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**STUDIES ON THE ASSESSMENT OF
ABDOMINAL AORTIC ANEURYSM RUPTURE
RISK**

**TEJAS CANCHI
SCHOOL OF MECHANICAL AND AEROSPACE ENGINEERING
2018**

STUDIES ON THE ASSESSMENT OF ABDOMINAL AORTIC ANEURYSM RUPTURE RISK

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requirements for the degree of Doctor of Philosophy

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Dedication

To Amma and Bapa, my first teachers

ABSTRACT

Abdominal Aortic Aneurysms (AAA) are a type of cardiovascular disease that affect the infra renal aorta, where the normal aorta dilates to more than two times its original diameter. Progressive dilation leads to weakening of the aortic wall and eventually, rupture. Pathophysiological, biomechanical and genetic factors contribute to the genesis, growth and rupture of the AAA. Current clinical management of AAA is based on the maximum transverse diameter of the dilated lumen to recommend surgical intervention. However, several additional factors play a role in the progression to rupture. Therefore, a patient specific assessment based on biomechanical factors and antecedents can lead to the development of a predictive tool that can be implemented at the bedside. This thesis has investigated a biomechanical as well as machine learning/statistical approach to developing an accurate patient specific predictive tool for rupture assessment in Asian AAA patients. This was deemed necessary due to the differences in morphology between Asian and Caucasian patients. These differences have caused difficulties with the graft delivery during Endovascular Aneurysm Repair (EVAR) and subsequent follow up of AAA Asian patients. The clinical significance of these differences can be brought out through a comparison of the geometric parameters in each cohort along with the mechanical stresses developed in these aneurysms.

A comparison of 19 patients each from the Asian and Caucasian patient groups was conducted to establish the differences in morphology and hence, the biomechanics of rupture in each cohort. This was done using a combination of in-house segmentation codes and commercial finite element analysis (FEA) software. Subsequently, statistical

analysis was also applied to generate geometric surrogates to predict the wall stresses in the patient groups. The study resulted in significant differences in peak wall stress among Asian patients with high maximum diameters when modeled with non-linear constitutive material models. The means of the biomechanical stresses between the two patient groups were not significant between the two patient groups. It was seen that the geometric indices that were significantly correlated to the spatially averaged wall stress in the Asian patient group were maximum diameter, proximal neck diameter, L2 norm of the mean curvature (MLN), square root sum of the Gaussian curvature (KM), and the L2 norm of the minor principal curvature (K2LN) while in the Caucasian patient group it was only distal neck diameter. The resulting six geometric indices can be used as geometric surrogates to quantify wall stresses in the patients. The five indices in addition to maximum diameter can predict the spatially averaged wall stresses with an accuracy of 72.87% in the Asian patient group and 74.74% in the Caucasian patient group.

Machine learning algorithms (MLA) as a possible approach to hasten the diagnostic process was explored using multiple classifiers such as decision trees, support vector machines (SVM), Naïve Bayes and logistic regression. The most suitable classifier analyzing a cohort of 312 patients (155 AAA and 157 normal) with geometric and patient antecedent attributes, was determined as the Naïve Bayes algorithm. Further, a feature selection algorithm was applied to obtain the attributes that are significantly correlated to rupture. These included the proximal neck diameter, the neck length and the right iliac artery diameter in addition to the maximum diameter of the AAA. A further investigation involving 155 patients' data was done to estimate whether only antecedent attributes can accurately predict rupture in the cohort. Using only attributes based on patient history, it

was observed that the MLA can accurately extract the most significant clinical features that are correlated to AAA rupture. It was determined that machine learning algorithms can be used in synergy with the biomechanics to estimate rupture risk in the cohort.

A fluid structure interaction (FSI) based model is developed on patient specific geometry data originating in Singapore to establish the biomechanics of rupture in Asian AAA. A comparative analysis of two patient models with differing maximum diameters and literature based inlet and outlet boundary conditions was carried out by extracting biomechanical parameters such as principal stresses and wall shear stresses from the simulation. The patient model with the larger maximum transverse diameter developed lower principal and wall shear stresses than the one with a smaller value of the diameter.

In order to validate computational results, experimental methods need to be developed to accurately construct a physical model of the system being investigated. A patient specific silicone AAA phantom was used in a benchtop flow loop to mimic the fluid structure interaction between the aortic wall and blood. Realistic boundary conditions were imposed using a physical Windkessel model that mimics the impedance in the abdominal aortic system. Resistance and capacitance modules were built to establish the impedance values that generate realistic pressure values at the outlet.

Future work will involve analysis of a larger cohort of patients to compare the Asian and Caucasian cohorts, to develop a more robust machine learning model that can predict rupture and incorporation of patient specific boundary conditions in FSI simulations. Experiments using in vivo impedances will also be done to establish realistic boundary conditions in the AAA.

Keywords: Abdominal Aortic Aneurysm, Asian and Caucasian patient cohorts, finite element analysis, image segmentation, morphology, machine learning, rupture risk prediction, patient history, geometric quantification, fluid structure interaction, experimental method, Windkessel model, realistic outlet boundary conditions.

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Tejas Canchi, Hong N Nguyen, Sourav S Patnaik, EYK Ng, SD Kumar, Sriram Narayanan and Ender A. Finol, *A comparison of morphological parameters in Asian and Caucasian patients using biomechanical and machine learning methods*, Summer Biomechanics, Biotransport and Bioengineering Conference (SB3C) 2017, Tucson, Arizona, June 2017.

Tejas Canchi, EYK Ng, Germain ZE Tham and Sriram Narayanan, *Effect of Patient History on Estimation of Rupture Risk in Asian Abdominal Aortic Aneurysm (AAA) Patients Using Machine Learning Methods*, International Conference on Mechanics in Medicine and Biology (ICMMB), Melbourne, Australia, May 2017.

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BOOK CHAPTER

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CHAPTER 1

INTRODUCTION

1.1 Introduction

The World Health Organization estimates 17.5 million people died from cardiovascular diseases (CVDs) in 2012. This is equivalent to 31 percent of all global deaths during that year [1]. CVDs are the leading cause of death globally, except for Africa [2]. There are several risk factors which are believed to have contributed to the development of cardiovascular disease. Some examples of these risk factors are [3]:

- i. Physical Inactivity
- ii. Unhealthy Diet
- iii. Cholesterol
- iv. Raised Blood Pressure & Hypertension
- v. Obesity
- vi. Smoking

These risk factors may trigger certain adverse conditions within the vascular system. An example of such a condition is the blockage of arteries, known as atherosclerosis. Atherosclerosis leads to potentially fatal conditions such as myocardial infarction or stroke. CVDs are diagnosed using an array of laboratory tests and imaging studies. Cardiac magnetic resonance (MR), chest X-ray, echocardiography (ECG) and computed tomography (CT) are some of the common imaging methods used in diagnosis [4].

Aneurysms, are a type of CVD that is prevalent in the aorta, the main artery that pumps blood to the body. Aneurysms in the cardiovascular system are abnormal dilations of a specific region of the aorta. They can be formed at several locations along the aorta that stretches from the exit of the heart down to the iliac bifurcation. Aneurysms lead to weakening of the wall and eventually rupture. This can be attributed to several factors. Pathophysiological, biomechanical and genetic factors aid in the genesis, growth and eventual rupture of the aneurysm. Once diagnosed, the clinicians use size metrics corresponding to the type of the aneurysm in recommending surveillance or surgery. Abdominal Aortic Aneurysms, that are a specific type of aneurysm, is the focus of this thesis.

1.2 Types of Aneurysms

There are several types of aneurysms that occur in the body. The types that have highest incidence are described below.

1.2.1 Cerebral aneurysm

A cerebral aneurysm (also known as an intracranial aneurysm) is a dilation of a weak region of the blood vessel in the brain. The dilation results in a balloon shaped aneurysm. Rupture of this dilation releases blood in to the subarachnoid space of the brain causing a subarachnoid hemorrhage. Cerebral aneurysms are asymptomatic unless there is a large dilation or rupture. Cerebral aneurysms generally occur in the area around the Circle of Willis. This area is a junction of arteries that supply the brain with nutrition. Hence, this is a susceptible area for the weakening of the arterial wall. The likely causes of a cerebral

aneurysm include advanced age, smoking, atherosclerosis, high blood pressure or possible injury to the blood vessel. The diagnosis may be carried out using one or more imaging techniques, namely, CT scans, cerebral angiographies, or MRI. Surgical intervention is through clipping of the dilated region or endovascular coiling where a catheter coil is inserted into the dilated region preventing entry of blood. Cerebral aneurysms can be of two types: saccular and fusiform. In a saccular aneurysm, the dilation is on one side of the artery like a hanging fruit. On the other hand, in a fusiform aneurysm, the entire artery dilates along the transverse direction.

1.2.2 Thoracic aneurysm

A thoracic aortic aneurysm is a type of aneurysm where the thoracic aorta dilates to a diameter of more than 4.5 cm. Thoracic aneurysm diameters may go up to a value of 6.5 cm [5]. The thoracic aorta is composed of the ascending aorta, descending aorta and the aortic arch. The aneurysms may occur in any of these segments and in some cases in all of them. Patients with thoracic aortic aneurysms may also have an abdominal aortic aneurysm. Sixty percent of thoracic aortic aneurysms involve the aortic root and/or ascending aorta, 40% involve the descending aorta, 10% involve the arch, and 10% involve the thoracoabdominal aorta (with some involving >1 segment) [6]. The etiology, natural history, and treatment of thoracic aneurysms differ for each of these segments. Aneurysms in the ascending aorta grow up to 6 cm where it is considered to be a rupture risk. Similarly, for descending aortas, the critical size is 7 cm [7]. CT and MR angiographies are generally used in the diagnosis of thoracic aneurysms.

1.2.3 Abdominal Aortic Aneurysms (AAA)

Abdominal aortic aneurysm (AAA) is a localized enlargement of the abdominal aorta. In order to be considered as an AAA, the diameter of the aorta has to be enlarged to more than 50 percent of its normal size [8]. Non-intervention leads to progressive dilation and weakening of the arterial wall, and eventually rupture. The mortality as a result of AAA rupture is high. AAA is known to be a silent killer as diagnosis is mostly accidental with no symptoms being exhibited before rupture.

The wall of the aorta can be weakened or damaged by several processes, of which normal aging and hypertension are perhaps the most common. Atherosclerosis, the build-up of cholesterol that characterizes coronary artery disease, affects the inner lining (endothelium) of the aorta and may lead to weakening of the wall. Atherosclerotic deposits commonly occur in the abdominal segment, below the level of the branches to the kidneys.

With time and under the pressure of flowing blood, a bulge can develop at a weak spot in the aorta. This is called an aneurysm. Aneurysms, generally, grow to about 2.5 times the normal diameter of a healthy aorta. This bulging progresses with age (Figure 1.1).

The infra-renal aorta is a site predisposed to aneurysmal widening. The cyclic stress caused by the pulse wave in conjunction with factors which decrease the strength of the wall may lead to dilatation, and ultimately, to rupture [9]. It is the 13th most common cause of death in the United States [10]. The condition occurs mainly in patients over 65 years of age and affects approximately 2% of the elderly population [11]. There are several risk factors that have been known to affect the genesis, growth and rupture of AAA - advanced age, greater height, coronary artery disease, atherosclerosis, high

cholesterol levels, hypertension [12] and smoking [13,14]. Abdominal aortic aneurysms (AAAs) are known to have an incidence that is approximately four to six times higher in men than in women. However, the incidence in women also rises with age, although starting later in life than in men [15].

Figure 1.1. Physiology of the Abdominal Aortic Aneurysm

Brown and Powell [16] have said that a higher mean blood pressure in a patient means that they are at a higher risk of AAA formation. Smoking has been seen as a major risk factor in the development of AAAs by Hammond and Garfinkel [17] and Macsweeney et al [18]. The expansion rate of an aneurysm is another aspect that needs to be known in order to have a suitable time of intervention in the form of surgery. Cronenwett et al [19] showed that the expansion rate of an AAA once it is initiated is exponential. This has

major implications as the speed of growth of the lumen is quicker if the relationship is exponential.

Surgical repair of AAA can be performed in two ways – by traditional open surgery or endovascular aortic aneurysm repair (EVAR). Initially, open surgery was the norm but since the introduction of EVAR [20], there has been a widespread acceptance of the procedure. This is a less invasive procedure with a decrease in 30-day mortality in patients when compared to open surgical repair. In addition, the current generation of approved devices have smaller delivery system profiles, track better, and can be used to treat difficult AAA morphology more easily [21]. EVAR has rapidly become the preferred method of AAA repair amongst vascular surgeons. Vascular surgeons have used lumen diameter as a metric to guide surgical intervention for some time now. A cut off diameter of about 5-5.5 cm is used as a base to recommend surgery for patients with AAA [22]. Studies like the UK Small Aneurysm trial [23] have reinforced this value as a reasonable measure of the risk to benefit ratio between the risks of aneurysm rupture and those of surgical intervention.

As a criterion, the use of the maximum transverse diameter metric is a crude way to estimate the critical state of an AAA [24]. The authors [24] argued that, from a biomechanical perspective, the use of wall stress in the lumen, can more accurately predict the rupture of AAA. They defined the critical state of an AAA as that at which the mechanical stress within the aneurysmal wall exceeds the tensile strength of the tissue. Other parameters such as wall tensile strength, length of aneurysm and patient-specific pulsatile velocity and pressure boundary conditions also play an important role in the progress to rupture of the AAA. Biomechanics of rupture in AAA is affected due to

variations in a combination of these parameters. Hence, to account for the contributions of several parameters in what is essentially a patient-specific problem, biomechanical methods could play a crucial role.

Hence, a physics-based approach is required wherein the biomechanical factors are taken into account, such as material properties of the aortic wall, the stresses developed as a result of the blood flow and the boundary conditions, to make an informed decision on the status of growth of the AAA and the need for surgical intervention. Hence, a diagnostic tool can be developed to aid clinicians to this effect.

1.2 Research Scope and Objectives

This thesis will study the biomechanical factors that affect assessment of rupture risk in Asian AAA patients. This will be done using a multi-pronged approach. In addition to assessing stresses developed, through the use of finite element analysis (FEA)/Computational Fluid Dynamics (CFD) and *in vitro* experiments, development of a machine learning based predictive model will be explored as a novel strategy to aid clinicians make a swift assessment of the rupture risk. The following will be the main objectives of this thesis.

1. Highlight the morphological differences in the Asian and Caucasian AAA patient geometries. Establish geometric surrogates for the Asian and Caucasian patient groups to estimate stress development by carrying out biomechanical analysis and subsequently through statistical methods, bring out the most significant attributes affecting assessment of rupture risk in each patient group.
2. Develop a machine learning model based on retrospective patient data (involving geometric indices and clinical parameters) to assess AAA patient rupture risk. This

diagnostic model will aid clinicians in swift assessment based on attributes other than just the maximum transverse diameter of the diseased aorta.

3. Analyze the biomechanics of rupture in Asian AAA patients through a strongly coupled fluid structure interaction approach. This will aid in the estimation of biomechanical indicators such as intraluminal pressure, which are critical markers in the assessment of AAA rupture risk.

An ancillary objective would be to setup a bench top flow loop to study *in vitro*, the fluid structure interaction of the aortic wall using realistic inflow and outlet boundary conditions. This will establish an experimental model for computational validation, incorporating *in vivo* impedances of the vascular system.

1.3 Thesis Organization

This thesis is organized as follows. Chapter 2 contains a comprehensive literature review of the methods used to assess rupture risk in AAA. The gaps in research are brought out to justify this work.

Chapter 3 presents the biomechanical and statistical analysis done on 19 patients each, from the Asian and Caucasian groups to bring out the morphological differences and their influence on rupture risk assessment. Using FEA, the peak wall stress (PWS), spatially averaged wall stress (AWS) and the 99th percentile wall stress (99th -WS) are computed. Subsequently, a statistical method is used to bring out the significant factors of difference in the two cohorts and in addition to that, the factors that are highly correlated to the

spatially averaged wall stress values in each cohort. This will bring out a set of geometric surrogates to estimate the stresses for each patient group.

Chapter 4 presents the machine learning analysis work that was done on 312 patients' data to aid in the development of a diagnostic tool to predict rupture in the Asian AAA cohort. Four different classifiers are used to compute the accuracy of prediction of AAA rupture. A feature selection algorithm based on Chi square and wrapper methods is used to extract the most significant attributes that are highly correlated to AAA rupture risk. In addition, a machine learning analysis based on 155 patients' data with only patient history derived factors is used to predict rupture risk. Subsequently, a Chi square feature selection algorithm is presented to rank the highly significant factors predicting AAA rupture risk.

Chapter 5 presents a computational fluid structure interaction (FSI) analysis of two patients drawn from the Asian population. The analysis is conducted based on patient specific geometries reconstructed from CT images and subsequently a strongly coupled commercial solver is used to extract the biomechanical parameters. The two patients are then compared using these parameters. It is seen that the maximum transverse diameter may not be the only determinant of the rupture risk in AAA.

A summary and conclusions of the thesis is presented in addition to suggestions for future work.

Appendix A presents the design and construction of a benchtop flow loop to mimic the fluid structure interaction of the aortic wall, incorporating a physical Windkessel module to account for the realistic impedance values in the upstream and downstream of a patient specific silicone AAA phantom.

Chapters 2-5 and the appendix are based on content that have been published or have been submitted for publication. Hence, there is some recurrence of background and methods in these chapters.

1.4 Contributions of the Thesis

This thesis is the first attempt at developing a diagnostic model to assess AAA rupture risk in the Asian population. A multi-pronged methodology based on experiments, computational mechanics and machine learning/statistics is used to develop a diagnostic strategy that can be implemented at the bedside and specifically for the Asian population. Towards this end, this thesis has the following contributions.

1. The morphological attributes in the form of geometric indices in the Asian and Caucasian AAA patients have been correlated with the spatially averaged wall stresses induced in each patient group and a geometric surrogate model has been developed for the two patient groups. The attributes that are significantly correlated to the stresses are seen to be different in each group. Proximal neck diameter and the curvatures that were seen to be different in the Asian patient group could contribute to the design of a stent graft that is suitable for Asian patients.
2. A machine learning method based classification algorithm to assess AAA rupture risk based on geometrical parameters is a novel approach that can aid swift and accurate diagnosis at the bedside. Additionally, the use of feature selection algorithms provides insights into choosing only those attributes that are significantly correlated to AAA rupture risk in a patient.

3. The mechanics aspect of assessment of AAA rupture risk is also critical as it provides additional insight over just the clinical standard maximum transverse diameter. The FSI analysis quantifies parameters such as intraluminal pressure which are difficult to obtain *in vivo*.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

During the past three decades, there has been a concerted multidisciplinary effort by clinicians, biologists and engineers to study the pathogenesis, growth and progression to rupture of Abdominal Aortic Aneurysms. These studies have been carried out in order to develop a diagnostic tool at the bedside to aid clinicians make an accurate status assessment and diagnosis. Engineering based strategies have spanned fluid and solid mechanics based analyses and have brought out a new dimension to the traditional methods of clinical diagnosis using imaging modalities such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). The use of statistical and machine learning methods has given an additional boost to rupture risk assessment.

Several researchers have pursued the development of a diagnostic tool to assess AAA rupture risk [1-3]. Some researchers have performed experiments on phantoms made of silicone rubber [4] and distensible tubes [5,6] and on cadavers and during surgery to ascertain the properties of the AAA configuration [7]. Some have come up with analytical approaches of a simplified AAA problem [8-10]. But computational fluid dynamics (CFD)/ finite element analysis (FEA) based approaches have dominated the landscape in the analysis of risk of rupture of AAA. This is because experiments are difficult to set up due to ethical considerations of sample retrieval from patients. Also, obtaining accurate material properties to understand the coupled interaction between the arterial wall and

blood flow has been a challenge in the assessment of AAA rupture risk. Hence, it is critical that a multipronged approach is employed to ascertain the status of the AAA in order to estimate rupture risk. The biomechanical approach to this end, can be a combination of experiments, and computational methods involving fluid and solid mechanics, and statistical and machine learning methods. This chapter will summarize previous work done using all these approaches and establish the justification for this work.

2.2 Experimental Studies

Even as it has been said that experimental studies are hard to set up due to the inherent complexity of the variables involved in the disease system being studied, they form a critical aspect of the analysis that can bring out phenomena that explain inconsistencies in computational analysis. *In vitro* studies represent actual physical conditions and can quantify parameters such as boundary conditions, temporal convergence, flow dynamics and material properties, additionally bringing out speculated phenomena such as turbulence. Hence, the use of experiments as a validation tool is vital in order to eventually develop a computational diagnostic model for use in the clinic.

Experimental studies in the AAA domain have been carried out using animal models [11-14], to understand tissue mechanics and develop hyperelastic material property models using histology [15-18], and using a fluid mechanics based approach using flow visualization techniques such as particle incidence velocimetry (PIV), Laser Doppler Velocimetry (LDV) to discern the flow physics in the AAA system [19-22]. The improvement in technology has brought in imaging based diagnostic studies with the

advent of CT and MRI as non-invasive techniques to measure velocity and flow in arteries.

