interactive systems). Flow modelling software such as this allows us to simulate the physical properties of such models in order to predict their behaviour. In this specific context the physical properties of blood vessels in order to predict the stresses that enact upon them.
This thesis will concern solely with simulations involving fluid dynamics, though it should be noted that mechanical applications may also be applicable in other aneurysms such as simulating stenting and coiling, and more complex simulations which take into account non rigid arterial walls.

The models are generated using a series of "mesh grids" or a series of interconnected 3 dimensional blocks which tessellate, and fill a predetermined 3 dimensional model space acquired through medical imaging, commonly CAT (computerized axial tomography) scans (3d X Rays) or MRI (Magnetic resonance imaging). Thus the mesh, and hence model quality is dependent on the quality and resolution of the image. A courser mesh, that is one with larger elements will

result in a more simple model and affect the convergence of the simulation while a higher resolution (finer) mesh will improve the quality and convergence (or the mathematical coherence, or the degree to which the Navier Stokes equations have been resolved) of the model. A finer mesh will of course also increase the computing time and processing requirements, but also more accurately mimic complex geometrical shapes, which is especially relevant in medical applications such as this study.

A finer mesh would therefore result in more accurate models and in theory higher sensitivity and specificity if used in a clinical setting.

The type of mesh created is what is known as an unstructured grid (meaning all of the elements are not identical) due to the need to fit the mesh into an irregular shape.

It is known that these types of mesh grids are less accurate and consume more computing time and processing power but is a necessity in irregular models. Unstructured grids are designed in order to isolate regular and irregular parts of the mesh grid to minimize the irregular areas of the simulation.

The wire mesh model more generally consisted of tetrahedral geometry, with 3 layers of prism mesh simulated the fluid space and blood vessel wall respectively with a grid resolution of 0.1. This is done to improve the accuracy of the model around the wall by creating a discrete plane (known as a boundary layer) to represent the wall.

This is known as a composite or hybrid mesh technique. In this particular case, we have used prism elements on the surface (with terahedral elements in the fluid body) which results in a hybrid prism/hex mesh within the meshed volume. This will yield more accurate results than a full tetrahedral mesh, in a much shorter time due to a reduced total number of cells. This is commonly used in engineering simulations of in flow-aligned geometries such as internal flow through pipes or ducts with irregular and complex cross-sectional shapes.

Therefore it is assumed in these simulations, that the physics in this simulation would be "directional",in this case, it is assumed that the blood flow is to move in one direction in a smooth laminar fashion, thus the mesh faces in 3D that follow the flow direction, or the smoothness of the elements that form a smooth boundary at the wall.

It should be noted that pulsatile flow was not simulated. While pulsatile flow is considered more realistic and would be ideal it requires significantly more computing resources.

It should also be noted that past studies have found few differences in results based on laminar vs pulsatile flow. (Farnoush 2012, Ford et al 2005, Kallmes 2012, Marshall et al 2004).

Those studies concluded that pulsatile flow can vary significantly in rate and pressure making simulations of pulsatile flow unwieldy and impractical in the absence of a specific experimental question in relation to pulsatile flow.
Thus simple laminar steady flow is considered sufficient for the experimental questions with respect to the measures we are studying here, for example pressure, wall shear stress, energy loss etc in terms of the clinical predictiveness of the model.
More technically, in a mathematical sense. In numerical analysis terms, when error estimates are made between computed and exact solutions, often the angles of the mesh cells are evaluated. The error is considered to approximate 1/sin(theta) where theta is the angle of the cell element in the non structured irregular boundary element.

Hence in hexagonal or rectangular elements(barring any extreme levels of cell distortion due to irregular geometry, theta would approach a limit of pi/2 radians. This reduces error as even if the cell is very elongated in one direction (because the edges of the cell are straight and the angles would remain constant regardless

of how elongated they are, which is optimal because then 1/sin(theta) is close to 1. If tetragonal or triangular elements are used however, and the cell element is elongated, theta may be closer to zero (or the max angle closer to pi), and then 1/sin(theta) may be much higher than one. This would mean that the angles of the elements would distort if they are elongated due to the distortion of the triangular facets. (Baker 2005, Jean et al 2005, Sayma 2009).

Currently the simulations used in this series of experiments assume the arterial walls are perfectly rigid, which of course is not the case in reality. Simulating no rigid walls, however requires significantly more computing resources and previous studies have shown that this concession has a relatively small effect on the quality of the simulation and the measures derived from them.

3.3 Simulation parameters

The parameters used in this study used to simulate blood flow are outlined in appendix 1. These parameters were selected based on previous studies (Dhar et al 2008, Takao et al 2012, Xiang et al 2011).

It should be noted that while 3000 iterations were set as the limit of the simulation run, most of the models bar two converged (in this case meaning that the simulation terminated normally due to convergence before the set 3000 iterations). In the case where the 3000 iterations were run without reaching convergence, the data from the model generated was deemed sufficiently in line with the other normal models. In this case, the parameters such as pressure, wall shear stress and blood flow were deemed sufficiently within expectations that it was accepted, and the non convergent parts of the model were deemed to be minor and to not have an impact on the parameters of interest in the study.

A literature review was then conducted to determine the types of empirical measures used to assess the appropriate measure.

3.4 Experimental measures used

The most common measures are (WSS), Oscillary Shear Index (OSI), and measures of total energy loss, Pressure Loss, as described previously. (Takao et al 2012, Xiang et al 2011).

Multiple measures were made to obtain a better general understanding of the quality of each of the measures and hopefully in future be able to determine the sensitivity and specificity of such measures as well and refine the measures in order to improve said sensitivity and specificity. It is also hoped that the interaction between these measures can be better understood.

3.5 CFD software Manual processing

Currently many of the measures rely of manual process using the built in ruler mechanism in the ANSYS software. These measurements were repeated multiple times in order to assess the reliability of measuring aneurysm size by hand. From person trial and error it was found that hand measurements produced less than 10% error (that is repeating 20 times, no measurement varied more than 10% from the mean), so was generally reliable for our purposes, however, it would be ideal if an automated procedure could be put in place to eliminate manual error.

It should be noted however that real world pathology analysis relies on manual measurement making this an acceptable industry standard. Multiple examiners are often used to reduce error or to assess measurement reliability, however this was not done in this instance (Beck et al 2018).

3.6 Experimental constructs used

The models were altered in order to accommodate flow, In this case the inlet and outlets into the vessel were simulated by extending the tube to provide for realistic acceleration into the aneurysm and vessels. This was done using ANSYS

software. Various "smoothing measures" were taken in order to compensate for low resolution artefacts when necessary. Smoothing was done manually using "Blendr" open source (version 2.79b).

Again as this is done manually it should be kept in mind that some level of variability and error may be introduced using these tools and thus the results may be less replicable.

3.7 Applied Experimental constructs and software

One of the measures used in this study is "Energy loss"

Energy loss is mathematically defined previously and is the energy loss due to the friction and turbulence, this is the mean flow velocity in and out of the system, and represents the static pressure at the inlet and outlet. (From Xiang et al 2011) This formula was used to calculate the relevant values in a spread sheet program (Kingsoft office suite 2013 edition).

This measure is made by comparing the net kinetic energy loss of the blood flow in a simulation of the Aneurysm compared to a hypothetical model where the aneurysm bulge is removed (flattened and smoothed) in modelling software (Blendr v2.79b). Again it should be noted that this is done manually which in turn affects replicability and error.

3.8 Haemodynamic characteristics methodology

While haemodynamics is an important factor in the pathophysiology, formation and rupture of aneurysms, it should be noted that there is an interaction between form and function, in this case meaning that the morphology fundamentally affects the fluid dynamics of the blood flow. A number of studies demonstrates the link between aneurysm rupture and morphological characteristics.

Hassan et al. (2005) suggested that high wall shear stress (WSS) may be responsible for Aneurysm growth and rupture in high-flow aneurysms, Aneurysm rupture also occurred in aneurysms where there was low flow and fluid stasis.

Shojima et al. (2004) had earlier found a similar result, observing that average WSS in the aneurysm sac was associated with aneurysm rupture. With similar observations with regards to haemostasis and recirculation in the aneurysm sac. It was concluded that aneurysm geometry and the geometry of the vessels feeding into it was the major determining factor in determining haemodynamics. Cebral et al. (2005) found that aneurysm rupture was associated with unstable flow patterns, small impingement zones creating "jet streams" or streams of high pressure, high velocity flow.

Cebral et al. (2006) found that haemodynamics do not vary significantly with physiological parameters of flow rate, blood pressure, and waveform, therefore it is not unreasonable to ignore these factors in simulations.

That is not to say they are completely irrelevant, and may be employed in more complex simulations such as with oscillary shear stress studies. However as it has been found not to significantly alter the haemodynamics at a gross macro level. It may be a reasonable way to simplify simulations without grossly affecting the outcome, and more importantly in future applications, may allow simulations to be done quickly without largely and negatively affecting the clinical predictive decision making process, thus it is feasible that geometric morphology alone should be able to provide satisfactory predictive strength without the need for far more complex simulations of physiological parameters based on the findings of Cerbral 2006 with factors such as predicted energy loss and wall shear stress being predicted from those based on simplified haemodynamic flow parameters.

4. Results

After the models were rendered and meshed as described previously, the maximal Wall shear stress was recorded using the embedded ANSYS software tools.

The wall shear stress was recorded both for the model with Aneurysm and without in order to compare the effect of the presence of the aneurysm.

