NonInvasive Methods of Characterising Local Regional Variations in Aortic Tissue to Advance Aneurysm Rupture Risk Prediction

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A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY AT THE COLLEGE OF SCIENCE AND ENGINEERING, UNIVERSITY OF LIMERICK, IRELAND.

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SUBMITTED TO THE UNIVERSITY OF LIMERICK, APRIL 2012.
I hereby declare that this thesis is entirely my own work, and has not been submitted for any other awards at this or any other academic establishment. Where use has been made of the work of other people it has been fully acknowledged and referenced.

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ABSTRACT

Abdominal Aortic Aneurysms (AAAs) is a permanent and irreversible dilation of the infrarenal section of the aorta. AAA’s are generally asymptomatic, until rupture of the AAA wall occurs. Rupture can lead to large abdominal bleeding and death within a short period of time. AAA formation affects the integrity of the aortic wall, leading to a decrease in compliance and tensile strength, increased wall stiffness and a progressive dilation of the wall. From a biomedical engineering perspective, rupture of an AAA occurs when, locally, the wall stress surpasses the strength of the wall. This suggests it is of importance to have wall property information and perform wall stress analysis which can assess the risk of rupture reliably. Noninvasive assessment of aneurysm wall properties would improve insight into the vascular changes, preceding rupture. This thesis aims to explore noninvasive methods of characterising aortic wall properties and the effectiveness of these techniques to aid in clinical assessment. In this study, the efficacy of acoustic radiation force impulse (ARFI) imaging for determination of aortic changes in vitro was reported. The study successfully developed an artificial aneurysm in excised tissue and the changes induced by aneurysm development were detected using ARFI. A feasibility case study demonstrated a method for estimation of in vivo tissue properties using ARFI and exhibited the viability of translation of this modality to AAA clinical use. Most preoperative imaging protocols use computerised tomography (CT) angiography with three dimensional (3D) reconstructions for sizing and planning. The resulting images are static images, despite the fact that the human aorta exists in a dynamic environment. The elastic properties of the aorta were examined to assess the changes in the dynamic environment using cardiac gated CT. Different regions of the aorta were shown to have different mechanical properties. High variation in mechanical behaviour was found to exist locally. A novel method which allowed these variances to be reflected in finite element reconstructions was established. This is believed to be an important step in the improvement and accuracy of finite element studies. The morphology and the regional variation in mechanical properties were both found to play a key role in accurate wall stress calculations. An index, described as Regional Prestress Rupture Index (RPRI), indicates that regional variations are important for accurate rupture prediction. The knowledge of regional distribution of mechanical behaviour and accurate wall dynamics has potential to be employed to improve the durability and long term clinical performance of stent-grafts used for treating AAA. A novel and elegant approach to compute the damage of the aorta using cardiac gated CT image data is also presented. This technique can also be applied to analyse image data of patients with cardiovascular disease and is not limited to the abdominal aorta. The study quantified tissue damage due to aneurysm formation. Due to the high variations between individual patients, this technique may represent a method of analysing patient-specific changes. The results and conclusions presented through this thesis may further contribute to the understanding of AAA biomechanics and rupture potential, and in the future may help provide improved clinical guidance on surgical intervention for AAA treatment.
Dedicated to
My father, Liam

Success is not final,
Failure is not fatal:
It is the courage to continue that counts.
Acknowledgements

There are so many people I have to thank for the help I’ve had over the last few years.

Firstly to my supervisors, Prof. Tim McGloughlin and Dr. Anthony Callanan. Tim, thank you for giving me the opportunity to study and work in CABER and thanks for all the advice and insight given throughout my PhD. Anthony, for always supplying a wealth of new ideas and paths to explore. I really appreciate your time, effort and opinions that have shaped this research.

To Prof. Gregg Trahey, for providing me with the opportunity to work in your lab and giving advice and direction on my research. Doug Dumont – the time and effort you put in to AAA’s was unbelievable, the continual helpfulness and expertise in areas from ARFI to Linux to matlab to the best places to go in Durham was always appreciated. To the rest of the Trahey, Nightingale, Smith labs, especially Brett, Steve, Richard, Stephanie, David, the opportunity to pick your brains about the scanner, ARFI and all they entail was brilliant.

To Joost van Herwaarden and Herman Zandvoort, for supplying the 4DCT scans, taking the time to introduce me to the 3Mensio software and providing surgical insight into my work.

Thank you to the staff of the MABE department who always helped out whenever needed.

To the CABER research group, thanks for all the advice and help through the years. I have to start with the ‘Class of 2007’. Steve, the GIMP-lord, for all the help and advice with everything from images to the cluster. And always keeping me entertained with stories of your 200mile cycles/runs/swims! Mossy, for finishing up before me and letting me know what the ‘real’ world is like, nearly time again for another holiday! Aidan, for all the advice, debates and help especially the couple of late nights in the lab with the DIC and experimental side of things, greatly appreciated. Edel, for finishing up with me, always good to know someone else was in the same boat, with formatting and what forms to fill in! To the ‘original newbies’, Baz, Barry, Timmy, Dave, who showed us all how it was done. Who gave great help while they were here and still even after they have left from whatever corner of the world they happen to be in. To Dave O’R, for all the cups of tea and, of course, the Scunthorpe United and Aisling Annacotty trivia, and saving me hours of work with the thesis template! To Alex, a pleasure to sit beside you for 3 years and for the company near the end in the late evenings. To Grainne, for all the offers of proofing and reading. To CABER 2.0, Lynchie, Willo, John, Leonard, Jen, Ian, Brian, Eoghan, Bronagh, for all the laughs and intellectual conversations at lunch and tea – It’s going to be tough job deciding who to leave my teatime stopwatch to. To Siobhan (Shivvy) and Sarah, for keeping the CABER aneurysm flag flying! To Aoife, for putting up with my somewhat ‘messy’ desk. To Rory, for aorta help and abattoir trips, even if they did leave you looking a bit pale! To Farmer, Anna, Niall, for your knowledge and expertise whenever needed. To Mikah and Eamonn, for keeping the group going and giving help and advice.

To Laura, who I know is missing us all dearly since her move to the B-Block, all the help formatting and SPSS advice was brilliant. To Claire, for being probably the most
good humoured person I know, and for all the baking and cupcakes! To Maria, for putting up with a house of engineers, although it probably helps having a picnic bag! To Daithí, for putting up with a house of girls and girl chat! To all of ye for putting up with me in Number 75 and being around to have a laugh and banter!

To Lisa, for being there through it all, be it through email or a ‘few odd’ texts, for the chats about anything from the price of BMWs to goats to dresses to the odd conversation about PhD work! To Ciara Drico, long way from Clonners now! Thanks to you both for all the laughs about every crazy event the last few years!! To Olivia and Michele, for the several thousand cups of tea during undergrad, we’ll have to celebrate this one in LA!

To Michele and Rebecca, thanks for making the Duke months some of the most memorable of my life, from I gotcha to Chips Ahoy!

To Rosie, for being fascinated in porcine aortas! To Edel, for doing a PhD and feeling my pain! To Hayesie, for all the road trips and nights out, we’ll have to arrange another Limerick/Clems road trip for old time’s sake! To all the other girls from home, O Grady, Miriam, Cahalan, Dots – for all the encouragement. To all the camogie girls, for some great matches and some even better nights out, what better way to vent PhD frustrations than with a hurl!

To my Fenton and Tierney cousins, aunts and uncles, who always encouraged me, had some great nights out and were around to ask ‘Are you not finished yet!!??’.

To my two Grandparents who passed away during the course of my PhD, thanks for all the prayers and support.

To my own family and their families, thanks for putting up with me, even during the odd bad mood, the encouragement and making sure there was enough money in my wallet for a night out. My mother, for making sure there was always petrol in my car and food in my bag going back every weekend, and minding my laptop while I wasn’t using it!! William, for all the career advice! Kevin, for ensuring I wasn’t the last Tierney in college! Andrea, sorry for encroaching on your nurse/doctor territory, thanks for all the dinners, lunches and shopping trips. Rayme, for paving the way in UL. Joey, or Bank of Joey, that brought me through undergrad! Caroline, for all the pictures and random chats when I needed a break. Shane, for the hilarious emails, G Star, and filling each weekend with jobs! Frankie, for all the whispered phone calls, yes I was in the office. Sara, for the skype chats and Amman gossip, thanks also for proof reading my thesis, and therefore taking responsibility for any spelling mistakes! I couldn’t have done it without all of ye.

And to Iain, thanks for everything, the support, encouragement and listening to my rants. Thanks for all the laughs and keeping me motoring (literally!!). There are no flying cars yet, but I am finished!!

To my father, who would have loved to see a doctor in the family and to read this thesis.
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Glossary of Terms

Aneurysm  An abnormal localised dilation or bulge in a blood vessel
Aneurysmal  Relating to or affected by an aneurysm
Anterior  Situated towards the front of the body
Bifurcate  To divide into two branches or parts
Calcification  A calcified substance
Collagen  Connective tissue protein which gives tissue in the body its stiffness
Compliance  Change in vessel cross sectional area for a given change in pressure
Computed Tomography  Medical Imaging Technique where multiple x-rays are passed through a body to create cross sectional images
Dilatation  Relating to an enlargement or expansion
Distal  Anatomically located far from a point of reference, such as an origin or a point of attachment
Elastin  Connective tissue protein which gives tissue in the body its elasticity
Endovascular  A minimally invasive technique of inserting a medical device into a blood vessel
Hypertension  Abnormally elevated blood pressure
In vitro  Latin for within the glass; but frequently used to describe experimental approaches that stimulate physiological conditions
In vivo  Latin for within the living
Infrarenal  Situated below the kidneys or renal arteries
Intraluminal  A stationary blood clot along the wall of a blood vessel
Thrombus  The cavity of a tubular structure
Mortality  The death rate, which reflects the number of deaths per unit of population
Physiological  Characteristic of an organs functioning
Posterior  Situated at or toward the hind part of the body
Postoperative  Relating to, occurring in, or being the period following a surgical operation
Preoperative  Occurring, performed, or administered before and usually close to a surgical operation
Proximal  Anatomically located nearer to a point of reference, such as an origin, a point of attachment or a midline of the body
Stent Graft  A Dacron or ePTFE graft supported by metal stents. Used for the treatment of cardiovascular disease and implanted using the endovascular method
Ultrasonography  Diagnostic Imaging in which ultrasound is used to image an internal body structure
INTRODUCTION
INTRODUCTION

Cardiovascular diseases (CVD) are the world’s largest killers, claiming 17.1 million lives a year. In Ireland, cardiovascular disease is the number one cause of death, with more than 9,600 deaths each year (Brosnan et al. 2009). This equates to the death of more than one person every hour. In nearly all European countries, cardiovascular mortality represents around 40% of all-causes of mortality before the age of 74 years (Kromhout 2001). Cardiovascular diseases result in substantial disability and loss of productivity and contribute in a large part, to the escalating costs of health care, especially in the presence of an ageing population. In 2006, direct and indirect costs of cardiovascular disease were estimated at US$415 billion in the U.S.A (American Heart Association 2007). These costs place a huge burden on the economy.

Types of cardiovascular diseases include atherosclerosis, stroke, high blood pressure (hypertension), aneurysms and heart attacks. Aneurysms are a prevalent type of CVD, which can occur in any part of the body. An aneurysm is a permanent localised dilatation of a blood vessel. The three main types of aneurysm are thoracic aortic aneurysms (TAA), cerebral aneurysms and abdominal aortic aneurysms (AAA). An AAA is the dilatation of the abdominal aorta, which occurs below the renal arteries and above the aortic bifurcation. An AAA is defined as an infrarenal aortic diameter 1.5 times larger than normal (Johnson 1991). It is this, the AAA, which is of most interest in this research.

Abdominal aortic aneurysms (AAA) are found in 4% to 8% of older men and 0.5% to 1.5% of older women. The incidences of AAA’s have increased largely during the past two decades due in part to the aging demographic, the rise in the number of smokers, the introduction of screening programmes and improved diagnostic tools (Sakalihasan et al. 2005). There are approximately 200,000 patients in the US and 500,000 patients worldwide diagnosed with AAA each year (Bosch et al. 2001). These aneurysms are hazardous because of their propensity to rupture. Ruptured AAA’s (rAAA) were found to cause 0.8% of all deaths in women older than 65 years of age compared to 2.1% of that in men (Scott et al. 2002). Patients with an unruptured AAA are typically asymptomatic, although patients may present with back or abdominal pain or gastrointestinal symptoms as aneurysms enlarge and compress adjacent structures.
Rupture may occur spontaneously once the induced mechanical wall stress exceeds the local minimum strength of the AAA wall (Kleinstreuer and Li 2006). Rupture of an AAA is a dramatic and often fatal process, with up to 90% mortality on rupture (Upchurch and Criado 2009). After rupturing, approximately 40% of total fatalities occur before hospital admission. After emergency repair of the rAAA, 40-50% of patients die during or within 30 days of operation (Hak 1996). These factors have contributed to death from AAA being the 13th most common cause of death in the US and the 10th leading cause of death in men over the age of 65 (Vorp 2007, Vardulaki et al. 1998).

The normal healthy aortic wall structure is in three layers - Tunica Intima, Tunica Media and Tunica Adventitia. The innermost component, the intima, lining the lumen of the artery is a continuous layer of thin endothelial cells, which offer little resistance to outward pressure but are resistant to the shearing force of the flowing blood. The adventitia is a fibrous sheath composed largely of collagen. The adventitia has little elasticity, thus it lacks the dynamic recoil of the media, but it accounts for much of the static strength of the arterial wall (Thubrikar 2007).

The basic ingredients of the aortic media are smooth muscle cells (SMCs), elastin fibres and collagen fibres. These components are arranged in an orderly fashion. The smooth muscle cells are arranged circumferentially. Interposed among them are variable amounts of elastin, collagen, and ground substance. The media contains a series of concentrically arranged perforated elastic membranes, or laminae, and between these membranes are SMCs, thin collagen fibrils, and an amorphous ground substance. The basic structural unit of aortic media is two parallel elastic laminae with SMCs, collagen fibres, and ground substances sandwiched between them. The number of elastic laminae (lamellar units) generally increases with age (40 in the newborn; 70 in the adult). Elastin is highly elastic and can double its length and spring back to its original dimensions. Collagen has very different properties. Fibrillar collagen has a tensile strength more than 20 times greater than that of elastin and is very stiff. It cannot extend beyond a small percentage of its length before structural damage occurs. Aortic collagen is coiled up in such a way that, initially, the load of the aorta is borne by elastin and, as the load increases, collagen fibres uncoil and are progressively recruited as load-bearing elements. This allows the aorta to stretch easily initially and to become less and less distensible progressively with load (Thubrikar 2007).
The pathogenesis of AAA formation is not well understood. It is characterised by a destruction of elastin and collagen in the arterial wall. The formation of these dilations can be attributed to a number of risk factors including age, gender, smoking, hypertension and family history (Blanchard et al. 2000). A National Heart, Lung and Blood Institute (NHLBI) Request for Applications (HL-99-007) identified that AAAs are characterised by destruction of elastin and collagen in the media and adventitia, loss of medial smooth muscle cells with thinning of the vessel wall, and transmural infiltration of lymphocytes and macrophages. The destruction of elastin is considered a key factor in the pathogenesis of an aneurysm. Exposed elastin degradation products in the aortic wall may serve as the primary chemotactic attractant for infiltrating macrophages. Aneurysms occur with greater frequency in the abdominal aorta where the number of elastic lamellae (and therefore elastin) are markedly decreased in comparison with the thoracic aorta (Macsweeney et al. 1994). Elastin destruction and fragmentation is a striking histological feature of an aneurysm wall. Disruption of elastin by elastase produces aneurysms in animal models (Anidjar et al. 1990, Kratzberg et al. 2009, Sinha et al. 2004). The in vivo elastase perfusion has been found to lead to subsequent aortic dilatation, collagen and elastin degradation, MMP upregulation, and an extensive inflammatory cell infiltrate in the outer media and adventitia of the aortic wall, which is typical of AAA formation (Sinha et al. 2004). Elasticity of the aneurysm wall has been observed to be reduced, and it is correlated with reduced elastin content. The underlying problem in aneurysmal disease is this weakening of the aortic wall resulting in progressive dilation leading to eventual rupture (Golledge et al. 2006).

If an AAA is diagnosed before rupture and the risk of rupture is thought to be greater than the risk of interventional surgery, there are two methods of aneurysm repair; open repair and endovascular surgery (Kleinstreuer and Li 2006, Lederle 2003, Sakalihasan et al. 2005). The gold standard in AAA repair remains the open surgical method. Open repair (OR) requires a large abdominal incision as well as clamping of the aorta above and below the aneurysm. The aorta is then opened and a graft is sewn in. The long-term durability of ORs is excellent, with little need for aneurysm-related reintervention. However, OR is a major surgical procedure and involves prolonged cross clamping of the aorta, which poses the risk of serious operative complications (Corbett et al. 2008). Endovascular aneurysm repair (EVAR) was introduced in the late 1980s. It has evolved since then to become the preferred treatment in older and unfit
patients. This technique is minimally invasive and involves inserting a collapsed graft through a femoral artery access and over a guide wire to the aneurysm location. Here, the stent-graft is allowed to expand to form a new conduit for blood flow excluding the aneurysm sac. Due to the minimally invasive nature of this procedure, operation time and blood loss are reduced, and the need for cross clamping of the aorta is eliminated. Early mortality, length of hospital stay, and recovery time are lower after EVAR than after OR. These reasons has led to EVAR becoming a very popular treatment, over the last 20 years, where 70/80% of eligible patients were treated using this technique (Cambria 2011). Even with elective surgical repair complications can occur, and the risk of mortality lies between 3% and 6% (Brewster et al. 2003). This mortality rate rises to 40-50% when dealing with emergency repairs due to a leak or rupture (Brewster et al. 2003).

The risk of AAA rupture increases strongly with increasing diameter of the AAA (Schlösser 2008). Aneurysm diameter has been used widely as the ‘one size fits all’ criterion with which to assess rupture risk, specifically the risk of rupture is highest when the aneurysm reaches 5-5.5cm in diameter (Lederle 2003, Scott et al. 2002). However several studies have questioned the reliability of this criterion by showing that small aneurysms (<5cm) can rupture and that larger aneurysms (>5cm) can remain quiescent for years (Darling et al. 1977, Doyle et al. 2009, Limet et al. 1991). This coupled with a 4-5% mortality rate with interventional surgery indicates a critical need for improved noninvasive AAA rupture predictors (Upchurch and Criado 2009).

The investigation of peak wall stress as a potential indicator exhibited the location of AAA rupture as location of peak stress (Venkatasubramaniam et al. 2003). It has been shown that the stresses acting on the AAA wall are not evenly distributed and are highly dependent on the specific shape of the aneurysm (Raghavan and Vorp 2000, Venkatasubramaniam et al. 2003, Wang et al. 2002). Therefore AAA’s with equivalent diameters and pressures, and thus the same Laplace-predicted wall stress, can have largely different stress distributions (Vorp 2007). The rupture of an AAA occurs when the stresses acting on the AAA exceed the wall strength. Hence, considering the location of peak stress alone is insufficient. Other proposed predictors include growth rates (Hirose and Takamiya 1998), degree of asymmetry (Doyle et al. 2009), wall stiffness (Sonesson et al. 1999), increase in ILT thickness (Stenbaek et al. 2000), finite element analysis rupture index (FEARI) (Doyle 2009) and prediction from
mathematical models (Volokh and Vorp 2008). Based on these hypotheses, it is believed that an improved predictor of AAA rupture is desirable and may have clinical importance. The Society for Vascular Surgery (SVS) practice guidelines for the treatment of AAAs, a wide range of other risk factors associated with AAA are discussed such as sex, gender, family history, AAA expansion rate, presence of ILT, wall stiffness, wall tension, peak AAA wall stress, AAA geometry etc.; however it states clearly ‘further validation’ of such factors will be necessary before they can be implemented in a clinical setting (Chaikof et al. 2009). Alternative methods of rupture prediction have also been investigated; these include the relationship between AAA wall stresses and rupture risk.

Screening for many diseases has become popular in recent years, e.g. Pap Smear, mammogram. The objective of any screening program should be to enable intervention that conveys a clear clinical benefit to be appropriately targeted, while remaining cost effective (Lederle 2003). Several screening programs have also been implemented worldwide for aneurysm detection. They are targeted at the group at greatest risk, males greater than 65 years old (Calonge et al. 2005). Screening involves the use of ultrasonography to detect AAA and the implementation of these programs is becoming increasingly common. From a theoretical screening model of a population of 100,000, it has been estimated that 1500 lives could be saved, at a cost of $78,000 per life (Ernst 1993, Quill et al. 1989). Measurements of AAA size determined using ultrasonography are accurate up to 6 mm (Ernst 1993), and therefore this has become the most cost-effective method of AAA detection. AAA screening programs are becoming more widespread in the UK with many private institutions providing screening. The UK National Health Service (NHS) recently announced that a full screening program will be made available throughout the UK, but is unlikely to become widely available until 2013 (National Health Service, 2009). Recently, it was suggested that AAA screening may be beneficial in Irish males aged 65 - 75 years (Brosnan et al. 2009). According to the US Preventative Services Task Force (Calonge et al. 2005), the potential benefit of screening for AAA among women over the age of 65 is low because of the number of age-related deaths in this population. The majority of AAA related deaths occur in women over the age of 80, and as there are many competing health risks at this age, any benefit of screening would be minimal (Calonge et al. 2005).
Computational simulations of blood flow and vessel wall mechanics for vascular structures are currently widely used as a research tool to study vascular diseases. The AAA vessel wall differs from the healthy vessel wall because the extracellular matrix has been degraded. The inflammation and plaque formation processes related to the aorta expansion may lead to a heterogeneous wall composition. The local constituency of the vessel wall material may not only affect the stress values, but it is also likely to affect the amount of stress that the wall can bear locally. In the near future, however, these methods may find their way into hospitals and clinics to aid the medical experts in deciding when to intervene, in planning the surgical procedure and in predicting the outcome of the procedure. Furthermore, the clinical sensitivity and specificity of this predictor can possibly be improved further by using more patient-specific input, such as local material properties and initial wall stress.

While it is well known that the mechanical properties of healthy blood vessels vary with location and age, their regional variations have received little attention. Studies on the material properties of vessel wall and rupture prediction have mainly focused on describing AAA vessel wall as a homogeneous material. Local inhomogeneities can, however, have large influences on the stress magnitude and distribution as can be concluded from the previously described effect of atherosclerotic plaques and calcifications (Inzoli et al., 1993; de Putter et al., 2006b). The presence and distribution of inhomogeneities is highly patient-specific and should therefore be dealt with accordingly. Although histological staining is a sound method to determine tissue composition and structure, its highly invasive character prevents it from being a suitable diagnostic tool. A noninvasive imaging tool should therefore be used to obtain tissue morphology.

Novel dynamic imaging techniques that are capable of characterisation pulsatile wall motion of the aorta could an important adjunct for calculating the changes in aortic pathology due to aneurysm formation (Laskowski et al. 2007). Computed tomography is currently the most frequently used study for surgical decision making in patients with aortic aneurysms. CTs are capable of providing accurate information of relevant conformational aortic anatomy, and it may be used for functional follow-up. Dynamic imaging, in which the time dimension has a specific function in data (image) interpretation, is becoming increasingly important when contemplating endovascular aneurysm repair. Clinical parameters and complications, including proper sizing,
successful aneurysm sac exclusion, optimal stent-graft design, endoleaks, graft migration, and stent fracture are beginning to be better understood through dynamic magnetic resonance, ultrasound, and dynamic computed tomography. Dynamic CTs to measure non-uniform deformation during the cardiac cycle may be useful to determine heterogeneous aortic shape changes and mechanical properties, previously unseen with conventional static imaging.

Another relatively new technique for the assessment of tissue elasticity is with acoustic radiation force impulse (ARFI) imaging. ARFI imaging measures tissue responses by using radiation force from long pulses to impart localised displacements in order to gain insight into the local viscoelastic properties of soft tissue in vivo and in vitro (Nightingale et al. 2002a, Nightingale et al. 2002c). Acoustic radiation force is applied to absorbing or reflecting targets in the propagation path of an acoustic wave. Radiation force is a universal phenomenon in any wave motion, electromagnetic or acoustic (Sarvaryan et al. 2010). The acoustic radiation force is produced by a change in the density of energy and momentum of the propagating waves because of the absorption, scattering or reflection from inclusions or from spatial variations in propagating velocity. ARFI has been shown to be clinically useful in a variety of applications including: breast, cardiovascular, hepatic, and urological imaging (Dumont et al. 2009, Fahey et al. 2008, Hsu et al. 2007, Sharma et al. 2004, Zhai et al. 2012). ARFI imaging has been shown to be capable of visualising changes in the stiffness of skeletal muscle fibres under various contractile loads (Nightingale et al. 2002b). Recent advances in beam sequencing and parallel-receive imaging have shortened acquisition times and lessened transducer heating to a point where continuous ARFI imaging acquisitions can be executed at high frame rates (Dahl et al. 2007). ARFI imaging uses impulsive, high-intensity ultrasound pulses to generate acoustic radiation force and material-dependent displacement fields. Displacement magnitudes and dynamics are dependent on tissue stiffness and structure, which may differentiate healthy from diseased tissues. As arterial walls, soft tissue, atheromas, and calcifications have a wide range of stiffness properties; aneurysms represent excellent candidates for ARFI imaging.

The main aim of this thesis is to examine methods of noninvasive mechanical characterisation and assess the use of these patient-specific parameters for rupture prediction. In Chapter 1, the viability of using ARFI as an imaging modality to assess
aneurysm development was investigated. This was performed on an in vitro animal tissue model and various ARFI techniques applied. Chapter 2 explores the feasibility of the use of ARFI at realistic aortic depths. Clinical suitability for AAA feasibility was explored and a method of quantifying resultant deformations was devised. Chapter 3 is dedicated to an initial study using 2-slice cardiac gated CT scans. Relationships between aneurysm formation and elastic properties are investigated. The effect of regional variation of mechanical properties in FE analysis is reported. In Chapter 4 wall stress simulations on abdominal aortic aneurysms (AAA) are developed to provide an indication of rupture risk on a patient-specific basis. The elastic quantification and regional variation study from Chapter 3 was also extended. Chapter 5 explores a method of extending readily available elastic properties from gated CT for use clinically. A summary of the work with conclusions and recommendations for future work complete the thesis.
REFERENCES


INTRODUCTION


CHAPTER 1

ACOUSTIC RADIATION FORCE IMPULSE IMAGING ON EX VIVO ABDOMINAL AORTIC ANEURYSM MODEL

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Ultrasound in Medicine and Biology 2010; 36; 5: p821-832

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Data Collection: AT, DD
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Critical Revision: DD, AC, GT, TM
Final Approval: TM, AC, DD
Obtained Funding: AT, AC, TM
ABSTRACT

BACKGROUND
A method for reliable, noninvasive estimation of Abdominal Aortic Aneurysms (AAA) wall mechanics may be a useful clinical tool for rupture prediction.

METHODS
An in vitro AAA model was developed from an excised porcine aorta, with elastase treatment. The AAA model behaviour was analysed using Acoustic Radiation Force Impulse (ARFI) imaging techniques to generate and measure wave propagation in both aneurysmal and normal undilated aortic tissue.

RESULTS
Opening angle measurement showed a fourfold decrease from undilated aorta to AAA model and pathological analysis verified this elastin degradation. Maximum wave velocity at 180mmHg was 7mm/ms for undilated tissue and 8.26mm/ms for the aneurysmal tissue.

CONCLUSIONS
The mechanical changes produced in the artificially induced aneurysm were found to be detectable using ARFI imaging.
INTRODUCTION

An Abdominal Aortic Aneurysm (AAA) is a focal balloon-like dilation of the terminal aortic segment that occurs gradually over a span of years (Vorp 2007). The usual definition of AAA is an infrarenal aorta of diameter greater than 30mm (Van Damme et al. 2005). Each year, there are 200000 (US), 500000 (worldwide) newly diagnosed (Bosch et al. 2001). These aneurysms are hazardous because of their propensity to rupture. 30-50% of patients with a ruptured AAA die before they reach hospital. Even with surgery, there is 50-70% mortality rate associated with rupture. The majority of AAA’s are asymptomatic until rupture; this has led them to become the 13th most common cause of death in the US (Vande Geest et al. 2004).

The pathogenesis of AAA formation is not well understood. They are characterised by a destruction of elastin and collagen in the arterial wall. The underlying problem in aneurysmal disease is this weakening of the aortic wall resulting in progressive dilation leading to eventual rupture (Golledge et al. 2006). Previous researchers have been successful in generating in vivo aneurysms in small animals, e.g. rabbits, rats, mice (Anidjar et al. 1990, Sinha et al. 2004) and ex vivo in porcine aortas (Kratzberg et al. 2009) using a method of elastase perfusion in the aorta. The in vivo elastase perfusion has been found to lead to subsequent aortic dilatation, collagen and elastin degradation, MMP upregulation, and an extensive inflammatory cell infiltrate in the outer media and adventitia of the aortic wall, which is typical of AAA formation (Sinha et al. 2004). The elastin degradation in the wall will be characterised by the opening angle alterations due to elastase treatment, similar to Zeller and Skalak, 1998, Fan et al, 2005 and Alford et al., 2008.

The maximum diameter of an AAA has long-time been considered as the main determinant in predicting its risk of rupture, i.e. when the AAA reaches 5.5cm it is thought that the risk of rupture warrants repair (Van Damme et al. 2005). However several studies have questioned the reliability of this criterion by showing that small aneurysms (<5cm) can rupture and that larger aneurysms (>5cm) can remain quiescent for years (Darling et al. 1977, Limet et al. 1991). This coupled with a 4-5% mortality rate with interventional surgery indicates a critical need for improved noninvasive AAA rupture predictors (Lasheras 2007).
Therefore, there exists a need for a noninvasive, cost effective, safe and accurate mechanism for detecting changes in abdominal pathology. Several ultrasonic methods have been previously investigated. Intraoperative Ultrasound (IOUS) has been shown to be effective in detecting changes in liver pathology (Cervone et al. 2000) but the invasive nature of IOUS would restrict its use. Intravascular ultrasound (IVUS) elastography has recently shown promise in the characterisation of focal plaques in coronary arteries (Schaar et al. 2003). Again a challenge for this method, however, is the introduction of the ultrasonic probe within the vessel lumen which exposes the patient to the risk of dislodging a vulnerable plaque. Acoustic Radiation Force Impulse (ARFI) Imaging presents an attractive method as it involves remote interrogation with short acquisition times, which because is implemented on a diagnostic US machine is at relatively low cost.

ARFI Imaging is a relatively new imaging modality which has been developed in Duke University (Durham, NC, USA) over the last ten years. Acoustic radiation force is a phenomenon associated with the propagation of acoustic waves through a dissipative medium (Fahey et al. 2008a). It is caused by a transfer of momentum from the wave to the medium, arising either from absorption or reflection of the wave (Torr 1984). This momentum transfer results in the application of a body force in the direction of wave propagation (Nightingale et al. 2002b).

ARFI imaging provides information about the local mechanical properties of bodily tissue. The acoustic radiation forces generate localised displacements in the tissue and these displacements can be tracked using ultrasonic methods (Trahey et al. 2004). The tissue response to these forces can be monitored both spatially and temporally. The tissue displacements are inversely related to tissue stiffness (Nightingale et al. 2001).