In vitro experimental studies have been generally carried out using a rigid or compliant phantom, made of a polymer such as Sylgard^{TM}, or glass in early studies. One of the early studies was by Scherer in 1973 [23] who used three axisymmetric glass models of an aneurysm to measure pressure and determine the critical Reynolds number for transition to turbulence. The analysis was conducted using steady flow regimes for each of the aneurysm models. He concluded that the geometry of the aneurysm plays a large part in determining the critical Reynolds number where transition occurs. He hypothesizes that in an actual patient origin aneurysm, the geometrical parameters would be important in the flow field solution along with additional dimensionless parameters. The critical Reynolds number was calculated to be 2950 for peak aortic flow of 5L/min and an aortic diameter of 2 cm. Stehbens in 1974 [24] used glass aneurysm models to observe boundary layer separation and reattachment again under steady flow conditions. Other studies such as Drexler and Hoffman in 1985 [25] and Budwig et al in 1993 [26] saw recirculating vortices in the aneurysm lumen under steady flow conditions. Budwig in fact was able to estimate the wall shear stresses in the aneurysm reporting two peaks in the distal region of the lumen where the recirculating vortices reattached to the arterial wall. Peattie et al in a series of experiments in 1994 and 1996 [27,28] carried out under steady flow conditions, established the transition points into turbulence using color Doppler imaging modalities. Steady flow studies established that there are recirculating vortices due to the geometry of the aneurysm and the flow regimes are mixed; both laminar and turbulent regimes exist in the AAA lumen. But these were mostly using symmetric models of fusiform or saccular

AAA. Bluestein et al. [29] carried out experimental and computational studies of a symmetric model aneurysm, also under steady flow conditions. They observed platelet deposition at the sites where the wall shear stress (WSS) is low thereby promoting thrombus formation and creating conditions for rupture.

Yu [30] investigated the effect of steady and pulsatile flow characteristics using PIV over a range of Reynolds numbers (400 to 1400). While he reported observing the recirculatory vortex in steady flow with the core near the distal end of the bulge under pulsatile flow conditions, the vortex moved distally gaining in strength even as it occupied only 1/4th the space as compared to the steady flow vortex. While Moore and Ku [31] and Pedersen et al [32] investigated the variation of flow fields during rest and exercise conditions in the healthy abdominal aorta, there have been studies investigating pulsatile flow using AAA models.

Peattie and Bluth [33] investigated the mechanical factors that lead to rupture in AAA by simulating resting *in vivo* conditions in an experimental setup, using seven rigid aneurysm models with uniform lengths of 4d, and diameters that ranged from 1.5 to 3.2d, where d is the diameter of the undilated entrance tube. The investigation was carried out at mean Reynolds number of 340 and peak Reynolds number of 2000 with a Womersley number of 11. The flow field was analyzed using LDV to derive the wall stresses. They measured a wall shear stress value of 12 dyn/cm² during peak systole in the cardiac cycle. This was nine times the value of 1.3 dyn/cm² during steady flow conditions. The wall pressure stayed constant at 120 mmHg throughout the cardiac cycle. Pulsatility increased the wall shear stress significantly but still is a function of model size. The greatest stresses occurred in the smallest aneurysm models. This investigation was extended to exercise

conditions by Egelhoff et al [34] who examined the vortex dynamics of both resting and exercise conditions. Five rigid aneurysm models were used along with an axisymmetric model with all five having same aspect ratios. The flow showed three distinctive regimes; attached flow over the entire cycle in small AAAs, vortex formation and translation in moderate AAAs at resting conditions and vortex formation and transition to turbulence in moderately large AAAs. They proposed a new mode of transition to disturbed flow and finally turbulence in the distal end of the AAA. This occurs through “vortex bursting” during late diastole, in which there is formation of a secondary vortex that elongates, travels distally and subsequently, bursts causing the flow to become chaotic.

These observations have been reinforced in a study by Peattie et al., 2004 [35] where they observe that the bulge diameter plays a large role in the complexity of the vortex fields generated during diastole in the cardiac cycle. This was observed in an axisymmetric AAA model subject to resting conditions. Egelhoff et al [34] had not observed any vortex development in axisymmetric models but Peattie et al report vortices that are formed during peak systole, moving distally and showing complex patterns depending on lumen diameter. They observe flow becoming increasingly disturbed in the large aneurysm models. The greatest shear stress developed was in a 4.3 cm model. They proposed that there is a correlation between unstable flow dynamics and high wall shear stresses thereby leading to rupture.

To study the evolution of wall shear stress values as a function of the diameter of the AAA, Salsac et al [36] conducted a parametric study of axisymmetric AAAs with a range of diameters using physiologically accurate boundary conditions. This was the first time

since Fukushima et al [37] that an *in vitro* study had used boundary conditions that were not a generic sinusoidal waveform [30,38]. Five aneurysm models with aspect ratios varying from 2.9 to 3.2 and dilatation ratios from 1.3 to 2.4 were used in the study. The variation of hemodynamic stresses as a result of changes in these two parameters was investigated experimentally. All the rigid glass AAA models tested had a diameter of less than 4.5 cm and no thrombus was present. They found that at all values of the dilatation parameter, i.e. where the shape change is significant from the healthy aorta, the flow remains attached to the wall, due to systolic acceleration. But following peak systole the flow detaches. The impingement of start up vortices on the distal portion of the lumen induces wall shear stresses on the aortic wall. These two regions, the detachment and reattachment form the principal processes in the cardiac cycle as the aneurysm grows in size, with reattachment inducing stresses that may be important to assess rupture risk.

All the above studies have been carried out with rigid aneurysm models. But in reality, the aortic wall is compliant and interacts with the flow. Hence, accounting for that becomes important. Deplano et al [39] used both rigid and compliant AAA models under resting and exercise flow rates to determine parameters affecting flow behavior. They concluded that under resting conditions, the rigid model does not show any interaction of vortices with the wall while it is a critical phenomenon that contributes to increased pressure in the compliant model. This is true for exercise conditions as well and the pressure and wall stress induced depends on the input flow rates. O'Rourke and McCollough [40] conducted the same type of analysis but using patient specific AAA models. The inlet velocity waveform was extracted through LDV and was deemed to be physiologically accurate. This was done for three Reynolds number values of 300, 477 and 1700. *In vitro* and *in*

vivo measurements were compared and found to be within error range. Subsequently a computational strategy was used wherein the extracted boundary conditions were adapted to extract the flow dynamics for each case to be compared with experiment. This was done using both steady and unsteady flows. Agreement between the results was best during systole, where there was a strong pressure gradient, and also during diastole in the presence of vortex structures. The level of agreement deteriorated during diastole in the wake of the vortex; this reflects the complexity and chaotic nature of the flow in these areas.

Similar studies have been carried out by Boutsianis et al [41] and Stamatopoulos et al [42] to ascertain flow dynamics in patient specific AAA models using steady and pulsatile flows. These have added to the knowledge of the flow in the lumen. But most of these studies have used non patient specific models or flow conditions to ascertain the development of vortices that in turn affect pressure development and hence wall shear stress values in the AAA. Additionally, using rigid models and boundary conditions that are in only one axial direction will result in under estimation of stresses developed. Regardless, experimental methods have been useful in discerning flow structures and how they possibly are correlated to development of wall stresses.

2.3 Computational Methods Reported in Literature

Rapid improvements in computational power coupled with better understanding of hemodynamics have spawned the interdisciplinary science of computational medicine. A multidisciplinary effort with clinicians, radiologists and biologists on the one hand and engineers with computer scientists on the other has greatly increased the ability to

diagnose medical conditions and has improved delivery of healthcare. Computational methods have played a very important role in this, as experimentally determining parameters that affect a certain medical condition is not possible in many cases. Computational fluid dynamics (CFD) methods can be used to accurately determine the nature of blood flow in the cardiovascular system [43] and the nervous system [44] and air flow in the respiratory system [45]. Machine learning/data mining methods have also been used to develop models that learn from retrospective data to make a prediction on factors affecting progression of disease [46-48]. These models have also been successful in incorporating factors such as patient history and occupation. Some of these variables (patient history, occupation, family history) are difficult to quantify directly and so using methods such as machine learning, they can be incorporated into predictive models.

Computational models are based on constitutive laws of continuum mechanics, such as the Law of Laplace that had been originally used in the analysis of bursting of cylindrical shells, the laws of rheology to describe the properties of blood, fluid mechanics in the analysis of vortex formation in the lumen and material properties of stent grafts in a post-surgical aorta. There are several aspects of computational methods that need to be in place to make a comprehensive assessment of rupture risk in AAA. They include boundary conditions, material properties, flow physics and subsequently the statistics and machine learning as mentioned before. The following sections will describe previous research based on these aspects.

The work reported in this thesis involves a methodical approach to make an assessment of AAA rupture risk based on CT images. The process involves firstly, reconstruction of the 3D model from CT data for the region of interest. After sufficiently filtering out the

artifacts by using a suitable Gaussian/Poisson filter, a computational mesh is imposed on the model. This mesh model is put through a FEA/CFD solver based on the Navier Stokes equations. Patient specific/ literature derived boundary conditions namely, inlet and outlet velocities, fluid pressure on the internal wall, material properties of the aortic wall and properties of the intraluminal thrombus (ILT) if present, are inputs to the solver. The output of the simulation involves biomechanical parameters such as the peak wall stress and the velocities and pressures in the lumen along with the flow structures that induce the pressures and stresses in the AAA.

As the ultimate aim of the project is to develop a prediction tool to support clinicians in the diagnosis of rupture risk, the large number of retrospective patient data that is available with the hospital can be leveraged. The data can be used to develop a “learning model” that will be able to accrue the several different variables of a specific patient, over a number of patients. This model will then be able to predict the possible course of an aneurysm for a new patient and subsequently be used as a tool to predict the rupture risk in future cases. The work flow schematic is shown in Figure 2.1.

Figure 2.1 Work flow schematic in assessment of AAA rupture risk.

2.3.1 Image segmentation and Reconstruction

Medical images from AAA patients are extracted using either CT/MRI modalities. CT images can be obtained per the type of analysis being carried out i.e. they can be obtained in a longitudinal surveillance study at certain intervals to investigate progression, or they can be obtained before surgery and after surgery to analyze the effect of aneurysm repair. These 2D image slices need to be reconstructed as 3D models so that they are suitable for use in a numerical solver. Image reconstruction is carried out using image segmentation and reconstruction algorithms.

The image reconstruction algorithms are spelt out in detail in [49]. The level set method is a popular method for realizing image segmentation and subsequently, reconstruction. This

was a method developed by [50] as a novel method for segmenting gray scale images. Amongst the parametric methods that are used in image segmentation, the “Snakes” method is widely used. Many commercial and open source codes use this automatic segmentation method to determine the edges of the required area of interest. Image edge detection in these methods is based on curve parameterization.

An image is a bi-variate function that is unchanging in time that can be represented by $I(x, y)$. Initially, the curvature is obtained. Subsequently, to find the edges in an image, the region of highest gradient is identified. When the edges have been detected, the gradient values define the intensity of the image. Moving in the direction of the highest intensity provides the contrast in a gray scale image. The image $I(x, y)$ is associated with a vector field, given in eq. (2.1).

$$V(x, y) = (v_1(x, y), v_2(x, y)) = |\text{grad}(x, y)| = \left(\frac{d(I(x, y))}{dx}, \frac{d(I(x, y))}{dy} \right) \quad (2.1)$$

“Snakes” is an automatic segmentation procedure and is used as a fast method in commercial image segmentation codes. An example is shown in figure 3.2 as to how the segmentation algorithm proceeds to evolve and wrap around the boundary of the region of interest in the image.

Figure 2.2. Evolution of explicit boundaries in a “Snakes” image segmentation algorithm [51]

A snake is defined as the energy minimization spline whose energy depends on its shape and location within the image. The shape of a snake is controlled by the external and internal forces prevailing in the image. The external force guides the snake towards the features in the image, and internal force acts as smoothing constraint for the snake.

Let the vector $p(s) = (x(s), y(s))$ be the parametric representation of the snake where the value of s goes from 0 to 1. The energy function to be minimized is given as [52]

$$E_{snake} = \int_0^1 [E_{int}(p(s)) + E_{ext}(p(s))] ds \quad (2.2)$$

E_{int} is the internal force that forces the snake to be small and smooth. E_{ext} is the external energy needed so that the snake can find the edges of the image. The aim is to minimize the total energy of the system. Hence, the external energy is defined as the negative of the gradient of the image.

$$E_{ext} = -\|\nabla I\| \quad (2.3)$$

where, ‘ I ’ represents the image. The internal energy is defined as

$$E_{int} = \frac{1}{2} \{ \alpha |p'(s)|^2 + \beta |p''(s)|^2 \} \quad (2.4)$$

where, $|p'(s)|$ is the magnitude of the first derivative, which is large for long snakes and $|p''(s)|$ is the second derivative and is large for sharp bends in the image. α and β , which are constants, define the relative importance of the two energy terms. The total energy function needs to be minimized and the Euler-Lagrange equation is used for this purpose [53].

$$\alpha p''(s) - \beta p''''(s) - E_{ext}(p(s)) = 0 \quad (2.5)$$

Where, $p''''(s)$ is the 4th derivative of the image function. The solution of the above Euler-Lagrange equation is obtained through the gradient descent method and the snake converges to a minimum.

2.3.2 CFD Methods

CFD methods have been applied to bio-fluid dynamics problem as it has been seen to be able to describe the flow dynamics of blood in terms of the Navier Stokes (N-S) equations. To discern the flow dynamics in the cardiovascular system, blood is assumed to be an incompressible, Newtonian fluid [54], ignoring the effect of blood vessels that make up about 40% of the fluid. Strictly speaking, blood is a two-phase fluid whose bulk properties are contributed to by both the red blood cells (RBC) and water. The generalized Navier-Stokes equations are as given in eq. (2.7)

$$\frac{\partial u_i}{\partial x_i} = 0 \quad (2.6)$$

$$\rho \left(\frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} \right) = - \frac{\partial P}{\partial x_j} \delta_{ij} + \mu \frac{\partial^2 u_i}{\partial x_j \partial x_j} + f_i \quad (2.7)$$

where u is the velocity, P is the pressure and ρ is the density of the fluid and f is the body force acting on the fluid. The N-S equations are discretized using two methods: the finite volume method (FVM) and the finite element method (FEM). FVM is generally seen to approximate the solution accurately to a large extent. But FVM may not be the best way to understand the deformation of a tissue due to blood flow. FEM has been used to solve fluid mechanics based problems [55,56] and specifically for AAA simulations as well [57,58]. It has the capability to incorporate the displacement of the biological tissue in a medical simulation problem more accurately than a FVM-based solver where the fluid becomes the most important component in the solution unlike in FEM where the solid displacement is more important.

The most accurate solutions to a biomechanics problem would incorporate the material properties of the blood vessel/tissue in question. This would allow a fluid-structure interaction (FSI) model to be embedded in the resulting physics. As the blood vessel/tissue is normally not rigid, it is imperative that this aspect is accounted for in the computed solution. FSI methods [59,60] have been demonstrated to be effective in the description of flow physics in aneurysms. The coupling of the aneurysmal wall motion and blood flow is commonly made by using the Arbitrary Lagrangian Eulerian (ALE) method. The incompressible continuity and N-S equations in ALE form can be expressed as shown in eq. (2.9).

$$\nabla \cdot \mathbf{u} = 0 \quad (2.8)$$

$$\rho_f \left(\frac{\partial \mathbf{u}}{\partial t} + ((\mathbf{u} - \mathbf{u}_g) \cdot \nabla) \mathbf{u} \right) = -\nabla \mathbf{p} + \mu \nabla^2 \mathbf{u} \quad (2.9)$$

where ρ_f , $\mathbf{p}$, $\mathbf{u}$, and $\mathbf{u}_g$ are the fluid density, the pressure, the fluid velocity, and the moving coordinate velocity, respectively. In ALE formulation, the term $(\mathbf{u} - \mathbf{u}_g)$, which is the relative velocity of the fluid with respect to the moving coordinate velocity, is added to the conventional Navier- Stokes equation to account for the movement of the grid [61]. From a computational point of view, the moving interface between the fluid and the rigid body has to be incorporated in the model. The ALE method has been successfully applied to such moving boundary problems, which arise in free surface problems and fluid-structure interaction problems. The ALE method has been employed here because

- (i) it is convenient to describe the fluid motion on the moving interface by the Lagrangian description in order to treat the compatibility conditions and the equilibrium conditions between the fluid and the rigid body;
- (ii) it is apparently impossible to employ the Lagrangian description for the entire fluid domain because of severe mesh distortion due to vortex shedding or flows through outer boundaries.

Therefore, it is natural to employ the mixed viewpoint of the Lagrangian and Eulerian descriptions [62]. Whilst the above method has been used for a rigid tissue, the ALE has been extended to the FSI problem as well [63]. Hirt et al. [64] provide further details of the ALE method wherein they describe the applications of ALE to problems involving different flow speeds using the finite element method.

2.3.3 Machine Learning Methods

Significant experience over many years in the management of AAA amongst hospitals and clinicians has led to the availability of a large volume of data on patients who have undergone treatment for the condition. Statistical techniques such as univariate and multivariate logistic regression analyses have been successfully applied to risk prediction in clinical medicine. A commonly used instrument is the use of a prognostic score derived from logistic regression to classify a patient into a potential risk category [65]. This suggests that, using these techniques, an estimate of the associations between the various risk factors that cause rupture in an AAA can be encoded. Many techniques have been used for data mining in medical and biomedical studies. A popular data mining technique is decision tree induction. The dataset is recursively partitioned into discrete subcategories. These subcategories are based on the value of an attribute in the dataset. The criteria for selecting these attributes in the dataset are based on its predictability within a certain subcategory. As a result of this, the final outcome is a set of series of categories based on values of the attributes. Each of these series generates a classification value. There are many algorithms developed for decision tree induction. Some clinical examples that apply this approach are diagnosis of central nervous system disorders [66], post-traumatic acute lung injury prediction [67], and acute cardiac ischemia [68]. Some parameters may affect the ability to predict rupture risk in an untreated aneurysm. These parameters can be used in a model that learns from retrospective data and can be used in a prospective tool for patients. They are listed here.

- (1) Diameter of lumen.
- (2) Length of aneurysm.

- (3) Aneurysm neck angle and length.
- (4) Wall thickness.
- (5) Presence and volume of intraluminal thrombus (ILT).
- (6) Wall shear stress (WSS).
- (7) Calcification of the aortic wall and calcium volume and percentage of aneurysm sac volume.
- (8) Gender.
- (9) Age of patient.
- (10) Patient history (smoking, diabetes, specific occupations, and family history of aneurysms).
- (11) CT scan slice thickness.
- (12) Aortic and iliac vessel tortuosity.
- (13) Imaging system used for diagnosis.
- (14) AAA ILT index.
- (15) Patient ethnicity.
- (16) Body mass index (BMI)
- (17) AAA surface area.
- (18) Aneurysm neck length/height and supra- and infrarenal neck angles.

While these may be some of the input variables for a machine learning model, the output is the risk of rupture that can be obtained as a result of training the model on such retrospectively gathered data. The said model will learn about the parameters that play a part in the rupture or non-rupture of a patient-specific AAA. A great amount of classified data, that is, a suitable spread of ruptured and non-ruptured retrospective cases, will allow the model to gauge the parameters that are the most important factors among many that lead to rupture in an AAA case. This model can then be applied prospectively where the model, having learnt from a large amount of data in the past, can make a prediction of rupture risk in the patient. When comparing different classifiers [69,70], the key issues to address in such a model are (1) predictive accuracy; (2) interpretability of the classification models by the domain expert; (3) handling of missing data and noise; (4) ability to work with different types of attributes (categorical, ordinal, and continuous); (5) reduction of attributes needed to derive the conclusion; (6) computational cost for both induction and use of the classification models; (7) ability to explain the clinical decisions made when models are used in decision making; (8) ability to perform well with hitherto unseen (prospective) cases.

2.4 Computational Studies

2.4.1 Boundary Conditions

Unsteady boundary conditions of velocity and pressure are generally obtained from phase contrast MRI (PC-MRI) methods. There is paucity of such studies and in most instances, the few waveforms that are available in literature are re-used by others thereby taking away the patient-specific nature of the problem being solved. Figure 2.3 shows such a sample waveform that has been used by Soudah et al. [71], which in itself has been

adapted from [72] . Flow in the aorta is pulsatile in nature. Hence, time varying waveforms of velocity and pressure are needed in order to accurately model the flow physics. The inlet flow velocity profile has two peaks, each visualizing the systolic and diastolic phases in a pulse. The outlet pressure shows only one peak in the pulse.

Several different outlet boundary conditions have been used in literature such as constant pressure [73,74] and flow specification at particular instances [75]. The boundary conditions for the velocity V are imposed as follows: (i) no-slip at the walls, (ii) uniform (plug) profile at the inlet, and (iii) zero-traction outflow at the exit. For pulsatile flow, the inflow mean velocity is time-dependent and the volume flow rate is oscillatory as suggested by Finol and Amon [76]. Although newly developed imaging methods, such as 4D MRI, have proved to be successful in measuring the flow, they still have limited spatial resolution (of the order of 2 mm), which restricts their applicability in calculating WSS parameters, and do not provide pressure information. Therefore, in the usage of Windkessel parameters based on patient-specific clinical data, the simulation takes into account the essential characteristics of the rest of the vasculature, which can be expected to improve the correlation between the simulation results and the true in vivo characteristics [77].

The Womersley number is a non-dimensional number that describes the ratio of pulsatile flow to viscous effects and is used extensively in computations related to bio-fluids. Womersley profiles generally regard only the centerline velocity of the inlet. They incorporate the Bessel functions to derive the velocity profile in the inlet. But, it is not accurate as the geometry of the artery is patient specific and affects the velocity values. The Womersley number is shown in eq. (2.10) [78].

$$\alpha = r \left(\frac{\omega}{\nu} \right)^{\frac{1}{2}} \quad (2.10)$$

where, α is the Womersley number, r is the radius of the artery, ω is the angular frequency of flow oscillation and ν the dynamic viscosity of the fluid.

Figure 2.3 Inlet velocity and pressure outlet waveforms [71]

Flow boundary conditions are critical to computing the flow solution in AAA. Hardman et al. [78] surmise that the Womersley number-based studies are inaccurate in computing solutions of flow fields and hence, an axial velocity component is needed. They suggest that it is sufficient for the axial velocity component to be used in the simulation, and radial components are needed only when it is needed to understand the secondary flow components in the flow, such as particle tracking. Multiple outlet systems are however, more complex and need better description of boundary conditions. Though this seldom occurs in the case of AAA, scalability, simplicity and accuracy is paramount as there could be multiple outlets in an arterial network [79].