The results of this are detailed in appendix 2. For sample images of the rendered aneurysms, a number of select rendered models are displayed in the results (section 4.4.5)

4.1 Morphology parameters

This section will quickly and specifically review the morphology parameters used in this study and generally in this field of study.

4.1.1 Morphological characteristics Methodology

Past studies have investigated such parameters, size being the most commonly cited parameter. Typically intra-cranial aneurysms 10 mm or larger in size are considered clinically in need of intervention due to the potential morbidity, however a number of studies have shown that smaller intra-cranial aneurysms also risk rupture.(Beck et al 2009, Forget et al 2001, Raghaven, Mar & Harbaugh 2005, Rickel et al 1998, Uije et al 1999, Uije et al 2001, Weir et al 2002) and relation between size and rupture risk is not yet fully understood and requires more study.

Shape is also another highly studied morphological parameter that should be taken into consideration with possibly even higher correlation with intra-cranial aneurysm rupture than size (Dhar et al 2008).

Aspect ratio (AR) is a highly cited morphological parameter in the literature as, defined as the height of the aneurysm divided by neck diameter, this is the most commonly studied shape parameter. (Dhar et al 2008).

Though most studies agree upon it's significance as a predictive factor in intra-cranial aneurysm rupture there is no commonly agreed upon limit or value at which the studies converge upon with respect to the aforementioned parameters (Beck et al 2009, Raghaven, Ma & Harbaugh 2005, Rickel et al 1998, Uije et al 1999 Uije et al 2001 Wier et al 2003).

More studies would therefore be useful in order to quantify the threshold at which the AR ratio would be clinically likely to rupture, and further study to align and standardize the variations and criteria by which the morphological characteristics can be measured may also prove useful. As mentioned earlier, many of these measures while done on a computer interface require manual measurement using computer tools (that is, done by eye and hand on a mouse and keyboard) and hence without close control, there is bound to be a good amount of inter rater error.

Another minor issue encountered through the course of this study is the definition of width. As even the best most regular vessels are not perfectly circular and vary in width. In this study it was decided that both a "width" and a "breadth" would be taken with the widest possible point (judged by eye) and the width perpendicular to that (at the widest point) being the breadth, in order to obtain a fair estimate cross section, While this would of course overestimate the area of the opening, it should be important to note that we are simply using the number as a number which is proportional to the size of the opening, and that assuming they are reasonable regular shapes, the figure would scale proportionally with size.

4.1.2 Measurement of Irregular geometry

While most vessel geometries to tend to be more or less regular, there are more sophisticated measures which take into account more irregular geometric forms. These included, shape parameters such as undulation index (UI), nonsphericity index (NSI), and ellipticity index (EI) have been proposed (Raghaven 2005) in an attempt to account for the three-dimensional (3D) nature of aneurysms. (Dhar et al 2005). These extended measures were too complex to implement at this time. These potentially could provide more accurate measures which take into account more convoluted geometries however it is beyond the current scope of this study.

4.1.3 Study cohort and parameters

In the current study we analysed 8 pairs of blood vessels (with and without aneurysms) using the parameters as in appendix 1.

4.2 Wall Shear Stress (WSS)

As can be seen, while there is a net increase in WSS in the absence of an Aneurysm (That is, that the WSS increased in the presence of an aneurysm implying that it causes an increase in WSS).

While the difference appears relatively small, a paired T test actually shows a relatively low P value of ~0.11. While this does not show statistical significance, this is a relatively small sample and approaches statistical significance, and it would be reasonable to believe that a larger sample size would achieve a statistically significant result (That is that that the presence of an aneurysm is associated with lower wall shear stress).

4.3 Energy Loss (EL)

Energy loss is mathematically defined previously and placed into a spread sheet After being exported from the software (ANSYS 15.0).

Energy loss is the energy loss due to the friction and turbulence, where it is

defined as the mean flow velocity in and out of the system, and represents the static pressure at the inlet and outlet (From Xiang et al 2011).

The results show that energy loss can both increase or decrease in the presence or absence of an aneurysm.

4.4 Morphological characteristics

Here we will examine a number of interesting morphological characteristics found in the course of experimentation that showed potential to predict physical stresses. In this study we have trialled the usage of a measure we call "neck width where the "width" (narrowest part of the neck) is multiplied by the "breath" (widest part of the neck).

Here we have an example of how we obtain the neck width and breadth as well as the height in the ANSYS ICEM CFD program. Note that the model is rendered with transparent mesh to assist with measurement and viewing.
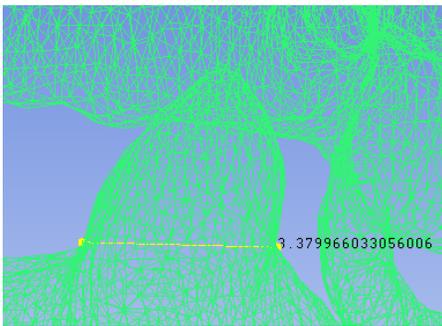
Figure 5a Width
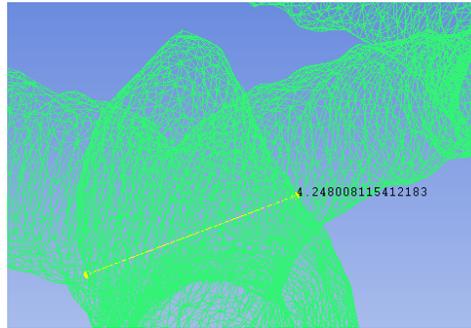
Figure 5b Breadth
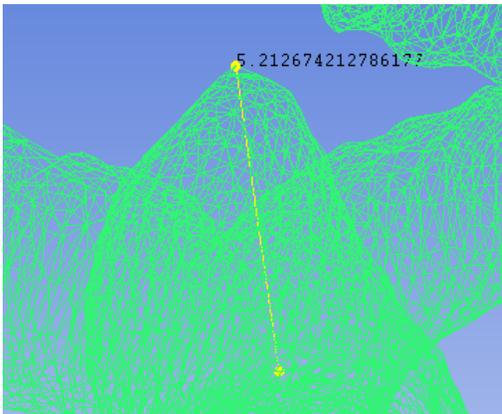
Figure 5c Height

4.4.1 Energy loss vs the neck width

An interesting result was found by correlating the neck width to the observed energy loss (this measurement multiplying the width by the breadth of the neck opening of the aneurysm) This is defined in this study as by the widest point and the widest width perpendicular to that, it was found that there was a $R^2 = 0.5916$ correlation. This figure shows the relationship between maximum values of wall shear stress (Max WSS) and the values of neck width (WxB). A line of best fit was added via the spread sheet algorithm to examine the relation between Max WSS and the WxB to energy loss.

This was only achieved with by removing two outlier results.
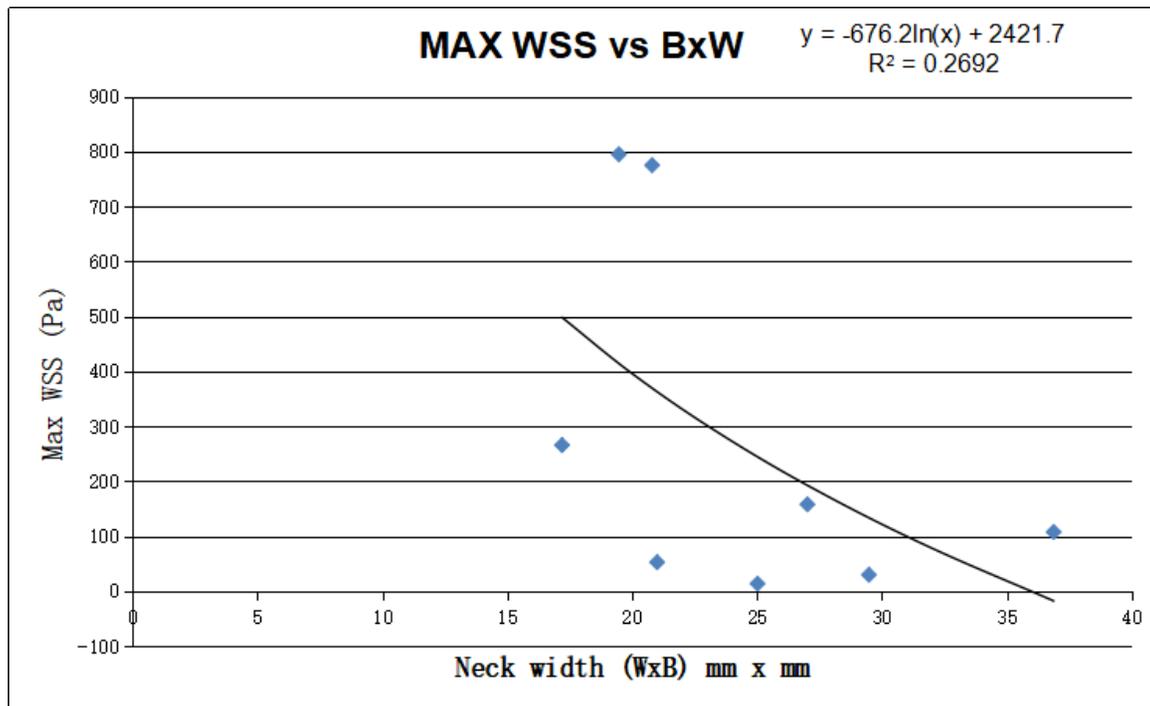
Figure 6

4.4.2 Maximum Wall Shear stress vs Neck width (Breadth x Width)

A negative correlation was found between the WSS in the presence of the Aneurysm (The maximum WSS of the original model) and the breadth x width measure however it did not appear to be statistically strong with r2= 0.2692, meaning that neck width explained only 26% of the variability of the WSS.