Radiation force has also been demonstrated to generate propagating waves within tissue (Sarvazyan et al. 1998, Zhang et al. 2005). Wave propagation speed is directly related to the mechanical properties of the tissue. Estimates of vascular stiffness can be derived by measuring the velocity of the propagating wave. A single transducer on a diagnostic scanner is used to both generate the radiation force and track the displacements (Trahey et al. 2004). ARFI Imaging has been shown to be effective in cardiac/ liver ablation monitoring, breast mass imaging and monitoring cardiac myocardial stiffness (Fahey et al. 2008b, Hsu et al. 2005). Challenges exist in adapting
the ARFI imaging method so it can effectively displace and effectively monitor the dynamics of deep lying tissues, such as the abdominal aorta.

This paper uses ARFI to examine the material responses in aortic tissue and in phantom AAA animal tissue models examining the effect of elastin reduction on mechanical parameters. This paper hypothesises that ARFI could be implemented to provide additional information on the changing mechanical properties of an AAA which lead to rupture.
MATERIALS AND METHODS

Ultrasound measurement

All ex vivo imaging was implemented on a Siemens Antares™ platform (Siemens Medical Solutions USA, Inc., Ultrasound Division, Issaquah, WA) with a VF10-5 handheld transducer at a frequency of 8MHz. The scanner has been modified to allow user control of the acoustic beam sequences and intensities and access to raw radiofrequency (RF) data.

ARFI Measurement

In soft tissues, where the majority of attenuation results from absorption, and under plane wave assumptions, this radiation force magnitude can be represented by the following equation (Nightingale et al. 2000, Nyborg 1965, Starritt et al. 1991, Torr 1984, Trahey et al. 2004)

\[ F = \frac{W_{\text{absorbed}}}{c} = \frac{2\alpha I}{c} \]  

where \( F \) [(dyne/(1000cm)^2)] or (kg/s^2cm^2)], is acoustic radiation force, \( W_{\text{absorbed}} \) [W/(100 cm)^2] is the power absorbed by the medium at a given spatial location, \( c \) [m/s] is the speed of sound in the medium, \( \alpha \) [Np/m] is the absorption coefficient of the medium, and \( I \) [W/cm^2] is the temporal average intensity at a given point in space. For a focused acoustic beam, the radiation force is applied throughout the focal region of the acoustic beam.

During the ARFI sequences, an initial reference line is acquired using standard B-mode parameters. Reference lines are used to establish the initial tissue position. This is followed by a high intensity focused ‘push’ pulse which mechanically excites the tissue. The excitation pulse is then followed by a series of tracking pulses, which are utilised to monitor the tissue displacement response.

Displacement measurements were calculated using cross-correlation between 0.5mm kernels from a reference line and subsequent tracking lines. This was performed over an approximate 60mm lateral field of view on the proximal wall. Each dataset was filtered to remove linear bulk motion artifacts. Displacements within the lumen were masked out. The mean of the displacements for the 4 acquisitions was calculated.
Test Samples

Excised Porcine Aortas were obtained from Sierra for Medical Science (P.O. Box 5692 Whittier, CA 90607-5692). Three Aortas were imaged after excision to determine their original properties. Measurements were taken on all samples tested after being excised in their undilated state and a second measurement was taken after a phantom aneurysm was created on part of the sample. Segments of the samples were finally tested in an opening angle test. A stretch ratio of 1.3 was used in experimental procedures (Guo and Kassab 2004).

All tests were performed within 48 hours of excision. This minimised significant changes in the mechanical properties of the aortic tissue, as described by Samila and Carter 1981. Due to mechanical failure during initial testing, Aorta 3 was unable to be used for all data analysis.

<table>
<thead>
<tr>
<th>Table 1: Aortic Specimen Details</th>
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<tr>
<td><strong>Excised Length [cm]</strong></td>
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<tr>
<td>Aorta 1</td>
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<tr>
<td>Aorta 2</td>
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<tr>
<td>Aorta 3</td>
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Experimental Pressure, Displacement and Wave Test analysis

The excised artery was attached to cannulae in closed pressure apparatus in a phosphate buffered solution (PBS) filled water bath similar to Behler et al. 2006, Dumont et al. 2006, Figure 1. The apparatus enabled pressurisation of the aortic specimen up to 200mmHg. The specimen was preconditioned by an inflation-deflation cycle of pressure range 0mmHg to 100mmHg, ten times. Prior to data acquisition, the axial imaging focus was adjusted to the location of the vascular wall.
The properties of tissues overlying and adjacent to target tissues can impact the strength of the push field reaching the target and dynamic response of tissues to the applied force. System factors, such as transducer focal configuration, ARFI pushing pulse intensity and location of the target tissue relative to the axial focal position of the pushing beams, can also affect induced displacements. However all experimental imaging took place under identical conditions with saline between the transducer and artery as this would be capable of discerning the differing stiffness and effects of the elastase treatment.

During experimentation, the specimen was hydrostatically pressurised with saline in the range 0-200mmHg. Data acquisition was performed at each step of 20mmHg at the central location of the aortic specimen. The transducer was 13mm from the near wall of the artery during all experimentation (Figure 1). After each increase in pressure, the axial image focus was readjusted to the vascular wall, to ensure the wall was exposed to an approximately uniform field of radiation at each pressurisation step. Eight data acquisitions (4 displacement, 4 wave) were taken at each pressure step. Co-registered B-mode images were acquired concurrently to provide anatomical reference and correlate features revealed by ARFI with the structure observed in the B-mode image.
CHAPTER 1 – ARFI EX VIVO FEASIBILITY STUDY

**Generation of Phantom Aneurysm**

After initially imaging the aortas in their original excised state, they were subjected to enzymatic treatment of Porcine Pancreatic elastase (Anidjar et al. 1990, Kratzberg et al. 2009, Sinha et al. 2004). A plastic cuff was used to clamp the aorta 2/3 along its length proximally. The middle 1/3 of the aorta was infused with Porcine Pancreatic elastase (LeeBioSolutions, #345-10, Concentration 20U/ml). A second plastic cuff was applied distally to the solution to clamp the middle section and allow the elastase solution to only infuse this section. The intraluminal infusion of porcine pancreatic elastase solution was allowed for 4 hours. The enzymatic treatment was adapted from earlier reports on degradation of elastin. After elastase infusion treatment, the aortas were flushed through with PBS to remove any residual enzyme on the surface. An Ancure Balloon (Endovascular Technologies, Menlo Park, CA, USA) was then inflated at the elastase treated section to dilate the aorta to 1.3 times its original diameter. The inflated balloon was left in the aorta for 6 hours. The artery was in a phosphate buffered solution (PBS) at 37°C for duration of all treatments.

**Measurement of the opening angle**

A ring specimen of the undilated normal aorta and elastase treated aorta was cut open by a radial cut for measurement of the opening angle. After the radial cut, the rings popped opened into C-shaped sectors and the sectors were allowed to stabilise for 30 min to fully release the residual stress. The angle was measured from the original centroid location of the uncut aortic ring (Figure 2).

![Figure 2: Illustration of Opening angle measurement, where Ø is opening angle](image)
Histology

Histological staining was performed to study the effect of elastase on the elastin in the aortic wall. The sections were fixed in a 10% formalin solution and then embedded in paraffin. Previous studies have shown that Verhoeff-Van Gieson (VVG) Staining is appropriate for elastin under light microscopy (Kratzberg et al. 2009, Samila and Carter 1981). Once proper staining was completed, the microstructure of three micron (3µm) cross sectional slices of the tissue were examined using Nikon ES/L1 light microscope with a viewing range from 4-40x.

Data Analysis

Motion filters were applied to the data to reduce artifacts from physiological and transducer motion (Fahey et al. 2007). Displacements were computed by correlating the reference pulse with sequentially acquired tracking pulses transmitted after the pushing pulse. Estimation of the speed with which waves propagate through the lateral locations at each pressure step for the differing arteries was also calculated, in order to measure the changing stiffness of the arteries with pressure change (Nightingale et al. 2003). The elastic stiffness properties of the arterial wall are expressed in terms of the Hudetz incremental elastic modulus (Zulliger et al. 2002). The Hudetz Incremental Elastic Modulus is shown in equation 2.

\[
H_{oo}(p) = 2 \left( \frac{d_{out}(p)d_{in}^2(p)}{\frac{\partial d_{out}(p)}{\partial p}} + p.d_{out}^2(p) \right) \times \frac{1}{d_{out}^2(p) - d_{in}^2(p)} \quad (2)
\]

Where \(d_{out}\) is external diameter, \(d_{in}\) is inner diameter; \(p\) is the pressure.

The Hudetz Incremental Elastic Modulus is plotted versus circumferential stretch, \(r/R\), where \(r\) is current radius; \(R\) is original radius.

Wave Generation and Data Collection

Usually waves generated are classified as shear waves, the velocity of which can be used to calculate the shear modulus of the material. This assumes an isotropic, homogeneous material. The aorta is a complex, orthotropic material. So the wave generated in these experiments will not be defined as shear waves. Because of this in
contrast to shear wave imaging, the shear modulus cannot be reported and the velocity of the waves will be analysed to examine the changes in material properties.

A region of tissue is excited to generate a wave through the tissue. An adjacent location is tracked to monitor the displacement as the wave passes through this location. The excitation of the initial region is repeated a number of times and tracking of displacement is performed at different lateral locations along the length of the aorta. The time it took the displacement to reach peak displacement at each of these locations for each of the 4 wave generated was calculated. The time to peak displacement is plotted against lateral location; a regression line is fitted to these plots, with goodness to fit greater than 0.95 (Regression lines not displayed in Figure 11). The slope of these regression lines is the estimated wave velocity (Palmeri et al. 2008).

**Elastin Concentration Calculation**

Histology images were thresholded using Mimics (v12.0, Materialise, Belgium) allowing the percentage elastin in the sample to be calculated. This process assigns a pixel intensity value measured in Hounsfield units (HU) to each pixel in the greyscale image. From this, the HU value can be controlled so that only the regions of interest, in this case the elastin, are thresholded. HU values of -1034 and -180 were applied to the greyscale histology images. The percentage of elastin present after elastase treatment could then be calculated.
RESULTS

The opening angles for the undilated normal aorta and elastase treated rings were 83.2 ± 4.6° and 20.0 ± 8.5° respectively. The opening angle measurement from the undilated normal and elastase treated aorta ring specimens is shown in figure 3 and 4 for specimen 2. The opening angle of arteries is a concise parameter directly indicating the residual stress in the vessel, which affects the mechanical behaviour of the arterial wall.

![Normal Artery: Θ = 85 degrees](image)

Figure 3: Undilated Normal Aorta ring, opening angle measurement – Showing an opening angle of 85 degrees

![Elastased Artery: Θ = 19 degrees](image)

Figure 4: Elastase Aorta ring, opening angle measurement, Showing an opening angle of 20 degrees

The collagen and elastin were inspected visually with a microscope and some examples are shown in Figure 5 of specimen 3. Verhoeff-Van Gieson (VVG) Staining is useful for staining elastin fibres which appear as blue/black.
Figure 5: Histology Staining - Fig a-c show the aortic wall in its excised state; 4x, 20x and 40x respectively. Fig d-f show the aortic wall which has been treated for elastin degradation; 4x, 20x and 40x respectively.

A thresholding technique was applied to a grey scale image of Figure 6 c and f to calculate the percentage elastin remaining. Figure 6 show these values normalised to percentage elastin, the pre-elastase treatment was assumed to have 100% elastin; there has been an average 73.02% decrease in elastin content relative to the undilated normal cases, which agrees with values published by Vyavahare 2007.

Figure 6: Comparison of Percentage Elastin in arteries before and after elastase treatment; with pre-elastase treatment normalised to 100% [n=3]
The Hudetz Incremental Elastic Modulus is shown plotted against $r/R$ in figure 7 for Aorta 2 ($r$ is current radius, and $R$ is original radius, $r/R$ corresponds to circumferential stretch). It also shows the pressure variation against $r/R$ on the secondary axis, solid black lines correspond to the modulus axis; dashed grey lines correspond to the pressure axis. The differing behaviour between the two tissues is apparent in this graph with a 35.7% difference in moduli at 120mmHg. The elastase artery modulus ramps up exponentially at lower pressures compared to the more gradual increase of the undilated normal artery. There is also greater circumferential stretch induced in the elastase artery.

Figure 7: Hudetz Incremental Elastic Modulus, solid line corresponds to the modulus axis, dashed line corresponds to the pressure axis, $r$ is current radius, and $R$ is original radius, $r/R$ corresponds to circumferential stretch

Diameters of the arteries could be measured directly from the ultrasound screen, at each pressure step. The B-mode image indicated definite preferential dilation of the elastase treated artery (figure 8a & 8b).
Pressure Diameter Curves- These curves, in figure 9, demonstrate the variation of diameter (cm) of three different vessels with respect to the pressure exerted on their walls. At pressures of 60mmHg and 140mmHg, the average difference in dilations between elastase and undilated normal tissue were 19.04% ± 3.72% and 10.70% ± 1.17% respectively. The pressure-diameter curves for each sample corresponds to the amount of elastin degradation in each sample. Aorta 3 had the greatest amount of elastin remaining, 32%, with Aorta 2 having greatest degradation. This corresponds to greater stretch evident before the onset of collagen recruitment in Aorta 3 and least stretch in Aorta 2.
The Acoustic Radiation Force generates displacements in the tissue. The error in the displacement calculation typically seen in ARFI images is on the order of a few tenths of microns (Dahl et al. 2009). Figure 10 shows the average of 4 acquisitions of the displacements which were computed for Aorta 1 at undilated normal and elastase configuration, and expressed versus pressure. Softer tissues should move farther than stiffer tissues for a given force magnitude (Nightingale et al. 2005). Displacement magnitude decreased with increasing pressure as expected due to the corresponding increase in stiffness for both arteries, with an average standard deviation of 0.1 microns between all 4 acquisitions. But there was a preferential stiffening of the enzymatic treated artery, as seen in figure 9, which would be expected in aneurysm tissue [Data for Aorta 2 displayed in Appendix A].

![Figure 10: Displacement profile, elastase treated artery versus undilated normal tissue (Aorta 1), preferential stiffening of the elastase treated evident with less displacement of the wall](image)

The time it takes the wave to generate peak displacement at each lateral location outside the region of excitation was calculated for both the undilated normal artery and enzymatic treated artery, and displayed below versus pressure. The stiffness of skeletal tissue has been shown to increase with increasing load (Levinson et al. 1995). Increasing tissue stiffness is correlated with decreasing time to maximum displacement. The enzymatic treated artery time to peak displacement is considerably less than that of the undilated normal artery at the same pressure and is displayed in Figure 11 for both 80mmHg and 160mmHg for Aorta 1.
Figure 11: Wave Time to Peak displacement versus Lateral Position, Undilated Normal artery, 80mmHg & 160mmHg [Aorta 1], Increasing stiffness correlates with decreasing time to peak displacement at lateral locations.

The inverse slope of a regression line fitted to the time to peak displacement plots (Figure 11) allowed wave velocity estimation to be calculated. Acoustic force generated a propagating wave within the tissue samples. The average wave speed for each pressure step was calculated, for the two artery configurations (undilated normal and elastase) for Aorta 1 (figure 12). The wave velocity follows a similar trend to that of the ARFI displacement (figure 10), which in turn follows the stiffness trend in the materials properties as shown in figure 7.

Figure 12: Wave speed versus Pressure curve, elastase treated artery versus undilated normal, demonstrating similar trends as displacement profiles.
Analysis of the ARFI generated displacement and calculated Hudetz Incremental Elastic Modulus is shown in Figure 13. It is shown that for each of the individual arteries, in both their elastase and undilated normal state, similar trends are evident in the displacement-modulus behaviour. The difference between elastase and undilated normal displacements falls to 0.3 microns for Aorta 1 at modulus of 0.3MPa, with greater displacements in the undilated normal. It is also evident here, from the difference in displacement profiles, that there is inter-individual variation in the properties of the native vessels, due to the important muscular component of their wall.

Figure 13: ARFI displacement versus Hudetz Elastic Incremental Modulus, for Aorta 1 and 2 [Mechanical failure of Aorta 3 meant it could not be analysed in this fashion]
DISCUSSION

The composite nature of the artery wall is important in providing the essential elastic non-linearity of the aortic wall (Roach and Burton 1957). The initial stiffness of the artery wall represents the elasticity of the elastin, while the much higher stiffness at high strains represents the contribution of fully tensed collagen fibres. The straightening of elastin layers and the alignment of collagen fibres with distension, under physiological pressures, correlates with the increasing elastic modulus and represents the basis for load transfer from compliant elastin at low strains to much more rigid collagen fibres at higher strains.

An artery ring springs open into a sector after a radial cut. Elastin is the protein constituent of connective tissue responsible for this elasticity and recoil of the tissue (Fonck et al. 2007). The elastase enzymatic treatment performed on the porcine aortas is thought to replicate the elastin degradation in aneurysms. The opening angle characterises the residual strain in the unloaded state. The opening angle measurements prove this experimentally, with an average elastase treated opening angle of 20.0 ± 8.5º and an average undilated normal aorta opening angle of 83.2 ± 4.6º. Histological analysis of the arteries further proved this elastin degradation (Figure 6) with a 73% decrease in elastin content. The excised artery staining (Figure 5, a-c) reveals the elastic fibres (in black) evenly distributed through the artery wall in a longitudinal orientation. The staining of the elastase treated aorta (Figure 5, d-f) displays disorganisation of elastin with almost complete elastin degradation in areas (Arrows in Figure 5, f).

The Hudetz Incremental Elastic Modulus is an indicator of the inherent elastic properties of the artery. Figure 7 indicates appreciably higher Hudetz Incremental Elastic Modulus values for the elastase treated vessel compared to the undilated normal vessel at similar pressures i.e. at 120mmHg the undilated normal Modulus is 0.04MPa compared to 0.077MPa in the elastase vessel. In the undilated normal group, the incremental modulus increases slowly, whereas the elastased group incremental modulus has a substantial and continuous increase. Also evident from this graph, there is substantially greater circumferential stretch in the elastased group. At 100mmHg, there is 57.3% more circumferential stretch induced in the elastased group. This is indicative of early and substantial collagen recruitment in the absence of elastin. The median circumferential stretch of the undilated normal aorta of 1.23 is similar to values
reported by Labrosse et al. 2009. Previous incremental elastic moduli reported for aortae has been found to be in the range of 0.4MPa-1.5MPa (Black 1998) and, for aneurysms < 60mm, was slightly higher at 0.9 – 2.01MPa (Koullias et al. 2005). The samples tested fell within these ranges for both diseased and undilated, which gives some confidence in the artificial induction of an aneurysm.

Figure 8 shows B-mode images showing a longitudinal view at the same pressure for both arteries. There is a definite preferential dilation of the elastased artery versus the undilated normal artery as is symptomatic of aneurysmal aortas. A circumferential b-mode image also allows diametrical measurements be taken easily at each pressure increment.

The pressure-diameter curves for the entire undilated normal aortae (Figure 9) exhibit the typical curve of an elastic conduit artery. The early part of the curve, indicative of compliance and distensibility, is increasing gradually with pressure. In the undilated normal artery, at low inflation pressures, the load is carried almost exclusively by the elastin fibres and the diameter increases gradually. As inflation pressure continues to increase, collagen fibres will start to engage yielding a progressively stiffer vessel wall and there is less diametrical increase. This pressure-diameter response is characteristic of quasi-linear elastic materials.

In contrast to the undilated normal arteries, the elastased arteries do not exhibit the typical pressure-diameter curve and, in consequence, their distensibility decreases monotonically with pressure. In the elastased arteries, after initial rapid diameter increase, collagen starts to engage at lower pressures due to the absence of elastin. This limits the elastic response of the artery and yields a substantially stiffer vessel even at low inflation pressures. This conclusion further supports the incremental elastic modulus graph in which it is clearly seen that the elastic modulus of elastased arteries increases considerably and in exponential fashion with pressurisation. The increase in elastic modulus takes action nearly immediately, with preferential dilation of the elastased artery to compensate for the loss of elastin. The point where collagen fibres begin to engage for the undilated normal arteries is a lot later than the elastase arteries (Fonck et al. 2007, Raghavan et al. 1996, Samila and Carter 1981). The continuous recruitment of collagen fibres limits the further distension of the artery and leads to an exponential decrease in distensibility (Vyavahare 2007).
The differing mechanical properties of the arteries can also be identified using ARFI techniques. Increasing tissue stiffness is correlated with both decreasing tissue displacement and increasing wave velocity. Large displacements occur in healthy tissue and smaller displacements indicate where stiffer materials occur. Thus a stiffer tissue will exhibit smaller displacements than more compliant, healthy tissue. The displacement-pressure graph (Figure 10) displays decreased displacement for the elastased vessel at the same pressure as the undilated normal artery, signifying a greater reduction in the distensibility of the phantom aneurysm, in comparison to the undilated normal artery, over the same pressure range.

ARFI was also employed to generate waves in the artery. Figure 11 shows the time it takes the wave to induce peak displacement at lateral positions outside the region of excitation (ROE). The time it takes the wave to generate maximum displacement decreases with increasing stiffness, 2.0msec versus 2.2msec [80mmHg] and 1.3msec versus 1.6msec [160mmHg].

Fitting regression lines to Figure 11, it was possible to document the wave speeds for both the elastase treated artery as well as the undilated normal artery. Figure 12 displays these speeds with respect to the pressure. The elastase wave speed is higher than the undilated normal wave speed across the physiological pressure range (80mmHg-180mmHg), further highlighting the elevated stiffness of this artery (Nightingale et al. 2002a). This further highlights the preferential stiffening of the enzymatic treated artery over the undilated normal artery. It is possible that in addition to the velocity, diameter, thickness and boundary conditions play a role in stiffness of the artery. Utilising velocity of the wave has advantages over using displacement data. For displacement data, the force is a function of intensity and attenuation which affects displacement. Therefore for different samples, the forces vary due to different attenuation coefficients. But for wave generation, intensity and attenuation only affect the amplitude of the wave, the velocity remains the same.

There is a cross over point in both displacement and velocity plots. In the displacement plot (Figure 10), the elastase artery has greater displacement at lower pressure, but as the pressure increases the displacement falls lower than that of the undilated normal artery. In the velocity plot (Figure 12), the elastase vessel velocity is lower at lower pressures and as the pressure increases the velocity is greater than the
undilated normal artery. Similar behaviour is evident in the modulus/circumferential stretch plots (Figure 7). The elastase artery experiences initial dilation at lower pressures, as the pressure increases the artery dilation reduces and there is a rapid increase in modulus. This is similar behaviour as suggested by the cross over point in the displacement and velocity plots. Roach and Burton (1957) suggest that the compliant elastic fibres are stretched first and determine the resistance to stretch at low pressures. As the vessel is distended, the collagen fibres come into play so that, at higher pressures, resistance to stretch is mainly due to collagen recruitment. Destruction of the compliant elastin induces profound change in the collagen recruitment in the elastase treated arteries (Fonck et al. 2007, Raghavan et al. 1996, Samila and Carter 1981). There is decreased vessel distensibility, at lower pressures, as the amount of elastin is reduced in load bearing and the load is shifted to the rigid collagen sooner. This leads to earlier stiffening of the elastased vessel, as suggested by each of the displacement, velocity and modulus/circumferential plots.

Comparison of the ARFI displacement and Hudetz modulus in Figure 13 reveals very little difference between the trends for each artery. Previous analysis had demonstrated preferential stiffening of the elastase arteries, but similar trends between their displacements is evident here at similar moduli before and after elastase treating. This suggests that ARFI displacements could also be engaged to provide information on the materials modulus.

The technique described in this investigation is noninvasive and would be applicable to study the effects of AAAs on vascular elastic pathology on larger populations. However, clinically, the quality of these ARFI images would be influenced by the pulsatile nature of the Aorta, which would have to be addressed with ECG triggers and motion filters. Also, successful ARFI Imaging at realistic aortic depths faces challenges at generating sufficient radiation forces to measurably displace this deep lying tissue and track these displacements.

**Limitations**

In this study, there were certain limitations which may have influenced the data obtained and may affect the use and development of ARFI to predict AAA material properties using elastase infusion.
1. The undilated normal aorta did not undergo balloon dilation for six hours, which could lead to differing ARFI responses.

2. Material length differences due to the aneurysm formation could also influence on the acoustic response times.

3. Displacements could be influenced by the surface area and volume differences between the undilated normal artery and the elastase artery.

4. It is uncertain how the boundary conditions, the thickness of the artery and diameter influence velocity. The Moens-Korteweg equation predicts that as diameter increases velocity decreases, but in the aorta the opposite occurs.

\[ c^2 = \frac{EH}{\rho d} \]

Where:  
H=thickness,  
E = Youngs modulus,  
\( \rho \) = density  
d = diameter.

This means that density or modulus could also be influencing the velocity.

These possible limiting factors could cause errors in the interpretation from the ARFI signal and the readings which seem to be linked to the geometrical changes and elastin reduction, which may be only as a result of geometrical changes.
CONCLUSIONS

An experimental model of an in vitro AAA was successfully developed using elastase infusion techniques for examination using ARFI Imaging. ARFI induced displacement and wave generation was demonstrated in in vitro phantoms. ARFI imaging was found to have the ability to detect the mechanical changes induced during aneurysmal formation. This study indicates that ARFI may be a useful additional tool in the diagnostic assessment of AAA. Clinical evaluation is also needed to determine whether ARFI can cause tissue responses at the depths encountered in AAA cases. A preliminary study is in preparation.

ACKNOWLEDGEMENTS

This work is supported by (i) the Irish Research Council for Science, Engineering and Technology (IRCSET) Grant no. 2007/2950 (ii) FÁS Science Challenge 2008/2009.
REFERENCES


CHAPTER 1 – ARFI Ex Vivo Feasibility Study


Zulliger MA, Montorzi G, Stergiopulos N, Biomechanical adaptation of porcine carotid vascular smooth muscle to hypo and hypertension
CHAPTER 2

IN VIVO FEASIBILITY CASE STUDY FOR EVALUATING ABDOMINAL AORTIC ANEURYSMS TISSUE PROPERTIES AND RUPTURE POTENTIAL USING ACOUSTIC RADIATION FORCE IMPULSE IMAGING

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Analysis and Interpretation: AT, AC
Data Collection: AT
Writing the article: AT
Critical Revision: AC, TM
Final Approval: TM, AC
Obtained Funding: AT, AC, TM
ABSTRACT

BACKGROUND

Abdominal Aortic Aneurysm (AAA) is defined as a permanent and irreversible localised dilatation of the abdominal aorta. A reliable, noninvasive method to assess the wall mechanics of an aneurysm may provide additional information regarding their susceptibility to rupture. Acoustic radiation force impulse (ARFI) Imaging is a phenomenon associated with the propagation of acoustic waves in attenuating media. This study was a preliminary evaluation to explore the feasibility of using ARFI imaging to examine an AAA in vivo.

METHODS

A previously diagnosed in vivo aneurysm case study was imaged to demonstrate the viability of excitation of the abdominal aorta using ARFI imaging. Ex vivo experiments were used to assess an artificially induced aneurysm to establish its development and whether ARFI was able to capture the mechanical changes during artificial aneurysm formation.

RESULTS

A combination of in vivo and ex vivo results demonstrated a proposed hypothesis of estimation of the tissue’s stiffness properties.

CONCLUSIONS

The study details a method for noninvasive rupture potential prediction of AAAs using patient-specific moduli to generate a Physiological Stiffness Rupture Potential Index (PSRPI) of the AAA. Clinical feasibility of ARFI as an additional prognostic tool to interrogate AAA was verified and methods to utilise this data as a diagnostic tool was demonstrated with the PSRPI.
INTRODUCTION

For many years, clinicians have been aware of the correlation between the mechanical properties of soft tissues and its state of health. Abdominal aortic aneurysm (AAA) is defined as a permanent localised dilation of the aorta constituting at least a 50% increase in normal diameter (Xiong et al., 2008). There are approximately 200,000 patients in the United States and 500,000 patients worldwide diagnosed with AAA every year (Bosch et al., 2001). The development of AAAs is associated with alterations of the connective tissue in the aortic wall. It is characterised by a destruction of elastin and growth and remodelling of collagen in the arterial wall. This destruction of elastin is considered a key factor in the pathogenesis of the aneurysm. Elasticity of the aneurysm wall has been observed to be reduced, and to be correlated with reduced elastin content (Vorp, 2007).

The current method for assessing the risk of rupture of aneurysms is based on its maximum diameter. Thus if an aneurysm is 5.5cm or larger in diameter, it is deemed high risk and therefore recommended for repair (Lederle et al., 2001). While it is obvious that the larger an aneurysm is, the more likely it is to rupture; several studies have reported rupture in aneurysms with diameters less than 5.5cm (Darling et al., 1977; Limet et al., 1991). This coupled with a 4-5% mortality rate with interventional surgery indicates a critical need for improved noninvasive AAA rupture predictors.

Acoustic Radiation Force Impulse (ARFI) Imaging is a relatively new imaging modality which has been developed in Duke University (Durham, NC, USA) over the last ten years. ARFI imaging is a radiation force-based imaging method that uses commercially available ultrasound scanners to generate short duration (approximately 30–300 μs) acoustic radiation forces. These impulses, or pushing pulses, generate localised displacements in tissue of approximately 1–10 μm. Displacement magnitude is inversely proportional to local tissue stiffness (Fahey et al., 2003). It has been shown to be successful in clinical imaging applications, including differentiating malignant lesions from fluid-filled cysts in breast, monitoring chemical and thermal ablations in vivo and isolating regions of atherosclerosis via surveying arterial wall mechanical

1 Abbreviations: AAA – Abdominal Aortic Aneurysm, ARFI - Acoustic Radiation Force Impulse, PSRPI - Physiological Stiffness Rupture Potential Index.
properties in *in vivo* and *ex vivo* human investigations (Behler et al., 2008; Bradway et al., 2007; Nightingale et al., 2007; Nightingale et al., 2000).

The primary objective of this paper is to show the clinical feasibility of ARFI *in vivo* to evaluate AAA tissue stiffness properties and to demonstrate how this data can be utilised to give a diagnostic measure of potential failure. A physiological stiffness rupture potential index (PSRPI) will be defined as the ratio of the patient-specific incremental modulus of an AAA to a population average incremental modulus multiplied by 100. It seems reasonable to suggest that the stiffness of an aneurysm may yield an additional diagnostic measure which could be used to assess the likelihood of rupture. We propose the PSRPI to be a possible criterion for assessing patient-specific rupture potential and could be combined with the widely accepted maximum diameter criterion to serve as an additional clinical aid to surgeons.
MATERIALS AND METHODS

A previously diagnosed in vivo AAA was scanned and ARFI displacement evaluated. An ex vivo ARFI evaluation was carried out on excised Porcine Aortas pre and post elastase treatment. An evaluation method is described where these ex vivo results were then used in conjunction with in vivo case study findings to give an indication of elasticity based on ARFI displacement. The elasticity value obtained could be used in a physiological stiffness based index (PSRPI) as a signal to predict rupture potential by ARFI. As the PSRPI increases above a value of 100, probability of rupture of that AAA would increase.

ARFI in vivo Case Study Imaging

For in vivo imaging, a curvilinear transducer, CH4-1, was used at relatively low transmit frequencies (2.22 MHz). For in vivo imaging, clinical sequences were synchronised to vessel systole to limit artifacts from vessel pulsation using ECG-gated acquisitions. In addition, acquisition time for clinical sequences was reduced using parallel-receive beam forming techniques (Dahl et al., 2007). Parallel-receive ARFI imaging allows for the simultaneous tracking of four locations for every pushing pulse transmitted. Shortening the acquisition time with parallel-receive ARFI reduces both patient exposure and the likelihood of physiological and patient motion artifacts (Dahl et al., 2007).

The patient details are shown below in Table 1.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73 years</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>182/77</td>
</tr>
<tr>
<td>Pulse</td>
<td>63 bpm</td>
</tr>
</tbody>
</table>

ARFI Displacements Evaluation

For ARFI sequences, a reference-tracking beam was transmitted, followed by high-intensity ARFI pushing beam that displaced the tissue. A series of tracking beams after the push beam were used to track the tissue displacement. The reference pulse relates to the initial tissue position. Displacements were computed at each pressure by correlating
the reference pulse with sequentially acquired tracking pulses transmitted after the pushing pulse.