2.4.2 Material Properties

There are other boundary conditions to be considered in the simulation of AAA fluid mechanics. These are the material properties of the arterial wall. This requires the arterial wall material to be properly modeled, an issue which is complex given that the wall stiffness increases when lumen diameter increases and calcification and medial sclerosis occur with aging and in disease. Furthermore, the aneurysmal wall has been found to be mechanically anisotropic, a factor to be taken into account if a rational estimate of the wall stresses is to be made [80]. Generally, an isotropic properties assumption is made of the arterial wall when carrying out an analysis of the AAA. Whilst this may be a reasonable assumption in most cases, a more accurate constitutive model is needed to describe the properties of the wall. Constitutive models are obtained from experimental tests of actual tissue specimens. A uniaxial test specimen is generally made from two rectangular strips of tissue that has been cut out from the arterial layer. The flat arterial tissue layer is assumed to be a fiber-reinforced material with relatively stiff collagenous fibers embedded in a homogeneous isotropic (soft) ground matrix [81].

Most elastic tissues studies in literature have used the strain energy function approach. But arterial tissue exhibits highly non-linear, non-isotropic, and possibly hyper-elastic properties, and a computational model needs to incorporate all these properties as the elastic modulus is inadequate. Also, the assumption of strain energy functions holds good only for single continuous medium tissues. This is not the case with arterial tissue. Since the mechanical properties of soft biological tissues depend greatly on their microstructure, proposing a reliable mechanical model for these tissues, including the arterial wall, depends on the level of microstructure integration attained in the constitutive model [82].

Taghizadeh et al. [82] proposed a new bi-axial constitutive model based on microstructural properties as opposed to the simple uniaxial tests carried out by [83] and [84]. The uniaxial tests only look at a single layer of the tissue that is in contact with the blood flow. The bi-axial tests however consider a second layer as well, which is important in assessing the response of the arterial wall in a fluid structure interaction scenario. In general, whilst using the simplified boundary conditions is computationally inexpensive and is accurate in most cases, incorporation of the nonlinear properties when custom codes are written make the solution more realistic.

Wall thickness is another aspect that is central to the response of the blood vessel to flow. Since aneurysmal rupture occurs at a specific site of the aortic lumen, the properties of the wall affect the computed solution. In general, the aortic wall thickness in computational methods is assumed to be in the range of 1.5-2 mm. While this may be largely accurate for most simulations, it has been acknowledged as a major limitation in the completeness of the predictive solution [85]. Some previous measurements of thickness are listed in Table 2.1 [86]. The thickness from Thubrikar et al. [87] has been extensively used in literature as the value that accounts for the posterior and anterior sections of the AAA. Most ruptures are seen to occur in the proximal posterior part of the AAA. Hence, this value is assumed to accurately describe the wall thickness. Raut et al., [86] suggest that the wall thickness as a constant value is not accurate and described a novel method that incorporated the regionally varying wall thickness, especially in the area of rupture. A comparison of uniform thickness, patient-specific uniform thickness and the varying thickness was carried out in 28 samples. This showed a statistically significant difference in FE analysis with principal stresses and strains and strain energy density being the

output parameters. As stated previously, rupture does not occur at the region of the aortic wall with maximum lumen diameter. This method can thus be used to obtain the wall thickness that reflects the true thickness at the site of rupture.

Table 2.1 Wall thickness measurements as reported in literature [86]

Author	Reported Thickness(mm)	Method of measurement	Remarks
Di Martino et al., 2006 [88]	Elective AAA 2.5±0.1 Ruptured AAA 3.6±0.3 mean 2.9	Optical (laser)	Thickness is inversely correlated with local strength; only anterior wall tested; use of laser measurement eliminates compression due to caliper
Raghavan et al., 2006 [16]	Min 0.23 Max 4.26 Median 1.48	Caliper	No discernible difference in thickness for small and large aneurysm; thickness slightly lower in posterior and right walls; thickness low in ruptured aneurysm near site of rupture
Thubrikar et al., 2001 [87]	Posterior 2.73±0.46 Lateral 2.52±0.67 Anterior 2.09±0.51	Customized micrometer with resistivity meter	Thickness decreases from posterior to lateral to anterior walls; accuracy 0.05mm

2.4.3 Flow Physics

The physics of blood flow through the AAA is perhaps the most important aspect of the analysis of rupture risk. Data about material properties from experimental studies and boundary conditions from advanced MRI and CT technology have led to CFD methods being used to understand the flow fields in AAA. Accurate hemodynamic simulations can lead to better treatment planning and improved stent design for the diseased aorta. The interaction between blood flow and the arterial wall is a challenging problem. The studies reported below have used the rigid wall assumption to overcome the computational expense of the fluid structure interaction solution.

Blood flow in the normal aorta can be ascribed to be laminar, similar to that in a pipe. Flow development is also well understood. In contrast to the normal aorta however, the flow in an aneurysmal segment is highly disturbed and non-laminar. Specifically, in the aortic segment immediately beyond the aneurysm neck, flow separation involving regions of high streaming velocities and high shear stresses is observed. At the expanded aneurysmal segment, average flow velocity and wall shear stress are much lower compared to that in the normal aorta [89]. Early studies used steady flow computations as the norm since pulsatile boundary conditions were hard to obtain. Taylor and Yamaguchi [90] were amongst the earliest to compare the steady and unsteady flows in aneurysms. A set of symmetric vortices that were different in behavior were observed both in the steady flow and the unsteady flow conditions. Symmetric vortices induce high pressure at certain locations in the lumen and were seen later to be possible sites of rupture of the aneurysm. Blood flow induces wall shear stress (WSS) in the aneurysm. This is the main parameter that determines the risk of rupture in an AAA lumen. WSS is related to the properties of

the blood flowing through the lumen. Apart from blood pressure, WSS in AAA is also influenced by the aneurysm diameter, shape, wall thickness, wall mechanical properties and the presence of intra-luminal thrombus (ILT) [91].

ILT is an important component of AAA that is difficult to incorporate in to any computational model. Most aneurysms have ILT within their lumen. Stenbaek et al., [92] argued that the development of ILT maybe a better predictor than the maximum diameter of the AAA as a rupture risk parameter. But DiMartino and Vorp [93] postulated that ILT might protect the AAA wall from the pressure applied by blood flow. A finite element study by Li et al. [94] on the effect of ILT on wall shear stress showed that the non ILT models had higher stress development than the ILT models. This is in keeping with Laplace's law, which is often applied in fluid mechanics studies on AAA. It must however be emphasized here that Laplace's law was originally used to describe bursting stresses in cylindrical shells and to apply it in this situation may not be wholly accurate.

While most methods have assumed laminar flow regimes in the aneurysm, there is a possibility that turbulent flow can also develop due to the presence of ILTs or wall calcification. Turbulent flow is common in the heart and the upper airway unlike the smaller diameter aorta where a discernible turbulent regime of flow is not seen. However, turbulence may well be a factor in very large aneurysms where there is the possibility for a turbulent mixing phenomenon to occur. In a study using a rigid wall Newtonian fluid approach [95], and considering turbulent conditions carried out on 3 symmetric aneurysm geometries with different diameters, the smallest aneurysm did not show transition while the biggest diameter aneurysm shows flow separation and turbulent vortices. It was seen that the vortex that impinges on the distal wall of the AAA generates secondary vortices,

which then break up further. In the small aneurysm where flow remained laminar throughout the cycle, the high stress region was only seen in a relatively thin layer attached to the aortic wall. The large aneurysm, however, was seen to have islands of high stress in the center of the lumen due to the impact of turbulence transition. This study on the impact of turbulence transition on WSS concluded that with the onset of flow turbulence as seen in the large aneurysm models, the surface stress appeared to point to all directions and no dominant direction could be identified. The temporal and spatial gradient of WSS is significantly larger than the laminar flow (small aneurysm) situation. It is however, important to consider the effect of turbulence as well which is seen to occur in larger aneurysms, especially above 5 cm. Given the inherent nature of flow, the transition to turbulence can occur even at resting conditions in large aneurysms.

2.4.4 Fluid-structure interaction (FSI)

In computed solutions where the aneurysmal wall is assumed to be rigid, pressure values do not vary in time inside the lumen as the wall and blood flow are not coupled in the solution. But in reality, the wall is not rigid and interacts with the flow during every pulse. The nature of this fluid structure interaction is bi-directional i.e. the wall responds to blood flow pressure, shown by its displacement and this in-turn affects the flow through the aneurysm. Strongly coupled FSI methods most accurately describe the flow physics occurring inside the aneurysm and in theory, can precisely predict the site of rupture with the wall shear stress values reflecting the most realistic conditions.

DiMartino et al. [96] first carried out an FSI calculation on a realistic geometry obtained from segmentation of CT images. They were able to establish local stresses on the wall

due to the structural and blood flow conditions. An ALE based FSI numerical method was used in commercial software Fidap to obtain the solution (Figure 2.4). The motion of the wall was not homogenous as would be seen in a rigid wall calculation. The asymmetry of the aneurysm also seemed to play a part in the development of wall stresses. They found that a larger area of maximum velocity corresponds to the systolic peak and that a flow deceleration is always discernible at the site where the aneurysm is larger, suggesting a higher pressure at these sites. This along with a weakening of the wall itself may be the genesis of continued aneurysm enlargement.

Figure 2.4. Velocity and Pressure distribution along with wall displacement in a FSI calculation [96]

These studies have shown that a FSI method would be most accurate in predicting wall motion in the aneurysm as against only a FEM or a fluid dynamics model. This was further demonstrated by Scotti et al., [97] who compared the FEM with a FSI method on 10 aneurysm models. It was observed that applying a realistic fluid pressure distribution to the arterial wall resulted in wall stresses that were 20% higher than if only peak systolic pressures were considered. This was in direct correlation with previous results that also

showed a 21% increase in wall shear stresses when FSI methods were used [98, 99]. A limitation of this study was that this was an idealized model with asymmetry built into the geometry.

Using FSI methods, the various geometrical changes and material characteristics in patient-specific aneurysms can be accounted for. Scotti et al., [97] compared aneurysm geometries having uniform wall thickness and variable wall thickness and also investigated the effect of 5 levels of asymmetry in the model. They observed that varying wall thickness increases the von Mises stress by up to 4 times as compared to when it is uniform. For asymmetrical variations too, the changing thickness caused stresses to increase. This reinforces the fact that accurate thickness and FSI considerations will make the computed solution more accurate.

Li and Kleinstreuer [100] reinforced this by comparing different asymmetrical aneurysm geometries in a FSI solver. They concluded that assumption of symmetry leads to underestimation of wall shear stress. An iliac bifurcation angle also seems to have an effect. For iliac bifurcation angles, less than 90 degrees, the wall shear stress is in the range of 0.57 to 0.63 mPa. But as it goes beyond 90 degrees, the stress increases by about 8%. At aneurysm neck angles of 12 degrees or so, the region with the higher wall stress is at the asymmetric bulge with the maximal stress being at the distal point of the bulge. As the neck angle increases, the proximal stresses move away from the bulge but the maximum point of stress remains the same. They argue this is due to the fact that neck angles influence strong surface curvatures in the AAA neck leading to changes in the location of wall stress regions. A summary of the different studies using FSI methods are listed in Table 2.2.

2.5. Machine learning Studies

As described in the previous section, fluid structure interaction methods greatly increase accuracy of simulations of AAA [96, 99, 100], leading potentially to more accurate surgical planning for clinicians. But FSI computations can take several days to complete depending on the computational power available. In addition, carrying out these computations needs an expert in fluid dynamics and programming to interpret the simulation results for the clinician. Clinicians are often unable to obtain this kind of expertise or do not have the lead time to go through the detailed process to assess the prognosis of AAA in a particular patient. CFD is crucial in understanding the mechanics of aneurysm formation and rupture but it needs to be used in conjunction with faster methods to obtain a conclusion. This can be done using machine learning methods. Although experimental approaches such as flow visualization have been used earlier [101], it is hard replicate *in vivo* conditions during experiments.

Table 2.2. Comparison of parameters investigated using FSI methods

Reference	Method	Parameter	Remarks
DiMartino et al., 2001 [96]	FSI (ALE)	Max Pressure	First accurate calculation of FSI
Scotti et al., 2008 [99]	FSI	Wall shear stress	20% more WSS if FSI method is used
Scotti et al., 2005 [97]	FSI	Asymmetry and wall thickness	Varying wall thickness and asymmetry increases von Mises stress
Li and Kleinstreuer, 2007 [100]	FSI	Neck angle, asymmetry, bifurcation angle	Large neck angle leads to elevated von Mises stress, Lateral asymmetry has higher stress

A summary of the machine learning method has been described before in section 2.3.3. It uses a combination of statistical methods, probability and optimization methods to predict the direction of movement of a system. A ‘learning’ model is created with the available retrospective data. A large quantity of such retrospective data is available at hospitals and this is helpful in developing learning models that can make prospective predictions having “learnt” from retrospective data. There are numerous statistics based machine learning methods that can be used along with CFD simulations so that more accurate and faster conclusions can be drawn for clinicians [102].

Data mining is a popular method used to derive conclusions in hemodynamic simulations. Kolachalama et al. [103] proposed a data mining technique that accounted for the geometric variability in patients for predicting cardiovascular flows. A Bayesian network-based algorithm was used to understand the influence of key parameters through a sensitivity analysis. Although Monte Carlo methods are suitable for output statistical analysis, the Bayesian approach brings out the relationships between the parameters using a multivariate approach. They tested the method on the human carotid artery bifurcation. A range of automated geometries were created for steady state 3D flow analysis. After CFD analysis was carried out, the output maximum wall shear stress was approximated as a function of the geometric variables. The data from the runs was used as a training data set to build the Bayesian model. A probability plot of the maximum wall shear stress could then be generated.

Geometric parameters (especially diameter of the aneurysm) are critical in defining the risk of rupture and have undergone most investigation in the field of data mining. The variation of geometric parameters amongst patients gives an opportunity for models to be developed to predict the characteristics of disease progression. Martufi et al. [104] carried out a geometrical characterization of the wall thickness distribution in AAA. They were able to train a model to differentiate the wall thicknesses in ruptured and un-ruptured AAA. The thickness difference was seen to be 7.8% between ruptured and un-ruptured AAA. This could be an important parameter to determine the risk rupture and plan early intervention. This work has been extended by Shum et al. [105] who developed a model from 66 ruptured data sets and 10 non-ruptured data sets, their geometric indices and wall thickness variations. The results of this study showed that in addition to maximum diameter, sac length, sac height, volume, surface area, bulge height and ILT volume were all highly correlated with rupture status. It was also observed that parameters such as ILT volume particularly was also highly correlated with rupture in addition to the size of the AAA. In this study, the overall classification accuracy was 86.6%. It used a decision tree algorithm which is one of the possible machine learning methods that can be used for large data sets requiring a decision output.

2.5 AAA in the Asian Population

2.5.1 Incidence and Morphology

AAA is considered in general to be more prevalent among the Caucasian populations. Li et al. [106] conducted a meta-analysis of the prevalence of AAA in the general population comparing patients from different parts of the world. They concluded that in the cohort of samples they analyzed, the Asian population has the least incidence of AAA at 0.5% in a

56-patient sample. It was seen that Australia (6.7%) and Europe (2.5%) have higher incidence. It has been reported that the stent grafts used for the Endo Vascular Aneurysm Repair (EVAR) process are unsuitable for Asian populations as against the Caucasian ones. A stent-graft is difficult to place if the proximal neck of the aneurysm is shorter than 1.5cm. In addition, the angle between the neck of the aneurysm and the sagittal plane of the aorta must not be less than 60 degrees, the iliac arteries must not be tortuous, and their diameter must be at least 8 mm. All available commercial stents are designed for the Caucasian aortal dimensions and hence, clinicians in Asia have a problem in adjusting them for the Asian aorta.

In a clinical investigation to compare three commercially available stents, Cheng et al. [107] carried out a spiral CT and angiographic assessment of 65 Chinese (58 men, mean age 74 years, range 50-87) who underwent EVAR. The morphological parameters were compared with European and American patients. It was found that the common iliac arteries (CIA) were significantly shorter in Asians, particularly on the right-hand side. The right CIA had a mean length of 29.9 mm while the left had a 34.2 mm length compared to more than 50 mm in the Caucasian samples. The distance between the lowest renal artery and the CIA bifurcation averaged 20 mm shorter in Asians: 148 mm for the right side and 153 mm for the left. The CIAs were also wider, averaging 20.2 mm for the right and 17.9 mm for the left. This was reinforced in an investigation carried out by Mladenovic et al. [108] who investigated the difference in Asian and European patients' histories along with their aneurismal morphological features to aid in the clinical use of endovascular stent grafts. They concluded that the European patient group had longer CIAs as before with 47.41 mm in Asians and 59.68 mm in Europeans. The AAA mean

neck length in Asians was seen at 22.73 mm and 38.72 mm in Europeans. The mean AAA length was not statistically significant though with 104.97 mm in Asians against 108.24 mm in Europeans. These differences in morphology can cause changes in the flow physics in the diseased lumen. A biomechanical analysis of the Asian aorta would be therefore useful in understanding the changes in progression of the disease in the patients and also aid the design of a stent graft that might be specifically designed for Asian morphology.

2.6 Summary

From the survey of literature, it can be seen that biomechanical factors affect rupture risk in AAA. Also, morphological factors in the Asian aorta could be a factor in the progression of disease in this cohort. An analysis of the effect of morphology incorporated into a computational model would bring out its effect on rupture risk. Computational analysis and experiments have been carried out by several research groups to investigate biomechanical parameters that affect the propagation of AAA under various conditions. The FSI method has been seen to be more accurate in representing the ongoing process in the diseased aorta because it incorporates the effect of arterial wall interactions with the blood flow. Machine learning methods offer a new dimension in understanding the effect of parameters that cannot be normally incorporated in CFD/FSI simulations. The availability of retrospective data brings out the possibility of developing a model that can learn from the past history of patients and make a prediction of the diagnosis for a patient based on the prevailing factors.

Hence, while one aspect of any new investigation would incorporate the morphological differences in the Asian AAA as against the Caucasian AAA into the biomechanical analysis and investigate their effect of assessment of rupture risk, a machine learning

model in parallel can reinforce the biomechanical aspects by incorporating patient history and geometric factors in the analysis. These two approaches in parallel would form part of a diagnostic tool that would aid clinicians in assessment of rupture risk in the Asian AAA patient.

CHAPTER 3

THE ROLE OF MORPHOLOGY IN ASIAN AND CAUCASIAN ABDOMINAL AORTIC ANEURYSM RUPTURE RISK ASSESSMENT

3.1 Introduction

Abdominal Aortic Aneurysms (AAA) are a type of vascular condition where the infra renal aorta dilates to more than two times its normal diameter. This condition is seen mainly in patients whose age is greater than 55 years. The condition is largely asymptomatic and hence, is hard to diagnose [1]. The dilation increases progressively over time and non-intervention in this process leads to rupture of the AAA. Rupture of the aneurysm can be fatal to the patient. When diagnosed with the AAA, typical clinical procedure involves measuring the maximum transverse diameter using imaging modalities such as CT, MRI or ultrasound. The clinical metric for surgical intervention in AAA is the maximum transverse diameter (DAAA) value of 5.5 cm [2]. The structural integrity of the abdominal aorta is restored through open surgery or by placing a stent graft in the region of the diseased aorta. The procedure to place the stent graft is known as the Endovascular Aneurysm Repair (EVAR) which is the present clinical standard for AAAs [3].

Typically, the use of DAAA as a metric has seen success in most diagnoses. But smaller aneurysms of less than 5.5 cm DAAA have ruptured and about 60% of aneurysms having a diameter of more than 5 cm never ruptured [4]. There have been other clinical metrics that have been suggested in addition to the maximum diameter as a metric for assessment

of AAA rupture risk [5]. Biomechanical analysis estimates patient specific peak wall stresses and spatially distributed wall stresses in the AAA. These stresses have been seen to be highly correlated to AAA rupture risk [6]. Gasser et al, 2014 and others [7,8] have developed a rupture risk index that is based on the calculation of peak wall stress. Peak wall stress is closely correlated with diameter of the AAA. [9,10]. Geometric factors such as AAA volume [11,12], rate of expansion [13], intraluminal thrombus volume [14] and asymmetry and tortuosity [15] have been seen to be significant indicators of AAA rupture risk. A comprehensive review of geometric factors has been carried out by Raut et al [16]. They conclude that the local curvatures in the AAAs are the most significant factors in the prediction of wall stress which in turn are indicators of rupture risk. Any clinical diagnostic tool that aids the medical practitioner to assess rupture risk at the bedside needs to incorporate the geometric attributes of the patient specific AAA. This would be in addition to the biomechanical estimation that will provide a validation of the analysis. The addition of geometric factors improves the classification accuracy as seen by Tang et al [17]. Based on the clinical metrics, they performed univariate and multivariate logistic regression to improve the modeling accuracy by adding geometric parameters such as bulge location and mean averaged area over just using the maximum diameter ($D_{\max}$) and gender.

Chauhan et al [18] investigated the role of geometry in the assessment of emergently repaired AAA. They generated, through geometric quantification, 52 shape and size geometric indices and then correlated them with the biomechanical stresses developed in 75 patient models. Subsequently, Pearson's correlation coefficient analysis brought out 12 indices to be highly correlated to peak wall stresses developed in these patients. Finally,

through stepwise regression, they were able to obtain the four most significant indices that could predict wall stress; diameter, aneurysm sac length, average wall thickness at the maximum diameter cross section, and the median of the wall thickness variance. Another study was carried out by Muluk et al. [19] where, the feasibility of using geometric surrogates was investigated using 180 patients (90 ruptured and 90 unruptured). A univariate linear regression was carried out which identified 40 correlates of rupture. Subsequent regression analysis generated 15 features that classified 98% of the cases investigated correctly. Geometric attributes can be used as surrogates to gauge the biomechanical stresses in AAA. A combination of geometric attributes can be quantified as a model to predict rupture risk in AAA. These parameters can be estimated from point of care imaging modalities like CT or MRI and a relatively swift prognosis can be made through correlation with the biomechanical stresses.