Energy loss vs Neck width $y = 6747.1x - 198012$
$R^2 = 0.5916$
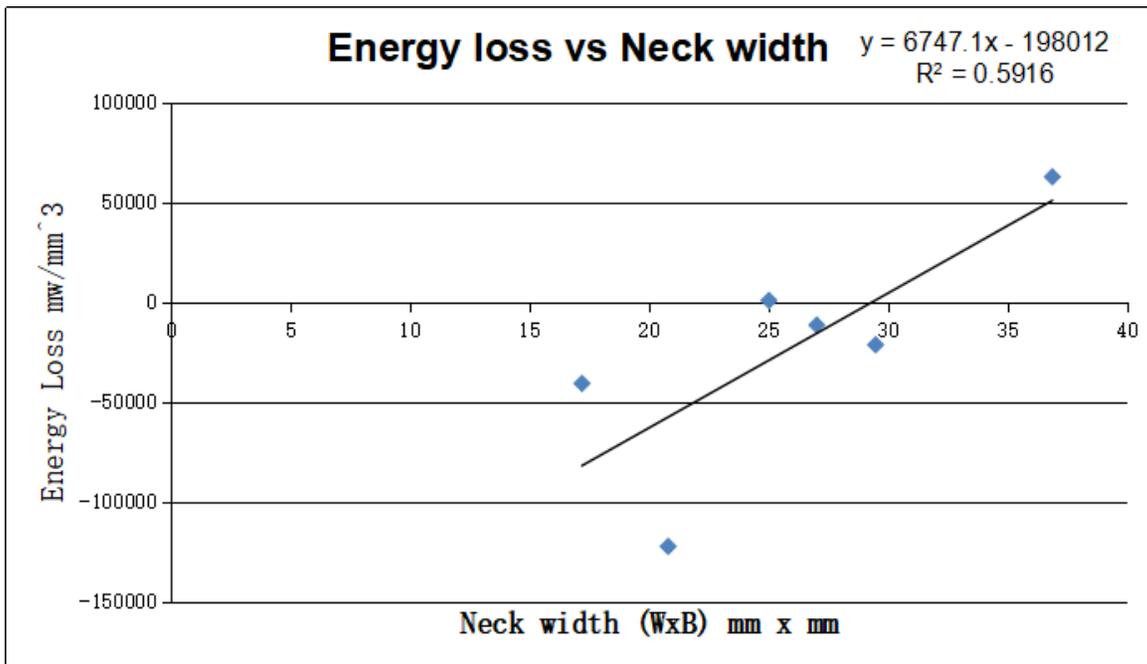
Figure 7

This is a modified method of aspect ratio using both breadth and height multiplied and shows an R squared value of 0.2692.

This graph shows the correlation between this measure and the energy loss (Being the kinetic energy lost by the blood as the blood flows through the vessels)

4.4.3 Aspect ratio vs Maximum WSS

Aspect ratio to Max WSS

$y = -326.29\text{Ln}(x)+415.06$
$R^2 = 0.2175$
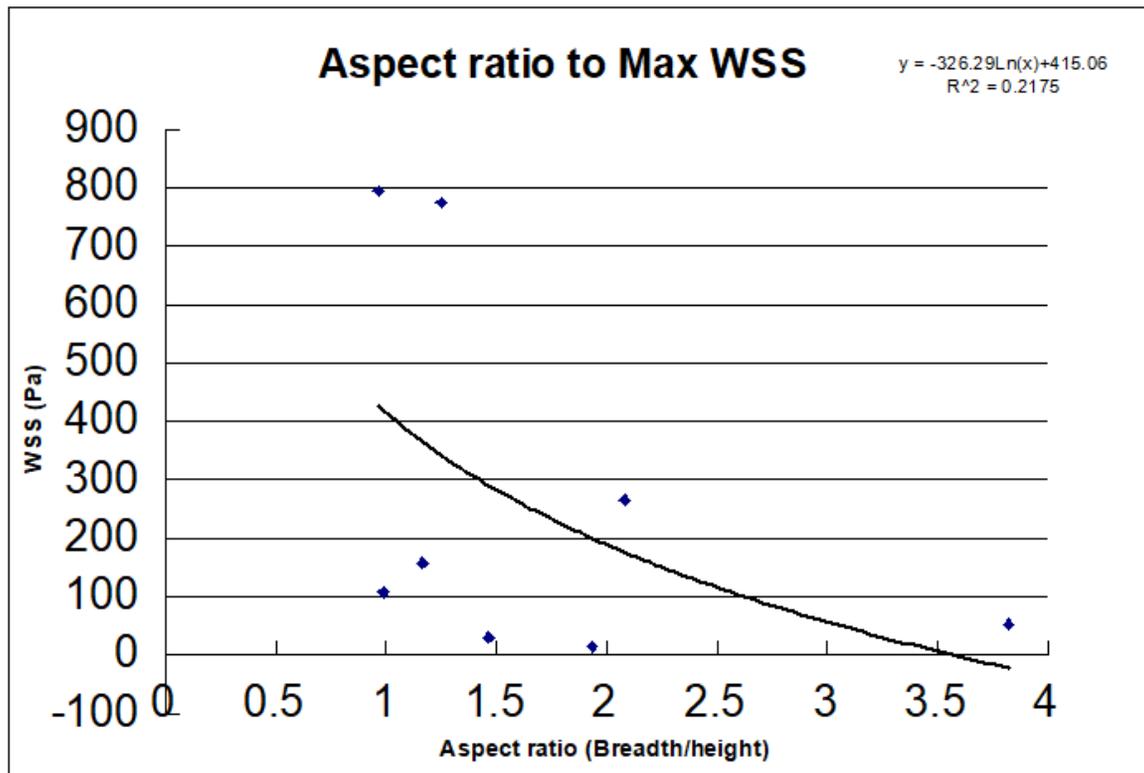
Figure 8

This was compared to a normal aspect ratio measure (done with only Breath) and it was found to have marginally lower correlation at r^2=0.2175 (As shown in figure 8).

While this may be a fairly small difference, this may suggest that the use of both width and breadth may yield higher sensitivity and specificity in predicting aneurysm outcome.

4.4.4 Dome WSS vs Neck width

The strongest correlation appears to be the correlation between the dome WSS with the neck width, with r^2=0.8489, however this again required 2 outliers to be removed. (one in common from previously, one different) (As shown in figure 9).
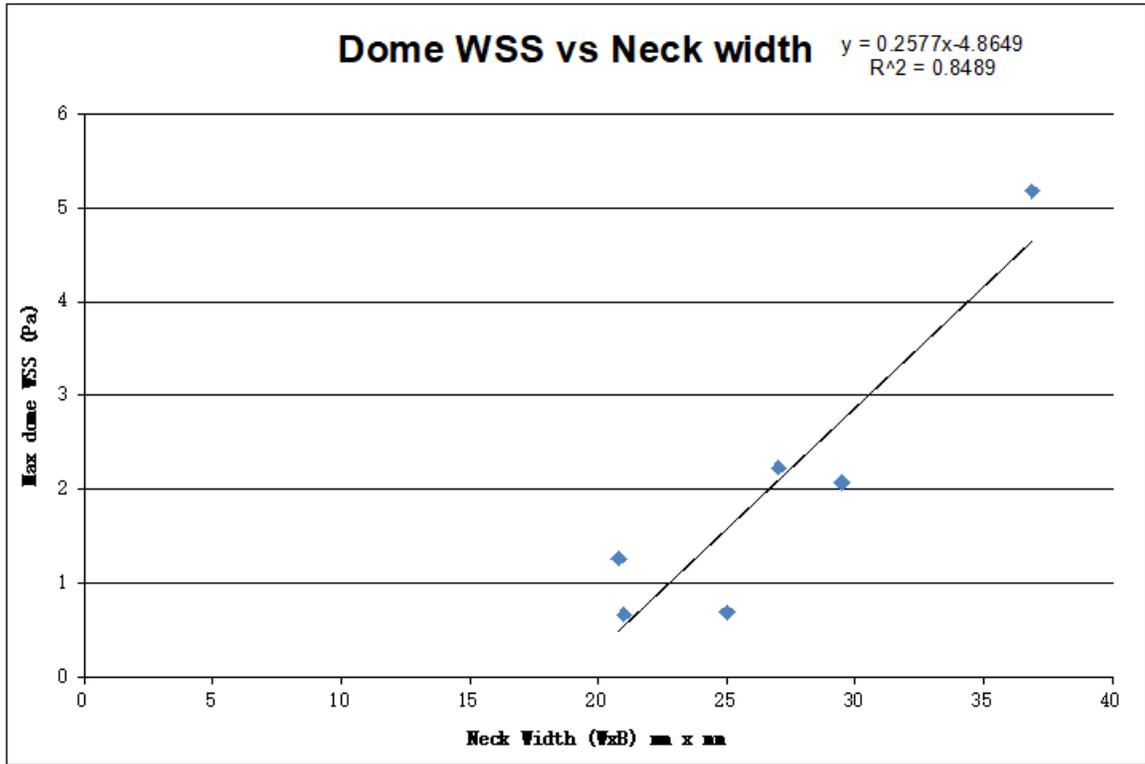
Figure 9