**Development of an elastase (experimental aneurysm) ex vivo model**

In brief, as described in our earlier work (Tierney et al., 2010), an excised porcine aorta (obtained from Sierra for Medical Science, P.O. Box 5692 Whittier, CA 90607-5692) was infused with Porcine Pancreatic Elastase (LeeBioSolutions, St. Louis, Missouri; #345-10, Concentration 20U/ml) for 4 hours. The aortas were flushed through with PBS. An Ancure Balloon (Endovascular Technologies, Menlo Park, CA, USA) was then inflated for 6 hours. The artery was in a phosphate buffered solution (PBS) at 37°C for duration of all treatments. The enzymatic treatment was adapted from earlier reports on degradation of elastin (Anidjar et al., 1990; Kratzberg et al., 2009; Sinha et al., 2004).

**Experimental Case Evaluation**

The experimental undilated and elastase cases were evaluated in detail in our previous work (Tierney et al., 2010). The aortic specimen was evaluated in a closed pressure apparatus up to 200mmHg. Aortas were imaged after excision to determine their properties – before and after elastase treatment.

**Compliance**

Compliance was computed using Eq. 1 (Vorp et al., 1996)

\[
\text{Compliance} = \frac{\Delta A}{(A_{\text{max}}) \Delta P} \tag{1}
\]

Where \(A\) is the cross sectional area of the vessel; \(P\) is the pressure in the vessel [mmHg].

**Hudetz Incremental Elastic Modulus**

The Hudetz Incremental Elastic Modulus (\(E_{\text{inc}}\)) is shown in Eq. 2,

\[
E_{\text{inc}} = 2 \left( \frac{(d_{\text{out}} - d_{\text{in}})^2}{\Delta d_{\text{out}} / \Delta P} \right) + P \cdot d_{\text{out}}^2 \left( \frac{1}{d_{\text{out}}^2 - d_{\text{in}}^2} \right) \tag{2}
\]

Where \(d_{\text{out}}\) is external diameter; \(d_{\text{in}}\) is inner diameter; \(P\) is the pressure in the vessel (Fonck et al., 2007).

**ARFI ex vivo Imaging**

All ex vivo imaging was implemented on a Siemens Antares™ platform (Siemens Medical Solutions USA, Inc., Ultrasound Division, Issaquah, WA) with a VF10-5
CHAPTER 2 – ARFI IN VIVO FEASIBILITY STUDY

handheld transducer at a frequency of 8MHz. The scanner has been modified to allow user control of the acoustic beam sequences, intensities and access to raw radiofrequency (RF) data.

**Future Perspectives for ARFI Implementation**

A method to use the ARFI displacements to quantify the degree of disease of the aneurysm was established.

**Concept for in vivo \(E_{\text{inc}}\) calculation**

a) The displacement recorded *in vivo* on the AAA case study was combined with the *ex vivo* displacement-modulus average behaviour (Figure 3). This allowed an *in vivo* modulus for the case study to be estimated.

b) Four average pressure-diameter curves of AAA were taken from literature (Corbett et al., 2010; Drangova et al., 1993; Lanne et al., 1992). These behaviours were evaluated according to percentage strain. The percentage strain was applied to the systole diameter of the *in vivo* case study to predict estimated diastole diameter. A prediction of Hudetz incremental elastic modulus (\(E_{\text{inc}}\)) could be calculated from these diameters for the *in vivo* case study.

c) *In vivo* \(E_{\text{inc}}\) was also compared to moduli for healthy abdominal aortas obtained from Langewouters et al, 1983 (Langewouters et al., 1984).

**Physiological Stiffness Rupture Potential Index (PSRPI)**

The PSRPI is defined as the ratio of a patient-specific incremental modulus to a population average incremental modulus taken from literature.

\[
\text{PSRPI} = \left( \frac{E_{\text{case}}}{E_{\text{population\ average}}} \right) \times 100
\]  

(3)

Where \(E_{\text{case}}\) is the patient-specific incremental modulus

\(E_{\text{Population\ Average}}\) is the average population incremental modulus from literature

The average \(E_{\text{inc}}\) of four aneurysms from literature (Corbett et al., 2010; Drangova et al., 1993; Lanne et al., 1992) was used in the PSRPI as \(E_{\text{Population\ Average}}\).

The risk of rupture was then determined by

\(<50\) Low Risk

50-100 Medium Risk
>100 High Risk
These risks were based on the assumption that any stiffness above population average \( E_{\text{inc}} \) was deemed to be high risk and as the \( E_{\text{inc}} \) increased above 100, rupture probability increased.
RESULTS

In vivo Case Study

The in vivo imaging of the aorta was performed under an existing IRB approved protocol which allowed for ARFI imaging of an AAA patient (patient details shown in Table 1).

Figure 1(a) shows B-mode images at maximum aneurysm diameter to allow for measurement of the Aorta, 1(b) allows identification from the B-mode image where the ARFI excitation was observed.
Figure 1: Taken at maximum diameter of the aneurysm (a) B-mode image of cross sectional view of AAA (b) ARFI image of AAA
**Ex vivo Experimental Results**

Figure 2 shows the comparison of the aortic compliance before and after elastase treatment. Compliance was calculated at physiological pressures for each of the excised samples.

![Figure 2: Comparison of compliance for the 3 aneurysm models](image)

The opening angle was measured in each of the three undilated and elastase samples. The opening angles for the undilated aorta and elastase treated rings showed an average 76% decrease from normal to elastase \([n=3]\) (Tierney et al., 2010).

The displacement versus incremental modulus behaviour for two excised arteries was evaluated, for the undilated case and elastase case (Figure 3).
Future Perspectives for ARFI Implementation

Proposed *in vivo* $E_{inc}$ calculation

Due to the very similar trends, for both undilated and elastase, of all the *ex vivo* specimen’s displacement-modulus behaviour, it was deemed acceptable to take an average of all these behaviours (Figure 3).

Combining this average behaviour with the fact that the elastase properties were very similar to previously reported *in vivo* behaviour (Tierney et al., 2010) made it acceptable to use the displacement from the *in vivo* case with the average behaviour to estimate the *in vivo* $E_{inc}$ for the case study (Figure 3, black dashed line).
Three calculations of $E_{inc}$ were carried out in this study as shown in Figure 4 a,b,c (shown).

(a) Using the displacement observed \textit{in vivo} (ARFI) with the average experimental aorta model behaviour predicted an \textit{in vivo} modulus of 1.25 MPa.

(b) Using Eqn. 2 in conjunction with the average pressure – diameter behaviour (Corbett et al., 2010; Drangova et al., 1993; Lanne et al., 1992) allowed a range of estimations for the \textit{in vivo} case. This method predicted calculations of modulus in the range of 0.71 – 1.33 MPa.

(c) Healthy moduli were in the range 0.07-0.136MPa (Langewouters et al., 1984).

Once the predicted $E_{inc}$ for the case study could be determined from literature average behaviours, the PSRPI risk could be calculated. In Table 2, an indication of the possible rupture risk using PSRPI is shown.
An example calculation for the rupture index of the case study is shown below - based on the behaviour of the Lanne *et al.* aneurysm study.

\[
\text{PSRPI} = \left( \frac{E_{\text{case}}}{E_{\text{population average}}} \right) \times 100
\]  

(3)

Where the \( E_{\text{Population Average}} \) is 1.02MPa (Corbett et al., 2010; Drangova et al., 1993; Lanne et al., 1992), the predicted \( E_{\text{inc}} \) for the case study is 0.88MPa.

The equation now becomes

\[
\text{PSRPI} = \left( \frac{0.88}{1.02} \right) \times 100 = 86.8
\]

Therefore, the resulting PSRPI for the case study based on Lanne *et al.* behaviour is medium risk.

**Table 2: PSRPI Values for the case study**

<table>
<thead>
<tr>
<th>Case</th>
<th>( E_{\text{inc}} ) [MPa]</th>
<th>PSRPI</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corbett (Corbett et al., In Press)</td>
<td>0.65</td>
<td>62.9</td>
<td>Medium</td>
</tr>
<tr>
<td>Drangova (Drangova et al., 1993)</td>
<td>1.33</td>
<td>130.4</td>
<td>High</td>
</tr>
<tr>
<td>Lanne (Lanne et al., 1992)</td>
<td>0.88</td>
<td>86.8</td>
<td>Medium</td>
</tr>
<tr>
<td>Lanne (Lanne et al., 1992)</td>
<td>1.22</td>
<td>120.6</td>
<td>High</td>
</tr>
<tr>
<td>ARFI Case Study</td>
<td>1.25</td>
<td>122.5</td>
<td>High</td>
</tr>
</tbody>
</table>
DISCUSSION

There still exists an extreme need clinically to predict AAA rupture. Towards this goal, this study investigated a noninvasive method to establish the mechanical properties of a clinically identified aneurysm.

A major challenge to ARFI Imaging is the application of it to the realistic aortic depths. This study was performed to establish if, in a clinical setting, it would be feasible to apply this technique to AAA patients. From the in vivo b-mode images, it was possible to measure the aortic diameter, showing a 41mm AAA. Figure 1 (a) exhibits the B-mode and ARFI images for the diseased aorta case study. An ILT is evident in the AAA scan as crescent shaped, which reduces the lumen of the aorta. Diseased aortic images revealed greater displacement in the ILT than the wall of the aorta, Figure 1 (b). Displacement was evident on the anterior wall of the aorta, in the preliminary scans.

Ex vivo experimental model study

The elastase model was evaluated to establish the similarity to in vivo aneurysm behaviour. Vorp, 1996 reported the compliance of AAAs to be 1.8-9.4 x 10^{-4}/mmHg (mean 4 x 10^{-4}/mmHg). All the elastase samples in this study had compliance values (3.7-8.4 x10^{-4}/mmHg) in this range. The opening angle decrease from undilated to elastase confirms the elastin degradation during elastase treatment.

Displacement profiles revealed increasing tissue stiffness correlates with decreasing tissue displacement. In both cases, the displacement magnitude for the elastase is less than that of the undilated case at similar pressures, confirming preferential stiffening due to the degradation of elastin. In the elastased arteries, collagen starts to engage at very low pressures due to the absence of elastin; thereby limiting the elastic response of the artery and yielding thus a substantially stiffer vessel even at low inflation pressures. This behaviour is demonstrated in the displacement profile.

The similar trends of the displacement – modulus behaviours (Figure 3) both before and after elastase treatment suggest that, even in the absence of elastin in the aneurysm wall, the vessel exhibits the same properties albeit at different pressures, which is expected in the incrementally changing property behaviour of arterial tissue. Previous incremental elastic moduli reported for aneurysms < 60mm, was 0.9 – 2.01MPa
(Koullias et al., 2005). The elastase samples previously tested fell within this range, which gives some confidence in the artificial induction of an aneurysm and allows use this data in conjunction with the in vivo data.

**Future Perspectives for ARFI Implementation**

The in vivo estimation of tissue elasticity parameters is important for realistic tissue deformation modelling and diagnostic tasks such as surgical intervention. The knowledge of aortic mechanical properties, in particular, could offer improvement in the treatment of aneurysms and may have wide spectrum applicability. Although our knowledge of aneurysm behaviour and its impact on rupture has improved tremendously during the course of the last few years, there is still a need for a noninvasive effective method for the identification of in vivo properties. ARFI has been shown to have the potential to indicate underlying mechanical properties of internal tissues. However, previously, this method has been limited to looking at relative differences spatially only, within a single image. This paper demonstrated the ability to interrogate at the depth of the aorta for a previously diagnosed aneurysmal patient. The linking of the in vivo data and ex vivo data is an approach which needs further validation but provides a concept which would allow a modulus to be known, which could aid the clinician during the decision making process.

Comparison of the $E_{inc}$ for ARFI case study to predicted $E_{inc}$ from the average circumferential strain behaviour revealed very similar estimated values, with the ARFI prediction in the high end of the strain prediction. Strain behaviour is thought to be more indicative of true aneurysm behaviour as it takes into account the nonhomogeneous behaviour and is less dependent on the original shape of the aneurysm. Thubrikar et al, 2007 reported, at the anterior wall, an incremental modulus of between 1MPa-2MPa for human aneurysmal samples. The predicted $E_{inc}$ for the case study, both by ARFI technique and prediction, corroborates with these values. A PSRPI value was determined for each case from Eqn.3. All predicted moduli for the in vivo case study suggested it had a medium to high risk of rupture. Although the PSRPI results presented here are preliminary and needs to be refined further, the approach may be clinically useful for the surgeon. This aneurysm measured 41mm and was under regular surveillance. This would be deemed clinically to be of moderate risk.
A study by DiMartino et al., 2006 stated that the risk of rupture was not related to stiffness. However these stiffness values were based on maximum tangential modulus taken from tensile tests. These stiffness values taken from stress-strain data would not accurately reflect the in vivo physiological strain ranges experienced by the aneurysm. The Hudetz incremental modulus used in this study which takes into account the diameter changes, pressure changes and thickness of the aneurysm may provide a better indication of the physiological stiffness seen by the aneurysm. A study by Moritake et al., 1975 hypothesised that the stiffest aneurysms might be the ones most prone to rupture. They found that when they varied distensibility but kept blood flow and diameter constant, pulse pressure increased with increased stiffness. They concluded that the pulsatile stress, fluctuation in pressure and the likelihood of rupture increased with increasing stiffness of the blood vessel. However the authors agree with Sonesson et al, 1999 that there is probably a complex relation between aneurysmal stiffness and weakness of the aneurysmal wall that determines the likelihood of rupture. Therefore the PSRPI values, which take into account patient-specific moduli, would be beneficial to the surgeon in addition to existing diagnostic techniques for rupture prediction.

The novel technique proposed in this study may provide some key information about in vivo properties of the AAA. Of course, one patient is insufficient to draw any quantitative or qualitative conclusion regarding the capability of this technique. A more comprehensive multi subject study would provide more conclusive evidence and also allow refinement of the bands of PSRPI. However the results of this study demonstrate that the technique is feasible. In addition it suggests that amalgamation with elastase data, drawn from laboratory based studies, may provide in vivo mechanical property information. This information could be used in conjunction with other surgical decision making criteria, ((Doyle, 2009; Doyle et al., 2009; Fillinger, 2006; Vande Geest et al., 2004; Vorp, 1998)) for the surgeon to make the most informed intervention decision.

The proposed method of equating the displacement to a modulus is a concept and the authors are fully aware of the limitations in this study.

**Limitations**

- One limitation of this study was the lack of an exact diameter taken at diastole. However the 4 average pressure-diameter behaviours of aneurysms applied to
the systole diameter are thought to have given a good estimation of this diameter.

- In ARFI, there is the assumption made that factors (e.g. attenuation coefficients, ultrasonic intensity, frequency content) which determine the radiation force are uniform in the area of displacement. This results in an inability to compare displacement values from person to person. A method such as the one proposed could be developed to take this assumption into account in the calculation of the modulus.

- The lack of a confirmation of the in vivo tissue modulus using mechanical testing. This would have involved excision of the tissue and testing post excision. Modulus results found are comparatively close to values reported previously by Koullias et al, 2005 and Thubrikar et al, 2009. A superior and more in depth study would have involved combining ARFI Imaging pre-resection for patients undergoing surgical repair with post resection biomechanical testing. This could be incorporated into any future testing undertaken.

- The effect of boundary conditions on displacement magnitudes would also have to be established.

- The choices of the bands for PSRPI are arbitrary and are based on the assumption that any stiffness above population average $E_{inc}$ was deemed to be high risk. A greater study have to be undertaken, including undilated aortae, aneurysmal aortae and ruptured aneurysms, to refine these PSRPI bands
CONCLUSIONS

ARFI induced displacement was demonstrated in an in vivo diseased aorta. We have proven the capability of ARFI to successfully displace at realistic abdominal depths. ARFI imaging may be a convenient adjunct to conventional ultrasound for assessing the abdominal pathology of the aorta. PSRPI can also provide additional information for the surgeon in the intervention process. It is important to note that this in vivo case study is encouraging for establishing feasibility; however a more prolonged study, both ex vivo and in vivo, with a statistically significant sample size is necessary to establish the efficacy of this method. Nevertheless, the proposed technique is clinically feasible and may offer an improved diagnostic technique over current rupture prediction methods. In the future, more accurate estimation of the inherent mechanical properties of the AAA to evaluate the potential of rupture for patient-specific AAA could be produced.

ACKNOWLEDGEMENTS

The authors extend their thanks to (i) Douglas Dumont and Gregg Trahey, Trahey Laboratory, Duke University, USA; (ii) The Irish Research Council for Science Engineering and Technology (IRCSET).
REFERENCES


CHAPTER 2 – ARFI IN VIVO FEASIBILITY STUDY


CHAPTER 3

USE OF REGIONAL MECHANICAL PROPERTIES OF ABDOMINAL AORTIC ANEURYSMS TO ADVANCE FINITE ELEMENT MODELING OF RUPTURE RISK

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Critical Revision: AC, TM
Final Approval: TM, AC
Obtained Funding: AT, AC, TM
ABSTRACT

BACKGROUND

To investigate the use of regional variations in the mechanical properties of abdominal aortic aneurysms (AAA) in finite element (FE) modelling of AAA rupture risk, which has heretofore assumed homogeneous mechanical tissue properties.

METHODS

Electrocardiogram-gated computed tomography scans from 3 male patients with known infrarenal AAA were used to characterise the behaviour of the aneurysm in 4 different segments (posterior, anterior, and left and right lateral) at maximum diameter and the suprarenal aorta. The elasticity of the aneurysm (circumferential cyclic strain, compliance, and the Hudetz incremental modulus) was calculated for each segment and the aneurysm as a whole. The FE analysis inclusive of prestress (pre-existing tensile stress) produced a detailed stress pattern on each of the aneurysm models under pressure loading. The 4 largest areas of stress in each region were considered in conjunction with the local regional properties of the segment to define a specific Regional Prestress Rupture Index (RPRI).

RESULTS

In terms of elasticity, there were average reductions of 68% in circumferential cyclic strain and 63% in compliance, with a >5-fold increase in incremental modulus, between the undilated and the aneurysmal aorta for each patient. There were also regional variations in all elastic properties in each individual patient. The average difference in total stress inclusive of prestress was 59%, 67%, and 15%, respectively, for the 3 patients. Comparing the strain from FE models with the CT scans revealed an average difference in strain of 1.55% for the segmented models and 3.61% for the homogeneous models, which suggests that the segmented models more accurately reflect in vivo behaviour. RPRI values were calculated for each segment for all patients.

CONCLUSIONS

A greater understanding of the local material properties and their use in FE models is essential for greater accuracy in rupture prediction. Quantifying the regional behaviour will yield insight into the changes in patient-specific aneurysms and increase understanding about the progression of aneurysmal disease.
INTRODUCTION

The decision to intervene in a patient with abdominal aortic aneurysm (AAA) is based on the threshold of maximum diameter of the aneurysm, which is currently ≥5.5 cm.\(^1\) This threshold represents the point at which the risk of rupture exceeds the perioperative mortality of open surgery.\(^1\) The major argument against this “one size fits all” criterion for the threshold of rupture is that some large aneurysms do not rupture, whereas some smaller aneurysms do.\(^2\) Clearly, doubt remains over using aneurysm diameter for decision making regarding surgical intervention.\(^3\)–\(^5\)

AAA rupture represents a catastrophic failure of the degenerated aortic tissue when the aneurysm wall can no longer withstand the stresses on it.\(^6\) Understanding the stress distribution in the aneurysm, along with its material properties, is an essential step toward predicting the rupture of an AAA.\(^6\)–\(^9\) Various other AAA rupture predictors in addition to wall stress have been investigated in recent years, including wall strength,\(^10\),\(^11\) combinations of stress and strength, \(^12\),\(^13\) acoustic radiation force impulse imaging displacement,\(^14\) asymmetry,\(^15\) presence/growth of thrombus,\(^16\),\(^17\) and weighted biomechanical factors.\(^18\) Many of these assessment techniques have involved finite element (FE) models as a basis for rupture prediction. FE analysis is a computer-based method of solving complex structural problems for which the stress distribution can be easily studied. In analysing AAA behaviour with FE models, realistic aortic anatomies with patient-specific physiological and mechanical properties have been used in recent years.\(^6\),\(^9\)–\(^11\) Data for these anatomies have typically come from computed tomography (CT) scans. At present, 3-dimensional (3D) reconstruction software and dynamic imaging with electrocardiogram (ECG)-gated CT or magnetic resonance imaging (MRI) have added new possibilities to the investigation of aortic deformation and expansion throughout the cardiac cycle.\(^19\)–\(^22\) Despite these advances in imaging and the knowledge that regional variations in mechanical properties exist \textit{in vivo},\(^7\),\(^8\) it has been common to apply homogeneous properties to the idealised or physiological geometries in these FE models.\(^23\)–\(^25\) We believe that knowledge of the AAA regional properties can help provide greater insight into AAA rupture behaviour and lead to more accurate methods of predicting rupture risk.

One of the shortcomings of many stress analyses involving patient-specific vascular structures is the common assumption that the reconstructed \textit{in vivo} configuration is
stress free, although the structures are in a prestressed state (i.e., there is pre-existing tensile stress). Many investigators have addressed the importance of removing this assumption of a stress-free configuration from CT scans.\textsuperscript{12,13,25-31} We submit that this assumption can be obviated using an approach that also takes into account the patient-specific blood pressure, thus increasing the accuracy of patient-specific stress estimates.

The purpose of this study was to examine the use of regional variations in mechanical properties in FE reconstruction to assist in the assessment of AAA rupture risk. This study utilised patient-specific local properties and strain data obtained from ECG-gated CT scans and related them to the local strength to determine the risk of rupture. The approach may be clinically useful in improving AAA diagnostic methods.
MATERIALS AND METHODS

CT Data Acquisition

Scans from 3 male patients (ages 81, 79, and 78 years) with known infrarenal AAA were obtained from colleagues at the University Hospital Heidelberg, Germany. The scans were acquired using a 4–detector row CT system (SOMATOM Volume Zoom; Siemens Medical Solutions, Erlangen, Germany) and a standardised protocol\textsuperscript{32} for ECG gating at 2 surgically relevant locations: the suprarenal aorta and at the level of maximum aneurysm diameter (Fig. 1A). An automatic pneumatic sphygmomanometer (Maglife C; Schiller, Wissembourg, France) with a measurement accuracy of 2\% was used to record blood pressure during the scans. The recorded blood pressures were 115/30 for patient 1, 160/95 for patient 2, and 133/81 for patient 3, respectively.

Figure 1: (A) Anatomical locations of CT scans taken at 2 sites: (a) undilated proximal neck and the (b) maximum diameter of the aneurysm. (B) Representative circumferences at systolic pressure (black line) and diastolic pressure (white line), shown at the maximum diameter of the aneurysm.

The DICOM image of each scan was imported into commercial software (Mimics version 12.0; Materialise Ltd., Leuven, Belgium). A thresholding technique was applied to the grayscale DICOM image to calculate the area of the aorta. A best fit curve was applied to the boundary of the wall area and exported to Matlab r2009a (Mathworks, Natick, MA, USA) as a 2-dimensional series of points that could be summed to calculate the circumference. Inasmuch as both strain and pressure peak occur nearly simultaneously in the cardiac cycle,\textsuperscript{33,34} all measurements were made at peak systole and end diastole. The time series with maximum area was referred to as systole and
mineral area as diastole (Fig. 1B). Each aortic image (Fig. 2) was sectioned into quadrants: anterior (A), posterior (P), right lateral (RL), and left lateral (LL). The circumferential lengths of these segments were tracked from diastole to systole using local anatomical markers, such as calcifications in the wall, intraluminal thrombus (ILT), etc.

Figure 2: CT image taken at the maximum diameter of the aneurysm showing the segmentation into quadrants (A: anterior, P: posterior, RL: right lateral, and LL: left lateral).

Elasticity Quantification

The elastic properties of the aortic wall were characterised at the undilated neck and the maximum diameter using the following equations applied to the entire aneurysm and to the 4 individual segments for each of the 3 patients.

Circumferential cyclic strain\(^{33-35}\): \(E_{00} = \frac{1}{2} \left[ \left( \frac{L_s}{L_d} \right)^2 - 1 \right] \)  
(Eqn. 1)

Compliance\(^{36,37}\): \(C = \frac{\Delta L}{L_s(\Delta P)}\)  
(Eqn. 2)

Hudetz Incremental Modulus\(^{38,39}\):

\(H_{00} = 2 \left[ \left( \frac{d_{out}}{d_{in}} \right)^2 \left( \frac{\Delta d_{out}}{\Delta P} \right) + (P \times d_{out}^2) \right] \times \left[ \frac{1}{\left( d_{out}^2 - d_{in}^2 \right)} \right] \)  
(Eqn. 3)

where \(L_s\) is the segment length at systole, \(L_d\) is the segment length at diastole, \(\Delta L = L_s - L_d\), \(\Delta P = P_s - P_d\) (variables are shown in Figure 3).
Biomechanical Material Properties

The circumferential cyclic strain and the modulus calculated from the CTs were used in conjunction with Raghavan and Vorp’s average aneurysm behaviour (Fig. 4) to generate a stress-strain relationship for each segment (Fig. 4A X–Y) and the entire aneurysm. Figure 4 displays the method used to transform the individual stress-strain behaviour back to calculate a strain energy function (SEF) and prestress component. The position of the regional behaviour on the graph gave an indication of the prestress in the segment based on the strain and modulus calculations (Fig. 4A). The prestress was subtracted from the segment stress-strain behaviour (X-Y) (Fig. 4B). This repositions the behaviour from X to Q. Q–Z then represents the original stress-strain behaviour of the segment (X-Y), which has been transposed to the origin. The points at X and Y are known from the tissue deformation and strain calculated in vivo. The intermediary behaviour between these points is then defined by the average behaviour. This transposition removes the prestress element of the behaviour and allows a SEF to be generated for each region. The prestress can then be included for total stress calculations at a later stage in the analysis.

A finite strain constitutive model was determined for the local segments and the entire aneurysm at maximum diameter for each patient. Various SEFs were examined including Marlow, Mooney-Rivlin, Ogden, and Neo-Hookean. The most applicable SEF
for the wall segment stress-strain data derived from Figure 4 proved to be a reduced polynomial SEF, as it provided a good curve fit for all the data ($r^2 > 0.999$) and was also stable at all stresses and strains. These properties at maximum diameter were applied to a general realistic FE model using Abaqus (version 6.9.1; Dassault Systèmes Simulia Corp., Providence, RI, USA). The FE analysis produced a detailed stress pattern on each of the aneurysm models under pressure loading. The peak stress results in each segment could be used to examine the risk of rupture in this segment based on the local properties. The effect of using segmental properties compared to homogeneous properties from the entire aneurysm was also examined.

Figure 4: (A) Behaviors of 2 quadrants equated to average behavior.\(^{40}\) (B) Subtracting the prestress from the local quadrant behaviour to derive a constitutive model. X–Y is the original stress-strain configuration of the segment. Q–Z is the stress-strain configuration when the stress-strain curve is returned to 0, and the prestress is removed. The points at X and Y are known from the tissue deformation and strain calculated \textit{in vivo}. The intermediary behaviour between these points is then defined by the average behavior.\(^{40}\)

FE Analysis

Using a method previously validated by our research group,\(^{41,42}\) a 3D reconstruction was generated from the CT scan of a 79-year-old man using Mimics (version 12.0) and ProEngineer Wildfire 4.0 software (Parametric Technology Corp, Meddham, MA, USA); the reconstruction was imported into Abaqus software for stress analysis. To
save resources, the same 3D geometry (Fig. 5) was used in conjunction with the elastic and biomechanical material properties of each patient. Using a single geometry for each of the 3 patients was justified because the study evaluated how material properties influence the method of modelling and to demonstrate the importance of more realistic material properties for prediction methods. It was not intended to actually model risk for any particular patient.

Figure 5: 3D geometry of FE model of the aneurysm used throughout this study in the (A) sagittal plane and (B) coronal plane.

The model imported into Abaqus was segmented into 4 sections (Figure 2 shows the orientation of the segmented areas) using the partition tool. The anterior segment was easily identified by the bulge of the aneurysm sac due to the asymmetrical expansion caused primarily by the proximity to the spinal column posteriorly. This allowed local patient properties to be applied to each section based on the deformations measured from the patients’ ECG-gated CT data.

As with previous research\(^{23,43}\), all models in this study omitted the iliac arteries. As the model was predominantly aneurysmal, only the properties measured at maximum diameter were used. To simulate the connection of the AAA segment to the descending
aorta and the iliac bifurcation, the model was fully constrained in the proximal and distal directions. The blood pressure within the AAA acts on the sac’s inner wall; therefore, patient-specific pressures were applied to the inner surface of the computational AAA model. Aortic tissue is also known to be nearly incompressible, with a Poisson’s ratio of ~0.49.

The geometry reconstructed was at diastolic pressure; therefore, the patient-specific pressure applied was the difference between diastolic and systolic pressures recorded from the patient during the CT scan. As in previous rupture prediction methods, the anisotropy in material properties was not taken into account. The shear stress induced by blood flow was neglected in this study, although the effects of blood flow have been shown to reduce wall stress in idealised AAA models.\textsuperscript{44}

Once the AAA was imported into the FE software, an FE mesh was generated on the AAA model. Because wall thickness cannot be fully determined from scan data, a uniform 2-mm thickness was applied to the model based on population mean values obtained from an experimental study of excised AAA wall tissue specimens.\textsuperscript{24} Mesh independence was performed by increasing the number of elements in the mesh until the difference in peak von Mises stress was <2\% of the result computed with the previous mesh.

**Prestress Inclusion in FE Analysis**

Unrelated to the patient-specific properties study, an investigative model was studied to establish the need to include prestress. Despite the fact that there are prestresses present in the aneurysm at the moment of image acquisition, it has not been widely taken into account in previous FE studies.\textsuperscript{15,40,43} Commonly used nonlinear material properties in AAA modelling have been taken from Raghavan and Vorp’s SEF.\textsuperscript{40} The materials were assumed to be incompressible and hyperelastic; therefore, the strain energy functions took the form:

\[ W = \Sigma_{i=0}^{N} C_{i0} (\bar{I}_1 - 3)^i \]  

(Eqn. 4),

where \( \bar{I}_1 \) is the first invariant and \( C \) is the material constant.\textsuperscript{45}

To justify the inclusion of prestress in FE modelling studies, SEFs were developed from commonly used properties (\( C_{10} = 0.174 \), \( C_{20} = 1.881 \)), which were pressurised to 120
mmHg, as is typical for many studies, while the prestress models were pressurised to 40 mmHg, reflecting the difference between systolic and diastolic values in a “normal” patient with 120/80 mmHg blood pressure. Therefore, the prestress accounted for pressure <80 mmHg and the model required only an additional 40 mmHg to bring it to maximum pressure. The newly developed SEFs applied a 5%, 10%, 15%, 20%, and a 25% prestress to the properties (Table 1). After application of these properties to an FE model, the peak stress and prestress were summed to calculate the total stress on the aneurysm wall and determine the importance of inclusion of this prestress in the calculations. The total stress recorded using the traditional properties was compared to the total stress recorded when prestress was included. The total pressure results were then examined to establish the various levels of error that would be inherent when prestress was disregarded.