3.1.1 Morphology in the Asian Population

The geometry of the Asian aorta is suspected to be different from the Caucasian aorta in terms of neck length, common iliac artery diameter and the distance between the lowest renal artery and the iliac bifurcation. To this end, in a clinical investigation to compare 3 commercially available stents, Cheng et al. [20] carried out an assessment of 65 Chinese patients who underwent EVAR in comparison with European and American patients. It was found that the common iliac arteries (CIA) were significantly shorter in Asians, particularly the right common iliac artery. This outcome was corroborated by Mladenovic et al. [21] who found the CIAs to be shorter, along with the mean neck length of Asian AAA being significantly lower than Europeans (22.73 mm vs. 38.72 mm). These differences have caused difficulties with the graft delivery during EVAR and subsequent

follow up of Asian AAA patients. The clinical significance of these differences can be brought out through a comparison of the geometric parameters in each cohort along with the mechanical stresses developed in these aneurysms.

Therefore, the objective of this work is to analyze, in a cohort of 19 Asian and 19 Caucasian AAA patients, the wall stress and geometric indices that characterize each group and quantify any differences that may exist. Additionally, the geometrical attributes that are significantly correlated to the biomechanical stresses in each cohort will also be extracted to identify the geometric surrogates that are able to quantify the wall stresses in each patient group.

3.2 Methods

3.2.1 Patient Selection

Anonymized abdominal contrast-enhanced computed tomography (CT) scans were obtained from Allegheny General Hospital, in Pittsburgh and the Tan Tock Seng Hospital, in Singapore. Existing patient medical records were obtained retrospectively for 38 AAA, inclusive of 19 Asian and 19 Caucasian subjects, using a maximum diameter matching approach.

3.2.2 3D Image reconstruction

The CT scans were stored in form of standard Digital Imaging and Communications in Medicine (DICOM) images. They were processed with an in-house MATLAB (Mathworks Inc., Natick, MA) supported geometric quantification code called AAASc (v1.0.3, The University of Texas at San Antonio, San Antonio, TX). Based on the contrast gradient between the AAA lumen and surrounding tissue, the lumen, the inner wall and the outer wall boundaries of the AAA can be identified. The lumen can be segmented

automatically by the user selecting a point near the center of the lumen and the algorithm will segment the lumen for all images. If a reasonable automatic segmentation cannot be found, the user has the option to segment the lumen manually. The outer wall can also be segmented either manually or automatically. The manual approach takes more time to perform and yields more desirable contours in comparison to the automatic approach. The inner wall can only be segmented after the lumen and the outer wall segmentation are complete and works by training a neural network. The user will choose inner wall points and non- inner wall points to train the neural network for one image. If the yielded result is a good fit, the inner wall contours for the rest of the images will be done automatically. Figure 3.1 illustrates an original abdominal CT image and its corresponding segmentation showing the three contours of interest.

Figure 3.1 An abdominal CT image: (A) original, contrast-enhanced image and (B) segmented image with the lumen, inner wall and outer wall contours.

AAAVasc generates binary masks from the segmented images. A volume mesh is generated from the binary masks using the MATLAB code AAAmesh. Two volume meshes were generated for each AAA: one with uniform and one with non-uniform wall thickness. The uniform wall meshes were created with the assumption that the AAA wall thickness was 1.5 mm. The non-uniform wall meshes were generated from the patient-specific wall thickness distribution obtained during image segmentation. All meshes were created in NASTRAN formatted files and ranged in size from 500,000 to 1 million quadratic hexahedral elements.

3.2.3 Finite Element Analysis

Finite element analysis (FEA) simulations were conducted for each AAA to obtain biomechanical parameters. The previously generated NASTRAN files were imported into the finite element solver Adina (ADINA R&D, Inc., Watertown, MA) to perform FEA simulations. An intraluminal pressure of 120 mmHg was applied to all inner wall nodes in 24 time steps. A Mooney-Rivlin constitutive model was used to characterize the AAA wall material properties with the following constants obtained from uniaxial tensile testing of AAA tissue specimens: $c1=17.4 \text{ N/cm}^2$ and $c2=188.1 \text{ N/cm}^2$ [22]. The biomechanical parameters were obtained as a result of the converged FEA simulations using Ensight (CEI, Inc., Apex, NC) to post-process the simulation files. Three biomechanical parameters were computed, namely the maximum of the first principal stress (PWS), the spatially averaged wall stress (AWS), and the 99th percentile wall stress (99th-WS). Figure 3.2 illustrates the workflow from clinical image to AAA computer model.

3.2.4 Geometric Quantification

54 geometric indices were calculated for each of the 38 AAA using several MATLAB scripts [23,24]. These indices consist of eleven 1-D size indices, nine 2-D shape indices, five thrombus-related indices, four 3-D size indices, two 3-D shape indices, thirteen wall thickness-related indices, and ten surface curvature-based indices. The complete mathematical formulation of these geometry metrics can be found in Appendix B.

The biquintic Hermite finite element method (BQFE) was used to evaluate the curvature-based indices, as described in [24]. This method utilizes a high order interpolation scheme to estimate the global curvature indices derived from local curvature distributions. BQFE discretizes the aneurysm outer wall into 12 elements as opposed to the traditional method of biquadratic surface patching (BSP). Surfaces are fit to each of the elements, from which the local principal curvatures (k_1 and k_2) are computed using Eqs. (3.1) and (3.2),

$$k_1 = a + c + \sqrt{(a - c)^2 + 4b^2} \quad (3.1)$$

$$k_2 = a + c - \sqrt{(a - c)^2 + 4b^2}, \quad (3.2)$$

where a , b , and c are best-fit constants determined for each surface node. The ten global curvature indices, as described in Appendix B, are then derived and defined for each AAA model: summation of Gaussian and Mean curvatures (KG , KM), the area-averaged Gaussian, Mean, first principal and second principal curvatures (GAA , MLN , $K1AA$, $K2AA$), and the L2-norm of the above-mentioned curvatures (GLN , MLN , $K1LN$, $K2LN$).

3.2.5 Statistical Analysis

Fifty-four geometric indices and three biomechanical parameters were computed and recorded for each AAA model. A Chi-square feature selection algorithm was applied to the indices. The attributes were ranked in descending order of the value of info gain [23].

Independent t-tests with a significant level of α^c were performed to test the differences between the means of the three biomechanical stresses among the Asian and Caucasian groups.

With the goal of identifying the geometric indices that have substantial correlation with wall stress, a series of test of hypotheses was carried out. Specifically, for each $j = 1, \dots, m = 52$ the null hypothesis $H_0^{(j)}: \rho_j = 0$ was tested against the alternative hypothesis $H_a^{(j)}: \rho_j \neq 0$, where ρ_j is the population correlation coefficient between the j^{th} geometric index and wall stress. The test rejects $H_0^{(j)}$ for large values of $|T_j|$, where

$$T_j = \frac{r_j \sqrt{n-2}}{\sqrt{1-r_j^2}}, \text{ for which } n \text{ is the sample size} \quad (3.3)$$

And

$$r_j = \frac{\sum_{i=1}^n (x_{ij} - \bar{x}_j)(y_i - \bar{y})}{(\sum_{i=1}^n (x_{ij} - \bar{x}_j)^2 \cdot \sum_{i=1}^n (y_i - \bar{y})^2)^{1/2}} \quad (3.4)$$

is the sample (Pearson's) correlation coefficient between the j^{th} geometric index and wall stress; x_{ij} is the value of the j^{th} geometric index from the i^{th} patient; $\bar{x}_j = \frac{1}{n} \sum_{i=1}^n x_{ij}$; y_i is the spatially averaged wall stress for the i^{th} patient; and $\bar{y} = \frac{1}{n} \sum_{i=1}^n y_i$. The p-values of these tests are computed from the fact that, under $H_0^{(j)}$, T_j has an approximate t -distribution with $n - 2$ degrees of freedom. A geometric index may be identified as having a substantial correlation with wall stress if the p-value of its corresponding test is smaller than a given level of significance.

Figure 3.2 Work flow schematic in assessment of AAA rupture risk. AAASVASC, AAAMesh: In house MATLAB codes developed at the University of Texas at San Antonio, USA

The correlations were further probed by carrying out stepwise regression analyses for the short-listed indices that bore a significant correlation with the spatially averaged wall stress (SPA), to evaluate the predictability of the highly significant indices to yield wall stress. The stepwise regression analyses were performed to further eliminate the geometric indices based on correlative redundancy amongst the variables.

3.3 Results

3.3.1 Biomechanics

Biomechanical parameters were computed separately on both uniform and non-uniform wall thickness meshes for each AAA. FEA results for only the non-uniform wall thickness

meshes are presented herein. As shown in Table 3.1, the mean PWS for Caucasian AAA was 106.6 N/cm² compared to 95.9 N/cm² for the Asian AAA. The mean AWS was 24.1 N/cm² for the Caucasian AAA and 21.6 N/cm² for the Asian AAA. Similarly, the 99th-WS was 44.0 N/cm² for the Caucasian AAA and 41.7 N/cm² for the Asian AAA.

The independent t-tests, assuming non-equal variances and a significance level of $\alpha = 0.017$ resulted in no biomechanical parameters being significantly different between the two AAA groups, as shown in Table 3.2. The wall stress distributions for the Asian and Caucasian AAA groups with matched D_{max} are similar to each other. It is also noted that Asian AAA tend to be more tortuous and irregularly shaped than Caucasian AAA with similar D_{max} as seen from Figure 3.3.

Table 3.1 Mean and standard deviation of PWS, AWS and 99th-WS (all in N/cm²) for the non-uniform wall thickness FEA models of the Asian (A) and Caucasian (C) AAA (Sample size: 19 patients each from C and A)

Biomechanical Parameter	Group	Mean	Std. Deviation	Std. Error of the Mean
PWS	C	106.6	50.5	11.6
	A	95.9	31.9	7.3
AWS	C	24.1	8.4	1.9
	A	21.6	7.9	1.8
99 th - WS	C	44.0	11.6	2.7
	A	41.7	15.4	3.5

3.3.2 Geometric Quantification

The range of maximum diameters (D_{max}) for the patient cohort was 24 to 74 mm. The means and standard deviations of all 54 geometric indices are described in Appendix C. The two AAA groups were diameter matched to each other.

Table 3.2 Outcome of t-tests on the comparison of the means of the biomechanical parameters (all in N/cm²) for the Asian (A) and Caucasian (C) AAA

Biomechanical Parameter	t	p-value	Mean Difference	Std. Error Difference	95% CI of the difference	
					Lower	Upper
PWS	0.7780	0.4426	10.7	13.7	-17.3	38.6
AWS	0.9419	0.3526	2.5	2.6	-2.9	7.9
99 th - WS	0.5250	0.6030	2.3	4.4	-6.7	11.3

Figure 3.3 Spatial distribution of first principal stress in an (a) Asian and (b) Caucasian AAA (N/cm²).

Application of the algorithm resulted in 18 most significant attributes out of the 57 indices for the combined Asian and Caucasian cohort. The list of significant features in descending order of info gain is presented in Table 3.3.

Table 3.3 Significant attributes in the full dataset based on Info Gain Attribute selection

Attribute	Info Gain value
D _{max} (mm)	1.00
Proximal neck diameter (mm)	1.00
K2AA	0.849
GLN	0.849
MLN	0.749
Distal neck diameter (mm)	0.712
KG	0.667
K2LN	0.667
KM	0.667
K1AA	0.606
K1LN	0.596
Maximum thickness variance	0.378
Maximum thickness (mm)	0.378
Bulge location	0.378
Tortuosity	0.377
Bulge Height (mm)	0.350
Minimum Compactness	0.290
Location of Maximum Thrombus thickness	0.261

The info gain evaluates the significance of the attribute with respect to the target class.

The attributes that contribute more information in the dataset have a higher info gain value

(also known as entropy). The lower info gain score attributes can be removed from the analysis. The range of the info gain is from 0 to 1. To identify the most significant geometric indices that are highly correlated to the biomechanical stresses, a Pearson's coefficient hypothesis test was carried out. Table 3.4 lists the highly correlated indices to the three biomechanical stresses in each of the Asian and Caucasian cohorts.

Table 3.4 Highly correlated geometric indices with SPA, 99-WS, and PWS for Asian and Caucasian Cohorts

Biomechanical Parameters	Asian			Caucasian		
	Geometric Indices	r-value	p-values	Geometric Indices	r-value	p-values
99th Percentile (Dynes per sq.cm)	Maximum Diameter	-	-	Maximum Diameter	0.47	< 0.05
	Distal Neck Diameter	-	-	Distal Neck Diameter	0.49	< 0.05
	Maximum Thickness	-0.49	< 0.05	Maximum Thickness	-	-
	Variance	-	-	Variance	-	-
	Tortuosity	-0.59	< 0.05	Tortuosity	-	-
Mean SPA (Dynes per sq.cm)	Maximum Diameter	0.66	< 0.05	Maximum Diameter	-	-
	Proximal Neck Diameter	0.48	< 0.05	Proximal Neck Diameter	-	-
	Distal Neck Diameter	-	-	Distal Neck Diameter	0.54	< 0.05
	MLN	0.64	< 0.05	MLN	-	-
	KM	0.52	< 0.05	KM	-	-
	K2LN	0.46	< 0.05	K2LN	-	-
MAX PSI (Dynes per sq.cm)	Maximum Diameter	0.67	< 0.05	Maximum Diameter	0.57	< 0.05
	KG	-	-	KG	-0.49	< 0.05
	K2LN	0.46	< 0.05	K2LN	-	-
	K1LN	-	-	K1LN	0.49	< 0.05
	Minimum Compactness	0.48	< 0.05	Minimum Compactness	-	-

For the 99th WS, the Asian cohort shows the maximum thickness variance and tortuosity to be significantly correlated among the five indices model, while it is the maximum diameter and the distal neck diameter that are significantly correlated in the Caucasian populations. For the spatially averaged stress, the Asian and Caucasian cohorts show five significant parameters in the six indices model; the maximum diameter, proximal neck diameter, MLN, KM and K2LN. The Caucasian population shows significant correlation for only the distal neck diameter. The peak wall stress (PWS) is correlated to maximum

diameter, K2LN and minimum compactness in the Asian population while it is maximum diameter, KG and K1LN for the Caucasian population. The coefficient of determination of the reduced attribute model can explain the variability of the biomechanical stresses. A plot of the actual spatially averaged wall stress and the estimated spatially averaged wall stress as a result of the reduced attribute model is generated to determine the accuracy of the reduced model for both cohorts as shown in Figs. 3.4 and 3.5. The coefficient of determination in the Asian cohort was 0.7287 while the value for the Caucasian cohort was 0.7474. Further, to ascertain the extent of predictability of biomechanical characteristics using the maximum diameter of the patients, an SPA vs maximum diameter plot was generated for both patient groups as shown in Figs. 3.6 and 3.7. It was seen that the maximum diameter can predict the spatially averaged peak wall stress only to an extent of 56.03% in Asian patients and 25.94% in Caucasian patients.

Fig 3.4 Representation of the actual SPA obtained from FEA vs the estimated SPA obtained from the regression model for the Asian cohort

Fig 3.5 Representation of the actual SPA obtained from FEA vs the estimated SPA obtained from the regression model for the Caucasian cohort

3.4 Discussion

This is the first known work on comparing the geometric and biomechanical characteristics of Asian and Caucasian AAA. An attempt was made to find a relationship between the geometric indices of the AAA and the biomechanical stresses that characterize a specific cohort of Asian and Caucasian patients. All the 38 patients (19 in each cohort) were unruptured AAAs taken one month prior to surgical intervention. The existence of such a relationship could suggest that the geometric indices can be used as effective surrogates in the assessment of rupture risk in each cohort as against the present finite element analysis (FEA) based approach. It would also bring out the morphological differences in the two cohorts that have been reported *a priori*.

For the Asian patient cohort, the largest SPA value was 38.89 N/cm² and the maximum diameter was 7.47 cm. Similarly, for the Caucasian cohort, it was 36.22 N/cm² and 7.39

cm. It is seen that the diameter is significantly higher than the clinical threshold of 5.5 cm and hence the AAA is subjected to high stresses. In the reduced parameter model of the Asian cohort, consisting of six indices, three of the indices are size related with the maximum diameter, and the proximal neck diameter being significantly correlated to the mean SPA. This model is significant also due to the reason that the proximal neck diameter has been seen to be one of the morphological parameters that differentiate the Asian and Caucasian patient groups. The second order curvature based indices, L2 norm of the mean curvature (MLN), L2 norm of the minor principal curvature (K2LN) and square root of the mean curvature (KM) are also significant in the reduced model. The wall surface curvature is a spatially distributed metric highly correlated with wall stress, in agreement with the work of Giannoglou et al. [25]. They had estimated that the mean centerline curvature and the maximum centerline curvature were highly correlated with the peak wall stress in a cohort of 39 patients. Lee et al. [24] reinforced this with an investigation of 205 patient image datasets; containing both elective and emergently repaired AAA, in which they brought out the 10 curvature based indices based on the bi quintile finite element method (BQFE). Further, a stepwise regression analysis reduced the model to three significant parameters for Asian patients and one significant parameter for the Caucasian group when correlated to the mean SPA. The maximum diameter (DAAA), proximal neck diameter, MLN, K2LN and KM were significant in the Asian cohort while it was only the distal neck diameter in the Caucasian cohort. Hence, we can conclude that the four indices are sufficient geometric surrogates (in addition to the maximum diameter) to estimate the state of the Asian AAA and make an informed assessment of the rupture risk.

To assess the reliability of the reduced regression model, the actual SPA is plotted as a function of the estimated SPA for both the Asian and Caucasian cohorts. The linear fit passes through the origin indicating that the regression model can be used to predict actual wall stress resulting from FEA simulations. The plots (Figs. 3.4 and Fig 3.5) show that the reduced geometrical surrogate models can predict 72.87% of the spatially averaged wall stress in the Asian cohort and 74.74% in the Caucasian cohort. To assess the predictability of wall stress by using only the maximum diameter, as is the clinical standard, a plot of mean SPA and maximum diameter was generated for both the patient groups as shown in Figs 3.6 and 3.7. From the figures, it can be inferred that the maximum diameter by itself predicts the spatially averaged wall stress to an accuracy of 56.74% in Asian patients and 25.94% in Caucasian patients. It can then be concluded that the five additional geometric indices (MLN, KM, K2LN, proximal neck diameter and distal neck diameter) result in improved accuracy of the prediction.

The biomechanical comparison resulted in Asian AAA having higher peak wall stresses for small maximum diameters. However, there were no statistical differences in PWS, AWS, or 99th-WS between the two groups when comparing them without size-matching. Hence, a larger cohort needs to be investigated to ascertain any significant differences in stress development in each patient group. The comparison between the Asian and Caucasian patient groups could have implications on the design of stent grafts that suit the Asian population as against the present one size fits all products that are available commercially.

Figure 3.6 Spatially averaged first principal stress (SPA) vs maximum diameter ($D_{\max}$) for the Asian population. Maximum diameter alone is able to predict the SPA with an accuracy of 56.03%

Figure 3.7 Spatially averaged first principal stress (SPA) vs maximum diameter ($D_{\max}$) for the Caucasian population. Maximum diameter alone is able to predict the SPA with an accuracy of 25.94%

3.5 Summary

In this work, a comparison of Asian and Caucasian AAA patient cohorts is made with the aim of establishing the geometric surrogates for predicting biomechanical characteristics and correspondingly, assessment of AAA rupture risk in each cohort. Initially, the biomechanical stresses are calculated from FEA simulations carried out on both the patient groups based on patient specific CT images that were reconstructed using image segmentation algorithms. 54 geometric indices were extracted for each patient using an in-house geometric quantification code. The biomechanical stresses between the two patient groups were not significantly different. A Chi square based feature selection algorithm was applied to reduce the 54 indices set to only the most significant attributes. Subsequently, the 18 reduced features were correlated with the biomechanical characteristics to generate a further reduced model of 5 features which can act as surrogates to predict the spatially averaged wall stress.

The analysis provides a geometric surrogate model that can be used to predict the biomechanical characteristics of each patient group, which in turn is a metric for assessment of AAA rupture risk.

CHAPTER 4

MACHINE LEARNING METHODS IN THE ASSESSMENT OF AAA

RUPTURE RISK BASED ON GEOMETRIC AND PATIENT

HISTORY FACTORS

4.1 Introduction

An Abdominal Aortic Aneurysm (AAA) is a dilation of the infra-renal segment of the aorta [1]. As a result of this condition, there is progressive weakening of the arterial wall which is a risk factor for the rupture of the aneurysm. However, the expansion of the aorta varies amongst individuals and not all AAA cases will result in a rupture. The U.K. Small Aneurysm Trial Participants [2] concluded that a cut-off diameter of about 5 – 5.5 cm should be used to recommend surgery for AAA patients. Emergency surgery of the AAA involves high risk and hence it would be useful if a prediction model can be used to assess the risk rupture of an aneurysm without using a one-size fits all approach such as maximum diameter.

Several risk factors and parameters affect the rupture of an AAA. Ruptured AAA seem to be less tortuous and have a larger cross-sectional diameter asymmetry [3], which is consistent with finite element studies showing that the highest wall stress is obtained in AAA with an asymmetric geometry [4,5]. A factor of significant importance in AAA rupture risk prediction is the non-uniformity of the wall thickness. Using a laser micrometer, Di Martino et al. measured the thickness of AAA wall specimens obtained from patients undergoing surgical repair [6]. A significant difference was found in wall thickness between ruptured (3.6 ± 0.3 mm) and electively repaired (2.5 ± 0.1 mm)

aneurysms, as well as an inverse correlation between wall thickness and local tissue strength. In an autopsy study, Raghavan et al. [7] analyzed the tissue properties of three unruptured and one ruptured AAA, revealing that all aneurysms had considerable regional variation in wall thickness and there was significant reduction in wall thickness near the rupture site. Patient-specific AAA have complex, tortuous, and asymmetric shapes with local changes in surface curvature [8], in addition to local changes in wall thickness. It is evident that an accurate characterization of the aneurysm shape and the variation of wall thickness need to be accounted for in the assessment of AAA rupture risk.