4.4.5 Selected images

During the simulation of haemodynamic properties of the models, an actual 3 dimensional mesh model is generated. Various simulated properties such as the wall shear stress and pressure can be mapped upon the the surface of these models. Although this project largely relies upon the mathematical values exported from these models, they are included here for completeness, as well as to illustrate the matching of the models between the original and smoothed models (the smoothed model being the model with the aneurysm removed)
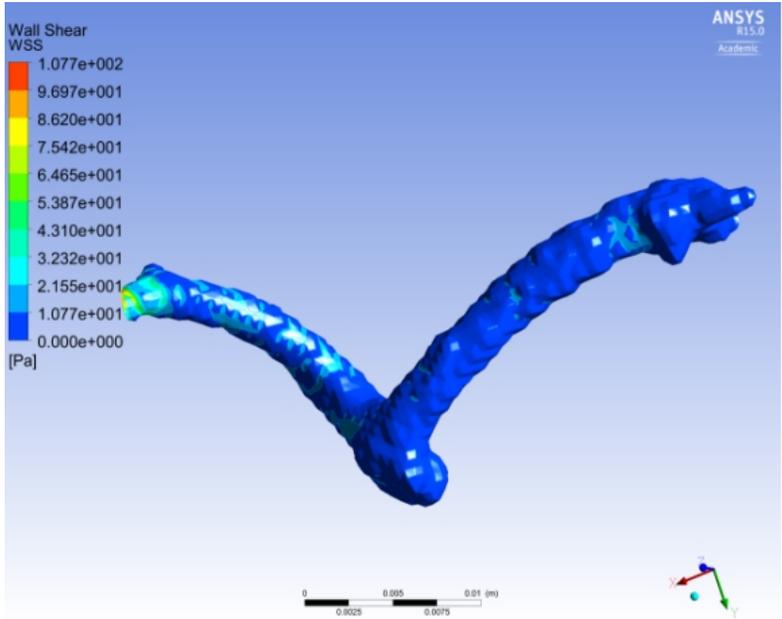
Aneurysm model intact with wall shear stress map
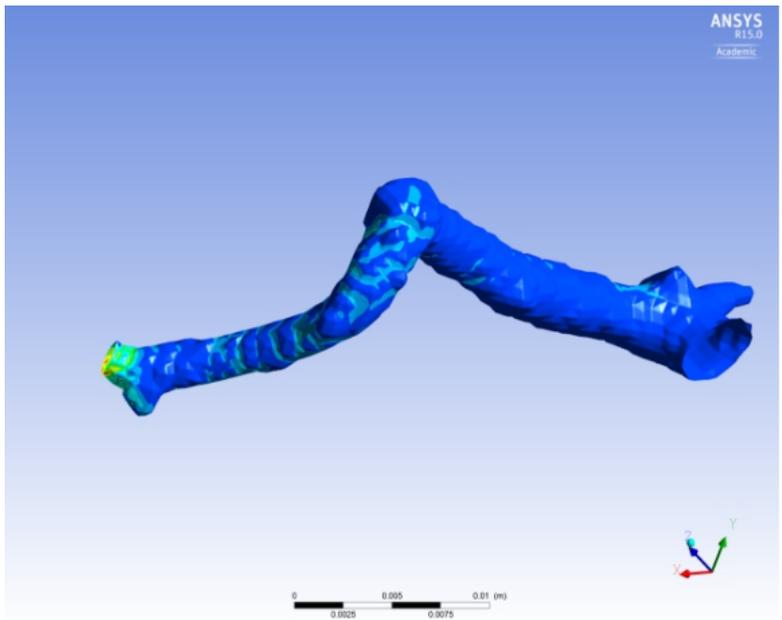
Aneurysm model cut
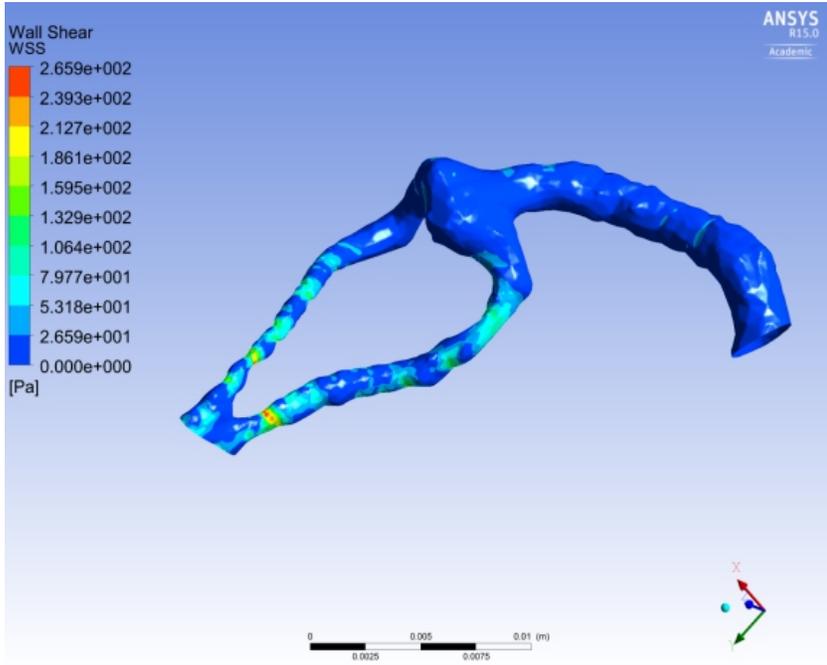
Aneurysm Model intact
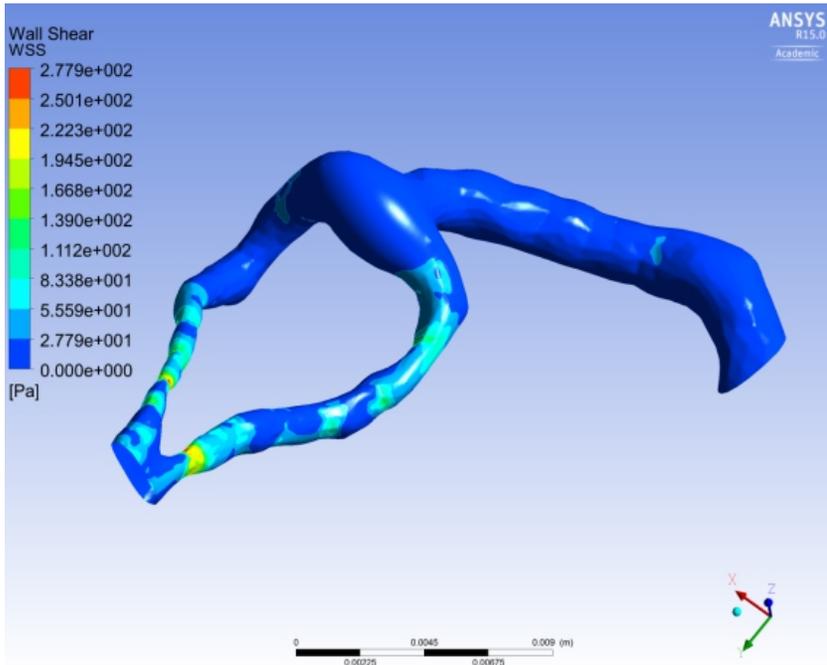
Aneurysm model cut

5. **Discussion**

5.1 Pathophysiology

The pathophysiology is the part of the model which is not accounted for in the physical model however would contribute greatly to the likelihood of aneurysm rupture by affecting the structural integrity of the blood vessels.

5.1.1 Parameter of Blood flow measurement

While it was mentioned earlier Cebral 2005 found that physiological flow parameters did not significantly affect the haemodynamic properties of the blood flow through the aneurysm, it should be noted that there are significant clinical factors which contribute to rupture risk, such as familial preponderance, smoking, hypertension, female sex, connective tissue disorder, aneurysm growth rate, and presence of multiple aneurysms (Juvela et al 2000), thus vessel and aneurysm morphology should not be considered in isolation to the clinical risk.

In terms of more sophisticated measure of vessel geometry and vessel size, Castro et al. (2006) have demonstrated that there are intra-aneurysmal hemodynamic effects, specifically that tortuous paths of vessels upstream to the aneurysm can have as significant effect on the blood flow coming into an aneurysm.

5.12 Parent vessel geometry and vessel location

Hassan et al. (2006) observed that angle shifts in the parent vessels leading into the aneurysm could lead to high WSS areas toward the aneurysm dome. These high WSS areas are prone to form "blebs" which are lesions caused by stress that are prone to rupture.

Hoi et al. (2004) noted that highly curved parent vessels also has a similar effect as observed in Hassan et al 2006, and numerous other studies have observed a

connection between aneurysm rupture risk and vessel location (Carter et al 2006, Castro et al 2006, Forget et al 2001, Orz et al 1997 Ujiie et al 1999, Wier et al 2003).

It should also be noted that anatomically, blood vessel geometry is affected by location. For example in intra-cranial aneurysms (the main focus of our study), most occur at the Circle of Willis, and generally are finer, more tortuous and more complex, whereas abdominal aortic aneurysms would be far larger and relatively simpler in terms of vessel geometry, so while in principle the simulations of intra-cranial and aortic aneurysms are comparable in methodology, the scale, the geometries, the risk factors and treatments would vary sufficiently for different studies and clinical decision making.