### Table 1: Strain Energy Function (SEF) Coefficients Used to Justify Including Prestress in the FE Model

<table>
<thead>
<tr>
<th>Prestress</th>
<th>0%</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
<th>25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficients, MPa</td>
<td>(C_{10}=0.174)</td>
<td>(C_{10}=0.161)</td>
<td>(C_{10}=0.320)</td>
<td>(C_{10}=0.615)</td>
<td>(C_{10}=0.871)</td>
<td>(C_{10}=2.99e^{-2})</td>
</tr>
<tr>
<td></td>
<td>(C_{20}=1.881)</td>
<td>(C_{20}=2.837)</td>
<td>(C_{20}=3.057)</td>
<td>(C_{20}=3.417)</td>
<td>(C_{20}=2.963)</td>
<td>(C_{20}=1.49e^{-2})</td>
</tr>
<tr>
<td></td>
<td>(C_{30}=4.118)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

0% is based on the traditional properties devised by Raghavan and Vorp.\(^4\)

#### Rupture Risk

The Regional Prestress Rupture Index (RPRI) was based on the engineering principle that a material will fail when the total stress acting on the wall exceeds the strength of the material. The prestress was based on the position of the segmental stress-strain curve on Raghavan and Vorp’s average behaviour curve.\(^40\)

\[
\text{RPRI}_R = \frac{(\text{Peak stress}_R + \text{Prestress}_R)}{\text{Wall Strength}_R} \quad (\text{Eqn. 5}),
\]

where prestress refers to the segment calculated using Figure 4 and peak stress to the segment measured from FE simulations. \(R\) refers to the local mechanical property circumferential region, which can be \(\geq 1\) (dependent on the number of local regional property calculations on the aneurysm). In these experiments, the 4 local mechanical property regions of the aneurysm (posterior, anterior, left lateral, right lateral) were directly compared to 1 mechanical property, which represented the complete aneurysm surface. The peak stress was taken from a simulation of patient-specific systolic pressure applied to the geometry, and the wall strengths were derived from experimental
uniaxial testing of 149 AAA tissue specimens. The wall strengths had been combined and averaged (anterior: 0.7744 MPa, posterior: 0.8658 MPa, left lateral: 0.9221 MPa, right lateral: 0.9187 MPa) in a previous study to collate the specific region strength. Equation 5 returns a numerical value, where 0 indicates a very low rupture risk and larger ratios represent a greater rupture risk.
RESULTS

Elasticity Quantification

Table 2: Circumferential Cyclic Strains for All Locations of the Anatomy in the 3 Patients

<table>
<thead>
<tr>
<th></th>
<th>Posterior</th>
<th>Left Lateral</th>
<th>Anterior</th>
<th>Right Lateral</th>
<th>Entire Aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undilated Neck</td>
<td>0.5%</td>
<td>22%</td>
<td>21%</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>1.8%</td>
<td>1.7%</td>
<td>1.8%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Patient 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undilated Neck</td>
<td>7.4%</td>
<td>20.9%</td>
<td>19.4%</td>
<td>6.9%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>5.0%</td>
<td>10%</td>
<td>11%</td>
<td>5.2%</td>
<td>8.2%</td>
</tr>
<tr>
<td><strong>Patient 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undilated Neck</td>
<td>20%</td>
<td>11.2%</td>
<td>11.9%</td>
<td>31.9%</td>
<td>17.3%</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>5.6%</td>
<td>1.1%</td>
<td>4.6%</td>
<td>0.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undilated Neck</td>
<td>9.3%</td>
<td>18.4%</td>
<td>17.8%</td>
<td>15.1%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>4.2%</td>
<td>4.5%</td>
<td>6.1%</td>
<td>4.4%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

The percentage cyclic strain represents behaviour between the points X and Y in Figure 4.

The patients’ circumferential cyclic strains for both locations are displayed in Table 2, for both the homogeneous and segmental models. Assuming the properties of the entire aneurysm are homogeneous, the average circumferential cyclic strain of the aorta decreased by 68% from the neck to the level of the maximum diameter on the model. In like fashion, the compliance values of each quadrant displayed an average decrease of 63% going from the neck to the maximum diameter of the aneurysm (Fig. 6). The incremental moduli of the aorta calculated at both the undilated neck and maximum diameter (Fig. 7) reflected a >5-fold increase between the undilated neck and the aneurysmal aorta, as well as between local regions at the same area. In addition to the average 68% reduction in circumferential cyclic strain, 63% reduction in compliance, and large differences in incremental modulus between the undilated and aneurysmal locations, there were also regional variations in all elastic properties in each individual patient.
Figure 6: Compliance values at both anatomical locations (undilated neck and maximum diameter) for each segment for the individual patients (calculated from Equation 2). All values are $\times 10^{-4}$/mmHg.
FE Analysis

Inclusion of prestress.

In the typical wall stress analyses, the geometry obtained from a CT scan is presumed to be unstressed, but at levels of prestress up to 20% (Table 3), total stress can be greatly overestimated if prestress is neglected. As the prestress increases toward 25%, the difference changes to an underestimation in the total stress.

Table 3: Differences in Total Stress to Support Including Prestress in the Investigative Model

<table>
<thead>
<tr>
<th>Prestress</th>
<th>0%</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
<th>25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prestress based on normal curve</td>
<td>—</td>
<td>0.02</td>
<td>0.08</td>
<td>0.19</td>
<td>0.38</td>
<td>0.65</td>
</tr>
<tr>
<td>(representing 80 mmHg), MPa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress from FE model on test</td>
<td>—</td>
<td>0.338</td>
<td>0.308</td>
<td>0.305</td>
<td>0.318</td>
<td>0.39</td>
</tr>
<tr>
<td>material, MPa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure applied to model, mmHg*</td>
<td>120</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Total stress prediction, MPa</td>
<td>0.99</td>
<td>0.358</td>
<td>0.388</td>
<td>0.495</td>
<td>0.698</td>
<td>1.04</td>
</tr>
<tr>
<td>Difference, %</td>
<td>-63.84</td>
<td>-60.81</td>
<td>-50.0</td>
<td>-29.5</td>
<td>5.05</td>
<td></td>
</tr>
</tbody>
</table>

0% represents the traditional properties. The 5% to 25% values of prestress from Table 1 were used to account for pressures of 0 to 80 mmHg.

*This study was not related to the patient-specific properties study.

FE: finite element.
Patient reconstructions.

The SEF coefficients for each patient, both segmentally and treating the entire aneurysm as a homogeneous material, are listed in Table 4 and the contours for each patient are shown in Figure 8.

Figure 8: Anterior and posterior views of stress contours for homogeneous and segmented models for each patient. The homogeneous model refers to use of 1 property of the aneurysm; the segmented model uses 4 distinct quadrant properties.
Table 4: Patient-Specific SEF Coefficients for Each Patient at Maximum Diameter from the ECG-Gated CT Scans

<table>
<thead>
<tr>
<th>Patient</th>
<th>Posterior</th>
<th>Left Lateral</th>
<th>Anterior</th>
<th>Right Lateral</th>
<th>Entire Aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>(C_{10}=1.2117)</td>
<td>(C_{10}=1.3266)</td>
<td>(C_{10}=1.2117)</td>
<td>(C_{10}=0.4241)</td>
<td>(C_{10}=0.8393)</td>
</tr>
<tr>
<td></td>
<td>(C_{20}=0.5131)</td>
<td>(C_{20}=1.5362)</td>
<td>(C_{20}=0.5131)</td>
<td>(C_{20}=3.2789)</td>
<td>(C_{20}=1.4206)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>(C_{10}=0.3793)</td>
<td>(C_{10}=0.1758)</td>
<td>(C_{10}=0.3793)</td>
<td>(C_{10}=0.2120)</td>
<td>(C_{10}=0.6540)</td>
</tr>
<tr>
<td></td>
<td>(C_{20}=8.5193)</td>
<td>(C_{20}=6.9218)</td>
<td>(C_{20}=8.5193)</td>
<td>(C_{20}=9.7944)</td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>(C_{10}=0.4656)</td>
<td>(C_{10}=1.5920)</td>
<td>(C_{10}=0.5302)</td>
<td>(C_{10}=1.4884)</td>
<td>(C_{10}=0.6540)</td>
</tr>
<tr>
<td></td>
<td>(C_{20}=4.0749)</td>
<td>(C_{20}=4.1887)</td>
<td>(C_{20}=3.4932)</td>
<td>(C_{20}=2.6324)</td>
<td>(C_{20}=3.2101)</td>
</tr>
</tbody>
</table>

There was great disparity in the magnitudes of peak stress and contours between models with homogeneous properties and the segmented properties for each patient. For example, for patient 2, the peak stress in the homogeneous model was 0.54 MPa on the anterior surface, with an elevated stress on the posterior wall of 0.45 MPa. The segmented model peak stress was 0.596 MPa on the anterior surface; an area of elevated stress of 0.489 MPa was evident on the posterior surface. The average difference in total stress in the different models after inclusion of prestress was 59%, 67%, and 15%, respectively, for the 3 patients. There was an average circumferential cyclic strain difference between the homogeneous and segmented FE models of 5.17%. Comparison of the strain from FE models with the \textit{in vivo} behaviour from the CT scans revealed an average difference in strain of 1.55% for the segmented models and 3.61% for the homogeneous models, which suggests that the segmented models more accurately reflect \textit{in vivo} behaviour.

The RPRI values (Fig. 9) were calculated from the data on peak stresses, locations of peak stress, and corresponding prestress values for each patient using the homogeneous and segmented modelling methods. An indication of the possible rupture risk using the index based on the local material properties can be determined. Using Equation 5, an example calculation of the risk for patient 2 (79-year-old man with a 160/95 mmHg pressure), using homogeneous properties, the peak stress (0.54MPa) in the anterior region, and a prestress value of 0.05MPa, would return: \(\text{RPRI}_R = (0.54+0.05)/0.7744 = 0.76\).
Figure 9: Regional RPRI values for each patient for both homogeneous (use of 1 property of the aneurysm) and segmented models (A: anterior, P: posterior, RL: right lateral, and LL: left lateral). The RPRI value predicts the area of the aneurysm that is thought to have greatest risk of rupture. The area of greatest rupture risk was not consistent between patients and varied when using local properties and homogeneous properties, which highlights the importance of the local regional properties.
DISCUSSION

Many previous studies have investigated the FE modelling of AAAs to predict rupture risk. An important aspect of any FEA study should be the inclusion of accurate material properties. These material inputs should be as similar to the patient-specific properties as possible if the results are to fully depict the state of health and behaviour of the aneurysm. However, to date, to the best of our knowledge, FE investigations have not been undertaken using the regional variation of the aneurysm mechanical response. To address this, we examined the hypothesis that the inhomogeneity and regional variation of aneurysm properties should be integral to constructing FE models to assess rupture risk.

The use of multidetector CT scans to acquire patient data is a noninvasive method to extract distensibility and elasticity properties of an aneurysm as described by the circumferential cyclic strain, compliance, and incremental modulus. Our study used a novel method to relate the patient-specific elasticity properties to average behaviour, generating finite strain constitutive relationships for use in FE modelling. These calculations will help to fully understand the dynamics of the aortic environment and lead to an improved understanding of the native environment.

Understanding and quantifying differences in elasticity properties during aneurysmal development is vital to gain insight into the pathogenesis and progression of the disease and changes in vessel wall properties. Our study demonstrated the differences in noninvasively measured elastic properties between the aneurysm site and the undilated proximal aorta. The undilated neck circumferential cyclic strain calculations (13%–17.3%) in our study agree with previously published estimates of strain in healthy human vessels (13.2%–17.8%). Local properties also led to large strain distribution differences between the segments compared to the entire aneurysm. In 2 of the 3 patients, the posterior wall circumferential cyclic strain was considerably smaller than the anterior strain, due in part to the constraint that the spinal column imposes on posterior motion.

The compliance values for the aneurysm site (5.4 to 8.62×10^{-4}/mmHg) are in good agreement with the literature (1.8 to 9.4×10^{-4}/mmHg). There is an average decrease in segmental compliance of 64%±15% going from the more elastic neck to the diseased aneurysm bulge. Also, the increased incremental modulus values at the aneurysm site
further highlight the increased stiffness due to aneurysm formation. These elasticity studies provide insight into the distension of the abdominal aorta. The wall motion and strain may explain aneurysm pathogenesis and may also have some relevance for the design of stent-grafts. In all elasticity calculations, there were differences evident in segmental values for each patient, corroborating the regional variations within the aneurysm.\textsuperscript{7,8}

From our evaluation of the need to include prestress in modelling, we found that the effect of prestress can be large and should be considered. The use of common properties can lead to considerable under- or overestimation of stress, which could have an implication for patient care and diagnostic decisions. Several previous studies have also proposed various methods to correct for the inclusion of the prestress present during data acquisition.\textsuperscript{25-29,49} All studies recommended including prestress in future FE analyses because it improves wall displacement accuracy.

The location of absolute peak stress at the inflection point was similar on both homogeneous and segmented models, as noted in other studies,\textsuperscript{23,42} although the magnitudes of peak stress and contours differed markedly between models with homogeneous properties and the segmented properties for each patient. On its own, the peak stress acting on the wall does not give a true indication of the rupture risk; it should be coupled with the local material properties. The local regional material property measurements may be more realistic and may give a better estimation of behaviour than using homogeneous properties. For example, in the 79-year-old patient 2, the peak stress acted on the anterior wall, but there was elevated stress acting on the posterior wall. However, due to local wall properties, the peak stress location was determined to have a lower risk of rupture. From the 3 cases examined, all AAAs experienced peak wall stress on the anterior surface, with elevated stress on the posterior surface. Relating these high stress areas to the regional properties identified the region that has the highest ratio of total stress to strength.

In contrast to previous research\textsuperscript{40,43,44,46} that applied the “normal” 120-mmHg blood pressure to the configuration, our study applied a lower patient-specific pressure that reflected the pressure acting on the aneurysm. The use of the patient specific pressure as a load to the diastolic configuration to predict the systolic configuration assumes that the principle of superposition applies to these cases. This assumes that the arterial
system response is linear. In the disease stage of the aneurysm, due to elastin degradation, the aorta acts in the collagen region of the stress-strain curve. Therefore the assumption of superposition holds for these cases. Using an elevated pressure may increase the stresses and result in false values of peak stress, which could lead to inaccurate risk results. Also, higher pressures are associated with larger deformation of the aneurysm due in part to the pressure and also to the material properties applied starting at a no load condition (low stiffness). In contrast, our modelling method accounted for the prestress on the tissue. Since the pressure was also lower, this resulted in lower overall deformation, which in turn can affect stress.

Previous studies have evaluated rupture potential indices\textsuperscript{10,11,50} similar to the RPRI we studied here. Both indices use the fundamental principle that a material will fail when the total stress acting on the wall exceeds the strength of the material. The principle is based on the hypothesis that, under no load, elastin and smooth muscle cells (SMC) are connected, such that elastin sheaths and fibres are prestressed. The exact 3D configuration of the links between SMC and elastin is not exactly known; however, a section of the artery that is under a high level of prestress can only undergo a certain level of stress until rupture. Other researchers have presented several methods that use static CT data in FE analysis to aid decision making.\textsuperscript{10,11,24,43,44,51} However, if these methods are to be used to their full potential and relied upon, the most accurate material properties to characterise normal aortic motion during the cardiac cycle must be used. Our technique incorporates regional mechanical properties and initial stress in the artery in FE methods to aid clinical decision making. It takes into account patient-specific regional properties to convert the regional stress to a specific regional rupture risk, which represents a departure from the “one size fits all” criterion currently in use. To justify this new approach, the resources for incorporating gated CTs into current scanning protocols and the additional computational work would have to be weighed against the benefits of an improved FE analysis.

**Limitations**

At the time of the CT scans acquisition, they were taken only at the neck and maximum diameter of the abdominal aorta; the full geometry was not acquired. Therefore, we could not apply the patient mechanical properties to their own geometries, so we applied each patient’s mechanical properties to a single AAA
geometry. Had 3 geometries been used, it would have been difficult to extract conclusive evidence on the use of regional properties. A more comprehensive study would involve using patient-specific properties in conjunction with the patient-specific geometry to address the significance of the geometry.

We did not include the ILT component in our simulations, but there was <8% difference (average 6.2%) between compliance calculations from FE and CT, suggesting that the wall properties taken from the CT scans included the effects of ILT on deformation. There are differing opinions in the literature about the importance of ILT in rupture assessment. The studies made by Vorp et al. indicated that the presence of ILT reduces AAA wall strength. Adolph et al. claimed that ILT can play an active role in AAA pathogenesis due to inflammatory infiltration cells (macrophages and neutrophils). Stenbaek et al. showed increasing thrombus surface area increases aneurysm rupture risk, particularly when the increase amounts to ≥15 mm² per year. Wolf et al. found that an increase in ILT volume was connected with the growth of the aneurysm. In contrast, Schurink et al. demonstrated that the presence of ILT does not cause any reduction in the arterial blood pressure acting on the wall, so it did not play any significant role. On the basis of comparative studies of groups of ruptured and unruptured AAAs, Hans et al. did not find statistically significant differences in the ILT to total aneurysm volume ratio between the studied groups. As this study was the first iteration in a feasibility study, the authors believed it was acceptable to exclude ILT from the simulations.

This study measured motion in the transverse plane and did not address the out-of-plane motion of the aorta. Aortic motion is generally 3D, but because of the relatively small motion of the aortic wall, it is reasonable to assume that out-of-plane motion is highly limited, so the motion can be extracted from 2D image sequences. The in-plane motion of the aorta is typically <1 mm per frame. It is physiologically reasonable to expect the out-of-plane motion to be even smaller than the motion in the transverse plane, so it can be neglected.

The entire circumference of the aneurysm was sectioned into 4 segments, which were each given its individual properties. There was an abrupt transition between certain segments; although this did not present any problems for this study, it may be more accurately modelled if treated as a gradient between the segments.
Published results have shown that wall thickness varies regionally and between AAAs from as low as 0.23 mm at a rupture site to 4.26 mm at a calcified site. Scotti et al. reported that an asymmetrical AAA with regional variations in wall thickness would be exposed to higher mechanical stresses and an increased risk of rupture than a more fusiform AAA with uniform wall thickness. It is difficult to accurately assess this dimension in patient-specific CT images due to calcification, thrombus, and the lack of clear image definition between the inner and outer wall surfaces. Therefore, a uniform thickness of 2 mm is typically assumed when modelling individual AAAs.

The average properties taken from Raghavan and Vorp, although based on 69 samples, only used uniaxial properties; biaxial data would also be necessary. The use of anisotropic properties in the material properties would yield greater accuracies in the wall stress analysis, which could lead to a more accurate rupture index. Longitudinal deformations and longitudinal strain were not taken into account for any of the computational reconstructions; previous studies have shown longitudinal strain to be in the order of 2%, which is negligible and justifies this approach. Notably, we are not facing a pure deformation problem since continuous remodelling processes are taking place in living tissue. These remodelling effects were not taken into account. The model assumed the prestress was uniform through the individual segment in the segmented model or uniform throughout in the case of the single property model.

There are conflicting opinions on the role of calcifications in AAA behaviour. They may diminish tissue strength, which increases the rupture risk at those sites. Using FE simulations, Maier et al. found that calcifications exhibit significant load-bearing effects and reduce stress in the adjacent vessel wall by 9.7% to 59.2%. These calcifications are visible in CT scans, and this information could be considered in an FE model by assigning constitutive properties for calcified tissue to finite elements representing calcified regions. The reliability, however, of such an approach would heavily depend on the quality of constitutive information, as it would be extracted from in vitro experiments of the calcified aneurysm wall.

The pressure used was measured by an automatic pneumatic sphygmomanometer. This use of non-invasively acquired peripheral arterial pressure to reflect central aortic pressure in the calculation of elastic properties may carry some inaccuracy. Vorp et al., 1996, demonstrated that pulse pressure measured by the finger cuff was significantly
related to central aortic pressure over a wide range of values. Therefore, the pulse pressure would be sufficient for the compliance measurements and FE simulations but a more invasive intra-aneurysmal measurement would be needed for exact reading of blood pressure.\textsuperscript{61}
CONCLUSIONS

We have reported the regional mechanical properties in undilated aorta, with no visible signs of aortic pathology, and at the visibly distended aneurysmal bulge. This analysis contributes to the understanding and quantification of the local regional properties in the undilated and diseased aorta. Quantifying the regional behaviour will yield insight into the changes in patient-specific aneurysms and increase understanding about the progression of aneurysm disease. Ultimately, identifying the local areas of the aneurysm that have high prestress could indicate higher degradation of elastin in these regions, which may leave them susceptible to rupture. A greater understanding of the local material properties and their use in FE models is essential for greater accuracy in rupture prediction. The incorporation of additional patient-specific parameters into the FE modelling criteria may reduce the uncertainty associated with rupture prediction.

ACKNOWLEDGEMENTS

The authors wish to acknowledge Drs. Marika Ganten and Stefan Delorme, Department of Radiology, Heidelberg, Germany, for providing the CT scans.
REFERENCES


CHAPTER 4

IN VIVO QUANTIFICATION OF REGIONAL ABDOMINAL AORTIC ANEURYSM ELASTIC PROPERTIES: IMPLICATIONS FOR FE ANALYSIS

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Conception and Design: AT, AC
Analysis and Interpretation: AT, AC
Data Collection: AT, HZ
Writing the article: AT
Critical Revision: AC, TM, HZ, JH
Final Approval: TM, AC, HZ, JH
Obtained Funding: AT, AC, TM
ABSTRACT

PURPOSE

To gain a new insight into the elastic properties of the abdominal aorta aneurysm in patients using electrocardiographically (ECG)-gated CT, CT data of 5 subjects with previously diagnosed AAA were reconstructed in 12.5% steps throughout the RR interval.

METHODS

Diameter and circumference were measured at 5 points of interest proximally from the maximum diameter of the AAA. The pulsation and elasticity of the aorta were evaluated. Aortic diameter and circumference changes were noted throughout the cardiac cycle. The local properties of aortic pulsation and wall elasticity could also be analysed regionally at the different locations. The centroid motion during the cardiac cycle was also studied to establish if the direction of the centroid motion could be correlated with AAA development. Local segmental elastic properties were used in patient-specific FE reconstructions to examine the effect of regional properties on FE modelling of rupture risk. The present work details a method for noninvasively assessing the regional rupture potential of AAAs using patient-specific measurements, calculated as the ratio of locally acting wall stress to strength.

RESULTS

The minimum average circumference change was at the level of the maximum diameter of the aneurysm, 2.751±1.003%. The maximum was seen at level 90mm proximal of the maximum diameter, 6.853±2.578%. There was a location-dependent change in elasticity measured by incremental modulus, compliance and circumferential cyclic strain. The local elastic properties had high standard deviations segmentally in 4 regions examined. The magnitude and direction of vessel expansion differs greatly at the different levels of the aorta, with large rightward motion at the aneurysmal site and smaller motion at the proximal level. FE analysis revealed considerable differences between stress levels based on the published and widely used mechanical properties of Raghavan and Vorp and those determined from the locally derived properties using this novel noninvasive approach. The highest RPRI value was not always necessarily the location of peak stress, due to the regional variations.

CONCLUSIONS

The rate of asymmetric distension varied by patient and by location. This may have implications in rupture risk assessment, clinical decision making and endograft design. The findings regarding segment difference and location were noteworthy and should be taken into account in clinical trials and treatments for cardiovascular diseases which induce changes in vessel elasticity.
INTRODUCTION

Cardiac gated CT and finite-element (FE) analysis are valuable tools in analysing cardiac mechanics. Helical computed tomographic angiography (CTA) is currently the primary imaging modality for pre- and postoperative planning and evaluation of abdominal aortic aneurysms (AAA). Precise 3-dimensional (3D) measurements and relationships become important when determining an accurate prediction of cardiac behaviour and motion. Static images obtained with current high-speed CT acquisition times could represent any random moment during the cardiac cycle. However, research on dynamic imaging reported that the aorta changes significantly (P > .05) during the cardiac cycle, with significant increases in aortic diameter per heartbeat within the proximal neck (P > .05) [1-4]. These increases in diameter and cardiac motion are functions of the arterial elasticity of the structure. Various vascular diseases including abdominal aortic aneurysms (AAAs) are known to change the tissue mechanical properties. Changes in composition and structure of the wall will alter its elasticity. Several noninvasive imaging techniques have been employed for aortic elasticity evaluation [5-12].

The properties of aortic pulsation and wall elasticity can be well shown by ECG-gated CT [1, 13-17]. Previous findings regarding regional differences and age relevance were considerable and should be taken into account in clinical trials and treatments for cardiovascular diseases which induce elasticity changes. Arterial elasticity is increasingly used as an important clinical marker in cardiovascular disease prediction and medication therapy evaluation. Elasticity is an important structural and functional parameter of the aortic wall and decreases correlate with high blood pressure, future atherosclerotic diseases, coronary artery disease and some arteriolar narrowing [18-21]. It is widely accepted as an independent predictor of adverse cardiovascular outcomes at an early stage [22, 23]. The age-dependent decrease of elasticity for the aorta without known vascular disease has been detected, demonstrating the natural process of aging of the aorta [24]. Sometimes, this natural process can be intensified because of multiple influencing factors such as hypertension, diabetes, smoking and genetics. Therefore, an ability to evaluate aortic elasticity noninvasively in an early disease state and inclusion of these elasticity modifications is of great interest for determination of rupture risk of aneurysms.
A previous study by the authors had reported that inclusion of patient-specific regional variation of the aneurysm properties, independent of patient geometries, in FE analysis may be more realistic and may give a better estimation of in vivo behaviour [25]. This previous study also demonstrated the differences in noninvasively measured elastic properties between the aneurysm site and the undilated proximal aorta. The study presented here extends the previous study by including the patient-specific geometries in the FE study. The centroid motion during the cardiac cycle was also analysed to establish if the direction of the centroid motion was correlated with AAA development [26]. The pulsation and elastic properties of the abdominal aorta were evaluated to elucidate our understanding of aortic elasticity at various anatomical points.
MATERIALS AND METHODS

Subjects
The study comprised of five male subjects, (ages 64, 63, 62, 64, 62 years), with known infrarenal aortic aneurysms who were being preoperatively scanned as part of regular treatment.

Image Acquisition
Data were acquired using an electrocardiographically (ECG)-gated dynamic 64-slice CT scanner (Philips Medical Systems, Best, The Netherlands). Images were acquired during a single breath-hold of 20 seconds, during which the entire abdomen was imaged. The imaging protocol was set at 1.25-mm collimation and a pitch of 0.25. Radiation exposure parameters were 120 kVp and 300 mAs, resulting in a CT dose index (CTDIvol) of 21 mGy. Intravascular nonionic contrast (120 mL of Iopromide 300; Schering, Berlin, Germany) followed by a 60-mL saline chaser bolus was injected at a flow rate of 6 mL/s. The scan was started using bolus triggering software with a threshold of 100 HU over baseline.

ECG-triggered retrospective reconstructions were made at 8 equidistant time points over the R-R cardiac cycle. The dataset of each patient was loaded into a separate workstation (3Mensio Medical Imaging B.V., Bilthoven, The Netherlands) and processed using the cardiac review program function.

Data Analysis
Analysis of the dynamic scans was performed using 3Surgery 4.0 software (3Mensio Medical Imaging B.V., Bilthoven, The Netherlands), which was developed to perform automated segmentation and measure changes in area and diameter at predetermined aortic levels [27].

Five relevant anatomical levels of the aorta were selected for analysis: Maximum diameter, M, and at 30mm levels proximally from the level of maximum diameter (Figure 1 M, B-E). Diameter and circumference changes could be measured at each time point of the cardiac cycle. The diameter was determined over 360 axes at an angular increment of 1 and the maximum value could then be determined.
To observe the local regional variation in mechanical properties, each aortic image was sectioned into segments: anterior (A), posterior (P), right lateral (RL), and left lateral (LL). A best fit curve was applied to the boundary of the wall area and exported to Matlab r2009a (Mathworks, Natick, MA, USA) as a 2-dimensional series of points that could be summed to calculate the segment lengths. The circumferential lengths of these segments could then be measured and changes calculated to allow for elasticity calculation.

![Figure 1: Representative geometry demonstrating the different levels examined through the anatomy, M represents Maximum Diameter and each level moves 30mm proximally to this.](image)

**Aortic Asymmetry**

The centroids of 100 slices were extracted to create an aortic centreline [28]. The degree of asymmetry of the aorta was defined by the perpendicular distance from the centreline to a connecting line joining the end points of the centreline. The location and magnitude of maximum asymmetry could then be calculated.

**Aortic Elasticity Evaluation**

The diameter and circumference were used in the calculation of elastic parameters such as circumferential cyclic strain (E_{θθ}), Hudetz Incremental Modulus (E_{inc}) and Compliance (C).

Circumferential cyclic strain\textsuperscript{[11, 29]}: \[ E_{θθ} = \frac{1}{2} \left[ \left( \frac{L_o^2}{L_d^2} \right) - 1 \right] \] (Eqn. 4)

Hudetz incremental modulus\textsuperscript{[30, 31]}: \[ H_{θθ} = 2 \left[ \left( \frac{d_{out}^2 - d_{in}^2}{\Delta d_{out}/\Delta P} \right) + \left( P \times d_{out}^2 \right) \right] \times \left[ \frac{1}{d_{out}^2 - d_{in}^2} \right] \] (Eqn. 2)

Compliance\textsuperscript{[32, 33]}: \[ C = \frac{\Delta L}{[L_o(\Delta P)]} \] (Eqn. 3)
Where, \( L_s \) = segment length at systole, \( L_d \) = segment length at diastole, \( \Delta L = L_s - L_d \), \( d_{\text{out}} \) = outer diameter, \( d_{\text{in}} \) = inner diameter, \( P \) is Pressure, \( \Delta P \) = change in Pressure from diastole to systole, \( \Delta d_{\text{out}} \) = change in outer diameter for \( P \).

**Aortic Centroid Motion**

The magnitude and direction of motion of the coordinates of the centroid at maximum diameter (M) and level E were also calculated (Figure 2). There was a gradient of centroid motion from E to M, and as these two levels were deemed to have the least and greatest motion respectively. Therefore these were chosen for more detailed analysis.

![Schematic of Centroid Motion](image)

**Figure 2:** Schematic showing magnitude and angle of centroid motion. The right lateral direction was defined as 0°, anterior as 90°, posterior as -90° and left lateral as ± 180°

**FE Analysis**

The circumferential cyclic strain and the incremental modulus calculated from the CTs were used in conjunction with Raghavan and Vorp’s average aneurysm behaviour [34] to generate a stress-strain relationship for each segment and the entire aneurysm (Figure 3). This is described at length in Tierney et al., 2012 [25].
Using a method previously validated by our research group, a 3D reconstruction was generated from the CT scan for each individual subject using Mimics (v14.1) and 3Matic (v6.1) (Materialise Ltd., Leuven, Belgium); the reconstruction was imported into Abaqus (version 6.9.1; Dassault Systèmes Simulia Corp., Providence, RI, USA) software for stress analysis. The materials were assumed to be incompressible and hyperelastic; therefore, the strain energy functions took the form:

\[ W = \sum_{i=1}^{N} C_{ij0} (\tilde{I}_1^{-3})^i \]  
(Eqn. 4),

where \( \tilde{I}_1 \) is the first invariant and \( C \) is the material constant [35].

Each patient geometry was modelled using 3 different material properties:

- **AAA(RV)** - Common nonlinear material properties traditionally used (\( C_{10} = 0.174 \text{ MPa}, C_{20} = 1.881 \text{ MPa} \)); As per the commonly used approach, 120mmHg was applied to each of these models [36-39]

- **AAA(WA)** - Material properties derived from the full circumferential behaviour of the aorta. Patient-specific pressures were applied to these models.
• AAA(SEG) - Segmented in 4, Material properties were calculated from each individual segment behaviour. As the model was predominantly aneurysmal, only the properties measured at maximum diameter were used. Patient-specific pressures were applied to these models.