Several computational methods have been used to model the AAA mechanical environment, namely finite element modeling (FEM) and machine learning methods. However, FEM has its limitations as many factors cannot be implemented in a FE model, e.g. race and family history [9]. Machine learning methods are thought to be more efficient as they can be implemented with a large number of parameters over a large patient cohort, without the need for executing simulations with an FEM code. For example, using machine learning and data mining methods to develop models that learn from input data consisting of clinical and biomechanical parameters, the models would make predictions based on parameters chosen *a priori* that are known to affect AAA risk of rupture. A summary of machine learning methods used in the classification of AAA population groups is described elsewhere [10].

Machine learning methods have been used earlier to predict risk of rupture in AAAs as well as to estimate parameters such as wall shear stress, which has been seen to be one of the critical biomechanical factors that are strongly correlated to rupture risk. To find correlations between the wall shear stress (WSS), blood viscosity, density, velocity and

geometric parameters in AAA and carotid bifurcation models, Jordanski et al [11] tested three machine learning algorithms; multivariate linear regression, multilayer perceptron neural network and Gaussian conditional random fields. They were able to predict the temporal evolution of WSS in both the AAA and carotid bifurcation model with high accuracy. The values of WSS correlated in 8 of the 10 time steps of the cardiac cycle and the Gaussian conditional random field performed the best among the methods tested. This was an extension from their previous work on data mining methods to estimate the wall shear stress from a number of CFD runs that involves the geometric parameters as well. They had used a neural network model to estimate the systolic stress, achieving a reduction in time from 114 minutes for CFD to 0.1 minutes using data mining methods for 85 patients [12]. Soudah et al [13] also used artificial neural networks (ANN) to reduce computational times for estimating wall shear stress. They used 243 idealized AAA models and performed FEA on them. Using the results obtained from the finite element technique, two different neural networks were developed and trained, a Mesh Neural Network (MNN) and a Tension Neural Network (TNN). The MNN created an aneurysm mesh in terms of four geometrical factors (asymmetry factor, aneurysm diameter, aneurysm thickness, aneurysm length) and the TNN was coupled with the MNN to calculate the peak wall shear stress on every node of that mesh for a given arterial pressure. This method was able to demonstrate high accuracy in the estimation of WSS when compared to the FEA. But the work was done using idealized AAA models. Statistical correlations between biomechanics and shape indices have been carried out by Guillermo et al, [14] where they performed CFD on 13 AAA patient models, and plotted correlations between the peak wall shear stress (PWSS) and peak intraluminal pressure

(PIP) with defined shape indices in 1D, 2D and 3D. All the AAAs selected had diameter values of less than 40 mm and hence maximum diameter and stresses developed were not correlated. But they concluded that the length L , asymmetry and saccular index significantly influence the PWSS and PIP. Izbicki et al. [15] presented an assessment of aortic aneurysm rupture risk by applying machine learning methods with the use of patient medical records while identifying the significant factors that play a role in rupture risk. Shum and colleagues in 2011 [16] proposed to use computed tomography (CT) image data to improve the performance of an AAA rupture prediction model by using three-dimensional image processing techniques to characterize indices of aneurysm size, shape and regional wall thickness. To this end, multivariate analysis of variance (MANOVA) was used to determine the significant difference between the indices and the ruptured condition. Shum further investigated the quantitative measurement of AAA geometry and wall thickness to assess rupture risk using the Decision Trees method [17]. It was shown that the geometry indices and regional variations of the complex shape of AAA should be taken into consideration to improve the accuracy in predicting rupture risk. Giannoglou et al. [18] reported on the relationship between the peak wall stresses that can cause the aneurysm rupture and several parameters characteristic of an aneurysm's geometry. They showed that three-dimensional analysis of curvature is an important factor in rupture risk assessment. Patient history factors like the presence of diabetes, hypertension or smoking, and prior surgical procedures play an important role in the progression to rupture of the AAA. But factors arising out of patient history cannot always be quantified directly in a mechanics based model. Prior attempts at using the machine learning method have been to estimate the wall shear stress distribution [11-13] or to estimate the effect of geometrical

parameters as a classifier [14,19] in the prediction of rupture of AAA but not exclusively using patient history. This would aid the non-expert user at the bedside to make an assessment of the rupture risk. Additionally, patient history factors are familiar to clinical staff. Hence, an analysis estimating whether just the patient history factors are sufficient to make an assessment of rupture risk is warranted.

4.1.1 AAA in the Singaporean Population

AAA is rare in the Asian population. In Singapore, AAA has an incidence rate of 3.1 per 100,000. The main risk factors in Singapore that may be linked to AAA are smoking, BMI and hypertension. About one in seven (13.6%) Singapore residents aged 18 to 69 years smoked cigarettes daily. The proportion of male daily smokers was six times that of females (23.7% vs 3.7%). Malays had the highest prevalence (23.2%) among the ethnic groups. This was true for both Malay males (41.3%) and females (5.5%). 5.7% of Singapore residents aged 18 to 69 years were obese (body mass index (BMI) of 30 kg/m² or higher). The proportion of obese adults in males (6.7%) was higher than in females (4.7%). Obesity was most common in older adults aged 60 to 69 years (11.0%). Malays had the highest obesity prevalence (13.4%), followed by Indians (7.5%) and Chinese (4.3%). One in eight (12.0%) Singapore residents aged 18 to 69 years reported that they had hypertension and were on prescribed medication. Males (12.4%) and females (11.5%) reported about the same prevalence. The prevalence of reported hypertension rose with age and was highest in the 60-69 age groups (48.0%). Malays (12.5%) and Chinese (12.2%) had higher reported prevalence compared to Indians (9.3%) [20].

4.2 Chapter Organization

This chapter consists of two parts. In the first part, four machine learning classifiers (Naive Bayes, SVM, Decision Trees and Logistic Regression) are tested for performance and the best classifier which is most suited to the assessment of AAA rupture risk is found. Subsequently, a feature selection algorithm (wrapper and filter methods) is applied to rank the most significant factors correlated with AAA rupture risk. The dataset contains 312 patients; of which 158 are normal and do not have any AAA. This forms the control cohort. Out of the 155 patients with AAA, 26 patients have a ruptured AAA. The rupture status of the AAA is the class variable. Performance metrics include classification accuracy of ruptured AAA, sensitivity and specificity of each method and a comparison through values of area under the Receiver Operator Characteristic (ROC) curve. This study stresses on the geometric factors of the diseased AAA to estimate rupture risk in the cohort and attempts to provide parameters based on geometry in addition to the maximum transverse diameter. A parametric model is generated based on the feature selection algorithm.

In the second study, three different machine learning classifiers namely, Naïve Bayes, Logistic Regression, and Decision Tree are used to determine rupture risk using factors based only on patient history. The effectiveness of these classifiers will be compared and a chi squared feature selection algorithm will be used to rank the risk factors according to their significance in the lead up to rupture in the AAA. The ranking will provide a validation of the predictive algorithm when compared against clinical factors leading to AAA rupture.

4.3 Methods

4.3.1 Study 1

4.3.1.1 Attributes of the Subject Population

The input dataset was collected from 312 in-patient medical records. All patients were treated at Tan Tock Seng Hospital in Singapore. The dataset included 17 attributes under three classes: un-ruptured AAA (U), ruptured AAA (R) and normal aorta without aneurysm (N). The 9 attributes for patient characteristics were age, gender, race, smoker, ex-smoker, diabetes, hypertension, previous dissection of aorta, and body mass index (BMI). Geometric indices measured from standard-of-care CT images constituted the other 8 attributes, which are as follows: proximal neck diameter (D1a: aortic diameter at level of lowest renal artery and D1c: aortic diameter at start of aneurysm), neck length (NL), AAA maximum diameter (DAAA), aortic length from lowest renal artery to bifurcation (L1), maximum diameter of left common iliac artery (D2), maximum diameter of right common iliac artery (D3), and diameter at the aortic bifurcation (D4). These indices are illustrated schematically in Figure 4.1.

Figure 4.1: Schematic of the eight geometric indices measured in each AAA after image analysis of the standard of care CT.

4.3.1.2 Pre-Processing of Dataset

Patient information was stored in an electronic data system in a structured format and in the form of unstructured free text clinical narratives. Narrative charting is a commonly used method to document a patient's status with brief words or abbreviations. The data mining application WEKA provided the functional analysis in data pre-processing such as discretization, imputation and data selection [21]. WEKA incorporates an imputation function wherein missing values in the input data are replaced by means of the

distribution. The replace missing values filter in WEKA was used to impute the missing entries in the dataset.

4.3.1.3 Evaluation

There are two phases of evaluation in machine learning. The first phase is to choose the most effective method to measure the performance during training. The next phase is to assess the performance for the final outcome of the trained model. The present dataset can be considered as an unbalanced distribution model with limited data. Unbalanced datasets are those in which there are large differences between large sample size of negative data and small sample size of positive data.

4.3.1.4 Testing

Classifier performance was tested using the cross-validation method. This process was used to compare the performance of the four classifiers: Naïve Bayes, Decision Tree, Support Vector Machines and Logistic Regression. The algorithms were evaluated by parameters such as classification accuracy, sensitivity, specificity, area under the receiver operator characteristic (ROC) curve (AUC), precision, recall, and F measure.

4.3.1.5 Scoring

A confusion matrix is a table containing information to measure the performance of a classifier on the test set. In binary classification, data is separated into two sets, positive (P) and negative (N). A 2x2 table (as in Table 4.1) consists of four types of results: two groups of correct classifications as true positive (TP) and true negative (TN), and other two incorrect classifications as false positive (FP) and false negative (FN). The total of four elements equals the number of test examples.

Table 4.1. Confusion Matrix

	Negative (Correct Class)	Positive (Correct Class)
Negative (Prediction)	True Negative	False Negative
Positive (Prediction)	False Positive	True Positive

- True positives (TP): The target was predicted yes and the actual class is yes
- True negatives (TN): The target was predicted no and the actual class is no
- False positives (FP): When the system predicted yes and the actual class is no
- False negatives (FN): When the system predicted no and the actual class is yes

Accuracy

This evaluation metric provides a simple method for comparing the performance of various classifier algorithms. Accuracy, sensitivity and specificity are recommended indicators in the analysis. Accuracy calculates the percentage of accurately classified instances. It can be expressed in terms of the previous terms as below.

$$\text{Accuracy} = \frac{\text{TN} + \text{TP}}{\text{FN} + \text{TN} + \text{TP} + \text{FP}} \quad (4.1)$$

Sensitivity

Sensitivity (known as true positive rate or recall) calculates the percentage of positive instances being accurately recognized as being positive.

$$\text{Sensitivity} = \frac{\text{TP}}{\text{FN} + \text{TP}} \quad (4.2)$$

Specificity

Specificity (known as true negative rate) calculates the percentage of negative instances being accurately recognized as being negative.

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}} \quad (4.3)$$

Precision

Precision calculates the extracted instances that are related to each other from the dataset.

$$\text{Precision} = \frac{TP}{TP+FP} \quad (4.4)$$

Receiver Operator Characteristic(ROC) Analysis

ROC curves are an effective way to visualize performance of classifiers. A study argued that the application of classification accuracy may not be a fair indicator of the performance and recommended the use of ROC curves [22]. The accuracy index provides a simple numerical measurement for the overall efficiency of the classifier. The ROC plot displays the ratio between specificity and sensitivity through a single threshold measurement [23]. It is a plot in which the x-axis represents the specificity and y-axis represents the sensitivity. These variables estimate the true positive fraction and false positive fraction which are measured at all possible threshold scores.

In the case of an imbalanced dataset, the system may show a high accuracy result but the outcome may be very misleading. The distribution of positive and negative classes may be overlapping and hence a threshold point may be used to determine the decision region. The threshold value can be chosen arbitrarily, and the sensitivity and specificity change for different threshold values. The selection of an appropriate threshold point depends largely on the application (i.e. decision making for a high risk surgery to choose high true positive fraction). The perfect ROC curve is the one that arches up to the top left hand corner of the chart. If the curve angle is closer to the 45 degree line, it means that the test is less accurate. There is a simple way to represent the ROC performance to a single value; the area under the curve (AUC). AUC is used to analyze multiple classifier quality

and the performance of a classifier is measured independently of the chosen threshold. For AUC measurement, a random classifier has a value of 0.5 and a perfect classifier has a value of 1.0 [24].

Precision Recall Analysis

The precision recall curve (PR) is an alternative way of evaluating classifier performance. The PR plot shows the ratio between precision and sensitivity (recall) where the y-axis is the precision and x-axis is the recall. A study showed that PR curves have attracted considerable attention in evaluating uncommon or rare diseases as the ROC method may over-optimize the result [35]. PR curves emphasize the ability to identify the retrieved information that are relevant (i.e. identify the diseased group (FP & TP) and ignore the correctly classified healthy group (TN)). It is able to capture poor performance on the unbalanced samples which is a more effective way to deal with uneven class distributions. Area under the precision recall curve (AUPRC) is another summary index to reflect the performance of PR curves. Furthermore, another parameter called the F-measure is used in evaluation of metrics in imbalanced data. The F measure relates precision and recall into an average value. It can be used effectively to represent the true positive to the arithmetic mean of predicted positives and real positives.

$$F \text{ measure} = \frac{2 * \text{Precision} * \text{Recall}}{\text{Precision} + \text{Recall}} \quad (4.5)$$

Cross Validation

Cross-validation measures the expected error in the number of misclassifications made over the total number of examples that used the performance of the classifier. K-fold

cross-validation splits the original collection of data into k uniformly sized subsamples. Next, the process is continued to perform k iterations involving training and validation. Within each run, one instance is named as a test set and the rest designated for learning. The hold out set is used to calculate the error rate and k error estimations are averaged to obtain an overall error rate. Due to random selections of the fold, it is vital to ensure each fold is well presented in right proportion in both training and test sets. The most popularly used value of k is 10 (i.e. 10-fold cross-validation which splits the data into 10 subsets; 9 for training and 1 for testing).

4.3.1.6 Feature Selection

A Chi squared feature selection algorithm was applied to the dataset to rank the most significant features that are highly correlated to AAA rupture risk. Subsequently, a wrapper based feature selection algorithm was applied for each of the four classifiers. This method brought out the most significant subset of features for each classifier. An evaluation of the factors in each case can be a metric of performance of the algorithms. The wrapper method outputs a subset of the features of the dataset to reveal the most significant features.

4.3.2 Study 2

155 Asian patient records were extracted from an IRB approved vascular database at Tan Tock Seng Hospital, Singapore. Among the 155 patients, there were 8 Indians, 17 Malay and 130 Chinese patients. Indian and Malay patients had 3 ruptured AAAs each while the Chinese patients had 20 ruptured AAAs in the cohort. The average age of the cohort was

73.63 years and average BMI was 23.30. The factors based on patient history were as follows: age, gender, race, smoking history, diabetic, hypertension and BMI. The cohort was predominantly male with 135 male and 20 female patients and among them, females had only 1 ruptured AAA. There were 141 Hypertensive patients and 47 patients who were diabetic. 118 patients were non-smokers in keeping with low incidence of smoking in the Singaporean population. Among the 12 patients who had a history of smoking, diabetes and hypertension, 4 patients had ruptured AAAs. There were 10 patients who did not show a history of smoking, diabetes or hypertension. Among them 2 patients had ruptured AAAs. 33 patients showed a smoking history and presence of hypertension. Among these 26 AAAs were unruptured while there were 7 ruptures. Overall, 26 patients had ruptured AAA, while in 129 patients, the AAA was unruptured.

4.3.2.1 Machine Learning Algorithms

Three machine learning algorithms, namely, Decision Tree, Logistic Regression and Naïve Bayes' were used in the open source application Weka^{TM} [21]. Decision trees are represented as a flowchart that illustrates optional moves from a series of decisions. They can be used to represent classification as well as regression analysis. A classification tree is used to label the class that depends on the value of the attribute. Each internal node denotes an attribute test which controls node division. Terminal nodes are assigned the status of the class variable being studied. The growing structure stops when all the attributes belong to the same target class or when maximum tree depth is reached.

Logistic regression is a machine learning classifier which is used when the target variables are binary. It can be used to describe the relationship between the class variable and one or many independent variables that may be numerical or nominal in nature. The output is

generally zero or one. Logistic regression generates a probabilistic function that describes whether each variable belongs to one or the other binary state of the class variable. The process can be described graphically in terms of a sigmoid function. The method can also be extended to cases where there are more than 2 categories. This is called multinomial logistic regression.

Naïve Bayes is a classification method based on the concept of conditional probabilities. It assumes that all factors that affect the value of the target variable are independent of each other. For each attribute, it calculates the probability, conditional on the target variable. This is done for all the attributes in the training set. Thereafter, a joint conditional probability is estimated and eventually, using the Bayes' rule, the conditional probability of the target variable is calculated. This is repeated for all the factors/attributes. The Naïve Bayes is a suitable classifier for use when there are several nominal factors in the problem.

4.3.2.2 Testing and Feature Selection

In this study, 10-fold cross validation was used in each of the machine learning methods. Stratified ten-fold cross validation is a standard method of predicting the error rate of a learning technique given a limited amount of data. The data are divided into ten parts, or folds, in which the class is represented in approximately the same proportion as in the full dataset. Each fold acts as testing data once and the learning algorithm is trained on the remaining nine-tenths. The error rate is then calculated by applying the testing data on the learned model. This process is repeated ten times on different training sets and the ten error estimates are averaged to yield an overall error estimate, which is represented as the percentage of correctly classified instances [25]. The class/target variable used was the

rupture status of the AAA. A confusion matrix was generated as a result of the classification process that quantified the classification accuracy of each algorithm. A receiver operator characteristic (ROC) curve was generated for each method used. The area under the curve (AUC) value provides a quantification of the effectiveness of the classifier. A comparison of classifiers was made using the confusion matrices and ROC curves. A Chi-squared (χ^2) test was subsequently carried out to rank the most significant risk factors that lead to rupture in the AAA patients.

4.4 Results and Discussion

4.4.1 Study 1

In this work, four different classifiers were tested, namely, Logistic Regression, Decision tree, Naïve Bayes and Support Vector Machines (SVM). The records obtained from the hospital contained missing data points. To deal with this shortcoming, pre-processing steps were carried out to improve classifier performance.

Amongst the 26 ruptured AAA patients in the dataset, 24 were men while only two were women. A majority of the ruptured AAA patients (21) were in the age group of 58 to 78 years with the average age being 72.3 years. The average DAAA value for this set of patients was 65.7 mm with the highest DAAA being 82.0 mm. All ruptured AAA patients were ex-smokers and were hypertensive with only 9 showing occurrence of diabetes as well. The mean, range and standard deviations for the quantifiable numerical attributes in the ruptured group of the dataset are shown in Table 4.3.

A stratified 10-fold cross-validation method was used to measure model performance using the four different classifiers. The dataset was divided into ten folds and one out of 10 folds was held out for testing. The validation results showed that machine learning

algorithms were competent enough to handle missing data. As illustrated in Table 4.4, Naïve Bayes (NB) achieved the best performance amongst the classifiers with a classification accuracy of 95.19%, ROC area under the curve of 0.995 and F-measure of 0.952. The results emphasize the outcomes of classes normal (N), unruptured (U) and ruptured (R) through the confusion matrix. As the goal was to predict the AAA rupture risk, the performance of predicting the true positive (TP) was the key measurement.

Table 4.3 Means and Standard Deviations of features in the dataset

Factor	Minimum value	Maximum value	Mean value	Standard Deviation
Age	23.0	99.0	68.60	13.82
D1a	17.2	26.1	21.63	1.60
D1c	15.8	26.6	22.39	2.0
NL	0.0	40.0	11.85	12.54
DAAA	17.2	82.0	37.27	17.18
L1	96.0	146.0	120.22	11.30
D2	8.0	29.0	15.09	3.74
D3	8.0	28.0	15.00	3.73
D4	14.9	27.1	22.29	2.00
BMI	11.7	49.6	23.51	4.29

The decision tree algorithm in Figure 4.2, shows the sequence of factors that must be considered in order to assess rupture risk. The neck length (NL) is seen to be the most

significant factor, followed by the maximum transverse diameter (DAAA), maximum diameter of right common iliac artery (D3), followed by gender, diabetes, race and the aortic diameter at the start of the aneurysm (D1c). The decision tree algorithm showed a classification accuracy of 91.98%, a Kappa statistic of 0.8582 with a F-measure of 0.918. The area under the ROC curve for the decision tree was 0.963. This was the least effective classifier in the study. The logistic regression algorithm showed a classification accuracy of 94.23%, with a Kappa statistic of 0.9420 and F measure of 0.942. The area under the ROC curve was 0.968. The SVM showed a classification accuracy of 93.91%, a Kappa statistic value of 0.8938 and an F measure of 0.941. The area under the ROC curve was 0.960. Detailed output parameters and the confusion matrices are presented in Table 4.4 and 4.5.