However, these factors are difficult to quantify in a simulation which can be input into simulations. As no study provide the changes in physical parameters that are quantified, they cannot be used integrated into the simulation (Dhar et al 2008).

5.13 Tissue characteristics
While it is known that certain connective tissue will weaken the elastin in blood vessels, or that smoking will harden or stiffen a blood vessel. No studies can be found that can quantify these as actual physical parameters that can be input into computer simulations. While there are studies which do take into account parameters such as wall stiffness, these parameters are poorly quantified and thus cannot be meaningfully accurate outside of simply seeing the effect of increased stiffness etc in a simulation. (Cebral 2005, Frosen 2012)
It should also be noted that adding such simulations also increases the complexity of the simulations significantly making many of the studies quite unwieldy, thus most studies currently are limited to evaluation of morphology alone, typically using size alone in predicting clinical outcomes. While a clinician may take into account all of the other factors such as medical history, smoking age, congenital tissue diseases etc into their clinical decision making, it would be

on an ad hoc, non-quantified basis based on their clinical judgement alone. (Juvela 2000, Frosen 2012).

Thus it would be useful to improve measures of these measure to provide the best estimate of the rupture risk.

5.2 Wall Shear stress (WSS)

With respect to the literature, there is both evidence for the theory that both high and low WSS is associated with Aneurysm rupture. (Chien et al 2009, Farnoush 2012).

Wall Shear in this context is defined as a mechanical force acting upon the endothelial cells of the blood vessels. This is effectively any "sideways" force upon the blood vessel wall.

This can be due to a variety of factors such as the pulsatile or oscillary nature of the blood flow, or simply the angle at which blood flow hits the blood vessel wall. While it was stated earlier that some studies have found there were minimal differences in the predictiveness of the aneurysm modelling between pulsatile and non pulsatile flow. This is limited evidence and further study of pulsatile flow is warranted given that is a likely and reasonable contributor to the mechanical wall shear stress.(Cebral 2005, Castro et al 2006, Frosen 2012).

Of particular interest is the effect of such mechanical stresses upon the chemical mechanical and biological structure of the components of the blood vessel wall which is composed of endothelial cells, extracellular matrix (composed mainly of collagen) as well as vascular smooth muscle wall.

The stresses upon the wall are of course the forces which initiate the pathophysiological process in the formation of aneurysm. In other words The haemodynamic stress factors distend the internal elastic lamina which forms the out bulging pouch of the aneurysm wall. This in turn leads to aberrant flow conditions. (Frosen et al 2012).

This effectively is the limit of mechanical modelling of aneurysm, which effectively models the genesis of the aneurysm, however it is obviously an incomplete picture.

5.3 Inflammation mechanism and pathophysiology

It is known that the distension and disruption of the blood vessel wall leads to inflammatory processes which further damage the cell wall.

The endothelial dysfunction leads to non laminar blood flow along the vessel wall which leads to lipid deposition and the formation of atherosclerotic plaques. The atherosclerotic plaques promote macrophage infiltration and general inflammatory cascade. Apart from atherosclerotic plaque deposition the non laminar flow also leads to thrombus formation leading to the accumulation of polymorphic leukocyte accumulation and iron accumulation at the site and proteolytic activity.

All of these factors combined leads to oxidative stress, which in turn further damages the various cells in the vessel wall, In this case the mural cells and degradation of the extracellular matrix. The cell necrosis further excites the inflammation which continues to weaken the vessel wall, in many cases leading to rupture if there is sufficient wall degradation. (Frösen et al 2012).

The aneurysm will rupture when the vessel wall is weakened to the point where the structural integrity of the vessel wall is no longer able to withstand the shear stresses imparted by the blood flow. The wall is of course not a static matrix of collagen but contains cells which repair and maintain damage to the cell wall from the various stresses outlined above, thus damage to the mural cells would be a key factor in future more comprehensive study.

While this would appear to imply that high wall shear stress would be positively associated with aneurysm formation and rupture, there is not universal

agreement on this hypothesis. There are studies which support both high and low wall shear stress being causative of aneurysm formation and rupture.

Chien et al (2009) reported that the initialization of aneurysm formation was with high WSS in s study of 29 aneurysm in various locations along the circle of Willis. Zuleger et al (2010) using real time MRI found that high WSS averaged over time was associated with aneurysm formation.

Flow disturbance (Or non laminar or turbulent flow) is generally found to be one of the important factors in aneurysm genesis.

Flow impingement distal to the aneurysm opening or "neck" and inflow back into the opening is a major cause of turbulent flow. This was found by Hashimoto 2006, to initiate leukocyte adhesion and inflammatory pathogenesis.

Feng et al (2004, 2008) found that high wall shear tended to occur at areas of vessel curvature (as intuitively vessel curvature would produce high shear stress) This was not to say that straight vessels would not produce aneurysm however they would tend to be produced more distally. Tateshima et al 2010 found that WSS tended to be higher at the dome rather than the neck of the aneurysm. Further, Castro et al (2012) concluded based on high resolution patient case studies of 3 cases that aneurysms tended to form in areas of high WSS, whereas areas of low WSS tended to be free from aneurysms.

A study of 26 simulations of the anterior communicating artery by Castro, Putman & Cebral 2006 showed that high WSS led also to aneurysm rupture and not just formation. In a smaller study (6 cases modelling the internal carotid artery) Chien et al 2009 also agreed that high WSS was the primary predictor of aneurysm rupture (over flow characteristics being found to be statistically insignificant) while Sforza et al 2010 found that WSS was significant in the sense that small impingement zones caused by high blood velocity were predictive of aneurysm rupture (within a scale of hours). Counter intuitively however, such impingement zones led to the formation of both high and low WSS areas, thus

indicating that it is not necessarily purely a matter of high WSS being associated with aneurysm formation and rupture.

5.4 Previous case studies

Malek et al (1999) found that WSS should be approximately 2.0 N/m² in normal physiological conditions with 1.5 N/m² leading to apoptotic and atherosclerotic changes in the blood vessel wall.

Boussel et al (2008) had contrary findings. In a study using 7 patient models, it was found that aneurysms were formed in regions of low WSS.

Shojima et al (2004) suggested that low WSS encouraged the growth (n=20), and triggered the rupture of aneurysms, and Jou et al 2008 found that this occurred in low WSS area in areas of the Posterior communicating artery.

Lu et al (2011) observed that aneurysm WSS was lower where oscillilary stress was higher in parent arteries (The adjacent arteries which fed into the aneurysm of aneurysms that ruptured than those that did not). Goubergrits et al (2012) also found that low WSS and irregular geometry were predictive of aneurysm rupture.

5.5 Energy vs pathophysiology

Conceptually energy loss, as a measure of "work" is defined in physics in this context as:

"measure of energy transfer that occurs when an object is moved over a distance by an external force at least part of which is applied in the direction of the displacement. If the force is constant, work may be computed by multiplying the length of the path by the component of the force acting along the path. Work done on a body is accomplished not only by a displacement of the body as a whole from one place to another but also, for example, by compressing a gas, by rotating a shaft, and even by causing invisible motions of the particles within a body by an external magnetic force." (from Encyclopaedia Britannica, definition of "work" in physics).

In the context of haemodynamics, it is the physical "work" done to overcome flow resistance which would generally consist of pressure and physical resistance against the blood vessel wall and in general measures the loss of pressure and blood flow velocity between models, that is that this technique measures the energy loss between a vessel with aneurysm and hypothetical computer model of the same aneurysm without energy loss.

Please note that this is a relative measure, that is the energy loss of a model with Aneurysm vs one without rather than an absolute measure of energy loss (or how much energy is lost as it passes through the blood vessel) hence it is possible for "energy loss" to be negative meaning that it does not violate conservation of energy laws. A negative energy loss would simply imply that the particular geometry of the aneurysm for some reason causes blood flow to flow more efficiently through the vessel model than in it's absence. While this seems counter intuitive that a diverted blood flow would cause more efficient blood flow, it is the case in some particular models.

We would naturally expect energy loss to correlate with clinical outcome as any energy loss would effectively be "work" done to distend and act upon the blood vessel wall. While most "energy loss" is a physical sense would not cause damage (as the blood vessel wall is elastic and the energy would be dissipated into heat without any significant changes in structural integrity, add this to the fact the any damage is usually repaired by the mural cells as mentioned early provided the damage is not too severe), it would nonetheless be expected that damage is more likely and more severe in the presence of greater forces and higher pressure acted upon the blood vessel wall, as conservation of energy would dictate that any "energy loss" would be in some form acted upon the blood vessel wall.

Thus the aim of treatment (surgical intervention such as stenting and coiling) is to divert the flow to a shorter path to reduce energy loss and maintain more smooth (laminar flow). Again it should be noted that aneurysms will not

necessarily increase overall energy loss. It may well be that surgical intervention decreases energy loss.

However as noted above, energy loss is not the only factor predicted to increase the likelihood of aneurysm rupture as the wall shear stress, particularly at the dome of the aneurysm may be the "weak spot" at which the aneurysm ruptures, hence it may be that surgical intervention may increase energy loss while still being beneficial in sparing a more vulnerable area to high wall shear stress, hence energy loss may be a fairly generalized warning measure in a clinical setting (similar for example to blood pressure, blood pressure and BMI) which has to be seen in the greater context of the specific patient, rather than a specific predictor of aneurysm rupture which accounts for all of the variability.