As with previous research [36, 40], all models in this study omitted the iliac arteries. To simulate the connection of the AAA segment to the descending aorta and the iliac bifurcation, the model was fully constrained in the proximal and distal directions. The blood pressure within the AAA acts on the sac’s inner wall; therefore, patient-specific pressures were applied to the inner surface of the computational AAA model. The patient-specific pressures are listed in Table 1. Aortic tissue is also known to be nearly incompressible, with a Poisson’s ratio of ~0.49. The mesh was declared independent when the peak aneurysm wall stress did not vary by more than 2% between successive meshes.

<table>
<thead>
<tr>
<th></th>
<th>Systolic Pressure (mmHg)</th>
<th>Diastolic Pressure (mmHg)</th>
<th>Applied Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>149</td>
<td>84</td>
<td>65</td>
</tr>
<tr>
<td>Patient 2</td>
<td>119</td>
<td>63</td>
<td>56</td>
</tr>
<tr>
<td>Patient 3</td>
<td>161</td>
<td>94</td>
<td>67</td>
</tr>
<tr>
<td>Patient 4</td>
<td>131</td>
<td>76</td>
<td>55</td>
</tr>
<tr>
<td>Patient 5</td>
<td>110</td>
<td>70</td>
<td>40</td>
</tr>
</tbody>
</table>

**Rupture Risk**

As described in our recent publication (Tierney et al, 2012), the regional prestress rupture index (RPRI) was based on the engineering principle that a material will fail when the total stress acting on the wall exceeds the strength of the material. The prestress was based on the position of the segmental stress-strain curve on Raghavan and Vorp’s average behaviour curve [34].

\[
\text{RPRI}_R = \frac{(\text{Peak stress}_R + \text{Prestress}_R)}{\text{Wall Strength}_R} \quad \text{(Eqn. 5)},
\]

where prestress refers to the segmental prestress calculated using Figure 3 and peak stress to that measured from FE simulations. R refers to the local mechanical property.
circumferential region, which can be ≥1 (dependent on the number of local regional property calculations on the aneurysm).

For the traditional modelling method [models AAA(RV)] the RPRI calculated was Peak stress/Wall strength. Typically for these models prestress is not taken into account.

These wall strengths had been combined and averaged (anterior: 0.7744 MPa, posterior: 0.8658 MPa, left lateral: 0.9221 MPa, right lateral: 0.9187 MPa) in a previous study to collate the specific region strength.
RESULTS

Global Measurements

The global measurements were calculated to extract information of the behaviour of the entire aorta. These measurements include Aortic Asymmetry, Circumference Change, Circumferential Cyclic Strain and Incremental Modulus and Compliance.

Aortic Asymmetry

Table 2: Maximum Asymmetry of the Aortic Centreline at Diastolic and Systolic Pressure

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diastole</th>
<th>Systole</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>13.4mm</td>
<td>13.8mm</td>
</tr>
<tr>
<td>2</td>
<td>8.69mm</td>
<td>8.86mm</td>
</tr>
<tr>
<td>3</td>
<td>23.06mm</td>
<td>23.38mm</td>
</tr>
<tr>
<td>4</td>
<td>43.72mm</td>
<td>46.95mm</td>
</tr>
<tr>
<td>5</td>
<td>20.3mm</td>
<td>21.95mm</td>
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</tbody>
</table>

Maximum asymmetry occurred at systolic pressure, as shown in Table 2, and the location of maximum geometric asymmetry of the aneurysm corresponded with the area of maximum aneurysm development.

Circumference Change

Five different positions along the aortic anatomy were monitored throughout the cardiac cycle. There was an observed variation in the circumference and magnitude of distension per patient and per level (Table 3). There was a large difference between the most proximal level E to the aneurysm site M. In all five patients there was a steady increase in circumference approaching the aneurysm. The average percentage increase from most proximal E to the aneurysm M was 128.7% (± 34.9%).

Incremental Modulus and Compliance at each position

The incremental modulus and compliance values are shown for each patient at each examined level in Figure 4. The incremental modulus of the vessel shows a steady increase distally approaching the aneurysm site. Conversely to this, the compliance of the vessel decreases. There was an average reduction in compliance of 43.8% (± 26.4%) and increase in modulus of 67.8% (± 14.8%) from most proximal site (E) to most distal site (M).
Table 3: Maximum Circumferences (in mm) at each level for each patient, at systolic and diastolic pressure, percentage difference displayed at each level

<table>
<thead>
<tr>
<th></th>
<th>E</th>
<th></th>
<th>D</th>
<th></th>
<th>C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cs</td>
<td>Cd</td>
<td>% Difference</td>
<td>Cs</td>
<td>Cd</td>
<td>% Difference</td>
</tr>
<tr>
<td>Patient 1</td>
<td>67.225</td>
<td>64.730</td>
<td>3.86</td>
<td>74.573</td>
<td>70.843</td>
<td>5.27</td>
</tr>
<tr>
<td>Patient 2</td>
<td>79.059</td>
<td>74.816</td>
<td>5.67</td>
<td>82.000</td>
<td>73.596</td>
<td>11.42</td>
</tr>
<tr>
<td>Patient 3</td>
<td>81.611</td>
<td>76.473</td>
<td>6.72</td>
<td>106.448</td>
<td>100.173</td>
<td>6.26</td>
</tr>
<tr>
<td>Patient 4</td>
<td>94.957</td>
<td>90.918</td>
<td>4.44</td>
<td>89.640</td>
<td>84.874</td>
<td>5.61</td>
</tr>
<tr>
<td>Patient 5</td>
<td>79.051</td>
<td>74.746</td>
<td>5.76</td>
<td>75.596</td>
<td>71.517</td>
<td>5.70</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>80.381</strong></td>
<td><strong>76.337</strong></td>
<td><strong>5.30</strong></td>
<td><strong>85.651</strong></td>
<td><strong>80.201</strong></td>
<td><strong>6.80</strong></td>
</tr>
<tr>
<td><strong>Standard</strong></td>
<td><strong>9.881</strong></td>
<td><strong>9.383</strong></td>
<td></td>
<td><strong>13.092</strong></td>
<td><strong>12.524</strong></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cs</th>
<th>Cd</th>
<th>% Difference</th>
<th>Cs</th>
<th>Cd</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>166.235</td>
<td>156.000</td>
<td>6.56</td>
<td>189.204</td>
<td>185.064</td>
<td>2.24</td>
</tr>
<tr>
<td>Patient 2</td>
<td>178.265</td>
<td>175.279</td>
<td>1.70</td>
<td>189.439</td>
<td>183.953</td>
<td>2.98</td>
</tr>
<tr>
<td>Patient 3</td>
<td>146.068</td>
<td>139.412</td>
<td>4.77</td>
<td>186.057</td>
<td>181.974</td>
<td>2.24</td>
</tr>
<tr>
<td>Patient 4</td>
<td>167.058</td>
<td>161.090</td>
<td>3.70</td>
<td>182.507</td>
<td>174.816</td>
<td>4.40</td>
</tr>
<tr>
<td>Patient 5</td>
<td>108.277</td>
<td>104.344</td>
<td>3.77</td>
<td>178.938</td>
<td>175.611</td>
<td>1.89</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>153.180</strong></td>
<td><strong>147.225</strong></td>
<td><strong>4.05</strong></td>
<td><strong>185.229</strong></td>
<td><strong>180.283</strong></td>
<td><strong>2.74</strong></td>
</tr>
<tr>
<td><strong>Standard</strong></td>
<td><strong>27.655</strong></td>
<td><strong>27.185</strong></td>
<td></td>
<td><strong>4.505</strong></td>
<td><strong>4.767</strong></td>
<td></td>
</tr>
</tbody>
</table>

Where $C_s$ is systolic circumference, $C_d$ is diastolic circumference.
Figure 4: Relationship between Incremental modulus and Compliance for each patient at each level
Local Measurements

The local measurements were calculated to extract information of the behaviour of the regional areas of the aorta. These measurements include Centroid Motion and circumferential cyclic strain at most proximal and distal levels and local incremental modulus and compliance of aortic segments.

Centroid Motion

The coordinates of the centroid were also calculated. The centroid of the vessel at the aneurysm site moved a greater distance than of that proximally (Average at M: 9.484mm, Average at E: 1.968mm) (Fig. 5 A). The direction of the centroid motion was also different at each location, the aneurysm site moved from left to right in the direction of the aneurysm expansion, while the slight proximal area motion appeared to be more slight and random direction (Fig 5 B, C & D).

Figure 5: (A) Illustration of the examined levels (B) Tabulated results from centroid motion data (C) Centroid motion for each patient at location E (D) Centroid motion for each patient at location M
Circumferential Cyclic Strain

Table 4: Maximum Circumferential Cyclic Strain and centroid motion data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Position</th>
<th>Maximum Circumferential Cyclic Strain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E</td>
<td>3.930</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>2.262</td>
</tr>
<tr>
<td>2</td>
<td>E</td>
<td>5.832</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>3.027</td>
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<tr>
<td>3</td>
<td>E</td>
<td>6.945</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>2.269</td>
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<tr>
<td>4</td>
<td>E</td>
<td>4.541</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>4.496</td>
</tr>
<tr>
<td>5</td>
<td>E</td>
<td>5.924</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>1.912</td>
</tr>
</tbody>
</table>

Table 4 shows that circumferential cyclic strains observed were larger at the proximal areas of the aorta and demonstrated the nonuniform circumferential expansion of the vessel at all levels. The average circumferential cyclic strain was measured at the different levels were E: 5.43%±1.19%, D: 7.11%±2.8, C: 5.85%±2.21%, B: 4.19%±1.84% and M: 2.79%±1.03%.

Segmental Calculations

Figure 6: Average Segmental Compliance and Modulus for each region of the aorta, at level M and E
The average segmental incremental modulus and compliance measured at M and E for individual segments are displayed in Figure 6. There is high variation in the local properties in both modulus and compliance at both locations. Asymmetric expansion was present at all levels of the aorta and for all patients. There was extremely high standard deviation in the average compliance and modulus values. These are shown in Table 5.

<table>
<thead>
<tr>
<th>Level</th>
<th>Incremental Modulus (MPa)</th>
<th>Compliance (*10^-4 /mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>RL</td>
<td>0.441</td>
<td>3.609</td>
</tr>
<tr>
<td>P</td>
<td>2.583</td>
<td>3.449</td>
</tr>
<tr>
<td>LL</td>
<td>0.302</td>
<td>1.746</td>
</tr>
<tr>
<td>WA</td>
<td>3.603</td>
<td>1.030</td>
</tr>
</tbody>
</table>

Finite Element Analysis

Both the global and local measurements were used in reconstructions of patient geometries to assess the effect of utilising patient-specific properties.

FE Results

In order to easily observe and visualise the resulting wall stress of each AAA model, contours of von Mises stress were plotted on the surface of each AAA model. The von Mises stress is a stress index especially suited for failure analysis, as stress is a tensor quantity with nine components. The von Mises stress is a combination of these components. Studying von Mises stress, rather than each component of stress, allows for meaningful interpretation of the results. The normalised computed wall stress for the AAA(RV), AAA(WA) and AAA(SEG) models can be seen in Figure 7. In these figures, wall stress results were normalised by using the peak stress from that individual patient. Observation of the stress distribution revealed that the regions of elevated stress and peak stress occurred at inflection points on the AAA wall, not at regions of maximum diameter. The majority of peak wall stresses were found on the posterior section of the aorta, possibly due to the constraint of the spine. The maximum stress was seen on AAA(WA) in 4 of the patients. Peak stresses in patients 5 had no difference
between the different modelling techniques, possible reasons for this are thought to be because of the relativity low Blood Pressure of this patient (110/70). This resulted in a pressure 40mmHg (5.33KPa) being applied to each of the models. Peak stresses varied considerably depending on the modelling technique. There was an average 29% difference between AAA(RV) and AAA(WA) and an average 28% between AAA(SEG) and AAA(WA). The contours on the models between each of the modelling techniques are also noticeably different (Figure 7). These differences are attributable to the use of more realistic properties as geometries, applied pressure and boundary conditions are all identical.
Figure 7: Posterior and Anterior view of Von Mises wall stress distributions for AAA(RV), AAA(WA) and AAA(SEG). Peak stresses and location for each model are displayed in the image.

<table>
<thead>
<tr>
<th>Patient</th>
<th>AAA(RV)</th>
<th>AAA(WA)</th>
<th>AAA(SEG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0.75MPa Posterior</td>
<td>0.401MPa Posterior</td>
<td>0.27MPa Anterior</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.66MPa Posterior</td>
<td>0.302MPa Posterior</td>
<td>0.198MPa Posterior</td>
</tr>
<tr>
<td>Patient 3</td>
<td>0.68MPa Posterior</td>
<td>0.465MPa Posterior</td>
<td>0.343MPa Posterior</td>
</tr>
<tr>
<td>Patient 4</td>
<td>0.63MPa Posterior</td>
<td>0.331MPa Left Lateral</td>
<td>0.287MPa Posterior</td>
</tr>
<tr>
<td>Patient 5</td>
<td>0.45MPa Posterior</td>
<td>0.126MPa Posterior</td>
<td>0.125MPa Posterior</td>
</tr>
</tbody>
</table>
Rupture Risk

The wall stress was assessed for each modelling technique from FE and used to calculate the regional rupture risk.

**RPRI**

The RPRI values could be calculated using Eqn. 5, following determination of peak stress magnitude and location through FE analysis. Table 6 shows the resulting RPRI values with the corresponding maximum diameters of each patient. The RPRI data presented utilises wall strength data which has been previously published [41-43], in combination with the peak stress, magnitude and location, and prestress previously measured. A RPRI value close to 1 suggests that the AAA may be at high risk of rupture. All five cases have exceeded the usual 50mm diameter threshold for surgery. Consideration of the RPRI values with the peak stresses from Figure 7 reveals that the location of peak stress was not always necessarily the location most at risk. The area of peak stress could be neutralised by a wall segment which has not undergone a lot of degradation. In contrast an elevated region of stress may be at higher risk due to a highly diseased local region or highly prestressed configuration *in vivo*. 
Table 6: Resulting RPRI values of each modelling technique, maximum diameters and prestresses for each patient are also displayed here.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Maximum Diameter (mm)</th>
<th>Region</th>
<th>RPRI</th>
<th>Regional Prestress (MPa)</th>
<th>RPRI</th>
<th>Regional Prestress (MPa)</th>
<th>RPRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>0.594</td>
<td>0.175</td>
<td>0.626</td>
<td>0.010</td>
<td>0.362</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RL</td>
<td>0.403</td>
<td>0.175</td>
<td>0.582</td>
<td>0.200</td>
<td>0.544</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
<td><strong>0.866</strong></td>
<td>0.175</td>
<td><strong>0.664</strong></td>
<td>0.355</td>
<td><strong>0.699</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LL</td>
<td>0.564</td>
<td>0.175</td>
<td>0.515</td>
<td>0.010</td>
<td>0.282</td>
</tr>
<tr>
<td>2</td>
<td>63.91</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>0.478</td>
<td>0.130</td>
<td>0.491</td>
<td>0.155</td>
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<tr>
<td></td>
<td></td>
<td>RL</td>
<td>0.642</td>
<td>0.130</td>
<td>0.435</td>
<td>0.178</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
<td><strong>0.762</strong></td>
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<td>0.254</td>
</tr>
<tr>
<td></td>
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<td>LL</td>
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<td>0.130</td>
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<td>0.070</td>
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<tr>
<td>3</td>
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<td>A</td>
<td>0.323</td>
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<td></td>
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<td></td>
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<td>0.175</td>
<td><strong>0.733</strong></td>
<td>0.130</td>
<td>0.546</td>
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<td></td>
</tr>
<tr>
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<td>0.325</td>
<td>0.030</td>
<td>0.163</td>
<td>0.030</td>
<td>0.163</td>
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</tbody>
</table>
DISCUSSION

Using cardiac gated CT, we quantified aortic elasticity, motion and asymmetry at multiple locations along the diseased abdominal aorta in five subjects. We have shown that cardiac gated CT can track pulsatile expansion and distension along the abdominal section. Numerous methods using various geometrical parameters have been used to quantify arterial elasticity. Diameter change, incremental modulus, compliance, circumferential cyclic strain, centroid motion and asymmetry were analysed to achieve a more objective insight into aortic elasticity. The negative impact of the aneurysm on vessel elasticity was clearly demonstrated in the various aortic dynamics measured.

We have observed a variation in the rate of circumferential increase and magnitude of expansion per patient and per level. The circumferential increase was asymmetric at all levels of the aorta which has been reported previously [15]. The non elastic and non geometric uniformity of the arterial tree is particularly evident in the circumference calculations through the anatomy. Arterial stiffness is different in proximal non-dilated elastic aorta compared with the aneurysmal artery. An advantage of using the circumference during expansion is it yields a complete mapping of the distension, regardless of the asymmetry of the vessel.

Incremental modulus and compliance in the aorta are markers of vessel wall integrity because they are dependent on the elastic properties of the aorta. The compliance values proximally in the anatomy are above that of compliance values for the aneurysm site literature (1.8 to 9.4×10⁻⁴/mmHg) [33]. Calculations approaching and at the aneurysm site correspond to that reported in literature, with lower compliance than that in the non-dilated proximal elastic region. Incremental modulus values previously reported in literature for aneurysms 50mm-60mm were 2.01 ± 0.37MPa [n=5] and healthy aorta 1.18 ± 0.21MPa [n=20]. The two most proximal levels of examination correspond to the previous calculations in the healthy aorta (E=1.049±0.265, D=1.179±0.432). The average modulus at the level of the aneurysm (M=3.603±1.030) was greater than that previously reported. The circumferential cyclic strain decreased from E to M for all patients, by an average of 94.5% (E=5.434%±1.198%, E=2.793%±1.035%).
The magnitude and direction of vessel expansion differs greatly at the different levels of the aorta, with large rightward centroid motion at the aneurysmal site and smaller motion at the proximal level. Similarly to previous studies, there was greater anterior wall motion than posterior motion [26]. Goergen et al, 2011 demonstrated that aortic curvature and pulsatile lumen expansion influence the location and direction of vessel expansion in experimental murine aneurysms [44]. This finding was found to be consistent in human AAA.

There was a high variability in segmental elastic properties examined circumferentially at level M and level E. The only segment of the aorta with a greater Incremental modulus at level M than E was the posterior segment, P. This could be attributed to the fact that the diaphragm and spine are predominantly located to the right of the vessel above the renal arteries and directly posterior in the infrarenal region. This may result in restricted movement of the posterior segment at M, thereby inhibiting displacement and deformation. The proximal level is nondilated and is greater distance from the constraint of the spine. The compliance values for 3/4 segments at level M fall within that reported previously in literature (1.8 to $9.4 \times 10^{-4}$/mmHg) [33]. The compliance values for 3/4 segments at level E fall above that reported previously in literature (1.8 to $9.4 \times 10^{-4}$/mmHg) for an aneurysm suggesting that perhaps disease formation may have initiated at the LL segment at level E already. Assessment of the segmental differences seen in AAA patients may provide interesting mechanistic information to clinical decision making.

The modelling techniques used in this study all return different wall stress results. The stress results returned by the models AAA(RV) were considerably higher than those of the patient-specific models. Peak wall stress was shown to decrease when using material properties which reflect the regional patient-specific elastic properties. The stresses returned from AAA(RV) were on average 120 ± 80.95% greater than those of AAA(WA) and 177% ± 69.94% greater than the AAA(SEG) models. The magnitude different from AAA(RV) may be due in part to the considerable difference in pressures applied to the models. These widely used properties from AAA(RV) may overestimate the stresses acting on the vessel wall, leading to false stress magnitudes. From Figure 7, it can be seen how the change in material properties not only alters the magnitude of the stresses acting on the wall, but also the overall stress distribution patterns. The location
of peak stress between the different techniques did not differ majorly. It has been found that an asymmetric AAA resulted in elevated wall stress on the opposite surface [28], the spine restricts aneurysm development posteriorly so aneurysm formation is generally anteriorly. Therefore the peak stress on the posterior wall is attributed to this. All models showed peak stress regions at inflection points on the inner surface of the AAA sac. This finding is consistent with previous experimental [45] and numerical [46] and computational [40] work. Convergence studies were also performed on each model to establish confidence in the finite element mesh size and accuracy of the results.

In order to determine the significance of the wall stress results from the FE analysis, other factors were taken into consideration. Since AAA rupture occurs when the stress acting on the wall exceeds its strength, the assessment of AAA rupture should include estimates of both wall stress and wall strength distributions. If wall stress is to be incorporated into the clinical decision making process, inclusion of prestress information, regional variations and wall strength must also be considered. RPRI values were calculated to allow these three parameters to be included to aid clinicians. Patient-specific parameters are important and should be taken into consideration in rupture prediction as the variation in wall properties can be significant. The regional variations have been shown to influence the failure properties of the aneurysm [41]. The RPRI presented here may have to be used in combination with previously derived rupture predictors such as asymmetry [28], Rupture Potential Index [47] and wall stress [48]. But the authors feel that the nature and magnitude of local variations presented here demonstrate their importance and need for consideration.

The study reported here linked the elastic properties of the aneurysm with AAA simulation to assess its importance to rupture prediction. The study investigated three iterations (AAA(RV), AAA(WA) and AAA(SEG)) of material properties to consider this. Inherently, nonlinear material behaviour, strength of the AAA wall, and the spatial distribution of these quantities are essential for the accuracy of AAA simulation results, and therefore a realistic prediction of AAA rupture risk. So far, however no imaging technique exists that preoperatively offers automatic information on material properties of an individual AAA wall, despite the widespread recognition of high variations in regional properties [43, 49]. Hence, it is even more important to model the biomechanical behaviour of AAAs as accurately as possible, with respect to known quantities, model assumptions, such as prestressing and patient-specific blood pressure
that are preoperatively available and represent state of the art modelling techniques. Good assessment of computational models applied in case studies is crucial for realistic simulation results and reliable rupture risk prediction. Developing the advanced imaging and quantification techniques for AAA geometry and dynamics will help increase understanding of vascular diseases and impact future research. Studying the dynamics of the aneurysm wall can also benefit therapeutic methods and interventional methods by quantifying dynamic changes after administration and surgery. It may also have implications for endo-aortic device design, testing and stability. Aortic elasticity may also be an important factor in cardiac dysfunctions, e.g. diastolic heart failure and restrictive pattern of vascular filling [50].

Overall, the methods presented in this study provide a technique for quantifying vessel motion and geometry in AAA patients. The results suggest a possible relationship between aortic asymmetry, centroid motion and the direction of aneurysm development. The difference between elasticity parameters and the variation between segments were large and should be taken into account in endovascular therapy, so as to choose suitable candidates and correct stent graft sizing.

Limitations

One limitation of the study was that only the in plane movement of the aorta was measured. When coronal and sagittal gated images are observed, the out of plane movement seems to be minimal in the abdominal aortic region [15].

It is known that the wall thickness is non-uniform [41], and therefore if this was factored into the model reconstruction it would have an effect on stress distribution and peak stress magnitude.

Also it is known that calcifications and ILT occur in vivo. Calcifications may act as stress raisers in the wall so their incorporation may have some significance [51].

We did not include the ILT component in our simulations; there are differing opinions in the literature about the importance of ILT in rupture assessment [52]. The studies made by Vorp et al. indicated that the presence of ILT reduces AAA wall strength [53]. Adolph et al. claimed that ILT can play an active role in AAA pathogenesis due to inflammatory infiltration cells (macrophages and neutrophils) [54]. In contrast, Schurink et al. demonstrated that the presence of ILT does not cause any
reduction in the arterial blood pressure acting on the wall, so it did not play any significant role [55]. On the basis of comparative studies of groups of ruptured and unruptured AAAs, Hans et al. did not find statistically significant differences in the ILT to total aneurysm volume ratio between the studied groups [56]. As this study was an iteration in a feasibility study, the authors believed it was acceptable to exclude ILT from the simulations.

Only the maximum diameter properties were used in the FE analysis, a more detailed analysis could define smaller segments and reflect these in the FE models.
CONCLUSIONS

In conclusion, the status of the abdominal aortic aneurysm during the cardiac cycle was well depicted. We have reported the circumferential cyclic strain, incremental modulus, compliance, circumference change and centroid motion along the abdominal aorta in AAA patients. This analysis will aid understanding of the biomechanical contributions to aortic disease. Using the regional properties to predict rupture risk presents a novel method which accounts for local variations in aortic morphology.
REFERENCES


CHAPTER 5

NONINVASIVE TISSUE BEHAVIOUR QUANTIFICATION OF ABDOMINAL AORTIC ANEURYSM

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Analysis and Interpretation: AT, AC
Data Collection: AT
Writing the article: AT
Critical Revision: AC, TM
Final Approval: TM, AC
Obtained Funding: AT, AC, TM
ABSTRACT

BACKGROUND

Studies on the material properties of vessel wall and rupture prediction have mainly focused on describing the abdominal aortic aneurysm (AAA) vessel wall as a homogeneous material. The presence and distribution of AAA inhomogeneities is highly patient-specific and should therefore be dealt with when investigating rupture risk.

METHODS

A noninvasive imaging analysis of the importance of local tissue morphology information was demonstrated. 4DCT scans are performed on an undilated and diseased section of aorta. Aortic compliance was used to calculate the tissue damage regionally and globally. The stiffness increase in the artery was demonstrated with an extension-inflation experimental animal model analysis. Four circumferential regions of each aorta (anterior (A), left lateral (L), posterior (P), right lateral (R)) were examined through inflation cycles with digital image correlation (DIC).

RESULTS

The values of regional compliance calculated are in agreement with recent biomedical imaging studies, showing circumferential nonuniform deformation of the aorta during the cardiac cycle and asymmetric distension of the aortic wall. The tissue damage indices show varying degrees of tissue damage circumferentially around the aneurysm. Regional property variations and distensibility increases are confirmed, using animal model studies.

CONCLUSIONS

The advent of four-dimensional (4D) CT scans presents a great opportunity for thorough geometric analysis in vivo. The ability to visualize the movement of anatomy as the cardiac cycle progresses allows for immensely greater understanding of tissue behaviour than is possible with static scans. The mechanical properties presented in this study may help to increase our understanding of the mechanisms that precede rupture of an AAA. Furthermore, this noninvasive approach for the evolution of the aortic tissue behaviour may lead to the development of improved patient-specific tissue behaviour calculation methods.
INTRODUCTION

Knowledge of the mechanical properties of arteries is important to understand vascular function in disease states, for example, during aneurysm formation and rupture. The increasing need for a reliable rupture indicator has greatly accelerated the growth of knowledge pertaining to the biological mechanisms involved in development and rupture of aneurysms.

Currently, the indicator used to predict the risk of impending rupture for an Abdominal Aortic Aneurysm (AAA) is the largest transverse diameter. After reaching a diameter threshold of 5.5cm, the AAA needs to be surgically repaired (Rentschler and Baxter, 2008). This criterion does not consider any other patient-specific information or heterogeneity of the AAA that may, in some cases, lead to rupture before the AAA reaches the standard intervention threshold. Thubrikar et al. 2001, Raghavan et al. 2006 and Choudhury et al. 2009 have shown that regional variations of the mechanical properties exist in AAAs; despite a lack of discernible variation in regional tissue composition (Choudhury et al., 2009; Raghavan et al., 2006; Thubrikar et al., 2001). In general, very little work has been done on the inhomogeneity of the mechanical properties of human vascular tissue.

A noninvasive property calculation, coupled with greater awareness of mechanical property variations which exist in aneurysms, could considerably improve patient outcome. Measuring local strain variations in diseased arteries can provide important information regarding altered biomechanical response (Ning et al., 2011). Non-contacting methods may be suitable for evaluating the mechanical properties of soft tissues because there are no changes induced due to the presence of sensors or gauges.

The accuracy of computational analysis and experimental modelling strongly depends on the knowledge of the elastic properties of the aortic tissue. The changing compliance in the aortic wall with age may reflect a combination of changes in elastin and collagen content, which relate to future growth rate and risk of rupture (Lanne et al., 1992). Following the local and global compliance of aneurysms in patients not selected for surgery may be one way of gaining information on the natural history and evolution of this condition and forecast the risk of rupture (Tierney et al., 2012). A basic knowledge of the risk factors can lead to improved screening modalities and perhaps allow identification of patients with aneurysms which are likely to rupture.
In recent years, there have been major advancements in computed tomography (CT). This paper exploits four dimensional CT (4DCT) data sets to compute patient-specific properties. This study explores the feasibility of using patient-specific local compliance to indicate degree of tissue damage and rupture potential. A 4DCT scan combined with a thorough geometric analysis can yield more details regarding the geometric changes that occur and consequently may be able to assist with prediction of negative outcomes, such as rupture, growth or progression of disease. The 4DCT scans of the abdominal aorta in this study were studied to determine if different mechanical properties and the extent of tissue damage induced during aneurysm formation could be extracted.

Knowledge of aortic wall behaviour is critical in improving the accuracy of computational analysis and rupture prediction. This concept was examined in this preliminary study by the extraction of tissue data from CT scans, and through the corroboration of this data with experimental findings.
MATERIALS AND METHODS

Patient Population

Seven 4DCT data sets from subjects diagnosed with AAA were selected from a database in Heidelberg University Hospital (Dept. of Vascular Surgery, University Hospital, Germany). The subjects had a mean age of 69.

4DCT Scanning

Scan data was collected using a four detector row CT system (SOMATOM Volume Zoom; Siemens Medical Solutions, Erlangen, Germany). ECG gating uses the ECG signal of the patient to divide the raw scan data into bins that correspond to consecutive phases of the heart beat. The data is reconstructed into a number of volumes, each corresponding to a different phase of the heart cycle (Fig.1 (i - iii)). This allows 4D visualisation of the scanned object and enables the temporal behaviour of the aneurysm to be investigated. This data acquisition is described in detail in Ganten et al. (2008) (Ganten et al., 2008).

Figure 1 (i - iii) The regional definitions of the aorta for a selection of subjects [1(i), 2(ii), 3(iii)] - posterior region (P), anterior region (A), left lateral region (L) and the right lateral region (R), the circumferential expansion at the maximum diameter is also shown here (Red – systole, b – diastole). (iv) The location of each CT slice acquisition – undilated neck and maximum diameter.
In short, two image sets for each subject were obtained at two surgically relevant locations – one at the suprarenal aorta and one at the level of maximum diameter (Fig. 1 (iv)). 20 time frames per heart cycle (0%, 5%, 10%, 15%... 95% of the RR interval) were calculated for each location.

**Segmental Compliance Calculation**

Each scan circumference was divided into 4 segments of equal length – Posterior (P), Anterior (A), Right Lateral (RL), and Left Lateral (LL) (Figure 1).

Anatomical markers present in the AAA were used to divide the circumference into 4 segments. ILT and calcifications were largely used in this regard to calculate segment lengths (Figure 2) (Tierney et al., 2012).

![Figure 2: Example of the anatomical markers used to segment the aortic circumference (a) Calcifications visible in the aortic wall (b) ILT present in the aorta. The red arrows indicate possible markers which could have been used for motion detection.](image)

Aortic compliance was calculated to describe the elasticity of the aorta. The compliance measurements were calculated from peak systole and from end diastole (Figure 1 (i - iii)). The compliance was measured at both scan locations, the undilated aorta and maximum diameter, for each segment using equation 1 (Figure 1 (iv)).

\[
Compliance[C] = \frac{\Delta L}{L_s}\Delta Pr
\]  
*Equation 1*

**Where:**
L is the length of the segment circumferential length, \( L_S \) is the segmental length at systolic pressure; \( Pr \) is the internal pressure in the vessel (Vorp et al., 1996).