Table 4.4 Comparison of classifier performance parameters

Classifier/ Performance Parameters	Classification Accuracy	Kappa Statistic	F Measure	Area under ROC Curve	Precision	Recall
Decision Tree	91.98%	0.8582	0.918	0.963	0.916	0.920
Naïve Bayes	95.19%	0.9156	0.952	0.995	0.953	0.952
Logistic Regression	94.23%	0.9420	0.942	0.968	0.942	0.942
SVM	93.91%	0.8938	0.941	0.960	0.944	0.939

Table 4.5 Confusion Matrices of the classifiers

	N	U	R
N	158	0	0
U	0	120	8
R	0	7	19

(a) Naïve Bayes Classifier Confusion Matrix

	N	U	R
N	158	0	0
U	0	117	11
R	0	14	12

(b) Decision Tree Classifier Confusion Matrix

	N	U	R
N	157	0	1
U	4	118	6
R	0	7	19

(c) Logistic Regression Classifier Confusion Matrix

	N	U	R
N	158	0	0
U	0	116	12
R	0	7	19

(d) SVM Classifier Confusion Matrix

A comparison of the ROC curves for each classifier is shown in figure 4.3. Considering the weighted averages for each class of U, N and R, the Naïve Bayes classifier shows the

highest area under the curve (AUC) among the four classifiers tested with 0.995. The ROC curves for the other three classifiers are 0.96 for SVM, 0.968 for logistic regression and 0.963 for decision trees. If the ruptured class variable is considered to plot the ROC curve as in figure 4.3, the corresponding AUCs are 0.974 for Naïve Bayes, 0.885 for logistic regression, 0.831 for decision trees and 0.844 for SVM.

A chi square feature selection algorithm is also applied to the dataset. This is a linear filter method which is not classifier specific and ranks the features from the dataset. The Chi square feature selection algorithm ranked the features in order of significance as follows. The maximum transverse diameter DAAA is most significant, followed by neck length NL, right iliac artery diameter D3, left iliac artery diameter D2, age, the inlet diameter D1c, diameter at iliac bifurcation D4, gender and followed by patient history factors, previous dissection of the aorta, presence of hypertension, presence of diabetes, race and the patient being an ex-smoker.

A wrapper based feature selection algorithm was also applied using each classifier to evaluate a subset of features that are significant in each method. Table 4.6 lists the features for each classifier. This method brings out the best model that can include the most significant features that have been investigated clinically as well.

4.4.1.1 Discussion

The aim of this work was to identify a suitable machine learning model that can be used at the bedside to assess AAA rupture risk. To this end, four machine learning algorithms are tested for performance in classification of ruptured AAA based on a cohort of Asian patients' medical records and abdominal CT images retrospectively.

As seen from the results of each classifier, the Naïve Bayes algorithm performs the best among the four tested. The factors making up the dataset are derived from patient history and geometric factors. As has been recorded in medical literature, patients with hypertension and having a smoking history along with being from the Caucasian race are the highest at risk for an AAA rupture. Prior investigations into Caucasian patients [17,18] have concluded that geometric factors are highly correlated to wall stress, which is in turn an indicator of AAA rupture risk.

Curvature has been seen to be highly correlated with high wall stress by Giannoglou [18], while Shum and others carried out feature selection to conclude sac length as the most significant factor affecting AAA rupture risk assessment. They suggested that the aneurysmal sac shape and size play a significant role in the progression to rupture and must be considered in any assessment.

Figure 4.2 Decision Tree visual ensuing from the machine learning method

Table 4.6 Models generated from wrapper feature selection algorithms for each classifier

Naïve Bayes	SVM	Logistic Regression	Decision Tree
Prev. Dissection of Aorta	Age	Race	Neck Length (NL)
Neck Length (NL)	Maximum Transverse Diameter (DAAA)	Prev. Dissection of Aorta	Maximum Transverse Diameter (DAAA)
Maximum Transverse diameter (DAAA)	Distance between lowest caudal artery and iliac bifurcation (L1)	Neck Length (NL)	Right iliac diameter (D3)
Distance between lowest caudal artery and iliac bifurcation (L1)	-	Maximum Transverse diameter (DAAA)	-
Right iliac diameter (D3)	-	Right iliac diameter (D3)	-

In this study, which has AAA patient data originating in Singapore, a machine learning model had brought out the most significant factors that are highly correlated with rupture risk. The decision tree algorithm showed that the neck length (NL) is the most significant geometric parameter that is correlated to rupture. This is followed by the maximum transverse diameter (DAAA). Subsequently, the diameter of the right iliac artery is seen to be a significant factor in the decision tree. Importantly, these parameters are seen to be significantly different in Asians as compared to Caucasian patient geometries as has been stated before. Among the factors derived from patient history, gender, presence of diabetes and race were present in the tree. The decision tree provides a visual of the sequence from the most significant features to the least significant ones in the dataset. It would be a suitable tool to aid clinicians at the bedside. The decision tree was the least effective classifier among the four with a classification accuracy of 91.98%.

To extract the list of significant factors in the three other classifiers, a feature selection algorithm is used. Feature selection is a method through which the most significant factors are extracted from the larger set of features. In this work, both the filter and wrapper methods are used in feature selection. This will result in a model which will contain only the most significant factors that affect assessment of AAA rupture risk.

Comparing the feature selection methods across classifiers shows that the maximum transverse diameter (DAAA) is certainly an important indicator of AAA rupture risk. But features like neck length, the diameter of the right iliac artery and the distance from the lowest caudal artery to the iliac bifurcation are also critical in determining progression to AAA rupture. The model predicted by the feature selection algorithm is consistent with

the morphological differences seen in Asian aortas as compared to their Caucasian counterparts.

Figure 4.3 ROC curves for all the four classifiers

The Naïve Bayes feature selection is the best model that brings out the important features such as neck length (NL), right iliac diameter (D3), the maximum transverse diameter (DAAA), the distance between the caudal artery and iliac bifurcation (L1) and also considers previous dissection of the aorta as one of the most significant factors highly correlated to AAA rupture. This is in addition to it being the best classifier with the best classification accuracy and the highest area under the ROC curve.

The Chi square feature selection algorithm provides a linear filter method by listing the most significant features of the dataset by considering the entire dataset. The method lists

DAAA, followed by neck length NL, right iliac diameter D3, left iliac diameter D2 and age at CT as the five most significant features affecting AAA rupture risk. The distance between the lowest caudal artery and the iliac bifurcation (L1) does not have a weight value at all which is a departure from the wrapper method where it is significant.

Among the patient history related factors, smoking is not seen to be a significant risk factor in the feature selection process in any of the four algorithms tested. Clinically, smoking is seen to be highly correlated to AAA rupture risk. But, the population being surveyed, in this case, mostly Asian may not have strong correlation of smoking to assessment of AAA rupture. But as is seen from the wrapper feature selection, Naïve Bayes and Logistic Regression show that previous dissection of the aorta has a significant effect on the risk of rupture.

4.4.2 Study 2

The classification accuracy and the number of correctly classified instances are shown in table 4.7 for each of the three methods used, namely Decision Tree, Logistic Regression and Naïve Bayes. The decision tree algorithm reported highest classification accuracy of 83.2%. Additionally, Kappa statistics and mean absolute error were also reported for each of the methods. The Logistic Regression method reported the highest Kappa statistic with a value of 0.06 and the Naïve Bayes was found to have the least mean absolute error value of 0.2713. Table 4.7 lists the values of both parameters in each method.

Confusion matrices were drawn up for each method based on the cross-validation procedure. These show the accuracy of each method in classifying the target class correctly. Based on the confusion matrices, the logistic regression method was able to classify ruptured AAAs the best among the three methods. Tables 4.8-4.10 show the

confusion matrices and the number of instances in each case that the prediction method was able to classify correctly. The most significant features leading to rupture were chosen using a χ^2 test based feature selection algorithm in Weka^{TM}. The highest ranked factors from the feature selection algorithm are as follows: BMI, Race, Gender, Smoker, Diabetic and Hypertension in order of significance. A ROC curve was generated as an additional comparison of classification accuracy by using specificity and sensitivity values. The method with the highest area under the curve (AUC) was the Naïve Bayes as shown in Figure 4.4.

4.4.2.1 Discussion

The main objective of this study was to ascertain the rupture risk of AAA in an Asian population cohort using machine learning methods. Additionally, only patient history based factors that influenced progression of the AAA to rupture were considered in the analysis.

Table 4.7. Classification accuracy comparison of the three machine learning algorithms

	Logistic Regression	Naïve Bayes	Decision Tree
Number of correctly classified instances	127	126	129
Percentage of correctly classified instances	81.9%	81.2%	83.2%
Kappa Statistic	0.06	-0.036	0.0
Mean Absolute Error	0.2733	0.2713	0.2793

Table 4.8. Confusion matrix for Decision Tree

	Predicted: Unruptured	Predicted: Ruptured
Actual: Unruptured	129	0
Actual: Ruptured	26	0

Table 4.9. Confusion Matrix for Naïve Bayes' algorithm

	Predicted: Unruptured	Predicted: Ruptured
Actual: Unruptured	126	3
Actual: Ruptured	26	0

Table 4.10 Confusion matrix for Logistic Regression

	Predicted: No need for surgery	Predicted: Surgery needed
Actual: No need for surgery	125	4
Actual: Surgery needed	24	2

This was done in order to enable an understanding of the non-quantifiable factors contributing to the rupture of the AAA. Mechanics based methods and earlier machine

learning based methods have brought out the quantifiable factors affecting rupture, such as the wall shear stress [11-13] and the morphology of the aneurysm [26]. But the nominal factors by themselves that form part of the patient history may not be quantified directly. They are critical from a clinical point of view and a machine learning based model that can put out the diagnosis quickly will aid healthcare delivery.

The use of maximum transverse diameter as a metric can be a limiting factor in the diagnosis of rupture [27]. This has been seen to be inadequate as there are other factors at play in the leadup to rupture as stated before. The results of this study show that in addition to the maximum diameter, factors arising out of patient history such as BMI, gender, smoking and hypertension were highly significant in determining AAA rupture. This was obtained through a χ^2 feature selection algorithm that ranked the features according to their significance. As all the patient data is from the Asian region, the race attribute can be discounted in this study. A further decomposition of race amongst Chinese, Malay and the Indian peoples warrants another study with more data points from each race. Smoking and hypertension have been seen to promote progression to rupture in AAA along with the male gender, which forms 99% of this dataset. Diabetes is negatively associated with both presence and growth of AAA as has been previously reported. Takagi and Umemoto [28] suggest a positive association of AAA presence with BMI but no association with AAA growth. But BMI in this cohort was seen to have highest association with the rupture of AAA.

In this study, even as decision tree shows the best classification accuracy among the methods, other factors affect reliability of the models. A confusion matrix is generated for each model as a metric to measure the accuracy of the models in picking the ruptured

cases as ruptured and otherwise. The confusion matrix will output the true positives, false positives, false negatives and true negatives. The true positives determine when the model is predicting ruptured AAAs when they are actually ruptured. Using the confusion matrix, it turned out that the Decision Tree may not be as reliable. Out of the 129 instances where there was no rupture in the aorta, in other words, when no surgery was conducted, the decision tree model predicted all 129 instances correctly, hence reflecting the 83.2% predictive accuracy. However, out of 26 instances where surgery was required, the model predicted incorrectly for all the 26. Similarly, in the Naïve Bayes' model, out of the 129 instances, 126 were predicted correctly by the algorithm. But again, the ruptured class was predicted incorrectly in all 26 instances. For the logistic regression algorithm, it performed only slightly better as seen from the confusion matrix. The model was able to predict 125 instances of no rupture correctly while predicting 2 instances correctly out of 26 ruptured cases.

Figure 4.4. Comparison of ROC curves for the three machine learning algorithms

Looking at the results from the confusion matrix, it seems that the decision tree model may not be the best after all, and selecting the best model simply by looking at the highest predictive accuracy is not sufficient. Therefore, in terms of distribution of correct predictions, logistic regression proved to be a better classifier among the three models. This is brought out in terms of the Kappa statistic. Kappa Statistic, also known as Cohen's Kappa coefficient is a number which measures the inter-rater agreement for qualitative items. Since it pertains to agreement between observers, precision is often reported as a Kappa statistic [29]. Hence, greater the value of Kappa, greater is the precision. If the Kappa statistic is considered Logistic Regression with a value of 0.06 showed better precision in the prediction of AAA rupture, as compared to Naïve Bayes' that had a value of -0.036 and Decision Tree that showed a value of 0.0. Overall Kappa statistic for the study is low as the data is skewed in favor of the unruptured cases. But, this can be attributed to the low incidence of AAA in Asians.

In terms of mean absolute error (MAE), Naïve Bayes fared better than the Decision Tree and the Logistic Regression classifiers. MAE is the average over the verification sample of the absolute values of the differences between forecast and the corresponding observation. The MAE is a linear score which means that all the individual differences are weighted equally in the average. Therefore, the lower its value, the more reliable it is. Naïve Bayes model had the lowest MAE value of 0.271 faring better than the other two models, as MAE for Logistic Regression was 0.273 and that of Decision Tree was 0.279 as has been seen in Table 4.7.

The AUC of the ROC curve in the case of Naïve Bayes was 0.582 while Logistic Regression showed a value of 0.544 whereas decision tree fared the worst with a value of 0.45. The ROC curves are all in the lower threshold of the prediction probability range. This may be attributed to the skewed data that has been made available for the study. More division in the data w.r.t the ruptured cases will ensure better predictability amongst the classifiers. Even as the AUC values are in the lower range of predictability, the classification accuracy and the feature selection algorithm have demonstrated useful conclusions regarding effectiveness of the classifiers in predicting rupture of AAAs.

The use of the three methods and the feature selection algorithm gives useful information on the progression to rupture of a AAA. Machine learning being a faster method than computational biomechanics by means of FEA or FSI could lead to faster assessment of AAA rupture risk. But machine learning methods can be used in congruence with the biomechanics to present a more complete picture of the status of the aneurysm. This will ensure better care delivery to patients thereby reducing costs and stress on resources on the healthcare system.

4.5 Summary

In study 1, four machine learning algorithms were applied to classify a retrospectively acquired dataset into normal, unruptured or ruptured AAA on the basis of 17 attributes obtained from existing medical records or measured from the standard of care abdominal CT images. Overall, the performance of the Naïve Bayes machine learning algorithm was the best among the four classifiers. The average age of a patient with a ruptured AAA is 64.5 to 76.5 years and men are more affected than women. Additional significant risk

factors include smoking, hypertension and maximum aortic aneurysm transverse diameter, which may increase the probability of rupture. The medical implications of this work can be addressed in two ways. The best classifier can be applied to prospectively acquired data to predict the likelihood of aneurysm rupture. Next, it would be necessary to estimate the attributes implicated in rupture risk beyond just maximum aneurysm diameter. The attributes of the dataset used in this work are known as 1D geometric indices. However, the geometry of an AAA can be quantified with 2D and 3D indices such as curvature and volume, which may also play a significant role in the progression to rupture of the diseased abdominal aorta. Future work will incorporate those additional attributes that will likely improve the accuracy of the classifier and help clinicians in their decision making.

In study 2, it is seen that machine learning methods can be used to predict the rupture of a AAA based on factors extracted from patient history alone. A comparison of three machine learning algorithms has been carried out in this study. The logistic regression method was superior to Naïve Bayes and Decision Tree in this study due to the high Kappa value that resulted, even as the other accuracy parameters were in similar range among all the methods. The significant risk factors of rupture were BMI, gender, diabetes and hypertension which were extracted as a result of a χ^2 feature selection algorithm. Hence, that would act as a validation of the machine learning method as a predictor of rupture risk in AAA from a medical perspective. It may also be said that the machine learning approach can be used congruently with biomechanics based methods as a diagnostic tool to predict rupture risk in AAAs.

CHAPTER 5

APPLICATION OF FLUID STRUCTURE INTERACTION

METHODS TO ESTIMATE THE MECHANICS OF RUPTURE IN

ASIAN ABDOMINAL AORTIC ANEURYSMS

5.1 Introduction

AAA is a vascular condition that affects the elderly population, mainly above the age of 55. It is a highly asymptomatic disease where the infra-renal aorta dilates to more than two times its original diameter. This leads to weakening of the arterial wall eventually leading to rupture (figure 5.1). In the event of a rupture, mortality is high. Pathophysiological and biomechanical factors contribute to the genesis, growth and rupture of the AAA. These include advanced age, greater height, coronary artery disease, atherosclerosis, high cholesterol levels, hypertension [1] and smoking [2,3]. The clinical metric used for surgical intervention is the maximum transverse diameter (DAAA). The DAAA is the diameter of the AAA lumen measured along the central lateral axis. Clinicians have used a value of 55 mm as the threshold for DAAA to recommend surgical intervention. But, in many cases, this does not hold true [4]. Hence, a computational method based on mechanical principles is essential to accurately predict rupture of AAA.

5.2 Incidence in The Asian Population

There have been numerous studies quantifying the incidence of AAA in the Caucasian population, retrospective studies have looked at the Asian demographic in several locations to bring out the incidence of AAA in the Asian population. Li et al. [5] reported prevalence of AAA considering 56 studies. The prevalence in Asians was 0.5% as against

2.2% for American patients and 2.5% for European patients. This has been corroborated by Guo and Zhang [6], where in a study covering 23,810 patients, the prevalence was seen to be 0.11%. The incidence in Chinese men was 0.18% whereas it was 0.07% in Chinese women. Other studies done earlier in Japan reported incidence of about 0.36% [7,8] while in Korea it has been seen to be 0.55% [9]. In a study done in Malaysia, Yii [10] reported that among 123 patients in the Sarawak region of Borneo, incidence among high risk males and females were 25.6 and 7.6 per 100,000. In the Caucasian population, a similar metric has shown a range from 3.0 – 117.2 per 100,000.

Figure 5.1. Normal abdominal aorta and Abdominal Aortic Aneurysm

Computational methods based analyses have been carried out using solid mechanics, fluid mechanics or a combination of these, known as fluid structure interaction. Computational solid mechanics based equations have been used to quantify stress development in the arterial wall [11-14]. Initial forays considered only the fluid or the solid mechanics of the

AAA separately through CFD and FEA methods as listed before. But the arterial wall is not rigid as it responds to the blood flow in the artery. This fluid-structure interaction (FSI) is bi-directional. Accounting for FSI provides a more rigorous approach to the most physiologically accurate solution. This was first investigated by DiMartino et al [15] using an Arbitrary Eulerian Lagrangian (ALE) method to accurately determine an FSI solution. Additional studies carried out by Scotti et al in 2005 and 2008 [16, 17] that considered the movement of the wall overestimated the stress values by 20% as against a rigid simulation and applying a varying wall thickness also increased the von Mises stress in the aneurysm model. This was reinforced by Papaharilaou et al. [18] who reported a 12.5% difference in peak stress when a decoupled FSI solution was incorporated. Figueroa et al., [19] formulated a coupled momentum method (CMM) for FSI problems using the stabilized FEM. They investigated flow in the AAA under rest and exercise conditions to quantify changes in stress. They observed that during exercise, the deformation of the wall is no longer occurring in a radial expansion and contraction fashion, but rather as a net motion forward and backwards due to the much larger inertial forces exerted on the wall by the impinging blood stream. Li and Kleinstreuer [20] in an FSI study, observed that a large neck angle of the aneurysm, may cause strong irregular vortices in the AAA cavity and may influence the wall stress distribution by increasing it as much as 40%. The rupture risk of lateral asymmetric AAAs is higher than for the anterior – posterior asymmetric types. The most likely rupture site is located near the anterior distal side for the anterior – posterior asymmetric AAA and the left distal side in the lateral asymmetric AAA. The incorporation of asymmetry is important as Fraser et al. [21] reported differences in stress

between a rigid walled calculation and FSI to be less than 3.5%. But this analysis was carried out using an axisymmetric AAA model.

As has been seen from prior studies, FSI analysis provides a more realistic picture of the stresses induced in AAA. It provides insight into the mechanics of rupture by considering both the structural and fluid solutions as against exclusively one of them, or even the use of only maximum transverse diameter as a metric to determine rupture.

In this work, two Asian patient AAAs are subjected to FSI analysis to determine a measure of the rupture risk. This will be done by extracting the principal stresses induced in the arterial wall and the corresponding wall shear stresses by the blood flow. A comparison of these two patient AAAs will also be made to deduce any relationship between the AAA geometry and the stresses developed.

5.3 Geometry

Two patient specific AAA computed tomography angiographies originating from Singapore were obtained from Tan Tock Seng Hospital, Singapore's IRB approved vascular database. One was a large aneurysm with a DAAA of 75 mm while the other, a small aneurysm having a DAAA of 35 mm. The obtained patient CTs were subjected to level set segmentation using the open source application ITKSnap [22]. The resulting geometry was then smoothed using MeshLab [23], an open source application where a series of Poisson filters were used to rid it of artifacts. The resulting *stl* file was exported to SolidWorks (Dassault Systemes Corporation, Waltham, MA) wherein a constant thickness of 2 mm was added to make it suitable for meshing for an FSI problem. Meshing was carried out using the commercial software ICEMCFD in ANSYS Workbench 16.1 (Canonsburg, PA). The intra-luminal thrombus (ILT) was not considered

in this geometric model. A tetrahedral mesh was created for the structural wall and the fluid mesh was a volumetric hexahedral mesh in both cases. The meshes are shown in figures 5.2 and 5.3.

Figure 5.2. Structural mesh of AAA geometry from Patient 1

Figure 5.3. Structural mesh of AAA geometry from Patient 2

5.4 Governing Equations

The properties of blood in the simulations were assumed to be Newtonian and incompressible. The Newtonian assumption for blood has been seen to be consistent for large arteries [24]. The inlet flow was made pulsatile to be physiologically accurate. Fluid-

structure coupling of the aneurysmal wall motion and blood flow is made using the Arbitrary-Lagrangian Eulerian (ALE) method. The incompressible continuity and the Navier-Stokes equations in ALE form are expressed in Eqs. (5.1) and (5.2).

$$\nabla \cdot \mathbf{u} = 0 \quad (5.1)$$

$$\rho_f \left(\frac{\partial \mathbf{u}}{\partial t} + ((\mathbf{u} - \mathbf{u}_g) \cdot \nabla) \mathbf{u} \right) = -\nabla p + \mu \nabla^2 \mathbf{u} \quad (5.2)$$

Where ρ_f , p , $\mathbf{u}$ and $\mathbf{u}_g$ are the fluid density, the pressure, the fluid velocity, and the moving coordinate velocity, respectively. In ALE formulation, the term $(\mathbf{u} - \mathbf{u}_g)$, which is the relative velocity of the fluid with respect to the moving coordinate velocity, is added to the conventional Navier-Stokes equations to account for movement of the mesh [25]. The values of ρ and μ were taken to be 1060 kg/m³ and 0.0035 Pa-s for blood. The SIMPLE method [26] was used with a time step calculated assuming the heart rate to be 72 beats per minute for the transient fluid solution. The transient structural solver and the fluid solver were used in the ANSYS 16.1 Workbench suite.