It has been found that continuous flow in the sac of the aneurysm, is a warning sign of treatment failure. Thus it may be that flow lines of the blood flow in the model should be more closely studied. This however comes with the problem of coming up with a consistent measure. Unlike energy loss, it cannot easily be reduced to a one line or number summary and requires a manual assessment of the post rendered model. (Chiu, Tin Lok, et al 2018).

Models would have a tendency to display an increased energy loss as blood is pushed through the "pores" of a stent. This would concur with the findings that "impingment zone" would correlate with aneurysm rupture (Chiu, Tin Lok, et al 2018, Hashimoto 2006, Sforza et al 2010).

5.6 Aspect ratio
Predicting the rupture risk of aneurysms, in the scope of this study, with respect to intracranial aneurysms. A large and relatively recent study of intracranial aneurysm and rupture was the International Study of Unruptured Intracranial Aneurysms (ISUIA). This is a large scale study consisting of Study of Unruptured Intra-cranial Aneurysms (ISUIA) consisting of 1691 conservatively managed

patients with unruptured intra-cranial aneurysms, 1917 surgically treated and 451 endovascularly treated patients, treated for 1 year or more (Connolly 2014).

The ISUIA reported low rupture rates for intracranial aneurysms when they were below 7 mm demonstrating no risk of rupture within 5 years in the scope of this particular cohort. However some smaller studies have indicated that there is some risk in smaller aneurysms (Forget et al, 2001, Nahed et al 2005a, 2005b, Ohashi 2004, Weir Disney and Karrison 2002).

So it would be natural then to wonder if there are more specific and sensitive measures available than just size (which is the current operating guideline) Numerous studies suggest that there is good evidence that various morphological constructs such as aspect ratio and size ratios (Dhar 2008, Rahman 2010) According to Ujiie et al. (1999) Frosen et al (2012), Nader-Sepahi et al (2004), and as argued previously, the pattern and velocity of flow throughout the aneurysm and surrounding blood vessel wall affects the pathophysiology and evolution of the aneurysm.

Nader-Sepahi et al (2004), argues that the aspect ratio (AR) is strongly correlated with the flow velocity. Greater aneurysm volume or a smaller neck is associated with slower flow inside the aneurysm.

Of course as argued earlier, other pathophysiological processes such as the loss of collagen, inflammation and atherosclerosis and bleb formation contribute to the aneurysm rupture so it is unlikely that pure morphological studies can fully account for and predict aneurysm rupture. However it should be noted that slow flow and homeostasis contributes to the pathophysiological sequelae predisposing a vessel and balloon and rupture.

5.7 Pathophysiology vs haemodynamics

Pathophysiological processes have long been known, as early as 1966, Crompton (1966), found that 57% of ruptured aneurysms had multiple lesions (described as "bubbles" or "locutions" as opposed to only 16% of unruptured aneurysms upon histological examination. The same study also found a correlation between aneurysm size and number of lesions.

Crompton (1966) also found that a majority of the ruptured aneurysms were only 5mm indicating a much smaller threshold than found in the aforementioned studies.

It would be difficult to ascertain why such a large discrepancy may take place, however given the age of the study, environmental factors such as diet, blood pressure control etc should be considered, emphasizing the important role of environmental effects external to pure geometry.

That is of course not to dismiss the importance of geometry.
In a more recent example but similar finding, Sampei et al (1991) found that 75% of aneurysms with daughter aneurysms (indicating multiple lesions) had ruptured within 10 years of discovery and that such multilobular aneurysms increased the likelihood of aneurysm rupture.

A doubling of aneurysm depth was found to increase its odds of rupture by over 5 fold, and conversely it is decreased by over five fold if the neck of the aneurysm is doubled, however it should be noted that there are interactive effects. An aneurysm is 17 time more likely to rupture with a doubling of aneurysm depth with a constant neck width if within the same patient, and a doubling of the aspect ratio measurement increased the likelihood of aneurysm rupture seven fold (Nader-Sepahi et al 2004) This concurs with our findings that WSS drops with neck width.

6.Future directions and other issues

The most immediate concern with respect to this study would be the amount of error involved. While strong correlations were seen on some measure, this required to removal of certain outliers, and it would be of great interest to examine the outlier models more closely to see if there were any particular features which led to the errors being produced, either concerning the image quality of the model or the particular geometry of the model itself.

Also it should be noted that while some of the measures were of low statistical power, much of this can be attributable to a low sample size.

6.1 Physical modelling

Real life aneurysm modelling exists separate to conventional CFD modelling for a number of reasons.

The main reason being for surgical training and trails of real life surgical procedures and devices, such and practice of suturing, coiling and meshing. Surgeons typically show the most improvement in their technique after approximately 100 to 200 practice trails (Suzuki 2005).

While CFD allows for consistent and easily repeatable results, such practical applications are necessary.

Older aneurysm models were manufactured by suturing together a separate model of an aneurysm sac and the parent vessel. Vascular models were typically created using animal tissues, typically either bovine or porcine vessel tissue.

Newer silicon models are also manufactured and are considered highly accurate, even among finer vessels.And are widely used in both surgical training and research (Chueh.,Wakhloo & Gounis 2009, Roloff et al 2013)

6.1.1 Haemodynamics within models

As discussed earlier, flow dynamics are believed to highly determine the various stresses imparted onto blood vessel walls (Imbesi et al 1999).

A study, Isoda 2006 demonstrated that time-resolved 3D phase-contrast MRI imaging could visualise haemodynamics in a silicon vascular model.

This involved an aqueous solution of glycerol as a flowing fluid with a pulsatile pump. Time-resolved images of 3D.

Models such as this has the advantage of being able to realistically simulate haemodynamics across a number of more complex parameters such as pulsatililty blood vessel wall stiffness without the need for vast computing resources.

The conventional silicone models are considered to be "very close reproductions of the aneurysm and vessels, even the fine branches", although it does appear to provide greater blood flow resistance as compared to a real aneurysm. (Suzuki 2005) It would be useful in future studies to address what changes in material composition can be made in order to more accurately mimic aneurysms with silicon modelling.

It should also be noted that the use of silicon models not only allow for more reproducibility of aneurysms (allowing comparable models to be used multiple times) as opposed to actual tissue samples, but also allows tissue simulations without damage to the original model through distension and wear and tear (Suzuki 2005).

Various aspects of haemodynamics of silicon models of in cerebral aneurysms have been explored for the purposes of assessing aneurysm rupture risk, growth, or re-canalization. (Cerbral et al 20125, Schnell et al 2014, Levitt et al 2014 Chien and Sayre 2014, Karmonik et al 2015).

Currently it is difficult to quantify haemodynamic properties (blood flow rates or

volumetric analysis) in real clinical setting using typical hospital imaging techniques such CT angiography and Digital subtraction angiography (DSA),and more atypical and expensive imaging techniques such as phase contrast MRI () or Doppler ultrasound are required. (Anderson 2016, Ansari et al 2015, Futami et al 2015, Karmonik et al 2014).

This not only would potentially increase costs were it implemented in a clinical setting, but also may compromise quality of care due to delay, hence CFD or silicon models may still be desirable, even in a clinical setting.
At this stage however silicon model usage is not feasible due to time delay and expense, and thus only a small number of idealised models are used in a research setting to date.(Costalat et al 2006, Goubergrits et al 2010, Imbesi et al 2003, Isoda et al 2006, Piotin et al 2003).

6.1.2 Three dimensional printing of models
This could potentially change however with the introduction of new technology, For example 3d printing. As one can imagine, having models crafted and sutured together, or being manufactured by moulds would be expensive and time consuming. (for an overview of various techniques used to created silicon vessel models, please see Chueh.,Wakhloo & Gounis 2009).
These techniques would also introduce sufficient error as to make results highly inconsistent and replication and control difficult as well as reduce the odds of manufacturing defect such as bubble formation etc (Chueh.,Wakhloo & Gounis 2009).

Three dimensional printing would allow for more accurate and uniform models to be manufactured with relatively low expense and ease. This would also allow for the creation of accurate and custom made models (specific to each individual patient), however these models are still in the trial phase and their accuracy and effective requires more experimental evident to be accepted as a viable technique for the exploration haemodynamics (Roloff 2013).

One possible problem with creating such models has to do with not only replicating the broad anatomy and vessel architectural characteristics, but also in replicating the various, blebs, lesions and imperfections in the vessels both for research and training purposes.

While many studies, as discussed earlier have attempted to quantify and identify the effect such characteristics associated with aneurysm formation and rupture, few studies have attempted to incorporate such features into actual physical models.

An added bonus to incorporating such lesion and various characteristics into models would be to allow for the creation of large data sets to be compared both post mortem and post experiment in order to more accurately assess the congruity of the various models as well as determine the effect of various population characteristics (age, sex, environmental influences, congenital disease etc) upon the actual pathophysiological processes associated with aneurysm formation and rupture, essentially a longitudinal assessment.

It should be noted however that while various techniques of manufacture exist, and new techniques may improve the quality of the models, a literature review (key words: Silicone aneurysm models) shows that such models are already widely used and published as an acceptable technique for the study of aneurysm haemodynamics, though their clinical effectiveness is still to be conclusively demonstrated (Chueh.,Wakhloo & Gounis 2009, Juvela 2000).

6.2 Imaging
Historically, medical imaging of blood was pioneered by Egar Moniz of Lisbon, Portugal, who in 1927 managed to image the surgical cannulation of both carotid arteries, via intra-arterial injection of sodium iodide, and xray imaging of the head revealed the cerebral vessels (Lin et al 2017). Based upon the same

principles modern day imaging is used (CT) and magnetic resonance (MR) techniques. Albeit with much higher resolution and computer control (Roloff 2013).