**Rupture Prediction - Local Damage & Global Damage indices**

In order to quantify the degree of tissue damage present in the aortic tissue and to provide improved guidance relating to rupture propensity, two damage parameters were defined. These two distinctive and different analyses of damage can be carried out on an aneurysm structure; one comparing regional properties circumferentially around the aneurysm, and the second comparing aneurysmal regional properties to a undilated arterial segment from the same patient. The following outlines how these indices work. A local damage index (Equation 2) was determined to evaluate which area of the aneurysm is most at risk of rupture. The percentage tissue damage (Equation 3) is calculated to determine the global mechanical property deterioration induced by aneurysm formation.

**Local Tissue Degradation/damage**

**4DCT Regional Damage Ratio (RDR)**

The regional damage ratio (RDR) is based on the segmental compliance calculations at the maximum diameter of the aneurysm. We suggest that lower RDR may indicate the location of highest tissue damage and possible rupture location at the aneurysm bulge.

\[
RDR = \frac{RC}{MC} \quad [Equation \ 2] \quad Where:\
\]

\[
RDR \text{ is the regional damage ratio. } MC \text{ is the Maximum compliance at the maximum diameter for the subject. } RC \text{ is the compliance of the region examined e.g. posterior, anterior segment.}
\]

**Global Tissue Degradation/damage**

**% Tissue damage**

The percentage tissue damage gives an indication of the degree of tissue degradation in the aneurysm compared to the average undilated non diseased distal aorta. We suggest that higher % Tissue Damage values may indicate greater severity of the disease formation.

\[
\%Tissue \ \text{Damage} = (1 - (RC/AHC))*100 \quad [Equation \ 3] \quad Where:\
\]

136
RC is the compliance of the region examined e.g. posterior, anterior segment at maximum diameter. AHC is the average compliance of the undilated region.

**Ex-Vivo substantiation of the 4DCT data**

In order to determine if this approach has merit, it needed to be assessed by experimental means. A key requirement for the adaption of 4DCT in aneurysm rupture prediction is the proof and quantification of the values extracted. There is a marked mechanical deterioration of the structural properties of the aortic wall during aneurysm formation. Regional variations in excised porcine aortae tissue properties were assessed. *Ex-vivo* Elastase depletion porcine models were developed and examined, before and after aneurysm induction, to assess the difference in mechanical properties including regional variations.

**Animal Models Specimen Preparation**

Abdominal Aortae were harvested from about 6 month old pigs weighing approximately 90 kg (stored in a refrigerator at 5°C until used). All tests were performed within 48 hours of excision. This minimised significant changes in the mechanical properties of the aortic tissue, as described by Samila and Carter 1981 (Samila and Carter, 1981).

The specimens were prepared as follows:

- Remove loose connective tissue and adipose tissues of the aorta.
- Ligate all branches with thread.
- Fix both ends of the specimen to cannulas.
- Mount the specimen on the test chamber, observing a prestretch of 1.3 to the load free state.

**Regional Variation in Porcine Arterial tissue.**

Digital Image Correlation (DIC) is a noncontacting method based on tracking speckle patterns before and after deformation to determine the complete, full-field surface displacements and strains on many types of materials. As an imaging method, DIC requires the presence of a randomly-patterned specimen surface with sufficient “contrast” for accurate image comparisons (Kim and Baek, 2011). Zhang et al. 2002 demonstrated the use of 2D DIC for analysis of soft tissue properties (Zhang et al., 2002). Recent reports have demonstrated the feasibility of using three-dimensional
digital image correlation (3D-DIC) to measure both local displacement and strain fields on a micrometer length scale on soft tissues using mouse carotid artery specimens (Sutton et al., 2008). The purpose of the DIC study was to develop an *ex vivo* experiment for the strain analysis of the aorta and to investigate regional variations in the porcine aorta during the inflation test. This study employed 3D-DIC to determine the variations in aortic properties during pressurisation using an excised porcine aorta. The excised porcine arteries were inflated in the physiological range to establish the regional property variation.

Figure 3: The 3D DIC apparatus consisted of (a) two Imager E-lite 2M cameras fitted with 50mm lenses; (b) two gated white light sources and; (c) a computer complete with Davis Strainmaster® software (La Vision, GmbH).

**DIC protocol**

La Vision Strainmaster software was used to simultaneously capture images from the two cameras at a specified frequency (3 Hz) during pressurisation to extract deformation and strain data for the area of interest of the aorta (Fig.3). The cameras were placed at different positions but at the same height focusing on the central region of the specimen. The distance from the cameras to the specimen was approximately 20cm and the angle between the two cameras was approximately 30°.

- Black markers were attached to the aortic wall around its circumference, using a minimal amount of glue, and avoiding the regions of aortic branches (Fig.4). Additional markers were attached to the proximal and
distal regions of the specimen to obtain reference measurements for longitudinal strain.

![Image](image-url)

**Figure 4:** Porcine aorta after removing surrounding tissues and with black markers affixed to the aortic wall. The movement of each marker can be tracked in three dimensions.

- The specimen was preconditioned longitudinally and circumferentially to obtain repeatable mechanical responses.
- The specimen was inflated from 0mmHg to 120mmHg at room temperature. The CCD camera obtained images of the specimen during inflation, at 20mmHg intervals.
- The mechanical response of the aorta was examined at 4 circumferential regions - the posterior region (P), anterior region (A), left lateral region (L) and the right lateral region (R).
- Inflation tests were performed at these four regions after 90° rotations of the specimen from one region to another. Care was taken so no twisting of the specimen was allowed during rotation.
- The region where the markers were affixed was selected from the image.
- Regional strains (circumferential and longitudinal) could then be calculated from the specimens. These enabled the regional compliances to be calculated.

**Animal Model stiffness alterations due to Elastase depletion**

1. Three Aortas were examined after excision to determine their original properties on an inflation-extension apparatus.
2. All specimens were inflated from 0mmHg and 120mmHg, with diameter measurements taken every 10mmHg.

3. Measurements were taken on all samples tested after being excised in their undilated state and a second measurement was taken after a phantom aneurysm was created on part of the sample (Tierney et al., 2010).

4. The Hudetz incremental modulus (120/80 mmHg) was calculated for each sample before and after the elastin depletion.

The stiffness elastic properties of the arterial wall are expressed in terms of the Hudetz incremental modulus $E_{inc}$.

$$E_{inc} = 2\left(\left(\frac{d_{out}^2 - d_{in}^2}{\Delta d_{out}/\Delta P}\right) + P \cdot d_{out}^2 \right) \cdot \frac{1}{d_{out}^2 - d_{in}^2}$$

[Equation 4]

Where

d_{out} is the outer diameter, d_{in} is the inner diameter, $\Delta p$ is the pressure change, $p$ is pressure at d_{out}.

This will assess the change in elasticity due to the disease formation. (Zulliger et al., 2002)
RESULTS

The diameters and circumference were quantified at end diastole and peak systole for each subject from the 4DCT. These metrics are depicted in Table 1. They were calculated at 2 locations along the aorta – Undilated and Max Diameter (Fig 1(iv)).

Table 1: The diameters and circumferences for the aorta at end diastole and peak systole.

<table>
<thead>
<tr>
<th></th>
<th>Undilated (mm)</th>
<th>Max. Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter – Diastolic (mm)</td>
<td>27.16 ± 5.22</td>
<td>51.06 ± 13.33</td>
</tr>
<tr>
<td>Diameter - Systolic</td>
<td>30.10 ± 6.28</td>
<td>52.94 ± 13.87</td>
</tr>
<tr>
<td>Circumference - Diastolic</td>
<td>85.32 ± 16.39</td>
<td>160.40 ± 41.88</td>
</tr>
<tr>
<td>Circumference - Systolic</td>
<td>94.84 ± 18.9</td>
<td>166.30 ± 41.79</td>
</tr>
</tbody>
</table>

Compliance results

The segmental circumference was used in the calculation of compliance. The compliance was calculated at both scan locations and for each segment of the aorta (Table 2).

Table 2: Compliance values (*10^-4/mmHg) for each subject, at undilated and max diameter levels.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undilated P</td>
<td>0.5950</td>
<td>24.7303</td>
<td>18.4891</td>
<td>4.8331</td>
<td>14.0010</td>
<td>7.3537</td>
<td>2.2892</td>
</tr>
<tr>
<td>Undilated Average</td>
<td>13.0400</td>
<td>17.3800</td>
<td>29.8000</td>
<td>10.0300</td>
<td>10.3100</td>
<td>17.5400</td>
<td>19.6700</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max Diameter P</td>
<td>1.9968</td>
<td>13.9332</td>
<td>2.2426</td>
<td>3.1130</td>
<td>4.0763</td>
<td>2.0202</td>
<td>1.3958</td>
</tr>
<tr>
<td>Max Diameter RL</td>
<td>2.1618</td>
<td>15.3702</td>
<td>8.3203</td>
<td>1.6144</td>
<td>0.9997</td>
<td>3.1882</td>
<td>2.2028</td>
</tr>
<tr>
<td>Max Diameter A</td>
<td>7.8667</td>
<td>7.4328</td>
<td>0.9262</td>
<td>4.0426</td>
<td>2.2423</td>
<td>3.8838</td>
<td>3.0448</td>
</tr>
<tr>
<td>Max Diameter LL</td>
<td>3.5817</td>
<td>11.3522</td>
<td>4.7942</td>
<td>1.2031</td>
<td>2.5793</td>
<td>3.6226</td>
<td>2.5029</td>
</tr>
</tbody>
</table>
4DCT Regional damage ratio

Figure 5 shows the RDR for the seven patients examined, with the lowest ratio for all subjects was subject 3 located at anterior wall (0.11), indicating the largest amount of material property difference/damage. Subject 5 was the second lowest (0.24); this may indicate that subject 3 has the highest chance of failure, based upon local comparison.
Percentage Tissue Damage

Figure 5 shows the percentage tissue damage for the seven subjects examined, with the greatest amount of damage for subject 3 located at anterior wall (96%), indicating the largest amount of material property difference/damage. Subject 5 was the second lowest; this may indicate that subject 3 has the highest chance of failure based upon comparison to undilated regions.

The calculation of RDR and percentage tissue damage for each patient revealed some similar trends. 5/7 patients had a maximum RDR value in the Right Lateral segment, corresponding with the minimum percentage Tissue Damage. For all patients the segment with the maximal RDR had also the minimum percentage Tissue Damage, likewise minimum RDR had greatest percentage Tissue Damage.

Animal Study

DIC quantification of Regional Variation in Arterial tissue

![Graph showing % strain for each specimen at each location.](image)

Figure 6: The % strain calculated by the DIC for each specimen at each location - posterior region (P), anterior region (A), left lateral region (L) and the right lateral region (R).
The % strain calculated for each specimen between 60mmHg and 120mmHg in each segment proves the existence of regional property variations in undilated aortae (Figure 6). These mechanical differences could have implications for rupture prediction in aneurysms. As the aneurysm fails at weakest spot, it is important to acknowledge the presence of regional property variation during computer modelling and bench-top experimentation. The average segmental strain is 9.26%, 7.61% and 6.76% for animal model 1, 2 and 3 respectively. The percentage difference between the minimum and maximum strain in each specimen was 317%, 28% and 58% for animal model 1, 2 and 3 respectively.

Longitudinal strain in each segment was found to be less that 2.6%, with an average value of 1.48%.

**Animal Model stiffness alterations**

The altered stiffness is demonstrated in Figure 7 (Adapted from Figure 7, Tierney et al. 2010 (Tierney et al., 2010)). Taking the pressure of 120mmHg and 80mmHg, based on the slope difference in the modulus behaviour, the differences in stiffness are evident. The graph is based on Model 2.

![Figure 7: Hudetz Incremental Elastic Modulus](image)

*Figure 7: Hudetz Incremental Elastic Modulus, solid line corresponds to the modulus axis, dashed line corresponds to the pressure axis, r is current radius, and R is original radius, r/R corresponds to circumferential stretch (Tierney et al., 2010). Physiological behaviour of the modulus is extracted using the dashed line from 120/80mmHg on the pressure axis, and using this to extrapolate the modulus behaviour. The slope of the modulus indicates the stiffness of the sample.*
Chapter 5 - Noninvasive Use of Material Properties

The Hudetz Modulus was calculated at physiological range (120/80mmHg) for each specimen before and after aneurysm inducement. The increase in modulus is noted in all subjects, there was up to 4 fold increase (specimen 3), and represents the altered conditions the aorta has now to work under due to aneurysm formation (Figure 8). The increased modulus relates to the elastin depletion which occurs during aneurysm formation.

Figure 8: Hudetz Elastic Modulus for each specimen before and after elastase depletion
DISCUSSION

Understanding the failure and damage mechanisms of soft biological tissue is critical to a sensitive and specific characterisation of tissue injury tolerance and its relation to biological responses. Such knowledge may help us to develop concepts that allow an accurate rupture risk assessment of AAAs. This is crucial for clinical treatment planning, or to optimise the design of medical devices based on a proper understanding of short-term and long-term mutual interactions with biological tissues. Aneurysmal degeneration involves a progressive imbalance between the destruction and the repair of structurally important connective tissue proteins (Wassef et al., 2001).

Some studies have shown that weakening of the mechanical properties of degenerated tissues may progress the expansion of the aneurysm (Saijo et al., 2004). Deformation of the aorta has been described by changes in diameter, circumference and compliance. The degradation of the elastin through aneurysmal formation can be seen in the difference between the diametrical and circumferential expansion of the undilated and diseased portion of the aorta. Elastin destruction is an essential part of the erosive process of the aortic wall leading to aneurysm formation (Satta et al., 1998). An increase in collagen-elastin ratio will result in increased wall stiffness and decreased wall strength at the aneurysm site. Both diameter and circumference change in response to pressure changes. The average expansion of the undilated region is 11.17% compared to an average of 3.6% at the maximum diameter of the aorta, thus highlighting the stiffness increase.

In this study, compliance is a tool used to describe the distensibility of an artery. The values of regional compliance calculated, shown to be in agreement with recent biomedical imaging studies, show that the aorta has circumferentially nonuniform deformation during the cardiac cycle and that the aortic wall distends asymmetrically (Kim and Baek, 2011; Morrison et al., 2009).

Malkawi et al (2010) have also demonstrated that there is increasing evidence that patient-specific biomechanical factors may be more reliable in predicting AAA rupture than currently available clinical and biochemical parameters (Malkawi et al., 2010). Degenerative changes during the aneurysm progression induce a change in the strength of the tissue. We developed a measure of the regional damage ratio (RDR) to establish regionally which segment had undergone the greatest degradation. Each regional
compliance was taken as a fraction of the highest regional compliance at maximum diameter. Establishing the region of the aneurysm with the greatest tissue degradation and damage may give an indication into the area at greatest risk of rupture. The RDR was solely concerned with the maximum diameter of the aneurysm and the comparison of each region to each other.

Additionally a further measure, the percentage tissue damage, was evaluated based on the comparison of the compliance at the undilated region of the aorta to segmental compliance at the maximum diameter of the aneurysm bulge. The percentage tissue damage represents a noninvasive method for determining the tissue damage in AAA based on the compliance values. It was calculated to discern the changes in tissue behaviour that occurred during aneurysmal formation.

Both measures taken here based on compliance changes, regionally and during aneurysm formation, may be helpful in rupture prediction. There is evidence that the material properties of the aortic wall can predict the likelihood of a dissection in patients predisposed to such an event (Goel et al., 2008). The metrics which indicate regionally the compliance and motion of the artery may also be helpful for stent graft placement and highlight anything that may have implication for proximal stent attachment. Late migration (> 1 year after implantation) of stent-grafts, which is the main reason for postoperative reintervention, is frequently seen when the dilating proximal neck exceeds the maximum diameter of the proximal stent graft. Knowledge of these parameters prior to stent graft implantation may aid the clinician.

This study proved the existence of regional variations in excised porcine tissue using DIC and it is feasible that these regional variations are maintained during disease progression.

Evidence of modulus increase during aneurysm formation was proven in Figure 8. With the increase in modulus, the arterial regulating ability for the blood declines (Wang et al., 2010). This could aggravate tissue denaturation of the arterial wall, and decreases its capability of bearing the impact from blood flow, and thus exacerbates vascular distortion and ability to withstand the blood pressure within the vessel. Stiffening due to age was obviated here because age was identical between healthy and diseased animal models.
This study highlights the potential for extraction of additional information from 4DCT and presents evidence that routine 4DCT for aneurysm examination may be useful (van Prehn et al., 2009a). Shorter rotation times and the development of 4DCT enabled the technique of ECG gating methods recently demonstrated robust performance in recovering the anatomy and dynamics of the aorta from 4DCT data (Morrison et al., 2009). The radiation burden associated with gated CT has been the subject of raised awareness due to the large radiation dose to which CT scanners expose the population and because the radiation dose delivered by gated CT can be very high: up to 25mSv. It has however been shown that it is possible to reduce radiation exposure (3mSv – 13mSv) during gated CT while maintaining the diagnostic performance by modifying the study parameters (Huang et al., 2010). Greater utilisation of 4DCT must be justified as whether it leads to the greatest benefit and whether the radiation risk may lead to improved knowledge of aneurysm behaviour and the clinical gain may outweigh the risk (Molacek et al., 2011). Although, there are risks at even low doses and the authors believe the determination of the variation in the regional mechanical properties warrants the use of the imaging technique for complete AAA examination.

**Limitations**

The authors assume that the undilated aortic location above the renal arteries is healthy even in AAA patients. This is against evidence that this region may be affected by atherosclerotic lesions. The aortic location above the renal arteries compliance measured in the study was 16.8243 ± 6.8338 (*10^-4/mmHg) [n=7]. The compliance calculated in two studies undertaken by Lanne and Sonnesson on healthy abdominal aortas was 15.7867 ± 4.57248 (*10^-4/mmHg) [n=20] (Lanne et al., 1992; Sonesson et al., 1993). Therefore the authors believe it is reasonable to assume that for comparisons this portion can be classed as healthy.

The main hypothesis of damage evolution in this paper dealt with is the degradation of elastin. The pathogenesis of AAA appears to be multifactorial. Degradation of elastin fibres has been proposed as a process of major importance in the pathogenesis of arterial dilatation and aneurysm formation (Wiernicki et al., 2008). This study does not take into account the degradation of collagen or matrix metalloproteinases activity.

The animal model used for DIC was a free standing sample with no surrounding tissue. The surrounding tissue had to be removed to enable the appropriate
measurements to be taken. The authors accept that the constraint of surrounding tissue will affect the deformations but the main purpose of the study was to analyse material property variation. The anatomical constraints have not been thought to be an issue and have not previously been addressed in aorta deformation and motion studies (Biesdorf et al., 2011; de Heer et al., 2011; Molacek et al., 2011; Schwartz et al., 2010; van Prehn et al., 2009b). The authors agree that boundary conditions and musculoskeletal motion will affect the \textit{in vivo} deformations and strain distributions (Choi et al., 2009). However there is no evidence to suggest that the constraints will have an effect on the material properties.
CONCLUSIONS

Diseases of the aorta such as aortic aneurysm and aortic dissection cause a high mortality rate and, hence, the study of the mechanical properties of the aorta has been an active research area. In many previous studies, the aorta has been considered as a straight cylindrical tube undergoing uniform circumferential deformation and therefore uniform strain/stress distribution in the circumferential direction. However, the nonuniform deformation due to the inhomogeneous properties of the aortic wall is an important area which needs to be taken into account. The advent of 4DCT scans presents a great opportunity for thorough geometric analysis in vivo. The ability to visualise the movement of anatomy as the cardiac cycle progresses allows for immensely greater understanding of tissue than is possible with static scans. The mechanical properties presented in this study, between the working pressure (diastolic and systolic) will increase our understanding of the mechanisms that precede rupture of an AAA and also which area of the aneurysm may be most at risk of rupture. We have shown that measuring compliance variations and enabling quantification using our proposed mechanisms may be a new tool for tissue property extraction.

ACKNOWLEDGEMENTS

The authors wish to acknowledge (i) Dr. Marika Ganten and Dr. Stefan Delorme, Dept. of Radiology, Heidelberg, Germany for providing CT scans, (ii) The Irish Research Council for Science, Engineering and Technology (IRCSET) Grant 2007/2950.
REFERENCES


DISCUSSION AND CONCLUSIONS
DISCUSSION AND CONCLUSIONS

Dramatic improvements have been made during the past 50 years in the overall diagnosis, management, and treatment of abdominal aortic aneurysms (AAAs). Unfortunately, the mortality for ruptured AAAs has improved little in recent decades (Wainess et al. 2003, Heller et al. 2000). The incidence of AAAs, and thus AAA mortality, in the general population is predictably increasing with the aging population (Sakalihasan et al. 2005). Improved techniques for rupture risk prediction and diagnosis would be of considerable clinical benefit. The main focus of the research described in this thesis is the noninvasive acquisition of patient-specific wall properties of AAA. The noninvasive characterisation of the material property variation has many benefits for the clinician. In vivo, AAAs can exhibit a varying range of material strengths (Raghavan et al. 2006) from localised weak hypoxic regions (Vorp et al. 2001) to much stronger regions and areas of calcifications (Speelman et al. 2007). Thus greater knowledge of mechanical behaviour would allow the surgeon visualise any potential problems prior to surgery, but it may also provide some useful insight into that particular aneurysm. Changes in the mechanical properties of arteries generally precede the occurrence of clinical symptoms, so measurement of these properties could identify individuals at risk for cardiovascular disease (Trahey et al. 2004). Noninvasive procedures which reduce both the risk of damage or destruction for the tissue and the possibility to alter the object properties during characterisation are desirable. The novelty of the research is based not only on the noninvasive nature of the methodologies, but also the translation of the use of the measured mechanical properties for use clinically to predict rupture potential.

When feasible, sonography is the guidance method of choice at many institutions for monitoring and examining AAA development and growth. It is an accurate, convenient and cost-efficient imaging mechanism for aneurysm examination. Research utilising various methods of imaging the elasticity of soft tissue has become extremely popular recently (Lalitha et al. 2011, Fatemi and Greenleaf 1999, Karpiouk et al. 2009, Palmeri et al. 2006, Nightingale et al. 2002a, Nightingale et al. 2002b). These methods interrogate tissue mechanical properties and produce images that are generally representative of underlying tissue stiffness. Soft tissues will deform more when
pressure is applied and hard tissues will deform less. By measuring the amount of tissue displacement and wave velocity, elastography provides objective information regarding the stiffness of tissues (Cho et al. 2008). Acoustic radiation force impulse (ARFI) is an ultrasound based technique with elastography modality. Previous efforts have demonstrated the utility of imaging for abdominal applications and noted some advantages of the ARFI technique for imaging at depth (Fahey et al. 2005). In Chapter 1, the ability of ARFI to interrogate the mechanical properties of arterial tissue before and after aneurysm development was investigated. An artificial aneurysm was induced in an *ex vivo* porcine animal model, using elastase infusion. Typical pressure–diameter curves associated with AAA behaviour were reproduced in the animal models. The contribution of elastin and collagen to wall function and structural differences produced due to the aneurysm formation were demonstrated by the contrast in pressure–diameter behaviour. The mechanical properties of each model, before and after aneurysm induction, were found to be discernible using ARFI interrogation. The stiffness increase due to the elastin degradation was corroborated by displacement reduction, wave velocity increases and modulus increase. The *ex vivo* animal model experiments were the first step towards ARFI imaging of AAA tissue and characterisation of tissue mechanical properties using displacements and wave velocities, with the eventual goal of developing ARFI as a diagnostic tool for the assessment of AAA wall variations. It was shown to be a robust method of distinguishing between undilated and diseased tissue.

Following the animal models, it was obvious that successful ARFI imaging at realistic aortic depths would face challenges at generating sufficient radiation force to measurably displace these deep lying tissues and track the displacements. As an acoustic wave propagates through a dissipative medium, an energy gradient is established in the medium, arising from either absorption or reflection of the wave. This energy gradient applies a force in the direction of wave propagation, and the absorption of energy results in the generation of heat in the tissue. As the depth of the AAA was greater than those associated with previous ARFI applications, these heating effects were analysed for Chapter 2. A FEM model of heating associated with ARFI imaging was constructed to estimate increases in temperature resulting from acoustic energy absorption by tissue at abdominal aortic depths (shown in Appendix A). The scan
sequences required to displace up to 10cm were analysed in FIELD II, a linear acoustic field simulation software program. This software allows study of the tissue heating associated with different focal configurations. Heating effects proved to be minimal for settings needed; worst case maximum temperature increase was < 2°C. FEM simulation proved that all sequences were safe and well within FDA approvals and fit to be used on patients. This allowed a preliminary study to be carried out on a previously diagnosed AAA patient. Aorta excitation was carried out during a six-month routine check up for this patient. This preliminary study demonstrated that ARFI excitation was possible on an AAA wall. A combination of the magnitude of the AAA displacement in vivo and the tissue stiffness behaviour from previous animal models revealed a possible method of ARFI being used as a quantitative method to define tissue properties. The acquired properties from the patient measured were similar to that of diseased tissue. A limitation to this work was the lack of a control healthy subject which would have given an indication of the accuracy of the measurement of tissue properties.

As ARFI is an ultrasound based technique, it possesses both the advantages and disadvantages of ultrasound. For ultrasound, as with any sound wave, the reflected sound returns straight to the source if the reflecting surface is perpendicular to the ultrasound beam. If the surface is at an angle, the sound refracts and may not be received by the transducer. Therefore, the anterior and posterior regions of the aorta will return high quality, easily distinguishable images due to the directional nature of the image; but the lateral regions return unfocused images which are often difficult to discern. Ultrasound cannot transmit through bone so the suprarenal section of the aorta and proximal regions may have restricted visibility due to the ribcage. Computed tomographic (CT) angiography is currently the imaging technique most often used for preoperative assessment of aortic morphological characteristics in AAA patients. Static CTs do not consider normal aortic dynamics. Cardiac gated CT is an imaging modality which overcomes these disadvantages associated with ultrasound and static CT. It gives a very good morphologic resolution and helps to plan open or endovascular therapy for the treatment of AAA. ECG-gated data acquisition has been primarily used for heart and coronary arteries scans, but it can be used to acquire functional parameters of the aortic wall. Moreover, this technique is noninvasive, rapid and comfortable for the patient. There are limitations, for example, the exposure to radiation, which is obviously higher
when acquired by ECG-gated acquisition; the radiation dose was reduced in this case as only scans of 2 slices were acquired. In Chapter 3, the scans used were only taken of a point of maximal dilation and at the point of undilated diameter above the aneurysm. A large variation in regional elastic properties was calculated for each slice, as described by compliance, circumferential cyclic strain and incremental modulus. The elasticity studies provided an insight into the distension of the abdominal aorta and the changes in the distension due to aneurysm formation.

Recently there has been much interest in utilising the finite element method to calculate wall stress and using this wall stress as a rupture predictor (Doyle et al. 2009, Fillinger et al. 2003, Fillinger et al. 2002, Venkatasubramaniam et al. 2003). If peak stress from FE is to be used as an indicator of rupture potential, then the regional variations in mechanical wall properties may be an important parameter in the accuracy of these models. To obtain a better understanding of the effects of variations of mechanical properties on FE analysis, a method was derived which linked the elastic properties calculated from cardiac gated CT to the average behaviour of aneurysm tissue (Raghavan and Vorp 2000). This then allowed these patient-specific properties to be applied to an aneurysm geometry. For the gated scans used in Chapter 3, the patient-specific geometries were not taken at the time of scanning so this study used a common geometry and evaluated the effects of regional variations on the FE results. The contours and magnitudes of peak stresses from homogeneous and regionally segmented models were markedly different. The incorporation of these local material properties into FE modelling was shown to improve the accuracy and reduce the simplifications of the stress analysis.

From a broader point of view, patient-specific modelling of large arteries is now gaining recognition. The advances in computing power and numerical methods will allow performance of computations of complete cardiac cycles in minutes rather than in hours, and the improvement in medical imaging techniques and equipment is progressing towards fast and noninvasive acquisition of anatomy at high resolutions. The application of the currently available techniques to populations of patients and normal subjects, in order to better understand and evidence the relationships between
D I S C U S S I O N  A N D  C O N C L U S I O N S

geometry and pathological alterations is possible, and is progressively being achieved. From this point of view and to complement the results from Chapter 3, Chapter 4 extended the elastic quantification and regional variation study and removed the limitation of a common geometry between all patients. Full cardiac gated CTs were acquired in this study. The limitation of additional radiation dose was substantially decreased by using a dose-modulating technique and precise planning of the investigation scope. The pulsation and elastic properties measures further elucidated our understanding of aortic elasticity, both regionally and at various anatomical points. The centroid motion was in the direction of vessel expansion and aortic asymmetry was maximal at the area of maximum aneurysm development. Assessment of the regional property differences in AAA patients provided interesting mechanistic information which could be of considerable value in clinical decision making.

A noninvasive imaging analysis of the importance of local tissue morphology information was demonstrated. The finite element study using patient-specific geometries, in Chapter 4, observed a greater wall stress magnitude when using traditional nonlinear properties compared to patient-specific properties and pressure. Locations of peak stress in the geometries did not differ largely from patient to patient. Peak wall stress occurred at points of inflection on the inner surface of the AAA sac. This finding is consistent with previous experimental (Morris et al. 2004, Flora et al. 2002), numerical (Callanan et al. 2004) and computational (Doyle et al. 2007, Vorp 1998) work. This demonstrates that using patient-specific geometry is important to an accurate wall stress calculation and distribution. Patient-specific pressures were applied to models using patient-specific properties and a nominal 120mmHg was used in models which used common traditional non-linear material properties ($C_{10}= 0.174MPa$, $C_{20} = 1.881MPa$). The use of 120mmHg lead to an overestimation of wall stress in these models and was in one instance (Patient 5) three times the pressure applied to the model. Using an elevated pressure leads to greater deformations and may lead to inaccurate wall stress values.

In order to determine the significance of the calculated wall stress values, they were combined with other factors, i.e. wall strength, prestress. Failure of an aneurysm will
occur when the local wall stress exceeds the local wall strength; therefore wall strength may play an important role in predicting aneurysm rupture. A novel index, Regional Prestress Rupture Index (RPRI), described previously in Chapters 3 and 4 has been developed which uses this principle in predicting rupture. RPRI also removes the simplification that the aneurysm is in a stress free configuration in a CT scan (Maier et al. 2010, Gasser et al. 2010). RPRI is based on the regional properties of the aneurysm so may indicate regions of the aneurysm which are at greater risk than others. This knowledge of regional variations may be beneficial to clinicians for emergency repair.

The long-term objective of this research is to develop a clinical tool that will accurately predict the risk of rupture of an individual AAA within the same day of the initial diagnosis of the disease. A novel approach is presented in Chapter 5 to calculate the regional damage due to aneurysm formation and the percentage tissue damage which has occurred. This approach was calculated from deformations from cardiac gated CTs. The presence and distribution of AAA inhomogeneities is highly patient-specific and should therefore be dealt with when investigating rupture risk. This noninvasive approach for the evolution of the aortic tissue behaviour may lead to the development of improved patient-specific tissue behaviour calculation methods. Damage assessment could be an addition to diagnostics and decision-making on intervention. The technique presented can be readily incorporated into the decision making process, and may provide an additional parameter of the assessment of AAAs.

In conclusion based on this work:

- A method for reliable, noninvasive estimation of AAA wall mechanics may be a useful tool. It may aid the clinician in rupture prediction, endo-aortic device design, testing and stability; and treatment of cardiac dysfunctions.

- The mechanical changes induced in an artificially induced aneurysm were detectable using ARFI.

- ARFI represents a possible method for noninvasive material characterisation for AAA.
• Quantifying the regional behaviour of aneurysms yields insight into changes in patient-specific morphology and increases understanding about aneurysm disease progression.

• The findings of this research indicate that there are high variations inter-patient and intra-patient in regional elastic properties of both the dilated and nondilated aorta.

• Both accurate geometry and property representation in finite element analysis are integral to realistic wall stress calculations.

• RPRI may be a useful indicator of rupture and degree of disease for surgical decision making.