5.5 Boundary Conditions and Material Properties

The inlet and outlet boundary conditions were defined to be pulsatile with waveforms being extracted from literature [27]. The walls were bound by a no-slip condition and a FSI interface was defined at the inner wall of the aneurysm lumen, through the system coupling function of ANSYS Workbench. Figure 5.4a and 5.4b show the inlet velocity and outlet pressure boundary conditions. For the arterial wall, the density was taken to be 1120 kg/m³ [28]. By assuming isotropic elasticity, the value of the Young's modulus was

taken to be 4.5 MPa and Poisson's ratio to be 0.45 [29]. The boundary conditions were input through a User defined function (UDF) script in ANSYS. The boundary conditions were kept the same for both patients so as to allow comparison of the extracted biomechanical parameters.

Figure 5.4a Inlet velocity boundary condition waveform

Figure 5.4b Outlet pressure boundary condition waveform

5.6 Independence Studies

As part of the verification process, three different mesh sizes were investigated for mesh independence of the solver. The integral wall shear stress in the fluid was chosen as the parameter of interest in the study for both patients. The variation of the integral wall shear stress was recorded for three cardiac cycles and compared in the different mesh sizes. The systole occurred at 2.18 seconds for patient 1 and 2.3 seconds for patient 2. The maximum integral wall shear stress was then recorded at systole for all mesh sizes in both the patients. As seen from Tables 5.1 and 5.2, the solutions were indeed independent of mesh size. In patient 1, the fine mesh size showed a difference of 4.16% in the integral wall shear stress while the coarse mesh saw no error. In patient 2, as compared to the initial normal mesh size, the coarse mesh size saw a variation of the integral wall shear stress of about 2.81% whereas it was lower at 0.56% when the fine mesh was used. The least mesh

size that was not computationally expensive was used in each case for the FSI simulation. For patient 1, the 2.02 million element mesh and for patient 2, the 1.69 million element mesh was used in the final simulations.

Table 5.1. Independence studies (Patient 1)

Mesh Size	Number of Elements (millions)	Maximum Integral Wall Shear Stress at systole in third cardiac cycle (Pa)	Percentage Difference to Normal Mesh
Fine	3.34	0.024	0 %
Normal	2.02	0.024	0 %
Coarse	0.80	0.023	4.16 %

Table 5.2. Independence studies (Patient 2)

Mesh Size	Number of Elements (millions)	Maximum Integral Wall Shear Stress at systole in third cardiac cycle (Pa)	Percentage Difference to Normal Mesh
Fine	4.96	0.0365	2.81 %
Normal	3.14	0.0355	0 %
Coarse	1.69	0.0353	0.56 %

5.7 Results and Discussion

The present study is an attempt to estimate the mechanics of rupture of Asian AAA using FSI methods. Even though incidence is low in Asian patients, it is important to establish

the biomechanics of the Asian AAA cohort and eventually improve point of care technologies for them. FSI analysis of the Asian AAA will aid this pursuit. The arterial wall being a non-rigid entity is subject to interaction with the fluid flow and vice versa. Hence, this requires a FSI solution in order to investigate the effects of the moving arterial wall in the estimation of rupture risk as it incorporates the material properties of the arterial wall.

The deformation, maximum principal stress and maximum shear stress were extracted in the structural domain while the integral wall shear stress was the parameter of interest in the fluid domain. Also, the velocity streamlines and pressure distribution over the arterial wall was quantified in each patient. FSI simulations were carried out for 3 cardiac cycles measuring 0.9 seconds each. The plots were generated at systole in the third cardiac cycle. This was done to damp out any initial transients resulting from the computational method.

The parameters that caused the most effect on the risk of rupture of the AAA were first principal stress and wall shear stress. This was established from the maximum principal stress theory and maximum shear stress theory that are failure theories in mechanics. In the maximum principal stress theory, the material would fail if the maximum principal stress induced exceeds the maximum normal strength of the material. As for the maximum shear stress theory, the material would fail if the maximum shear stress suffered exceeds the maximum allowable shear stress.

Hence, it is important to observe the results of the maximum shear and principal stresses in the structural domain to comment on the rupture risk. In the same manner, the wall shear stress induced in the fluid domain, would be important affecting the results in the structural domain in a strongly coupled solution.

5.7.1 First Principal Stress (Structural Domain)

The first principal stress is a suitable metric to determine the peak stress that is being induced in the arterial wall. Principal stresses are the normal stresses acting on the arterial wall. The forces acting on the arterial wall is the pressure load from the fluid and hence, the principal stresses are the indicators of the stress distribution that may lead to rupture of the wall. The location of the highest principal stresses on the arterial wall is usually seen to be in the antero-distal region of the AAA lumen. Figure 5.5 shows the distribution of the first principal stresses in each patient. As seen from the figure, the regions of maximum principal stress induced in each of the patients are clearly marked out as the ones in red. In patient 1, the region is seen to be more distal than that for patient 2. From structural failure theories, we can deduce that these regions may be most susceptible to rupture. The maximum principal stresses have been used as a metric by Scotti and others [16] successfully to establish rupture potential in AAAs in their FEA analysis. The ranges of principal stresses developed in both the patient aortas are in the same range as those induced in Caucasian aortas. (0.2-0.4 MPa). The principal stresses show a marked difference in each patient as seen from figure 5.5. While the small AAA (patient 1) shows a maximum principal stress of 0.3 MPa, the larger aneurysm shows a lesser maximum principal stress at only 0.22 MPa. This brings out the importance of quantifying the biomechanical stress as opposed to only the maximum transverse diameter of the AAA as a metric for surgical intervention by clinicians. In this case, patient 1 has a higher stress and may be at a higher risk even though the maximum transverse diameter is well below the clinical threshold of 55 mm.

Figure 5.5. Spatial distribution of first principal stresses at the AAA wall (Pa)

5.7.2 Structural Deformation

This study accounts for the interaction between the fluid and the structure considering the arterial wall as a non-rigid entity. The ALE method, that involves a strongly coupled solution exchanges the structural deformation value with the fluid in every time step. The structural deformation value is an important parameter in the simulation. The maximum deformation of the arterial wall is visualized in Figure 5.6. Quantitatively, there is little difference in the maximum values of the deformation in both the patients. The maximum deformation value in patient 1 is 0.0022 m while it is 0.0020 m in patient 2. The location of maximum deformation is aligned with the location of the maximum principal stresses in both the patients. As the arterial wall is weakened during the progression of the disease, the deformation at the site of the high principal stress promotes the tendency to rupture.

Figure 5.6. Spatial distribution of the AAA wall deformation (m).

5.7.3 Wall Shear Stress (WSS) (Fluid Domain)

Wall shear stress is induced by the fluid on the arterial wall. The values of WSS are extracted from the fluid solution in the FSI simulation. It is a challenge to quantify the WSS *in vivo* and hence, computational methods must be used. Figure 5.7 shows the comparison of the induced WSS in both models. The peak WSS on the arterial wall, induced in patient 1 is 18.74 Pa as against patient 2 where only 12.88 Pa is induced on the arterial wall. Also seen from the figure, the location of peak wall shear stress is not at the same location as that of the peak first principal stress. It is also clear from the pressure distribution that the sites of integral wall shear stress and the pressure are correlated. This is supported by Boyd et al., 2016 [30] who reported that low wall shear stresses dominate sites of rupture in AAA.

Figure 5.7 Spatial distribution of WSS (fluid) on the arterial wall (Pa)

5.7.4 Velocity and Pressure (Fluid Domain)

Velocity streamlines were extracted using the post processing application, CFDPost, that is part of the ANSYS workbench suite. The streamlines provide insight into how the fluid is inducing pressure on the arterial wall. The changed geometry of the diseased aorta induces vorticity in the fluid. Flow vortices that are formed at the beginning of the cycle due to the geometry of the aneurysm migrate distally as the flow decelerates from peak systolic conditions to diastole. Initially, there is attached flow near the proximal end of the aneurysm but by peak systole there is a separation of the vortices from the wall. This is seen in the streamlines generated for both the patients. The flow separation is higher in the larger aneurysm of patient 2 as there is a pronounced neck region that induces the flow to turn the corner (Figure 5.8). This effect is lesser in the smaller aneurysm as there is a relatively less visible neck region and the lumen curvature is lower as the fluid moves from the proximal to the distal region of the AAA model.

Figure 5.8 Velocity Streamlines in the fluid domain (m/s)

Figure 5.9 Pressure distribution in the fluid domain (Pa)

Figure 5.9 shows the distribution of pressure over the arterial wall as computed in the fluid domain. When compared to the structural stress distribution, it is seen that the sites of the highest structural stresses were not found to be the same as those having irregular vortical flow or those with high fluid WSS. One possible reason could be that as the

arterial wall is treated as a non-rigid entity, it has non-uniform stress distributions due to the pulsatile nature of flow in the lumen.

5.8 Patient Model Comparison

In this study, a small aneurysm and a large aneurysm are investigated from the Asian cohort to establish the biomechanics of the Asian AAA. These two patient models are suitable cases for comparing the biomechanics of rupture as the maximum transverse diameters are on either side of the clinical metric of 55 mm. Quantification of stresses developed in these two patients would provide insight into the mechanics of rupture where clinicians have been recommending surveillance or immediate surgery, as in the case of a small or a large aneurysm, respectively.

Table 5.3 compares the two patient models in terms of the stresses developed in both the fluid and structural domains. From the table, it can be observed that patient 1 had a larger value of maximum shear stress, maximum principal stress and the total deformation. These three parameters were considered to be the determining factors that affect failure of the AAA in the structural domain. The location of the highest stresses would also be the location where the maximum total deformation of the AAA is seen. This would then be the most probable location where rupture would occur. However, rupture would only occur if the stresses indicated in figures 5.5 and 5.7 are higher than the aorta wall maximum normal strength and maximum allowable shear stress respectively.

It can be deduced from the results obtained from the FSI analysis, that patient 2 with a much larger AAA size would have a lower chance of rupture risk as compared to patient 1 under these simulation conditions. This implies that the size of AAA may not be the sole determinant of the risk of rupture.

Table 5.3. Comparison of biomechanical parameters from patients 1 and 2

Parameters/ Patient	Maximum Shear Stress (Pa)	Maximum Principal Stress (Pa)	Total Deformation (m)
Patient 1	1.65e5	3.16e5	0.0020
Patient 2	1.21e5	2.32e5	0.0022

5.9 Limitations

There are a few limitations to this study. The inlet and outlet boundary conditions used have been extracted from literature and are not patient specific. The use of constant wall thickness is another limitation. Non-uniform wall thickness values could affect the stress distribution on the arterial wall. There was no intraluminal thrombus (ILT) present in this study. Although ILT is not present in all patient AAAs, the effect of its presence on the wall mechanics needs to be quantified. A non-linear material model should improve the accuracy of the response of the arterial wall. Nevertheless, a FSI based solution is an important step towards determining the actual interaction between the arterial wall and blood flow, which will assess rupture risk in an Asian AAA. A more detailed patient-specific model, inclusive of a FSI modeling approach, will further our understanding.

5.10 Conclusions

This study is the first of its kind to aim at establishing the biomechanical parameters for Asian AAA using a FSI based computational model. As has been established from literature, the incidence of AAA in Asians is low. But as there is prevalence, it is important to establish a biomechanical model for the Asian AAA. This has been done here

using an FSI method that incorporated the movement of the arterial wall and its interaction with the blood flow in the AAA lumen in two patient specific Asian patient geometries.

A two-way FSI problem was formulated based on boundary conditions extracted from literature for each of the two patient models. In order to carry out a comparison of the mechanics of rupture in each of the two patients, biomechanical stress parameters such as maximum first principal stress and total deformation in the structural domain and integral wall shear stress along with pressure and velocity correlations were analyzed in the fluid domain. A comparison of stresses induced showed that the values of principal stresses (structural domain) in the smaller aneurysm model were higher than those for the bigger aneurysm (3.16×10^5 Pa vs 2.32×10^5 Pa). This was also true in the fluid domain (18.74 Pa vs 12.88 Pa). Incorporating the biomechanics in the prognosis could be a step forward in minimizing the risk of surgical intervention and bring down healthcare costs. This is an initial study into the mechanics of rupture in Asian AAA and there will be subsequent studies on a larger patient cohort.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

The research presented in this thesis consists of an attempt to develop a diagnostic methodology to assess Abdominal Aortic Aneurysm rupture risk in a cohort of patients that were drawn from the Asian population. This was done by way of a multiple pronged approach consisting of mechanics based methods and statistical/machine learning methods.

Firstly, a mechanics based approach is used where biomechanical characteristics of 19 patients from the Asian and Caucasian patient groups are evaluated using finite element analysis. Three biomechanical characteristics are extracted; peak wall stress (PWS), spatially averaged wall stress (AWS) and the 99th percentile wall stress (99th- WS). Additionally, 54 geometric indices are extracted using an in-house methodology. These geometric indices were further reduced using statistical feature selection and stepwise regression to develop a parameter model that can accurately estimate the spatially averaged wall stress in both the Asian and Caucasian patient groups, in addition to the maximum diameter metric. Six features were obtained as a result of feature reduction (Maximum diameter, Distal neck diameter, Proximal neck diameter, MLN, K2LN, KM). Out of these 5 were significant in the Asian patient group (other than distal neck diameter) but only one of them (distal neck diameter) was significant for the Caucasian patient group. It was then demonstrated that the reduced feature model would yield excellent geometric surrogates for predicting the spatially averaged wall stress; with 72.87% accuracy in the Asian patient group and 74.74% accuracy in the Caucasian patient group.

The contribution of maximum diameter in each case was also computed with the Asian patient group showing 56.03% while it was 25.74% for the Caucasian group. The notable aspect would be that the proximal neck diameter is seen as one of the parameters that differentiate the Asian and Caucasian patient groups. Hence, this would have impact on the design of stents that are specific to the Asian population.

In the next step of the investigation, a novel machine learning approach was chosen to train a diagnostic model based on retrospective patient data. There were two studies that were carried out to investigate the effectiveness of replacing the FEA by machine learning so that a clinical expert is also able to use it at the bedside. In the first study, 17 attributes (clinical and geometric) extracted from 312 Asian patients with 158 healthy controls. The Naïve Bayes, Logistic Regression, Decision Tree and Support Vector Machines algorithms were compared to bring out the most effective classifier to identify ruptured AAA cases. The Naïve Bayes algorithm was the most effective with a classification accuracy of 95.19% and an AUC of 0.995. A wrapper based feature selection algorithm was subsequently applied to all the algorithms. A parameter model consisting of NL, DAAA, L1 and D3 resulted using the Naïve Bayes classifier. The model suggests that the three features NL, L1 and D3 are significant in the progression to rupture of the Asian AAA, in addition to the maximum diameter DAAA.

In the second machine learning study, eight features relating to patient history were used in a machine learning algorithm comparison analysis where Naïve Bayes was the most effective classifier. A Chi-squared feature selection algorithm subsequently resulted in BMI, smoking and hypertension being among the most significant features. It can be

concluded that the machine learning algorithms can be used as a validation tool for the diagnosis as the features extracted are based on patient history only.

Even as novel machine learning methods can be used to estimate the accuracy of stresses in the AAA, using geometric surrogates, blood flow and its interaction with the aortic wall is an important factor in the development of stresses in the AAA. Additionally, the intraluminal pressure, which is the challenging parameter to measure in a patient can be estimated from a FSI based analysis. A two-way FSI problem was formulated using two Asian AAA patient models. In order to carry out a comparison of the mechanics of rupture in the two patients, biomechanical parameters such as maximum first principal stress and total deformation in the structural domain and integral wall shear stress were computed, in addition to pressure and velocity distributions in the fluid domain. A comparison of stresses induced showed that the values of principal stresses (structural domain) in the smaller aneurysm model was higher than those for the bigger aneurysm (3.16×10^5 Pa vs 2.32×10^5 Pa). This was also true in the fluid domain (18.74 Pa vs 12.88 Pa).

6.2 Limitations

In chapter 3, the limitations of the work include the small cohort of patients (19) from each patient group and the general value of systolic pressure (120 mmHg) used as an input boundary condition in the FEA analysis. More patients in each group will provide better statistical significance and the use of a patient specific intraluminal pressure will make the model more accurate. The intraluminal thrombus (ILT), a common phenomenon, was also not considered in any of the analyses since it needs a multidomain meshing strategy.

In chapter 4, only 1D geometric indices were used as attributes in the machine learning model. 2D and 3D indices such as volume and curvature indices might play a role in the progression to rupture of the AAA and need to be extracted from the CT image through segmentation. The inclusion of such higher dimensional indices will improve the classification accuracy of the machine learning model.

In chapter 5, the inlet and outlet boundary conditions used have been extracted from literature and are not patient specific. The use of constant wall thickness is another limitation. Non-uniform wall thickness values could affect the stress distribution on the arterial wall. There was no intraluminal thrombus (ILT) present in this study. Although ILT is not present in all patient AAAs, the effect of its presence on the wall mechanics needs to be quantified. A non-linear material model should improve the accuracy of the response of the arterial wall.

6.3 Recommendations for Future Work

6.3.1 Role of Morphology

Chapter 3 covered the role of morphology in determining the geometric surrogates for each of the Asian and Caucasian patient groups. They were found to be different as there were five significant attributes for the Asian patient group as against only one attribute for the Caucasian patient group. A larger cohort of both patient groups must be investigated to generalize the attribute model. The geometric attributes obtained can be a precursor to development of point of care technologies specific to the Asian patient population.

6.3.2 Machine Learning based diagnostic tools

Chapter 4 described the use of novel machine learning algorithms to assess the rupture risk of AAA patients in the Asian population. This was done using geometric and clinical attributes in one study that involved 1D geometric indices extracted from the patient CTs. Although the algorithms were able to provide a feature model based on the indices, 2D and 3D indices that account for the curvatures and the volume ratios of the thrombus and the lumen need to be incorporated into the model. This will provide a more detailed perspective on the features that affect progression to rupture in the AAA using machine learning methods.

6.3.3 Fluid Structure Interaction

Chapter 5 describes the study of two AAA patients that were drawn from the Asian population to assess their rupture risk using the FSI methodology. The FSI methodology is a critical aspect of the assessment of rupture risk as it can be used to estimate the intraluminal pressure distribution which is an important parameter in estimating the wall shear stress on the aortic wall. The use of nonlinear material models and patient specific boundary conditions including resistance/impedance based boundary conditions would provide better insight into the progression to rupture of AAA in Asian patients. The results can then be used in conjunction with the statistical/machine learning methods in estimating rupture risk.

6.3.4 Experimental Studies

Experimental studies are critical in validating computational methods to test the physicality of the resulting solution. In this work, an attempt has been made to mimic the impedances prevailing in the vascular system. Future work will entail using these

experimental results to validate the computational FSI solution on patient specific geometries and impedance boundary conditions. The geometries and boundary conditions will be extracted through the CT and PC-MR modalities that will discern geometry and the inlet velocity boundary conditions respectively. Outlet boundary conditions will be based on the calculated resistance, capacitance and compliance parameters.

APPENDIX A

***IN VITRO* INVESTIGATION OF FLUID STRUCTURE**

INTERACTION IN AAA INCORPORATING IN VIVO VASCULAR

IMPEDANCES

A.1 Introduction

Experiments involving flow dynamics in biological systems have been traditionally tedious to setup. This has been because of the problem of accurately recreating the conditions within the limitations of engineering. Additionally, obtaining biological tissue involves institutional reviews and patient consent. But an *in vitro* investigation is critical to validating any computational analysis in the assessment of AAA rupture risk. Development of techniques such as 3D printing has made it feasible to produce models of tissue based on CT images. Subsequently, MRI or ultrasound based imaging modalities are used to extract the velocity boundary conditions and pressure can be measured through placing a catheter in the target artery.

In vitro studies investigating flow dynamics have been carried out by several groups as has been described in the literature review. Starting with glass models of aneurysms in the early 1970s, to 3D printed patient specific phantoms, the investigations have used steady or pulsatile inlet flows. The goals of these studies have been to use imaging modalities like CT/MRI and subsequently computational methods to assess the rupture risk in AAA. Corbett et al. [1] proposed designs for creating compliant silicone rubber based phantoms for *in vitro* studies. They also carried out a FEA study to determine if the pressure-diameter change behavior of the models could be predicted numerically. ILT analogs were also manufactured and characterized. Ideal models were manufactured with ILT analog

internal to the aneurysm region, and the effect of the ILT analog on the model compliance and stiffness was investigated. The wall materials had similar properties (E_{init} 2.22 MPa and 1.57 MPa) to aortic tissue at physiological pressures (1.8 MPa (from literature)). ILT analogs had a similar Young's modulus (0.24 MPa and 0.33 MPa) to the medial layer of ILT (0.28 MPa (from literature)). All models had aneurysm sac compliance ($2.62\text{--}8.01 \times 10^{-4}/\text{mm Hg}$) in the physiological range ($1.8\text{--}9.4 \times 10^{-4}/\text{mm Hg}$ (from literature)). The necks of the AAA models had similar stiffness (20.44–29.83 MPa) to healthy aortas (17.5 ± 5.5 MPa (from literature)). Good agreement was seen between the diameter changes due to pressurization in the experimental and FEA wall models with a maximum difference of 7.3% at 120 mm Hg. It was also determined that the inclusion of ILT analog in the sac of the models could have an effect on the compliance of the model neck. Ideal AAA models with physiological properties were manufactured. To replicate in vivo conditions, Dorfmann et al. [2] surmised that based on the work done by [3-5], the intraluminal flow is highly non-laminar. They developed a physiologic wall stress analysis procedure; that is, a finite element computational technique that evaluates the wall stress distribution and maxima in models accurately replicating the shape of individual AAA patient lesions and incorporating published wall material properties, but using load distributions derived from wall pressure measurements in corresponding experimental phantoms. They concluded that replication of in vivo conditions result in accurate estimates of wall shear stress.