Imaging of course is a vital part of aneurysm modelling as touched on earlier and is worthwhile to briefly discuss their application in relation to haemodynamics modelling as this would affect the quality of imaging done and selected for in future studies.

Typically in a clinical setting, aneurysms are initially detected and diagnosed via either Computed Tomography (CT), Rotational Angiography (RA) or Magnetic Resonance Imaging.

6.2.1 MRI imaging

MRI is typically considered the most high resolution and such high quality images are the preferred method of obtaining the 3d images required in the manufacture of models.
While all models would ideally use the best possible imaging to created the highest possible quality models, this is of particular importance in Computational Fluid Dynamics (CFD) as they required mathematically concise high geometric consistency to fully resolve, as well as knowledge of all required parameters and boundary conditions.

Typically traditional cerebrovascular imaging techniques (such as those x-ray methods mentioned above) elucidates best the structure of the lumen (Wasserman et al 2005)

However as alluded to earlier, the pathophysiological processes occur not in the lumen of the vessel, (as it is effectively empty space filled with blood) but in the blood vessel wall.

Magnetic resonance imaging (MRI) tends to be required to obtain high quality images of blood vessel structure to supplement luminal imaging, and is widely used in clinical practice.

In a clinical setting, tellingly cerebrovascular disease alters the perfusability of the tissue and can be used to indirectly assess the haemodynamics and pathophysiology of the aneurysm and surrounding tissue.

Modern imaging techniques allows for safer, faster, and more accurate diagnosis of disease but has also lead to confusion due to the proliferation of differing techniques require more technical knowledge and specialization in the medical field. These techniques include:

6.2.2 CT Angiography

CT angiography (CTA) involves intravenous bolus injection of a radioactive iodine based contrast media. A "bolus" or "ball", in medical terms, is one quick mass injection made and given time to perfuse to the target vessels. The required time naturally varies with each specific patient, thus small scale tests and tracking software/systems are often employed to only acquire the image at the correct time.

Radiation is of clinical concern so tracking is primarily used to minimize patient exposure of ionizing radiation (hence why the image is only taken when the bolus reaches the vessel structure of interest.

Often a CTA scan for cerebrovascular aneurysms involves scanning from the head to the cervical vertebrae (known as a cervical-cranial CTA) is 3 to 6 mSv, (Manninen et al 2012) with other techniques such as diagnostic digital subtraction angiography (DSA) offering similar to slightly higher radiation exposure.(Hall and Brenner 2008, Gkanatsios 2002).

The estimated cancer mortality for radiation exposure is 1 in 20 000 per mSv, This risk is naturally compounded with multiple exposure and higher for children due to developing and growing body tissue (increasing radio sensitivity) so while low, it is a factor that should be taken into account when obtaining data (Hall and Brenner 2008).

6.2.3 MR Angiography

Unlike CTA scans, MRI scans do not emit ionizing radiation which would ameliorate concerns about radiation exposure though it should be noted that the cost is significantly higher.

MR angiography (MRA) refers the use of MRI to obtain imaging, of which exists a number of variants. These include, time-of-flight MRA (TOF-MRA), phase-contrast MRA (PC-MRA), and contrast-enhanced MRA (CE-MRA). (Lin et al 2017).

6.2.4 TOF-MRA

TOF-MRA works via "flow-related enhancement": radio frequency waves repeatedly bombard protons causing these protons in the area of the sample we wish to image to, create a magnetic differential generate high MRI signal in the vessel lumen.

This type of imaging can come in both "2 dimensional" and "3 dimensional" varieties where the 2 dimensional type acquires the images in large perpendicular "slices" and is lower resolution whereas the "3 dimensional" type is imaged from all 3 dimensions generating a higher quality image at the expense of longer (and thus higher cost) operation (Lin et al 2017, Saloner 1995).

6.2.5 PC-MRA

PC-MRA has a different physical basis than TOF-MRA. This works by manipulating the magnetic precession or spin of the various atoms in the sample (the technical details being beyond the scope of this paper), it should be noted

however that this technique is generally considered to be superior to TOF-MRA due to its ability to acquire similar quality images with lower scan times as well as being able to quantify blood flow within individual vessels with fewer artefacts from low velocity or turbulent blood flow (Lin et al 2017).

6.2.6 Digital Subtraction Catheter Angiography (DSA)

Digital subtraction angiography (DSA) is a fluoroscopy technique which can image blood vessels in anatomical areas composed of bone or dense soft tissue. Images are produced by comparing imaging pre and post injection of contrast media (radio opaque iodine) to elucidate where the contrast media has penetrated. This technique has high spatial and temporal resolution relative to other imaging techniques though is only 2 dimensional.

For comparison the 2 dimensional "pixel" resolution of DSA is approximately 0.2 mm^2 compared with 3 dimensional "voxel" resolution of 0.5 mm^3

It should also be noted that DSA has clinical risk due to the injection of the contrast media including ischaemic stroke, intra-cranial, haemorrhage, arterial dissection, puncture site haematoma and neurological complication resulting in permanent impairment, raising ethical concerns were it to be implemented in any study (Kaufman et al 2007, Willinsky et al 2003).

6.2.7 Time-Resolved Angiography

While static imaging can be used to elucidate structural information, which can be used for CFD modelling, real time, temporally resolved images are require to model haemodynamics in real patients and to a lesser extent models.

Diagnosis of certain conditions such as Heamodynamic-venous fistula (DAVF) also requires real time haemodynamic modelling. DSA is the standard clinical technique used to obtain time-resolved angiography, typically capturing 2-3 images per second.

However for various applications, especially in research where the fine details of the data are required other techniques are available.

Depending on the goal of the study, higher frame rates may be preferable to high resolution of images thus requiring different imaging techniques to accommodate this.

While as mentioned earlier TOF-MRA, PC-MRA, and CTA techniques can each provide imaging, and even real time animation, more temporally sensitive may be required depending on the relevant application

Time-resolved CE-MRA provides faster imaging at the expense of image resolution. While the previously mentioned imaging techniques

Provide a frame rate approximating 1 to 2 images per second,CE-MRA can images approximately 2 images per second (Korosec 1996, Lin et al 2017).

It should be noted that real time CTA imaging is rarely used due to the necessarily high radiation exposure from repeated scanning required in real time imaging.

Transcranial Doppler (TCD) ultrasound is non invasive and low cost, but can only be used on soft tissue (is obscured by bone), and the results are highly operator dependent (Amin-Hanjani et al 2007).

6.2.8 Aneurysm soft tissue analysis

Soft tissue can also be studied indirectly via observing oxygen consumption.

The most common way of imaging soft tissue in aneurysm is via

positron emission tomography (PET) which measures the fraction of oxygen the brain extracts from the blood, but at high cost.

Expensive and specialized equipment required to produce the needed oxygen 15

isotope which needs to be produced on site due to the short (2 minute) half life. While theoretically possible to precisely measure the oxygen tissue consumption, it is difficult to do due to specialized equipment needed and invasive procedures (such as catheterization).

Oxygen consumption can however be measured relatively by using the different brain hemispheres as controls for one another, however this assumes that there are no unilateral abnormalities or malignancies in the patient. (Derdyn and Powers 1999, Carlson et al 2011, Lustig, Donaho and Pauly 2007).

<u>6.2.9 Cerebral vasodilatory reserve</u>
Cerebral vasodilatory reserve is another method of assessing tissue oxygen consumption, which is based on the physiological observation that vasodilation in the vessel (upon autonomic stimulation such as via vasodilator drugs) is proportional to the tissue oxygen permeability, thus by eliciting and observing and vasodilatory event (e.g. injection of a vasodilator, hypercapnia by holding one's breath etc) the vasodilation would be a marker for the oxygen perfusability of the tissue. (Mandell et al 2008, Yoon et al 2015).

This can also be done passively by merely observing resting blood flow and observing over time, normal physiological variations (normal homeostatic auto-regulatory events) (Rim et al 2008).

<u>6.2.10 Laser Doppler Velocimetry</u>
Laser Doppler Velocimetry is the technique of measuring a homoeostatic effect with a laser beam by measuring the vibration and movement of fluids through transparent or semi transparent media and can be used to measure haemodynamic flow velocity and turbulence (Bordás et al. 2012).

While considered non intrusive and accurate and requiring no calibration, there are limitations with the angling of the machine making it difficult to obtain data

from near certain boundaries and walls and also require long acquisition times (on the order of hours) Variations of this broad technique exists such as Particle Tracking Velocimetry (PTV) and article Image Velocimetry (PIV). (Bordás et al. 2012, Lin et al 2017).

This technique while appearing straight forward in principle has a large number or variables such as the size of the particles involved, the need to inject "seeding particles" under certain conditions to allow for a media for the lasers to track, the multiple beams used to triangulate movement and the frequencies, interference and scattering of various beams, however the technical details are beyond the scope of this paper, but suffice to say, these techniques can be useful in the measurement of particle velocity in order for higher quality physiological parameters to be established to improve or create more realistic CFD and scale modelling of blood vessels and aneurysms, in particular the inlet flow conditions in CFD simulations (Roloff 2013).

6.2.11 Quantification of measures

Given the role of tissue pathology and pathophysiology in aneurysms, a histological study of the tissue under going aneurysm formation and pathological change would be a useful area of future study.