• A rupture index including regional variations in mechanical properties may be a helpful supplement to the current decision making process.

This thesis has explored methods of noninvasive characterisation of AAA material properties. The results presented throughout suggest that knowledge of the local regional variations may be beneficial to the clinical decision making process concerning intervention. There are some limitations to the methodologies and results presented throughout and these are addressed in Recommendations for Future Work.
REFERENCES


RECOMMENDATIONS FOR FUTURE WORK
RECOMMENDATIONS FOR FUTURE WORK

Whilst this thesis has investigated the main parameters of the noninvasive extraction of patient-specific properties, many areas of research still remain. The following recommendations for future work could address some of the simplifying assumptions inherent in the methodologies presented in this thesis. These recommendations may further enhance our understanding of patient regional property variations and their implementation in FE analysis.

Abdominal Aortic Aneurysm Animal Model Validation

In this thesis, animal models with artificially induced aneurysms were studied with ARFI to assess the effect of the tissue damage on their mechanical integrity. These were studied in a water bath, with water the only medium between the transducer and the animal model. In reality, the aorta would be separated by tissue and other internal organs. The properties of tissues overlying and adjacent to target tissues can impact the strength of the push field reaching the target and the dynamic response of tissues to the applied force. System factors, such as transducer focal configuration, ARFI pushing pulse intensity and location of the target tissue relative to the axial focal position of the pushing beams, can also affect induced displacements (Fahey et al. 2005). Tissue mimicking material, similar to one used in a study by Hoskins (2008), could be placed between the transducer and the animal model to replicate this.

ARFI in vivo feasibility study

This work presented a method which allowed the previously qualitative information from ARFI to be linked to a quantitative method capable of extracting valuable information on the elastic calibre of the aneurysm wall. Future studies would strive for larger study populations while leveraging the best of methodologies for improving our understanding of the mechanical properties of AAA tissue. Healthy subjects would also be included in this study to allow control measurements to be taken.

Validation of mechanical properties from CT

It would be necessary to validate the material properties derived from the gated CTs. An ideal method of performing this would be a cardiac gated scan pre-operatively combined with mechanical testing of excised tissue. This method would then correlate areas of damaged tissue with reduced mechanical strength. As open repair interventions
are reducing in recent years, opportunity to perform this testing may be limited. Localised damage could be induced on excised porcine aortas using elastase infusion. Digital image correlation together with biaxial testing may represent possible methods to establish this validation.

**Aortic Segmentation**

The non-uniform distribution of material properties regionally in the AA has been proven previously (Thubrikar et al. 2001, Tierney et al. 2012). This study aimed to reflect these regional variances in FE studies to improve the accuracy of these. The FE segmentation was into four segments. The segmentation of these regions was abrupt. It may be necessary to graduate the differing material properties from one segment to another. Also, only the properties at the maximum diameter were used in the FE model as the model was primarily aneurysmal. However in Chapter 5, it was shown that even 30mm proximal to the maximum diameter there is a difference in material properties. Therefore it may be beneficial for greater amount of segmentation of the aneurysm. Figure 1 (a) shows the approximate segmentation of the aneurysm previously used and Figure 1 (b) is a suggested segmentation. This approach would be more complex and require a lot more computational time; this would have to be weighed against the additional knowledge and learning from the models.

![Image of aortic segmentation](image)

**Fluid Structure Interaction**

Fluid Structure Interaction (FSI) is a particularly useful tool for the investigation of both wall stresses and fluid flow. It may provide an added benefit of a more accurate representation of *in vivo* environment than just FEA alone. In FEA alone the pressure
gradient across the region of interest is neglected and a constant static pressure is assumed. In CFD, the wall boundary is assumed to be rigid. In reality the artery wall is deforming due to pulsatile blood pressure and this can be represented by FSI. Therefore FSI, combined with the regional material properties, may lead to more accurate wall stress results.

**ILT Inclusion**

We did not include the ILT component in our simulations, but there was <8% difference (average 6.2%) between all compliance calculations, suggesting that the wall properties taken from the CT scans included the effects of ILT on deformation. There are differing opinions in the literature about the importance of ILT in rupture assessment (Maksymowicz et al. 2011). The studies made by Vorp et al. indicated that the presence of ILT reduces AAA wall strength (Vorp et al. 2001). Adolph et al (Adolph et al. 1997) claimed that ILT can play an active role in AAA pathogenesis due to inflammatory infiltration cells (macrophages and neutrophils). Stenbaek et al. showed increasing thrombus surface area increases aneurysm rupture risk, particularly when the increase amounts to ≥15 mm² per year (Stenbaek et al. 2000). Wolf et al. found that an increase in ILT volume was connected with the growth of the aneurysm (Wolf et al. 1994). In contrast, Schurink et al. demonstrated that the presence of ILT does not cause any reduction in the arterial blood pressure acting on the wall, so it did not play any significant role (Schurink et al. 2000). On the basis of comparative studies of groups of ruptured and unruptured AAAs, Hans et al. did not find statistically significant differences in the ILT to total aneurysm volume ratio between the studied groups (Hans et al. 2005). In their opinion, this finding disproves the usefulness of ILT for the assessment of AAA rupture probability. There is however no overwhelming evidence related to the consequences of ILT. ARFI, Magnetic Radiation Elastography (MRE) or dynamic scanning may represent a non-invasive facility which can provide material properties on a patient-specific basis.

**Wall Thickness Variation**

It was shown by van den Hengel that the wall thickness variation over the aorta influences the stresses in the Finite Element Models (FEM) (van den Hengel 2008). As local wall thickness can strongly influence the wall stress, local wall thickness measurements are required. Non patient-specific values are typically used for the wall
thickness, since this model parameter cannot easily be assessed on a patient specific basis. Figure 2 shows typical CT scans and shows the difficulty in measuring the wall thickness from these images. It is difficult to differentiate between wall and surrounding tissue and artifacts. Hall et al. have performed wall thickness measurements on CT, but they did not show combined images of the wall and the measurements (Hall et al. 2000). Ultrasound may offer a possible method of wall thickness measurement. Ultrasound is rapidly undergoing developments, and more stable and less noisy images could provide higher resolution images and better details of the wall in deeply located structures. An overall local wall thickness variation measurement is needed by the analysis of the risk of an AAA. Shum et al. 2010 have derived an algorithm for semiautomatic vessel wall detection and quantification of wall thickness in computed tomography images of human abdominal aortic aneurysms (Shum et al. 2010). While further refinement is needed to fully automate the outer wall segmentation algorithm, these preliminary results demonstrate the method’s adequate reproducibility and low interobserver variability which may represent an accurate method of wall thickness measurements.

Figure 2: Typical CT scans of an aneurysm, highlighting the difficulty of measuring wall thickness

Stent-Graft Design

EVAR has gained worldwide popularity for treatment of infrarenal abdominal aortic aneurysms. EVAR proved to be less invasive compared with open repair. Questions still remain over the long term success of the endovascular techniques and failure mechanisms have been reported that are not usually associated with open repair.
Distal migration of the implanted stent-graft is amongst the most serious failure mechanisms reported after EVAR. Migration of the device can compromise the seal between the stent-graft and the artery wall allowing blood at a systemic pressure flow into the aneurysm sac. New stent-graft technologies will probably make EVAR more applicable and more durable. The information gained from dynamic scanning of the aorta provides insight into a whole new area for further studies and will have its effects on inclusion criteria and stent-graft designs. Dynamics of EVAR can initiate further improvements of stent-graft fixation to make a giant leap ahead in EVARs evolution.
REFERENCES


APPENDICES
Data corresponding to Chapter 1, Aorta 2 is displayed below.

Figure A-1: Displacement profile, elastase treated artery versus undilated normal tissue [Aorta 2], preferential stiffening of the elastase treated evident with less displacement of the wall

Figure A-2: Wave Time to Peak displacement versus Lateral Position, Undilated Normal artery, 80mmHg & 160mmHg [Aorta 2], Increasing stiffness correlates with decreasing time to peak displacement at lateral locations
Figure A-3: Wave speed versus Pressure curve, elastase treated artery versus undilated normal [Aorta 2], demonstrating similar trends as displacement profiles.
HEATING EFFECTS ANALYSIS

A FEM model representing the sequences required were analysed.

Model 1

The model parameters were as follows:

- Attenuation: 0.7
- Cycles: 400
- Elements: 73
- Beams: 20
- Element Volume: $456 \times 10^{-6}$ cm$^3$
- Pulse Duration: 948μs

RESULTS

Greatest intensity @8.4cm

<table>
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<th>Intensity</th>
<th>Temperature Increase (°C)</th>
<th>Worst Case Temperature Increase (°C)*</th>
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<td>1.612</td>
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<tr>
<td>50%</td>
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<td>0.76</td>
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</table>

*Worse Case signified if all 20 beams transmitted to the same point

Figure B-1: Temperature Increase with intensity at 8.4cm
Model 2

The model parameters were as follows:

Attenuation 0.5
Cycles 400
Elements 73
Beams 20
Element Volume $456 \times 10^{-6} \text{ cm}^3$
Pulse Duration 948μs

RESULTS

Greatest intensity @ 7.6cm

<table>
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<th>Intensity</th>
<th>Temperature Increase (C)</th>
<th>Worst Case*</th>
</tr>
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</tr>
<tr>
<td>60%</td>
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<td>50%</td>
<td>0.0133</td>
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<td>40%</td>
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<td>0.22</td>
</tr>
<tr>
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<td>0.186</td>
</tr>
<tr>
<td>20%</td>
<td>0.0088</td>
<td>0.176</td>
</tr>
</tbody>
</table>

*Worse Case signified if all 20 beams transmitted to the same point

Figure B-2: Temperature Increase with intensity at 7.6cm
FDA guidelines state that “A diagnostic exposure that produces a maximum temperature rise of no more than 1.5°C above normal physiological levels (37°C) may be used without reservation on thermal grounds.” Therefore these sequences were deemed safe.
C – JOURNAL PUBLICATIONS


ACOUSTIC RADIATION FORCE IMPULSE IMAGING ON EX VIVO ABDOMINAL AORTIC ANEURYSM MODEL

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(Received 6 November 2009; revised 25 February 2010; in final form 27 February 2010)

Abstract—A method for reliable, noninvasive estimation of abdominal aortic aneurysms (AAA) wall mechanics may be a useful clinical tool for rupture prediction. An in vitro AAA model was developed from an excised porcine aorta with elastase treatment. The AAA model behaviour was analysed using acoustic radiation force impulse (ARFI) imaging techniques to generate and measure wave propagation in both aneurysmal and normal aortic tissue. Opening angle measurement showed a fourfold decrease from healthy aorta to AAA model and pathologic analysis verified this elastin degradation. Maximum wave velocity at 180 mm Hg was 7 mm/ms for healthy tissue and 8.26 mm/ms for the aneurysmal tissue. The mechanical changes produced in the artificially induced aneurysm were found to be detectable using ARFI imaging. (E-mail: tim.mcgloughlin@ul.ie) © 2010 World Federation for Ultrasound in Medicine & Biology.

Key Words: Abdominal aortic aneurysms, Acoustic radiation force impulse (ARFI) imaging, Radiation force, In vitro AAA model.

INTRODUCTION

An abdominal aortic aneurysm (AAA) is a focal balloon-like dilation of the terminal aortic segment that occurs gradually over a span of years (Vorp 2007). The usual definition of AAA is an infrarenal aorta of diameter greater than 30 mm (Van Damme et al. 2005). Each year, there are 200,000 (United States), 500,000 (worldwide) newly diagnosed (Vande Geest et al. 2004). These aneurysms are hazardous because of their propensity to rupture. About 30% to 50% of patients with a ruptured AAA die before they reach hospital. Even with surgery, there is 50 to 70% mortality rate associated with rupture. The majority of AAAs are asymptomatic until rupture; this has led them to become the 13th most common cause of death in the US (Vande Geest et al. 2004).

The pathogenesis of AAA formation is not well understood. They are characterised by a destruction of elastin and collagen in the arterial wall. The underlying problem in aneurysmal disease is this weakening of the aortic wall resulting in progressive dilation leading to eventual rupture (Gollelge et al. 2006). Previous researchers have been successful in generating in vivo aneurysms in small animals, e.g., rabbits, rats, mice (Anidjar et al. 1990; Sinha et al. 2004) and ex vivo in porcine aortas (Kratzberg et al. 2009) using a method of elastase perfusion in the aorta. The in vivo elastase perfusion has been found to lead to subsequent aortic dilatation, collagen and elastin degradation, MMP upregulation and an extensive inflammatory cell infiltrate in the outer media and adventitia of the aortic wall, which is typical of AAA formation (Sinha et al. 2004). The elastin degradation in the wall will be characterised by the opening angle alterations due to elastase treatment, similar to Fan et al. 2005.

The maximum diameter of an AAA has long time been considered as the main determinant in predicting its risk of rupture, i.e., when the AAA reaches 5.5 cm it is thought that the risk of rupture warrants repair (Van Damme et al. 2005). However, several studies have questioned the reliability of this criterion by showing that small aneurysms (<5 cm) can rupture and that larger aneurysms (>5 cm) can remain quiescent for years (Darling et al. 1977; Doyle et al. 2009; Limet et al. 1991). This
coupled with a 4% to 5% mortality rate with interventional surgery indicates a critical need for improved noninvasive AAA rupture predictors (Lasheras 2007).

Therefore, there exists a need for a noninvasive, cost-effective, safe and accurate mechanism for detecting changes in abdominal pathology. Several ultrasonic methods have been previously investigated. Intraoperative ultrasound (IOUS) has been shown to be effective in detecting changes in liver pathology (Cervone et al. 2000) but the invasive nature of IOUS would restrict its use. Intravascular ultrasound (IVUS) elastography has recently shown promise in the characterization of focal plaques in coronary arteries (Schaar et al. 2003). Again a challenge for this method, however, is the introduction of the ultrasonic probe within the vessel lumen, which exposes the patient to the risk of dislodging a vulnerable plaque. Acoustic radiation force impulse (ARFI) imaging presents an attractive method as it involves remote interrogation with short acquisition times, which because is implemented on a diagnostic ultrasound machine is at relatively low cost.

ARFI Imaging is a relatively new imaging modality that has been developed in Duke University (Durham, NC, USA) over the last 10 years. Acoustic radiation force is a phenomenon associated with the propagation of acoustic waves through a dissipative medium (Fahey et al. 2008a). It is caused by a transfer of momentum from the wave to the medium, arising either from absorption or reflection of the wave (Torr 1984). This momentum transfer results in the application of a body force in the direction of wave propagation (Nightingale et al. 2002b).

ARFI imaging provides information about the local mechanical properties of bodily tissue. The acoustic radiation forces generate localized displacements in the tissue and these displacements can be tracked using ultrasonic methods (Trahey et al. 2004). The tissue response to these forces can be monitored both spatially and temporally. The tissue displacements are inversely related to tissue stiffness (Nightingale et al. 2001).

Radiation force has also been demonstrated to generate propagating waves within tissue (Sarvazyan et al. 1998; Zhang et al. 2005). Wave propagation speed is directly related to the mechanical properties of the tissue. Estimates of vascular stiffness can be derived by measuring the velocity of the propagating wave. Wave generation similar to Zhang et al. 2006 was employed in this study. A single transducer on a diagnostic scanner is used to both generate the radiation force and track the wave velocity and displacements (Trahey et al. 2004). ARFI Imaging has been shown to be effective in cardiac/liver ablation monitoring, breast mass imaging and monitoring cardiac myocardial stiffness (Fahey et al. 2008b; Hsu et al. 2005). Challenges exist in adapting the ARFI imaging method so it can effectively displace and effectively monitor the dynamics of deep lying tissues, such as the abdominal aorta.

This article uses ARFI to examine the material responses in aortic tissue and in phantom AAA animal tissue models examining the effect of elastin reduction on mechanical parameters. This article hypothesises that ARFI could be implemented to provide additional information on the changing mechanical properties of an AAA that lead to rupture.

**MATERIALS AND METHODS**

**Ultrasound measurement**

All *ex vivo* imaging was implemented on a Siemens Antares platform (Siemens Medical Solutions USA, Inc., Ultrasound Division, Issaquah, WA, USA) with a VF10-5 handheld transducer at a frequency of 8 MHz. The scanner has been modified to allow user control of the acoustic beam sequences and intensities and access to raw radio-frequency (RF) data.

**ARFI measurement**

In soft tissues, where the majority of attenuation results from absorption and under plane wave assumptions, this radiation force magnitude can be represented by the following equation (Nightingale et al. 2000; Nyborg 1965; Starritt et al. 1991; Torr 1984, Trahey et al. 2004)

\[
F = \frac{W_{\text{absorbed}}}{c} = \frac{2\alpha I}{c}
\]

where \(F\) [dyn/(1000 cm)\(^{-3}\)], or (kg s\(^{-2}\) cm\(^2\)), is acoustic radiation force, \(W_{\text{absorbed}}\) [W (100 cm)\(^{-3}\)] is the power absorbed by the medium at a given spatial location, \(c\) [m s\(^{-1}\)] is the speed of sound in the medium, \(\alpha\) [m\(^{-1}\)] is the absorption coefficient of the medium and \(I\) [W cm\(^{-2}\)] is the temporal average intensity at a given point in space. For a focused acoustic beam, the radiation force is applied throughout the focal region of the acoustic beam.

During the ARFI sequences, an initial reference line is acquired using standard B-mode parameters. Reference lines are used to establish the initial tissue position. This is followed by a high-intensity focused “push” pulse, which mechanically excites the tissue. The excitation pulse is then followed by a series of tracking pulses, which are utilized to monitor the tissue displacement response.

Displacement measurements were calculated using cross-correlation between 0.5 mm kernels from a reference line and subsequent tracking lines. This was performed over an approximate 60 mm lateral field of view on the proximal wall. Each dataset was filtered to remove linear bulk motion artefacts. Displacements within the lumen were masked out. The mean of the displacements for the four acquisitions was calculated.
Test samples. Excised porcine aortas were obtained from Sierra for Medical Science (Whittier, CA, USA). Details of excised aortas are shown in Table 1. Three aortas were imaged after excision to determine their original properties. Measurements were taken on all samples tested after being excised in their healthy state and a second measurement was taken after a phantom aneurysm was created on part of the sample. Segments of the samples were finally tested in an opening angle test. A stretch ratio of 1.3 was used in experimental procedures (Guo and Kassab 2004).

All tests were performed within 48 h of excision. This minimised significant changes in the mechanical properties of the aortic tissue, as described by Samila and Carter 1981. Due to mechanical failure during initial testing, aorta 3 was unable to be used for all data analysis.

Experimental pressure, displacement and wave test analysis

The excised artery was attached to cannulae in closed pressure apparatus in a phosphate buffered solution (PBS) filled water bath similar to Behler et al. 2006, Dumont et al. 2006, Figure 1. The apparatus enabled pressurization of the aortic specimen up to 200 mm Hg. The specimen was preconditioned by an inflation-deflation cycle of pressure range 0 mm Hg to 100 mm Hg, 10 times. Prior to data acquisition, the axial imaging focus was adjusted to the location of the vascular wall.

The properties of tissues overlying and adjacent to target tissues can impact the strength of the push field reaching the target and dynamic response of tissues to the applied force. System factors, such as transducer focal configuration, ARFI pushing pulse intensity and location of the target tissue relative to the axial focal position of the pushing beams, can also affect induced displacements (Fahey et al. 2005). However, all experimental imaging took place under identical conditions with saline between the transducer and artery as this would be capable of discerning the differing stiffness and effects of the elastase treatment.

During experimentation, the specimen was hydrostatically pressurized with saline in the physiologic range 0 to 200 mm Hg. Data acquisition was performed at each step of 20 mm Hg at the central location of the aortic specimen. The transducer was 13 mm from the proximal wall of the artery during all experimentation (Fig. 1). After each increase in pressure, the axial image focus was readjusted to the vascular wall, to ensure the wall was exposed to an approximately uniform field of radiation at each pressurization step. Some force may be as a result of backscattering due to impedance mismatch between the artery wall and the saline solution, which also necessitated the need for constant experimentation conditions for all specimens. Eight data acquisitions (four displacement, four wave) were taken at each pressure step. Co-registered B-mode images were acquired concurrently to provide anatomical reference and correlate features revealed by ARFI with the structure observed in the B-mode image.

Generation of phantom aneurysm

After initially imaging the aortas in their original excised state, they were subjected to enzymatic treatment of porcine pancreatic elastase (Anidjar et al. 1990; Kratzberg et al. 2009; Sinha et al. 2004). A plastic cuff was used to clamp the aorta two-thirds along its length proximally. The middle one-third of the aorta was infused with porcine pancreatic elastase (LeeBioSolutions, St. Louis, MO, USA. #345-10, concentration 20 U/mL). A second plastic cuff was applied distally to the solution to clamp the middle section and allow the elastase solution to onlyinfuse this section. The intraluminal infusion of porcine pancreatic elastase solution was allowed for 4 h. The enzymatic treatment was adapted from earlier reports on degradation of elastin. After elastase infusion treatment, the aortas were flushed through with PBS to remove any residual enzyme on the surface. An Ancure balloon (Endovascular Technologies, Menlo Park, CA, USA) was then inflated at the elastase treated section to dilate the aorta to 1.3 times its original diameter. The inflated balloon was left in the aorta for 6 h. The artery was in a phosphate buffered solution (PBS) at 37°C for duration of all treatments.

Measurement of the opening angle

A ring specimen of the normal aorta and elastase treated aorta was cut open by a radial cut for measurement

<table>
<thead>
<tr>
<th>Table 1. Aortic specimen details</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Excised length (cm)</strong></td>
</tr>
<tr>
<td>Aorta 1</td>
</tr>
<tr>
<td>Aorta 2</td>
</tr>
<tr>
<td>Aorta 3</td>
</tr>
</tbody>
</table>

Fig. 1. *Ex vivo* apparatus schematic: Pressurised air tank (1) connected to a pressure regulator (2) and gravity head (3), the mounted porcine aorta in a water bath (4), a pressure catheter (5) and a linear transducer (6).
of the opening angle. After the radial cut, the rings popped opened into C-shaped sectors and the sectors were allowed to stabilize for 30 min to fully release the residual stress. The angle was measured from the original centroid location of the uncut aortic ring (Fig. 2).

Histology

Histologic staining was performed to study the effect of elastase on the elastin and collagen in the aortic wall. The sections were fixed in a 10% formalin solution and then embedded in paraffin. Previous studies have shown that Verhoeff-Van Gieson (VVG) staining is appropriate for elastin under light microscopy (Kratzberg et al. 2009; Samila and Carter 1981). Once proper staining was completed the microstructure of three micron (3 μm) cross-sectional slices of the tissue were examined using Nikon ES/L1 light microscope with a viewing range from 4 to ×40.

Data analysis

Motion filters were applied to the data to reduce artefacts from physiologic and transducer motion (Fahey et al. 2007). Displacements were computed by correlating the reference pulse with sequentially acquired tracking pulses transmitted after the pushing pulse. Estimation of the speed with which waves propagate through the lateral locations at each pressure step for the differing arteries was also calculated, to measure the changing stiffness of the arteries with pressure change (Nightingale et al. 2003). The elastic stiffness properties of the arterial wall are expressed in terms of the Hudetz incremental elastic modulus (Zulliger et al. 2002). The Hudetz Incremental elastic modulus is shown in eqn (2).

\[
H_{\theta \theta} (p) = 2 \left[ \frac{d_{out}(p)d_{in}^{\prime}(p)}{d_{out}^{\prime}(p)} \right] + p \cdot d_{out}^{\prime}(p) + 1 \cdot d_{out}^{\prime}(p) - d_{in}^{\prime}(p)
\]

(2)

Where \(d_{out}\) is external diameter, \(d_{in}\) is inner diameter; \(p\) is the pressure at \(d_{out}\).

The Hudetz incremental elastic modulus is plotted vs. \(r/R\), where \(r\) is current radius; \(R\) is original radius, which can be defined as circumferential stretch.

Wave generation and data collection

Usually waves generated are classified as shear waves, the velocity of which can be used to calculate the shear modulus of the material. This assumes an isotropic, homogeneous material. The aorta is a complex, orthotropic material. So the wave generated in these experiments will not be defined as shear waves. Because of this in contrast to shear wave imaging, the shear modulus cannot be reported and the velocity of the waves will be analysed to examine the changes in material properties.

A region of tissue is excited to generate a wave through the tissue. An adjacent location is tracked to monitor the displacement as the wave passes through this location. The excitation of the initial region is repeated a number of times and tracking of displacement is performed at different lateral locations along the length of the aorta. The time it took the displacement to reach peak displacement at each of these locations for each of the four wave generated was calculated. The time to peak displacement is plotted against lateral location; a regression line is fitted to these plots, with goodness to fit greater than 0.95 (Regression lines are not displayed in Fig. 11). The slope of these regression lines is the estimated wave velocity (Palmeri et al. 2008).

Elastin concentration calculation

Histology images were thresholded using Mimics (v12.0; Materialise, Leuven, Belgium) allowing the percentage elastin in the sample to be calculated. This process assigns a pixel intensity value measured in Hounsfield units (HU) to each pixel in the greyscale image. From this, the HU value can be controlled so that only the regions-of-interest, in this case the elastin, are thresholded. HU values of −1034 and −180 were applied to the grey-scale histology images. The percentage of elastin present after elastase treatment could then be calculated.

RESULTS

The opening angles for the normal aorta and elastase treated rings were 83.2±4.6° and 20.0±8.5°, respectively. The opening angle measurement from the normal and elastase treated aorta ring specimens is shown in Figures 3 and 4 for specimen 2. The opening angle of arteries is a concise parameter directly indicating the residual stress in the vessel, which affects the mechanical behaviour of the arterial wall.

The collagen and elastin were inspected visually with a microscope and some examples are shown in Figure 5 of
specimen 3. Verhoeff-Van Gieson (VVG) staining is useful for staining elastin fibres which appear as blue/black.

A thresholding technique was applied to a grey-scale image of Figure 5c and f to calculate the percentage elastin remaining. Figure 6 show these values normalized to percentage elastin, there has been an average 73.02% decrease in elastin content, which agrees with values published by Vyavahare 2007.

The Hudetz incremental elastic modulus is shown plotted against r/R in Figure 7 for aorta 2. It also shows the pressure variation against r/R on the secondary axis, solid black lines correspond to the modulus axis; dashed grey lines correspond to the pressure axis. The differing behaviour between the two tissues is apparent in this graph with a 35.7% difference in moduli at 120 mm Hg. The elastase artery modulus ramps up exponentially at lower pressures compared with the more gradual increase of the normal artery. There is also greater circumferential stretch induced in the elastase artery.

Diameters of the arteries could be measured directly from the ultrasound screen, at each pressure step. The B-mode image indicated definite preferential dilation of the elastase treated artery (Fig. 8a and b).

The pressure-diameter curves in Figure 9 demonstrate the variation of diameter (cm) of three different vessels with respect to the pressure exerted on their walls. At pressures of 60 mm Hg and 140 mm Hg, the average difference in dilations between elastase and normal tissue were 19.04% ± 3.72% and 10.70% ± 1.17%, respectively. The pressure-diameter curves for each sample corresponds to the amount of elastin degradation in each sample. Aorta 3 had the greatest amount of elastin remaining, 32%, with aorta 2 having greatest degradation. This corresponds to greater stretch evident before the onset of collagen recruitment in aorta 3 and least stretch in aorta 2.

The acoustic radiation force generates displacements in the tissue. The error in the displacement calculation typically seen in ARFI images is on the order of a few tenths of microns (Dahl et al. 2009). Figure 10 shows the average of four acquisitions of the displacements which were computed for aorta 1 at normal and elastase configuration and expressed vs. pressure. Softer tissues
should move farther than stiffer tissues for a given force magnitude (Nightingale et al. 2005). Displacement magnitude decreased with increasing pressure as expected due to the corresponding increase in stiffness for both arteries, with an average standard deviation of 0.1 microns between all four acquisitions. But there was a preferential stiffening of the enzymatic treated artery, as seen in Figure 9, which would be expected in an aneurysm tissue.

The time it takes the wave to generate peak displacement at each lateral location outside the region of excitation was calculated for both the normal artery and enzymatic treated artery and displayed below vs. pressure. The stiffness of skeletal tissue has been shown to increase with increasing load (Levinson et al. 1995). Increasing tissue stiffness is correlated with decreasing time to maximum displacement. The enzymatic treated artery time to peak displacement is considerably less than that of the normal artery at the same pressure and is displayed in Figure 11 for both 80 mm Hg and 160 mm Hg for aorta 1.

The slope of a regression line fitted to the time to peak displacement plots (Fig. 11) allowed wave velocity estimation to be calculated. Acoustic force generated a propagating wave within the tissue samples. The average wave speed for each pressure step was calculated, for the two artery configurations (normal and elastase) for aorta 1 (Fig. 12). The wave velocity follows a similar trend to that of the ARFI displacement (Fig. 10), which in turn follows the stiffness trend in the materials properties as shown in Figure 7.

Analysis of the ARFI generated displacement and calculated Hudetz incremental elastic modulus is shown in Figure 13. It is shown that for each of the individual arteries, in both their elastase and normal state, similar trends are evident in the displacement-modulus behaviour. The difference between elastase and normal displacements falls to 0.3 microns for aorta 1 at modulus of 0.3 MPa, with greater displacements in the normal. It is also evident here, from the difference in displacement profiles, that there is inter-individual variation in the properties of the native vessels, due to the important muscular component of their wall.

**DISCUSSION**

The composite nature of the artery wall is important in providing the essential elastic nonlinearity of the aortic wall (Roach and Burton 1957). The initial stiffness of the
artery wall represents the elasticity of the elastin, while the much higher stiffness at high strains represents the contribution of fully tensed collagen fibres. The straightening of elastin layers and the alignment of collagen fibres with distention under physiologic pressures correlates with the increasing elastic modulus and represents the basis for load transfer from compliant elastin at low strains to much more rigid collagen fibres at higher strains.

An artery ring springs open into a sector after a radial cut. Elastin is the protein constituent of connective tissue responsible for this elasticity and recoil of the tissue (Fonck et al. 2007). The elastase enzymatic treatment performed on the porcine aortas is thought to replicate the elastin degradation in aneurysms. The opening angle characterizes the residual strain in the unloaded state. The opening angle measurements prove this experimentally, with an average elastase treated opening angle of 20.0 ± 8.5° and an average normal aorta opening angle of 83.2 ± 4.6°. Histologic analysis of the arteries further proved this elastin degradation (Fig. 6) with a 73% decrease in elastin content. The excised artery staining (Fig. 5a–c) reveals the elastic fibres (in black) evenly distributed through the artery wall in a longitudinal orientation. The stain of the elastase treated aorta (Fig. 5d–f) displays disorganisation of elastin with almost complete elastin degradation in areas (Arrows in Fig. 5f).

The Hudetz incremental elastic modulus is an indicator of the inherent elastic properties of the artery. Figure 7 indicates significantly higher Hudetz incremental elastic modulus values for the elastase treated vessel compared with the normal vessel at similar pressures i.e., at 120 mm Hg the normal modulus is 0.04 MPa compared with 0.077 MPa in the elastase vessel. In the normal group, the incremental modulus increases slowly, whereas the elastased group incremental modulus has a substantial and continuous increase. Also evident from this graph, there is substantially greater circumferential stretch in the elastased group. At 100 mm Hg, there is 57.3% more circumferential stretch induced in the elastased group. This is indicative of an early and substantial collagen recruitment in the absence of elastin. The median circumferential stretch of the normal aorta of 1.23 is similar to values reported by Labrosse et al. 2009. Previous incremental elastic moduli reported for aortae has been found to be in the range of 0.4 MPa to 1.5 MPa (Black 1998) and, for aneurysms <60 mm, was slightly higher at 0.9 to 2.01 MPa (Koullias et al. 2005). The samples tested fell within these ranges for both diseased and healthy, which gives some confidence in the artificial induction of an aneurysm.