Another aspect of replication of in vivo conditions is the application of outlet boundary conditions. Most studies have previously used only outlet pressure boundary conditions in their investigations due to the lack of adequate flow rate and pressure information in the

system. Without realistic boundary conditions, the effect of the downstream vasculature is not taken into account, thereby making the system physiologically inaccurate. Hence, the in vivo impedances that are induced due to proximal and distal vasculature must be taken into account. Kung [6] proposed an experimental model to mimic the vascular impedances prevailing in the AAA and built resistance and capacitance modules based on the target pressure that was required to be induced at the outlets. The purpose was to develop an experimental model to validate computational simulations of flow and pressure in a rigid AAA. The simulations were able to accurately mimic the experimental flow and pressure based on the impedance based outlet boundary conditions.

In this work, a deformable patient specific silicone AAA phantom is used to mimic the vascular impedances at the inlet and outlets of the AAA phantom and additionally, computational validation of the fluid structure interaction in the system will be carried out.

A.2 Experimental Setup

A silicone patient specific AAA phantom manufactured by Vascular Simulations Inc. is used to carry out experiments mimicking flow conditions in a diseased aorta. This work is being carried out at the Vascular Biomechanics and BioFluids Lab, Department of Mechanical Engineering at the University of Texas at San Antonio, San Antonio, TX, USA. The benchtop flow loop setup is as shown in Figure A.1. A description of the components of the experiment follows.

Figure A.1. Flow loop setup

Pump (1): An MRI-compatible CardioFlow 5000MR pulsatile pump (Shelley Medical Imaging Systems, London, ON, Canada) was used to circulate the blood-mimicking fluid (BMF) in the flow-loop under simulated pulsatile, physiological conditions. The flow rate profile that was inputted to the pump was obtained from Maier et al [7], where the temporal flow curves of blood flow in a healthy abdominal aorta are presented.

Phantom (2): A silicone AAA phantom (Vascular Simulations LLC, Stony Brook, NY) (Figure A.1a) was obtained to be tested in a bench-top flow-loop apparatus. The phantom includes the AAA, renal arteries and the iliac arteries.

Figure A.1a AAA Phantom (Vascular Simulations Inc., Stony Brook, NY)

Flow meters (3): Four flow meters (Kobold USA, Pittsburgh, PA) were used to measure the instantaneous flow rate profiles at the inlet and outlets. One of the flow meters was

connected upstream of the inlet and two others were connected downstream of the outlet. The current output from the flow meter was converted into a voltage output using a current loop. The flow meters were calibrated using a beaker/stop watch method over a range of inlet flow rates starting from 25 mL/s up to 150 mL/s. The experimental flow rates measured using this method were fit against the voltages simultaneously read off the flow meters in **LabView (7)**, via the **NI-DAQ (8)**.

Pressure catheter (4): A catheter pressure transducer (“Mikro-Tip” SPC-350, Millar Instruments, Houston, TX) was introduced through one of the iliac arteries to reach the aneurysm sac. The tip of the catheter was dipped in saline solution and the weights were adjusted in the pressure control unit to balance the channels. The control unit was calibrated and then connected to the DAQ. The voltage output from the DAQ was read using LabView and the pressure waveform at the center of the sac was measured. The pressure waveform was also measured using an **oscilloscope (5)** and compared to that obtained from LabView.

Reservoir (6): A reservoir was designed and fabricated to enclose the BMF prepared by mixing 40% glycerol and 60% de-ionized water. The reservoir has ports to accommodate three outlets and one inlet.

A.3 Results

A.3.1 Flow-meter Calibration

There are two flow meters distal to the AAA phantom and one upstream of the phantom. These are linear flow meters that need to be calibrated so as to ensure they are measuring the flow rates through the phantom accurately. In order to calibrate the flow meters, a

graduated cylinder is used to measure the amount of BMF being collected in a fixed time period. This is then compared with the readings from the data acquisition system hooked up to the flow meters to complete the calibration. The calibration was carried out using 6 flow rate values starting from 25 mL/s to 150 mL/s. The voltage was read from the DAQ for each of these flow rates to plot a calibration curve. The equations of the curve would then be put in to the formula blocks of the loop in LabView. The inlet flowmeter is labeled A, while the downstream flow meters are B and C. B reads the flow coming out of the iliacs that have been combined into one outlet and C reads flow from the renals that have also been combined. (figures A.2-A.4)

Figure A.2. Calibration of Flowmeter A

Figure A.3. Calibration of Flowmeter B

Figure A.4. Calibration of Flowmeter C

Figure A.5. Pressure v Time obtained from LabView

A.3.2 Pressure Measurement

As seen in figure A.5, the pressure measurement against time is obtained from the catheter placed in the center of the lumen. The pressure waveform measured is not equivalent to the target pressure waveform. Hence, there is a need to induce resistance in the flow loop to increase pressure to target pressure range. Once the resistance-capacitance circuit is attached to the downstream of the flow loop, it will induce higher pressures in the lumen as the resistance to the flow is increased. The median pressure will rise due to the increased resistance in the circuit and the amplitude of the waveform will change due to the capacitance.

A.4 Building the Resistance Capacitance (RCR) Module

The circulatory system distal to the AAA induces a resistance upstream that must be overcome to force the flow through the system. There is also an inductance value induced due to the length of each artery/capillary/vein. These values are analogous to the resistance and impedance seen in an electrical circuit. Hence, these can be modeled for a fluid circuit to account for the difference in pressure being measured inside the aneurysm sac. The resistance module design was based on [6]. Resistance values were calculated for both the inlet and outlets. The flowrate and cross sectional areas of the tubes determine the values of resistance. The module consists of several capillary tubes placed inside a 3D printed cylindrical tube (figure A.6). It is connected to the capacitance module by a conduit. The resistance and capacitance values are computed based on matching the target outlet pressure through a genetic algorithm based optimization problem (figure A.7). The pressure waveform matching, results in the output of values of proximal resistance (R_p), distal resistance (R_d), and capacitance (C). The Reynolds number is controlled so that the flow is laminar ($Re < 1200$). Using the resistance equation linking the viscosity and length, the radius of the capillary tube and the number of tubes needed are determined. This is read off a table generated by [6]. The resistances are shown in table A.1.

Table A.1 Resistance values for the AAA flow loop

	L (barye*s ² /cm ³)	R_p (barye*s/cm ³)	C (cm ³ /barye)	R_d (barye*s/cm ³)
Iliac outlets	42.7	617.12	1.08e-4	7714
Renal Outlets	42.7	645.12	3.6e-5	16128

Figure A.6 View of the cylindrical resistance module with embedded capillary tubes.

Figure A.7 Result of Genetic Algorithm Optimization to match target pressure and extract resistance and capacitance values

The number of capillary tubes that make up the resistance module are calculated to be 47 for both the renal and iliac outlets for the proximal module. For the distal resistance module, 69 tubes are used for the iliac outlets and 47 for the renal outlet. Corresponding diameters of the capillary tubes are chosen so that maximum packing fraction is achieved. The capacitance module is designed as follows. From the pressure of the fluid at the base of the module, the height of the fluid column is determined. The important aspect is the height of the air column that induces the capacitance in the flow loop.

$$C = \frac{V_{tank} - A_{tank} * H_{fluid}}{P_{fluid} - \rho g H_{fluid}} \quad (A.1)$$

$$H_{fluid} = \frac{A_{tank} * H_{tank} - C * P_{fluid}}{A_{tank} - \rho g C} \quad (A.2)$$

$$P_{air} = P_{fluid} - \rho g H_{fluid} \quad (A.3)$$

Maintaining an air pressure of P_{air} inside the tank with fluid level at H_{fluid} , we should be able to achieve a capacitance as obtained from the optimization algorithm. The capacitance values in height of the air column were determined as 6.4 cm and 9.9 cm for the renal and iliac outlets. The pressure waveform from a range of 0-60 mmHg was pushed up to 80-120 mmHg using the capacitance modules. Figure A.8 shows the cylindrical capacitance modules that have been used in the experiment setup.

Figure A.8 Capacitance Modules added to bench top flow loop setup

The addition of resistance and capacitance modules in the flow loop aids in the development of the target pressure waveforms at the outlets. Figure A.9 shows the flow loop with both the proximal and distal resistances and the capacitance modules. The phantom itself is immersed in a cylindrical box filled with BMF. This is done to aid in the contrast imaging process that will be carried out using PC-MRI techniques. As a result of the imaging, the velocity waveform at the inlet can be obtained. This can be used in the eventual computational validation process.

Figure A.9 Bench top flow loop set up with addition of RCR module

A.5 Conclusions

Computational methods based on mechanics and machine learning have improved estimation of biomechanical characteristics in assessing the AAA rupture risk, but experimental validation is a critical aspect of any investigation. *In vitro* validation is important as a physical system can be fully reproduced using known control parameters. In the process, an opportunity to utilize imaging modalities such as CT/MRI is provided, along with extraction of experimental data that can be utilized in computational analysis of the physical system. In appendix A, a physical Windkessel model based flowloop setup is described for a patient specific silicone AAA phantom. An attempt is made to mimic the *in vivo* vascular impedances that induce physiological pressure values in the AAA lumen. This was induced using a fluid resistance-capacitance (RCR) circuit where proximal and distal resistance and capacitance values are computed using a target pressure

outlet waveform. Based on those parameters, RCR modules are fabricated to be incorporated in the flow loop. This will result in the measurement of physiologically accurate pressure waveforms at the outlet, thereby accounting for the *in vivo* impedances that have an effect on the vasculature.

A.6 Limitations

The RCR module was introduced so that the target pressure at the outlet of the AAA can be achieved. The target pressure was achieved and the resistance and capacitance values were obtained as a result of a genetic algorithm based optimization method as shown in fig A.7. During the experiment, the pressure waveforms obtained are underestimated compared to the target pressure. Future work would involve investigating this further to obtain the intended target pressure.

A.7 Future Work

The experiment setup will be used to measure the target pressure from the catheter placed in the AAA lumen. This would have imposed the required resistance, capacitance and inductance values in the flow loop. Subsequently, the test section containing the AAA phantom will be imaged using a 9T MRI machine at the Houston Methodist Research Institute, Houston, Texas to obtain phase contrast MRIs. Flow rate in a cardiac cycle will be extracted from these images. Aneurysm geometry will be extracted using the CT imaging modality. These images can then be reconstructed using segmentation and used in a Navier Stokes equation based solver for computational validation. This work will demonstrate computational validation of fluid mechanics phenomena in a patient specific deforming AAA lumen.

APPENDIX B

INDICES FOR AAA GEOMETRY QUANTIFICATION

One-Dimensional (1D) Size Indices

All diameter measurements were computed according to the hydraulic diameter definition (mm):

$$D = \frac{4 * Area}{Perimeter}$$

D_{max} : Maximum transverse diameter for all cross sections within the AAA sac

$D_{neck,p}$: Proximal neck diameter immediately below the renal arteries

$D_{neck,d}$: Distal neck diameter

H : Height of AAA

L : Centerline length of AAA

H_{neck} : Height of AAA neck

L_{neck} : Centerline length of AAA neck

H_{sac} : Height of AAA sac

L_{sac} : Centerline length of AAA sac

H_b : Bulge height

d_c : Distance between the lumen centroid and the centroid of the cross section where D_{max} is located

2D Shape Indices

DHr: Diameter-Height ratio; *DHr* is an expression of the fusiform shape of the AAA sac:

$$DHr = \frac{D_{max}}{H}$$

DDr: Diameter-Diameter ratio

$$DDr = \frac{D_{max}}{D_{neck,p}}$$

Hr: Height ratio; *Hr* is an assessment of the relative neck height in comparison with the AAA height:

$$Hr = \frac{H_{neck}}{H}$$

BL: Bulge Location; *BL* provides a measure of the relative position of the maximum transverse dimension with respect to the neck:

$$BL = \frac{H_b}{H}$$

β : Asymmetry factor

$$\beta = 1 - \frac{d_c}{D_{max}}$$

T: Tortuosity

$$T = \frac{L}{d}$$

where d is the Euclidean distance from the centroid of the cross section where $D_{neck,p}$ is located to the centroid of the cross section at the AAA distal end.

C_{ave} : average lumen compactness

C_{min} : minimum lumen compactness

C_{max} : maximum lumen compactness

where compactness is defined as $C = \frac{Perimeter^2}{4*\pi*Area}$

Thrombus Content Indices

$t_{t,ave}$: average thrombus thickness

$t_{t,max}$: maximum thrombus thickness

$t_{t,min}$: minimum thrombus thickness

$t_{t,minLoc}$: location of the minimum thickness

$t_{t,maxLoc}$: location of the maximum thickness

3-D Size Indices

V : Vessel volume

S : Vessel surface area

V_{ILT} : Volume of intraluminal thrombus (ILT) contained within AAA sac

γ : Ratio of AAA ILT volume to vessel volume

$$\gamma = \frac{V_{ILT}}{V}$$

3-D Shape Indices

IPR : isoperimetric ratio

$$IPR = \frac{S}{V^{\frac{2}{3}}}$$

NFI : non-fusiform index

$$NFI = \frac{\frac{S}{V^{2/3}}}{\frac{S_{fusiform}}{V_{fusiform}^{2/3}}} = \frac{IPR}{IPR_{fusiform}}$$

Wall Thickness Indices

$t_{w,min}$: minimum wall thickness

$t_{w,max}$: maximum wall thickness

$t_{w,ave}$: average wall thickness

$t_{w,Dmax}$: average wall thickness where D_{max} is located

$t_{w,mode}$: mode of the wall thickness

$t_{w,median}$: median of the wall thickness

$t_{w,minVar}$: minimum variance of wall thickness

$t_{w,MaxVar}$: maximum variance of wall thickness

$t_{w,MedianVar}$: median variance of wall thickness

$t_{w,modeVar}$: mode variance of wall thickness

$t_{w,meanVar}$: mean variance of wall thickness

$t_{w,skew}$: skewness of wall thickness distribution; indicates whether the distribution of wall thickness is normal, positive skew, or negative skew. Expressed as a percentage of the total thickness values that fall above/below the average.

Second Order Curvature Based Indices

GAA: Area averaged Gaussian curvature

$$GAA = \frac{\sum_{all\ elements} K_j S_j}{\sum_{all\ elements} S_j}$$

MAA: Area averaged Mean curvature

$$MAA = \frac{\sum_{all\ elements} M_j S_j}{\sum_{all\ elements} S_j}$$

GLN: L2 norm of the Gaussian curvature

$$GLN = \frac{1}{4\pi} \sqrt{\sum_{all\ elements} S_j \cdot \sum_{all\ elements} (K_j^2 S_j)}$$

MLN: L2 norm of the Mean curvature

$$MLN = \frac{1}{4\pi} \sqrt{\sum_{all\ elements} (M_j^2 S_j)}$$

KG: Square root sum of the Gaussian curvature

$$KG = \sqrt{\sum_{all\ elements} K_j^2}$$

KM: Square root sum of the Mean curvature

$$KM = \sqrt{\sum_{all\ elements} M_j^2}$$

K1AA: Area averaged major principal curvature

$$K1AA = \frac{\sum_{all\ elements} k_{1j} S_j}{\sum_{all\ elements} S_j}$$

K2AA: Area averaged minor principal curvature

$$K2AA = \frac{\sum_{all\ elements} k_{2j} S_j}{\sum_{all\ elements} S_j}$$

K1LN: L2 norm of the major principal curvature

$$K1LN = \frac{1}{4\pi} \sqrt{\sum_{all\ elements} (k_{1j}^2 S_j)}$$

K2LN: L2 norm of the minor principal curvature

$$K2LN = \frac{1}{4\pi} \sqrt{\sum_{all\ elements} (k_{2j}^2 S_j)}$$

APPENDIX C

MEAN AND STANDARD DEVIATION OF ALL GEOMETRIC INDICES FOR THE ASIAN (A) AND CAUCASIAN (C) AAA.

Geometry Index	Group	Mean	Std. Deviation	Std. Error of the Mean
D_{max}	C	51.7832	13.6862	3.1398
	A	51.4936	14.2001	3.2577
$D_{neck,p}$	C	29.2460	7.6480	1.7546
	A	25.8619	5.1354	1.1781
$D_{neck,d}$	C	23.5008	16.0198	3.6752
	A	21.8508	16.0529	3.6828
H	C	103.9737	15.8557	3.6375
	A	108.3895	20.8964	4.7940
H_{neck}	C	22.8947	19.7143	4.5228
	A	28.0000	25.2719	5.7978
H_{sac}	C	81.0789	26.2786	6.0287
	A	80.3895	35.7114	8.1928
L	C	132.4948	32.7286	7.5085
	A	120.6714	43.0408	9.8742
L_{neck}	C	37.1969	35.7878	8.2103
	A	25.0983	23.6556	5.4270
L_{sac}	C	95.2980	47.1805	10.8240
	A	95.5732	52.5445	12.0545
H_b	C	59.9474	18.8782	4.3310
	A	37.8421	29.3793	6.7401
d_c	C	4.4878	3.8550	0.8844
	A	7.1481	5.1907	1.1908
DHr	C	0.5033	0.1356	0.0311
	A	0.4794	0.1346	0.0309
DDr	C	1.8387	0.6033	0.1384
	A	1.9884	0.4427	0.1016
Hr	C	0.2252	0.1887	0.0433
	A	0.2716	0.2480	0.0569
BL	C	0.5862	0.1956	0.0449
	A	0.3423	0.2316	0.0531
β	C	0.9169	0.0638	0.0146
	A	0.8710	0.0759	0.0174
T	C	1.2295	0.1325	0.0304

	A	1.0865	0.3040	0.0697
C_{ave}	C	1.1530	0.0846	0.0194
	A	1.1332	0.0578	0.0133
C_{max}	C	1.6396	0.5800	0.1331
	A	1.9988	0.6478	0.1486
C_{min}	C	1.0384	0.0342	0.0079
	A	1.0120	0.0068	0.0016
$t_{t,ave}$	C	6.1527	3.6039	0.8268
	A	8.1852	5.1238	1.1755
$t_{t,max}$	C	18.3174	10.0478	2.3051
	A	22.2617	12.7749	2.9308
$t_{t,min}$	C	1.5153	0.1456	0.0334
	A	1.4020	0.1300	0.0298
$t_{t,minLoc}$	C	0.4771	0.3340	0.0766
	A	0.2757	0.2249	0.0516
$t_{t,maxLoc}$	C	0.6299	0.2751	0.0631
	A	0.4137	0.3563	0.0817
V	C	172.7243	97.4225	22.3503
	A	198.8559	126.8547	29.1025
S	C	169.0759	59.6680	13.6888
	A	188.5300	79.4554	18.2283
V_{ILT}	C	55.9276	40.0109	9.1791
	A	83.0174	74.0210	16.9816
γ	C	0.3110	0.1765	0.0405
	A	0.3551	0.1848	0.0424
NFI	C	1.1298	0.0817	0.0187
	A	1.1435	0.0662	0.0152
IPR	C	5.4648	1.0058	0.2308
	A	5.8813	0.4862	0.1115
$t_{w,ave}$	C	1.7728	0.5050	0.1158
	A	2.1221	0.5129	0.1177
$t_{w,max}$	C	3.5296	1.2315	0.2825
	A	5.4744	1.8293	0.4197
$t_{w,min}$	C	0.6336	0.2151	0.0494
	A	0.8233	0.2070	0.0475
$t_{w,Dmax}$	C	1.7766	0.6337	0.1454
	A	2.1952	0.6257	0.1435
$t_{w,mode}$	C	1.6494	0.5940	0.1363
	A	2.0654	0.6072	0.1393
$t_{w,median}$	C	1.7610	0.5366	0.1231
	A	2.1082	0.5565	0.1277

$t_{w,minVar}$	C	0.0395	0.0393	0.0090
	A	0.0194	0.0171	0.0039
$t_{w,MaxVar}$	C	0.3346	0.3846	0.0882
	A	1.0743	0.7770	0.1783
$t_{w,meanVar}$	C	0.1194	0.0988	0.0227
	A	0.1612	0.0977	0.0224
$t_{w,MedianVar}$	C	0.1032	0.0852	0.0195
	A	0.0910	0.0619	0.0142
$t_{w,modeVar}$	C	0.0395	0.0393	0.0090
	A	0.0194	0.0171	0.0039
Percent thickness above average thickness	C	44.7607	8.0253	1.8411
	A	37.9916	8.8207	2.0236
Percent thickness below average thickness	C	55.2393	8.0253	1.8411
	A	62.0084	8.8207	2.0236
GAA	C	.0001	.0002	.0000
	A	-.0001	.0005	.0001
MAA	C	.0243	.0053	.0012
	A	.0282	.0096	.0022
GLN	C	6.0044	2.0394	.4679
	A	20.1167	10.3552	2.3756
MLN	C	.6395	.1847	.0424
	A	2.4048	1.5731	.3609
K1AA	C	.0694	.0126	.0029
	A	.1535	.0590	.0135
K2AA	C	-.0208	.0088	.0020
	A	-.0971	.0467	.0107
K1LN	C	155.7185	69.4202	15.9261
	A	531.4043	444.6025	101.9988
K2LN	C	113.0567	50.6348	11.6164
	A	423.5651	306.2873	70.2671
KG	C	.6937	.2461	.0565
	A	3.1203	1.6655	.3821
KM	C	9.6321	2.1923	.5029
	A	43.3127	24.4383	5.6065

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Chapter 3: The Role of Morphology in Asian And Caucasian Abdominal Aortic

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Chapter 5: Application of Fluid Structure Interaction Methods to Estimate the Mechanics of Rupture in Asian Abdominal Aortic Aneurysms

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Appendix A: *In vitro* Investigation of Fluid Structure Interaction in AAA incorporating *in vivo* Vascular Impedances

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