While as discussed earlier it is understood broadly that macro mechanical forces such as wall shear stress and energy loss affects the pathophysiological development of the aneurysm, a better understanding of the exact sequelae and pathological process, especially quantified, or at least bench marked would aid in clinical diagnosis, treatment and risk prediction.

To do this experimentally of course, models will have to be made from real tissue or tissue cultures followed by histological analysis of the tissue both pre and post simulation calibrated to differing simulated physiological conditions.

A literature review found relatively few studies using this paradigm although a number of interesting animal and post mortem studies offers insights into this process which will be discussed here. However given the nature of these studies, it would be difficult to quantify the precise degree and pathological evolution to the physical stresses measured in CFD studies (Bordás et al. 2012, Lin et al 2017).

6.3 Histology and biochemical pathophysiology techniques
Nonetheless, it should be noted that there are numerous histological and pathological studies involving aneurysm formation including the study of various genetic, cell signally and histological changes that occur during their formation.

6.3.1 Histology and inflammation in aneurysm evolution vs physical stresses
Halpern et al 1994 observed that while there are a number of differences, the actual pathophysiological evolution of aneurysm bear many similarities to cerebrovascular ones (even if the haemodynamics would differ due to the scale mechanics) so the tissue study would generally be fairly comparable, at least on the tissue level, in terms of the changes in the inflammatory process, atherosclerosis and the changes in the extracellular collagen matrix.

Therefore at least initially tissue modelling of such aneurysms may run along parallel line, however some studies have found that the inflammatory process is initiated by the expansion of the blood vessel, that is that inflammatory infiltration into the vessel is associated with the degree of blood vessel expansion, (Anidjar et al 1992, Halpern 1992). This process is the trigger for the inflammatory cascade and aneurysm genesis.

The expansion would naturally scale with the macro physical forces such as wall shear stress, and pressure loss etc as discussed earlier. Thus it would be a reasonable hypothesis that the ability to measure and calibrate could predict the stage of evolution of the aneurysm, it would also be reasonable to assume that the studies of aortic and cardiovascular aneurysms would need to be calibrated

separately due to being quite different in size.

Still, it should also be noted that while this research project is modelling primarily the physical stresses and parameters of the aneurysm, no model accounts for 100% of the variability, and as such, in real clinical decision making, blood work, such as inflammatory signals and other biochemical markers should ideally be used in clinical decision making.

It would be interesting to see if quantification of inflammatory and other such factors would correlate with quantification of stress such as WSS, energy loss, pressure loss etc.

Interestingly it has been found that the biochemical markers affect the mechanical properties of the aneurysm as well. The presence of elastase (elastase being the enzyme which would cause damage to the elastin) is associated with blood vessel dilation whereas the presence of collagenase is associated with blood vessel rupture. (due to damage to the collagen) .

This indicates that various pathophysiological processes will effect different mechanical properties of the blood vessel, known in physics as young's modulus, shear and tensile strength etc (Dobrin et al 1984, Halpern 1994).

6.3.2 Histological and other biochemical markers in aneurysm
Standard histopathology of aneurysm show lack of internal elastic lamina and normal macro blood vessel architecture, and in particular distortion of the mural cells (vascular smooth muscle cells, myofibroblasts, and fibroblasts). With irregular formation and gaps appearing on the vessel lining (Hassler 1961, Scanarini et al 1978, Sakaki et al 1997, Stehbens, 1963, Stehbens et al 1989).

Inflammatory cells (polymorphonuclear leukocytes, plasma cells and lymphocytes) are also present (indicating inflammation and atherosclerosis (Stehbens, 1963).

Though it should be noted there are limited histopathological studies comparing ruptured and unruptured aneurysms and the specific cell populations involved (Frosen et al 2012).

Kataoka et al. (1999) and Frosen et al. (2004) reported both structural degeneration and infiltration of inflammatory particles, the loss of endothelium, loss of mural cells, breakdown of the collagen matrix and partial hyalinization of the wall in association with rupture as well as loss of endothelia and subsequent thrombus formation on the luminal surface of aneurysm wall. Signs of healing were also present such as myointimal hyperplasia or neointima (That is new cells in the intima and lumen of the vessel in unruptured aneurysms). Intramural lipid accumulation is associated with damage to the aneurysm wall with the associated lipids found to be oxidized or chemically atypical from normal body lipids (Moore 2011).

These lipids also tend to encourage thrombus formation. Some limited evidence also exists that hemosiderin also tends to be present due to phagocytosis of blood cells. The oxidation may be caused by neutrophils trapped in the thrombus and the subsequently formed fibrin networks, with the various chemical changes caused by the peroxidases released by neutrophils. Such peroxidases could also contribute significantly to the damage to the blood vessel wall. It should also be noted that the chemically altered groups may also trigger further inflammation and immune response. Also while this may be the triggering event for the inflammatory process, damage to the outer smooth endothelial wall and exposure of the internal collagen fibres will exacerbate the inflammation leading to a limited positive feedback loop (Hourd et al 2009).

Endothelium is known to be damaged in response to high and physiologically atypical WSS levels (Chien 2008) and as has been argued earlier, this is affected significantly by blood vessel and aneurysm geometry However, to date there is not clear correlation with wall degeneration and aneurysm, though it has been observed to be associated the activation of inflammatory pathways (Laaksamo et al 2008).

The degree of inflammatory cell infiltration and anti bodies were shown to be higher in ruptured than unruptured aneurysms, though both ruptured and unruptured aneurysms contained inflammatory infiltrates indicating their presence early in the pathophysiological process.

Chronic complement activation in the aneurysm has also been observed (primarily the classical pathway with some alternative pathway involvement via the C3d complement (typically involved in chronic rather than acute inflammation) (Nakagawa et al 2000, Tulamo et al 2010).

6.3.3 Gene expression

Gene expression studies have found an association of antigen presenting inflammatory cells with rupture. (Krischek et al 2008, Kurki et al 2011, Marchese et al 2010), various biochemical components that are expressed in response to aneurysm rupture include collagenases (matrix metalloproteinase), pro-apoptotic genes and nitric oxide synthetase, pro-inflammatory chemotactic chemokines, TNFa, mRNA, Jun N-terminal kinase (JNK) and p38 Mitogen activated protein kinases) MAPKs and down regulation of anti-apoptotic genes (Laaksamo et al 2008, Frosen 2012).

This is only a small sample of possible biochemical factors involved with one study micro assay study finding changes in expression 1,426 genes, between ruptured and unruptured aneurysm, most being genes involving signaling pathways associated with inflammation and immune function, oxidative stress,

and cell homeostasis (Kurki et al 2011), loss of mural cells, inflammatory cell infiltration and degradation of the matrix with aneurysm rupture. It should be noted that many of these may be a secondary effect to ischaemia and necrosis caused by aneurysm rupture.

While many of these examples and studies are derived from specialized studies of aneurysms, it should be noted that these are effectively all markers of inflammatory cascade, and it remains to be seen whether they are any more specific to the detection and prediction of aneurysm rupture than any other inflammatory marker, hence the need to quantify their sensitivity and specificity specifically to aneurysms, after all if they are merely stand in measures for inflammation, they may be no more useful than low cost and simple measure of inflammation currently used in clinical medicine such as C-reactive protein (CRP) and ESR (Erythrocyte Sediment Rate).

6.3.4 Clinical application

While it is understood generally that a practicing doctor, nurse or other clinician will not be able to be informed on minutiae concerning the predictive power of every available measure, this type of research could potentially be used as a part of a clinical score or guideline to aid decisions to treat, or at least be one factor in such a guide provided they are refined sufficiently to be easily performed, cost effective and shown to be sufficiently sensitive and specific to warrant their use. At this point while it would be desirable to quantify the morbidty and mortality associated with each of these measures, this would require extensive comparisons between the models and the case histories of the patients, possibly through a longitudinal study, which are beyond the scope of this study. At this stage all that can be quantified are the in model physical parameters such as aspect ratio wall shear stress etc.

6.3.5 Conclusion

In conclusion, in the scope of this study is is proposed the width X breadth (WXB) is a more sensitive and specific predictor of wall shear stress than aspect ratio which is widely used and studied in the literature (Dhar et al 2008) however it should be cautioned that this study has a relatively low sample size with significant outliers and thus further study should be done to determine the value of using WXB as a clinical measure to predict aneurysm rupture.

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8.APPENDICES

<u>Appendix 1 Simulation parameters</u>

Heat Transfer: None,

Mass flow rate 0.00217 kg/s

Static pressure

Relative pressure 0

3000x max iterations

Residual target 10^-2

Material -> "Water"

Density 1050 [kg m^-3]

Transport properties:

0.0035 Dynamic viscosity[kg m^-1 s^-1].

Values from various sources,

Valenica & Villaneuva 2006, Siebert 2008, Olgac et al 2011, Farnoush 2012

<u>Appendix 2 Energy loss and wall shear stress data</u>

WSS	AN	NoAN	Change WSS	EL
1	158.079	167.153	-9.074	-11583.97652
2	13.7806	15.1179	-1.3373	747.9816163
3	107.745	96.6759	11.0691	62648.2396
4	29.8912	32.084	-2.1928	-21482.23274
5	52.7589	48.2264	4.5325	191981.991
6	775.308	561.927	213.381	-122441.7486
7	795.14	699.955	95.185	7499340.326
8	265.887	277.925	-12.038	-40828.42745
Total	423.966	445.078		