Figure 8 shows B-mode images showing a longitudinal view at the same pressure for both arteries. There is a definite preferential dilation of the elastased artery vs. the normal artery as is symptomatic of aneurysmal aortas. A circumferential B-mode image also allows diametric measurements be taken easily at each pressure increment.

The pressure-diameter curves for all the normal aortae (Fig. 9) exhibits the typical curve of an elastic conduit artery. The early part of the curve is indicative of compliance and distensibility is increasing gradually with pressure. In the normal artery, at low inflation pressures, the load is carried almost exclusively by the elastin fibres and the diameter increases gradually. As inflation pressure continues to increase, collagen fibres will start to engage yielding a progressively stiffer vessel wall and there is less diametric increase. This pressure-diameter response is characteristic of quasi-linear elastic materials.

In contrast to the normal arteries, the elastased arteries do not exhibit the typical pressure-diameter curve and, in consequence, their distensibility decreases monotonically with pressure. In the elastased arteries, after initial rapid diameter increase, collagen starts to engage at lower pressures due to the absence of elastin. This limits...
the elastic response of the artery and yields a substantially stiffer vessel even at low inflation pressures. This conclusion further supports the incremental elastic modulus graph in which it is clearly seen that the elastic modulus of elastased arteries increases significantly and in exponential fashion with pressurisation. The increase in elastic modulus takes action nearly immediately, with preferential dilation of the elastased artery to compensate for the loss of elastin. The point where collagen fibres begin to engage for the normal arteries is a lot later than the elastase arteries (Fonck et al. 2007; Raghavan et al. 1996; Samila and Carter 1981). The continuous recruitment of collagen fibre limits the further distension of the artery and leads to an exponential decrease in distensibility (Vyavahare 2007).

The differing mechanical properties of the arteries can also be identified using ARFI techniques. Increasing tissue stiffness is correlated with both decreasing tissue displacement and increasing wave velocity. Large displacements occur in normal tissue and smaller displacements indicate where stiffer materials occur. Thus, a stiffer tissue will exhibit smaller displacements than more compliant, healthy tissue. The displacement-pressure graph (Fig. 10) displays decreased displacement for the elastased vessel at the same pressure as the normal artery, signifying a greater reduction in the distensibility of the phantom aneurysm, in comparison to the normal artery, over the same pressure range.

ARFI was also employed to generate waves in the artery. Figure 11 shows the time it takes the wave to induce peak displacement at lateral positions outside the region of excitation (ROE). The time it takes the wave to generate maximum displacement decreases with increasing stiffness, 2.0 ms vs. 2.2 ms (80 mm Hg) and 1.3 ms vs. 1.6 ms (160 mm Hg).

Fitting regression lines to Figure 11, it was possible to document the wave speeds for both the elastase treated artery as well as the normal artery. Figure 12 displays these speeds with respect to the pressure. The elastase wave speed is higher than the normal wave speed across...
the physiologic pressure range (80 mm Hg–180 mm Hg), further highlighting the elevated stiffness of this artery (Nightingale et al. 2002a). This further highlights the preferential stiffening of the enzymatic treated artery over the normal artery. It is possible that in addition to the velocity, diameter, thickness and boundary conditions play a role in stiffness of the artery. Utilizing velocity of the wave has advantages over using displacement data. For displacement data, the force is a function of intensity and attenuation that affects displacement. Therefore for different samples, the forces vary due to different attenuation coefficients. But for wave generation, intensity and attenuation only affect the amplitude of the wave, the velocity remains the same.

There is a crossover point in both displacement and velocity plots. In the displacement plot (Fig. 10), the elastase artery has greater displacement at lower pressure but as the pressure increases the displacement falls lower than that of the normal artery. In the velocity plot (Fig. 12), the elastase vessel velocity is lower at lower pressures and as the pressure increases the velocity is greater than the normal artery. Similar behaviour is evident in the modulus/circumferential stretch plots (Fig. 7). The elastase artery experiences initial dilation at lower pressures.
as the pressure increases the artery dilation reduces and there is a rapid increase in modulus. This is similar behaviour as suggested by the crossover point in the displacement and velocity plots. Roach and Burton (1957) suggest that the compliant elastic fibres are stretched first and determine the resistance to stretch at low pressures. As the vessel is distended, the collagen fibres come into play so that, at higher pressures, resistance to stretch is mainly due to collagen recruitment. Destruction of the compliant elastin induces profound change in the collagen recruitment in the elastase treated arteries (Fonck et al. 2007; Raghavan et al. 1996; Samila and Carter 1981). There is decreased vessel distensibility, at lower pressures, as the amount of elastin is reduced in load bearing and the load is shifted to the rigid collagen sooner. This leads to earlier stiffening of the elastased vessel, as suggested by each of the displacement, velocity and modulus/circumferential plots.

Comparison of the ARFI displacement and Hudetz modulus in Figure 13 reveals very little difference between the trends for each artery. Previous analysis had demonstrated preferential stiffening of the elastase arteries but similar trends between their displacements is evident here at similar moduli before and after elastase treating. This suggests that ARFI displacements could also be engaged to provide information on the materials modulus.

The technique described in this investigation is noninvasive and would be applicable to study of larger populations to study the effects of AAAs on vascular elastic pathology. However, clinically, the quality of these ARFI images would be influenced by the
pulsatile nature of the aorta, which would have to be addressed with ECG triggers and motion filters. Also, successful ARFI Imaging at realistic aortic depths faces challenges at generating sufficient radiation forces to measurably displace this deep lying tissue and these displacements.

Limitations

In this study, there were certain limitations that may have influenced the data obtained and may affect the use and development of ARFI to predict AAA material properties using elastase infusion.

1. The normal aorta did not undergo balloon dilation for 6 h, which could lead to differing ARFI responses.
2. Material length differences due to the aneurysm formation could also influence on the acoustic response times.
3. Displacements could be influenced by the surface area and volume differences between the normal artery and the elastase artery.
4. It is uncertain how the boundary conditions, the thickness of the artery and diameter influence velocity. The Moens-Korteweg equation 3 predicts that as diameter increases velocity decreases but in the aorta the opposite occurs.

\[ c^2 = \frac{EH}{pd} \] (3)

Where: \( H \) = thickness, \( E \) = Young’s modulus, \( p \) = density \( d \) = diameter.

This means that density or modulus could also be influencing the velocity.

These possible limiting factors could cause errors in the interpretation from the ARFI signal and the readings which seem to be linked to the geometric changes and elastin reduction, which may be only as a result of geometric changes.

CONCLUSION

An experimental model of an in vitro AAA was successfully developed using elastase infusion techniques for examination using ARFI Imaging. ARFI induced displacement and wave generation was demonstrated in in vitro phantoms. ARFI imaging was found to have the ability to detect the mechanical changes induced during aneurysmal formation. This study indicates that ARFI may be a useful additional tool in the diagnostic assessment of AAA. Clinical evaluation is also needed to determine whether ARFI can cause tissue responses at the depths encountered in AAA cases. A preliminary study is in preparation.

Acknowledgements—This work is supported by the Irish Research Council for Science, Engineering and Technology (IRCSET) Grant no. 2007/2950 and the FAS Science Challenge 2008/2009.

REFERENCES


Research paper

In vivo feasibility case study for evaluating abdominal aortic aneurysm tissue properties and rupture potential using acoustic radiation force impulse imaging

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ARTICLE INFO

Article history:
Received 8 September 2010
Received in revised form
17 December 2010
Accepted 22 December 2010
Published online 29 December 2010

Keywords:
Abdominal aortic aneurysm
Acoustic radiation force impulse
In vivo excitation
Rupture prediction index

ABSTRACT

An abdominal aortic aneurysm (AAA) is defined as a permanent and irreversible localized dilation of the abdominal aorta. A reliable, non-invasive method to assess the wall mechanics of an aneurysm may provide additional information regarding their susceptibility to rupture. Acoustic radiation force impulse (ARFI) imaging is a phenomenon associated with the propagation of acoustic waves in attenuating media. This study was a preliminary evaluation to explore the feasibility of using ARFI imaging to examine an AAA in vivo. A previously diagnosed in vivo aneurysm case study was imaged to demonstrate the viability of excitation of the abdominal aorta using ARFI imaging. Ex vivo experiments were used to assess an artificially induced aneurysm to establish its development and whether ARFI was able to capture the mechanical changes during artificial aneurysm formation. A combination of in vivo and ex vivo results demonstrated a proposed hypothesis of estimation of the tissue’s stiffness properties. The study details a method for non-invasive rupture potential prediction of AAAs using patient-specific moduli to generate a physiological stiffness rupture potential index (PSRPI) of the AAA. Clinical feasibility of ARFI imaging as an additional surgical tool to interrogate AAAs was verified and methods to utilize this data as a diagnostic tool was demonstrated with the PSRPI.

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1. Introduction

For many years, clinicians have been aware of the correlation between the mechanical properties of a soft tissue and its state of health. An abdominal aortic aneurysm (AAA) is defined as a permanent localized dilation of the aorta constituting at least a 50% increase in normal diameter (Xiong et al., 2008). There are approximately 200,000 patients in the United States and 500,000 patients worldwide diagnosed with an AAA every year (Vande Geest et al., 2004). The development of AAAs is associated with alterations of the connective tissue in the aortic wall. It is characterized by a destruction of elastin...
and growth and remodelling of collagen in the arterial wall. This destruction of elastin is considered a key factor in the pathogenesis of the aneurysm. Elasticity of the aneurysm wall has been observed to be reduced, and to be correlated with reduced elastin content (Vorp, 2007).

The current method for assessing the risk of rupture of aneurysms is based on its maximum diameter. Thus if an aneurysm is 5.5 cm or larger in diameter, it is deemed high risk, and is therefore recommended for repair (Lederle et al., 2001). While it is obvious that the larger an aneurysm is the more likely it is to rupture, several studies have reported rupture in aneurysms with diameters less than 5.5 cm (Darling et al., 1977; Limet et al., 1991). This, coupled with a 4–5% mortality rate with interventional surgery, indicates a critical need for improved non-invasive AAA rupture predictors.

Acoustic radiation force impulse (ARFI) imaging is a relatively new imaging modality which has been developed in Duke University (Durham, NC, USA) over the last ten years. ARFI imaging is a radiation force-based imaging method that uses commercially available ultrasound scanners to generate short-duration (approximately 30–300 µs) acoustic radiation forces. These impulses, or pushing pulses, generate localized displacements in tissue of approximately 1–10 µm. The displacement magnitude is inversely proportional to local tissue stiffness (Fahey et al., 2003). It has been shown to be successful in clinical imaging applications, including differentiating malignant lesions from fluid-filled cysts in breasts, monitoring chemical and thermal ablations in vivo, and isolating regions of atherosclerosis via surveying arterial wall mechanical properties in vivo and ex vivo human investigations (Behler et al., 2009; Bradway et al., 2007; Nightingale et al., 2007, 2000).

The primary objective of this paper is to investigate the clinical feasibility of ARFI imaging in vivo to evaluate AAA tissue stiffness properties and to demonstrate how this data can be utilized to give a diagnostic measure of potential failure. A physiological stiffness rupture potential index (PSRPI) will be defined as the ratio of the patient-specific incremental modulus of an AAA to a population-average incremental modulus. It seems reasonable to suggest that the stiffness of an aneurysm may yield an additional diagnostic measure which could be used to assess the likelihood of rupture. We propose the PSRPI to be a possible criterion for assessing patient-specific rupture potential, and that it could be combined with the widely accepted maximum diameter criterion to serve as an additional clinical aid to surgeons.

### 2. Materials and methods

A previously diagnosed in vivo AAA was scanned and the ARFI displacement evaluated. An ex vivo ARFI evaluation was carried out on excised porcine aortas pre and post elastase treatment. An evaluation method is described where these ex vivo results were then used in conjunction with in vivo case study findings to give an indication of elasticity based on the ARFI displacement. The elasticity value obtained could be used in a physiological stiffness-based index (PSRPI) as a signal to predict rupture potential by ARFI. As the PSRPI increases above a value of 100, the probability of rupture of that AAA would increase.

#### 2.1. ARFI in vivo case study imaging

For in vivo imaging, a curvilinear transducer, CH4-1, was used at relatively low transmit frequencies (2.22 MHz). For in vivo imaging, clinical sequences were synchronized to the vessel systole to limit artifacts from vessel pulsation. In addition, the acquisition time for clinical sequences was reduced using parallel-receive beam-forming techniques (Dahl et al., 2007). Parallel-receive ARFI imaging allows for the simultaneous tracking of four locations for every pushing pulse transmitted. Shortening the acquisition time with parallel-receive ARFI imaging reduces both patient exposure and the likelihood of physiological and patient motion artifacts (Dahl et al., 2007).

The patient details are given in Table 1.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Blood pressure</th>
<th>Pulse</th>
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<tbody>
<tr>
<td>Female</td>
<td>73 years</td>
<td>182/77</td>
<td>63 bpm</td>
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#### 2.2. ARFI displacement evaluation

For ARFI sequences, a reference tracking beam was transmitted, followed by a high-intensity ARFI pushing beam that displaced the tissue. A series of tracking beams after the push beam were used to track the tissue displacement. The reference pulse relates to the initial tissue position. Displacements were computed at each pressure by correlating the reference pulse with sequentially acquired tracking pulses transmitted after the pushing pulse.

#### 2.3. Development of an elastase (experimental aneurysm) ex vivo model

In brief, as described in our earlier work (Tierney et al., 2010), an excised porcine aorta (obtained from Sierra for Medical Science, P.O. Box 5692, Whittier, CA 90607-5692) was infused with porcine pancreatic elastase (Lee-BioSolutions, St. Louis, Missouri; #345-10, concentration 20 Unit/milliliter) for 4 h. The aortas were flushed through with phosphate buffered solution (PBS). An Ancure™ balloon (Endovascular Technologies, Menlo Park, CA) was then inflated for 6 h. The artery was kept in a PBS at 37 °C for the duration of all treatments. The enzymatic treatment was adapted from earlier reports on the degradation of elastin (Anidjar et al., 1990; Kratzberg et al., 2005; Sinha et al., 2004).

#### 2.4. Experimental case evaluation—healthy and elastase treated cases

The experimental healthy and elastase-treated cases were evaluated in detail in our previous work (Tierney et al., 2010). The aortic specimen was evaluated in a closed pressure apparatus up to 200 mm Hg. Aortas were imaged after excision to determine their properties before and after elastase treatment.
2.4.1. Compliance
Compliance was computed using Eq. (1) (Vorp et al., 1996):

\[
\text{Compliance} = \frac{(\Delta A)}{(A_{\text{max}})\Delta P}, \quad (1)
\]

where \( A \) is the cross-sectional area of the vessel and \( P \) is the pressure in the vessel (mm Hg).

2.4.2. Hudetz incremental elastic modulus
The Hudetz incremental elastic modulus \( E_{\text{inc}} \) is given by Eq. (2):

\[
E_{\text{inc}} = 2\left((\frac{d_{\text{out}}^2 - d_{\text{in}}^2}{(\Delta d_{\text{out}}/\Delta P)} + P\frac{d_{\text{out}}^2}{(1/\Delta d_{\text{out}} - d_{\text{in}}^2))) \right), \quad (2)
\]

where \( d_{\text{out}} \) is the external diameter, \( d_{\text{in}} \) is the inner diameter, and \( P \) is the pressure in the vessel (Fonck et al., 2007).

2.5. Ex vivo ARFI imaging—healthy and elastase-treated cases
All ex vivo imaging was implemented on a Siemens Antares™ platform (Siemens Medical Solutions USA, Inc., Ultrasound Division, Issaquah, WA) with a VF10-5 handheld transducer at a frequency of 8 MHz. The scanner has been modified to allow user control of the acoustic beam sequences and intensities and access to raw radiofrequency (RF) data.

2.6. Future perspectives for ARFI implementation
A method to use the ARFI displacements to quantify the degree of disease of the aneurysm was established.

2.6.1. Concept for in vivo \( E_{\text{inc}} \) calculation
(a) The displacement recorded in vivo in the AAA case study was combined with the ex vivo displacement–modulus average behaviour (Fig. 3). This allowed an in vivo modulus for the case study to be estimated.

(b) Four average pressure–diameter curves of AAAs were taken from the literature (Corbett et al., 2010; Drangova et al., 1993; Lanne et al., 1992). These behaviours were evaluated according to percentage strain. The percentage strain was applied to the systole diameter of the in vivo case study to obtain the estimated diastole diameter. A prediction of the Hudetz incremental elastic modulus \( E_{\text{inc}} \) could be obtained from these diameters for the in vivo case study.

(c) The in vivo \( E_{\text{inc}} \) was also compared to moduli for healthy abdominal aortas obtained from Langewouters et al. (1984).

2.6.2. Physiological stiffness rupture potential index (PSRPI)
The PSRPI is defined as the ratio of a patient-specific incremental modulus to a population-average incremental modulus taken from the literature:

\[
\text{PSRPI} = \left(\frac{E_{\text{case}}}{E_{\text{population average}}}\right) \times 100, \quad (3)
\]

where \( E_{\text{case}} \) is the patient-specific incremental modulus and \( E_{\text{population average}} \) is the average population incremental modulus from the literature.

3. Results
3.1. In vivo case study
The in vivo imaging of the aorta was performed under an existing Institutional Review Board (IRB) approved protocol which allowed for ARFI imaging of an AAA patient (patient details given in Table 1).

Fig. 1(a) shows a B-mode image at maximum aneurysm diameter to allow for measurement of the aorta and Fig. 1(b) allows identification from the B-mode image where the ARFI excitation was observed.
Healthy moduli were in the range 0.07–0.136 MPa, in conjunction with the average pressure–displacement observed for two excised arteries was evaluated, for the healthy case. Using the displacement observed for the case study ($E_{\text{inc}}$), the behaviour made it acceptable to use the displacement in vivo to calculate an estimate of the population average behaviour ($\bar{E}_{\text{inc}}$) as an indication of the possible rupture risk using the PSRPI is shown. Three calculations of $E_{\text{inc}}$ were carried out in this study, as shown in Fig. 4(a)–(c).

(a) Using the displacement observed in vivo (ARFI) with the average experimental aorta model behaviour predicted an in vivo modulus of 1.25 MPa.

(b) Using Eq. (2) in conjunction with the average pressure-diameter behaviour (Corbett et al., 2010; Drangova et al., 1993; Lanne et al., 1992) allowed a range of estimations for the in vivo case. This method predicted calculations of modulus in the range 0.71–1.33 MPa.

(c) Healthy moduli were in the range 0.07–0.136 MPa (Langewouters et al., 1984).

Once the predicted $E_{\text{inc}}$ for the case study could be determined from literature-average behaviours, the PSRPI could be calculated. In Table 2, an indication of the possible rupture risk using the PSRPI is shown.

An example calculation for the rupture index of the case study is shown below, based on the behaviour of the Lanne et al. aneurysm study.

$$\text{PSRPI} = \left( \frac{E_{\text{case}}}{E_{\text{population average}}} \right) \times 100,$$

where the $E_{\text{population average}}$ is 1.02 MPa (Corbett et al., 2010; Drangova et al., 1993; Lanne et al., 1992) and the predicted $E_{\text{inc}}$ for the case study is 0.88 MPa. The equation now becomes

$$\text{PSRPI} = (0.88/1.02) \times 100 = 86.8.$$

Therefore, the resulting PSRPI for the case study based on Lanne et al.’s behaviour reveals a medium risk.

### 3.2. Ex vivo healthy and elastase-treated experimental results

Fig. 2 shows the comparison of the aortic compliance before and after elastase treatment. Compliance was calculated at physiological pressures for each of the excised samples. The opening angle was measured in each of the three healthy and elastase-treated samples. The opening angles for the normal aorta and elastase-treated rings showed an average 76% decrease from normal to elastase treated ($n = 3$) (Tierney et al., 2010).

The displacement versus incremental modulus behaviour for two excised arteries was evaluated, for the healthy case and the elastase-treated case (Fig. 3).

### 3.3. Future perspectives for ARFI implementation

#### 3.3.1. Proposed in vivo $E_{\text{inc}}$ calculation

Due to the very similar trends, for both healthy and elastase-treated cases, of all the ex vivo specimen displacement–modulus behaviour, it was deemed acceptable to take an average of all these behaviours (Fig. 3).

Combining this average behaviour with the fact that the elastase properties were very similar to previously reported in vivo behaviour made it acceptable to use the displacement from the in vivo case with the average behaviour to estimate the in vivo $E_{\text{inc}}$ for the case study (Fig. 3, dashed line).

### 4. Discussion

There still exists an extreme need clinically to predict AAA rupture. Towards this goal, this study has investigated a non-invasive method to establish the mechanical properties of a clinically identified aneurysm.
4.1. Ex vivo experimental model study

The elastase model was evaluated to establish the similarity to in vivo aneurysm behaviour. Vorp et al. (1996) reported the compliance of AAAs to be $1.8-9.4 \times 10^{-4}/\text{mm Hg}$ (mean $4 \times 10^{-4}/\text{mm Hg}$). All the elastase samples in this study had compliance values $(3.7-8.4 \times 10^{-4}/\text{mm Hg})$ in this range. The opening angle decrease from healthy to elastase treated confirms the elastin degradation during elastase treatment.

The displacement profiles revealed that increasing tissue stiffness correlates with decreasing tissue displacement. In both cases, the displacement magnitude for the elastase-treated case is less than that of the healthy case at similar pressures, confirming preferential stiffening due to the degradation of elastin. In the elastase treated arteries, collagen starts to engage at very low pressures due to the absence of elastin, thereby limiting the elastic response of the artery and thus yielding a substantially stiffer vessel even at low inflation pressures. This behaviour is demonstrated in the displacement profile.

The similar trends of the displacement–modulus behaviour (Fig. 3) both before and after elastase treatment suggest that, even in the absence of elastin in the aneurysm wall, the vessel exhibits the same properties, albeit at different pressures, which is expected in the incrementally changing property behaviour of arterial tissue. Previous incremental elastic moduli reported for aneurysms <60 mm were in the range 0.9–2.01 MPa (Koullihas et al., 2005). The elastase treated samples previously tested fell within this range, which gives some confidence in the artificial induction of an aneurysm and allows use of this data in conjunction with the in vivo data.

4.2. Future perspectives for ARFI implementation

The in vivo estimation of tissue elasticity parameters is important for realistic tissue deformation modelling and diagnostic tasks such as surgical intervention. The knowledge of aortic mechanical properties in particular could offer improvement in the treatment of aneurysms and may have wide spectrum applicability. Although our knowledge of aneurysm behaviour and its impact on rupture has improved tremendously during the course of the last few years, there is still a need for a non-invasive effective method for the identification of in vivo properties. ARFI imaging has been shown to have the potential to indicate the underlying mechanical properties of internal tissues. However, previously, this method has been limited to looking at relative differences spatially only within a single image. This study has demonstrated the ability to interrogate at the depth of the aorta for a previously diagnosed aneurysmal patient. The linking of the in vivo data and ex vivo data is an approach which needs further validation, but it provides a concept which would allow a modulus to be known which could aid the clinician during the decision-making process.

Comparison of the $E_{\text{inc}}$ for the ARFI case study to the predicted $E_{\text{inc}}$ from the average circumferential strain behaviour revealed very similar estimated values, with the ARFI prediction in the high end of the strain prediction. Strain behaviour is thought to be more indicative of true aneurysm behaviour as it takes into account the nonhomogeneous behaviour and is less dependent on the original shape of the aneurysm.

Thubrikar (2007) reported, at the anterior wall, an incremental modulus of between 1 and 2 MPa for human aneurysmal samples. The predicted $E_{\text{inc}}$ for the case study, both by the ARFI technique and prediction, corroborates these values. A PSRPI value was determined for each case from Eq. (3). All predicted moduli for the in vivo case study suggested it had a medium to high risk of rupture. Although the PSRPI results presented here are preliminary and need to be refined further, the approach may be clinically useful for a surgeon. This aneurysm measured 41 mm and was under regular surveillance. This would be deemed clinically to be of moderate risk.

A study by Di Martino et al. (2006) stated that the risk of rupture was not related to the stiffness. However, these stiffness values were based on the maximum tangential moduli taken from tensile tests. These stiffness values taken from stress–strain data would not accurately reflect the in vivo physiological strain ranges experienced by the aneurysm. The Hudetz incremental modulus used in this study, which takes into account the diameter changes, pressure changes, and thickness of the aneurysm, may provide a better indication of the physiological stiffness seen by the aneurysm. A study by Moritake (1975a,b) hypothesized that the stiffest aneurysms might be the ones most prone to rupture. They found that when they varied the distensibility but kept the blood flow and diameter constant, the pulse pressure increased with increased stiffness. They concluded that the pulsatile stress, fluctuation in pressure, and the likelihood of rupture increased with increasing stiffness of the blood vessel. However, the authors agree with Sonesson et al. (1999) that there is probably a complex relation between aneurysmal stiffness and weakness of the aneurysmal wall that determines the likelihood of rupture. Therefore the PSRPI values, which take into account patient-specific moduli, would be beneficial to a surgeon in addition to existing diagnostic techniques for rupture prediction.

The novel technique proposed in this study may provide some key information about in vivo properties of the AAA. Of course, one patient is insufficient to draw any quantitative or qualitative conclusion regarding the capability of this technique. A more comprehensive multi-subject study would provide more conclusive evidence and also allow refinement of the bands of the PSRPI. However, the results of this study demonstrate that the technique is feasible. In addition, they suggest that amalgamation with elastase data drawn from laboratory-based studies may provide in vivo mechanical
property information. This information could be used in conjunction with other surgical decision-making criteria, (Doyle et al., 2009a,b; Fillinger, 2006; Vande Geest et al., 2004; Vorp et al., 1998) thereby enabling a surgeon to make the most informed intervention decision.

The proposed method of equating the displacement to a modulus is only a concept, and the authors are fully aware of the limitations in this study.

Limitations

- One limitation of this study was the lack of an exact diameter taken at the diastole. However the four average pressure–diameter behaviours of aneurysms applied to the systole diameter are thought to have given a good estimation of this diameter.
- In ARFI imaging, there is the assumption made that factors (e.g., attenuation coefficients, ultrasonic intensity, frequency content) which determine the radiation force are uniform in the area of displacement. This results in an inability to compare displacement values from person to person. A method such as the one proposed could be developed to take this assumption into account in the calculation of the modulus.
- Another limitation is the lack of confirmation of the in vivo tissue modulus using mechanical testing. This would have involved excision of the tissue and testing post excision. The modulus results found are comparatively close to values reported previously by Koulias et al. (2005) and Thubrikar (2007). A superior and more in-depth study would have involved combining ARFI imaging before resection for patients undergoing surgical repair with post-resection biomechanical testing. This could be incorporated into any future testing undertaken.
- The effect of boundary conditions on displacement magnitudes would also have to be established.

5. Conclusion

ARFI-induced displacement was demonstrated in an in vivo diseased aorta. We have proven the capability of ARFI imaging to successfully displace at realistic abdominal depths. ARFI imaging may be a convenient adjunct to conventional ultrasound for assessing the abdominal pathology of the aorta. The PSRFI can also provide additional information for a surgeon in the intervention process. It is important to note that this in vivo case study is encouraging for establishing feasibility; however, a more prolonged study, both ex vivo and in vivo, with a statistically significant sample size is necessary to establish the efficacy of this method. Nevertheless, the proposed technique is clinically feasible, and may offer an improved diagnostic technique over current rupture prediction methods. In the future, more accurate estimation of the inherent mechanical properties of the AAA to evaluate the potential of rupture for patient-specific AAAs could be produced.

Acknowledgements

The authors extend their thanks to Douglas Dumont and Gregg Trahey, Trahey Laboratory, Duke University, USA, and the Irish Research Council for Science Engineering and Technology (IRCSET).

References


Use of Regional Mechanical Properties of Abdominal Aortic Aneurysms to Advance Finite Element Modeling of Rupture Risk

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Purpose: To investigate the use of regional variations in the mechanical properties of abdominal aortic aneurysms (AAA) in finite element (FE) modeling of AAA rupture risk, which has heretofore assumed homogeneous mechanical tissue properties.

Methods: Electrocardiogram-gated computed tomography scans from 3 male patients with known infrarenal AAA were used to characterize the behavior of the aneurysm in 4 different segments (posterior, anterior, and left and right lateral) at maximum diameter and above the infrarenal aorta. The elasticity of the aneurysm (circumferential cyclic strain, compliance, and the Hudetz incremental modulus) was calculated for each segment and the aneurysm as a whole. The FE analysis inclusive of prestress (pre-existing tensile stress) produced a detailed stress pattern on each of the aneurysm models under pressure loading. The 4 largest areas of stress in each region were considered in conjunction with the local regional properties of the segment to define a specific regional prestress rupture index (RPRI).

Results: In terms of elasticity, there were average reductions of 68% in circumferential cyclic strain and 63% in compliance, with a >5-fold increase in incremental modulus, between the healthy and the aneurysmal aorta for each patient. There were also regional variations in all elastic properties in each individual patient. The average difference in total stress inclusive of prestress was 59%, 67%, and 15%, respectively, for the 3 patients. Comparing the strain from FE models with the CT scans revealed an average difference in strain of 1.55% for the segmented models and 3.61% for the homogeneous models, which suggests that the segmented models more accurately reflect in vivo behavior. RPRI values were calculated for each segment for all patients.

Conclusion: A greater understanding of the local material properties and their use in FE models is essential for greater accuracy in rupture prediction. Quantifying the regional behavior will yield insight into the changes in patient-specific aneurysms and increase understanding about the progression of aneurysmal disease.

Key words: abdominal aortic aneurysm, aneurysm sac, stress, strain, wall strength, computed tomography, finite element analysis, rupture prediction, biomechanical material properties, elasticity
The decision to intervene in a patient with abdominal aortic aneurysm (AAA) is based on the maximum diameter of the aneurysm, which is currently $\geq 5.5\text{ cm}$.\cite{1} This threshold represents the point at which the risk of rupture exceeds the perioperative mortality of open surgery.\cite{1} The major argument against this “one size fits all” criterion for the threshold of rupture is that some large aneurysms do not rupture, whereas some smaller aneurysms do.\cite{2} Clearly, doubt remains over using aneurysm diameter for decision making regarding surgical intervention.\cite{3-5}

AAA rupture represents a catastrophic failure of the degenerated aortic tissue when the aneurysm wall can no longer withstand the stresses on it.\cite{6} Understanding the stress distribution in the aneurysm, along with its material properties, is an essential step toward predicting the rupture of an AAA.\cite{6-9} Various other AAA rupture predictors in addition to wall stress have been investigated in recent years, including wall strength,\cite{10,11} combinations of stress and strength,\cite{12,13} acoustic radiation force impulse imaging displacement,\cite{14} asymmetry,\cite{15} presence/growth of thrombus,\cite{16,17} and weighted biomechanical factors.\cite{18} Many of these assessment techniques have involved finite element (FE) models as a basis for rupture prediction. FE analysis is a computer-based method of solving complex structural problems for which the stress distribution can be easily studied. In analyzing AAA behavior with FE models, realistic aortic anatomies with patient-specific physiological and mechanical properties have been used in recent years.\cite{6,9-11} Data for these anatomies have typically come from computed tomography (CT) scans. At present, 3-dimensional (3D) reconstruction software and dynamic imaging with electrocardiogram (ECG)-gated CT or magnetic resonance imaging (MRI) have added new possibilities to the investigation of aortic deformation and expansion throughout the cardiac cycle.\cite{19-23} Despite these advances in imaging and the knowledge that regional variations in mechanical properties exist in vivo,\cite{7,8} it has been common to apply homogeneous properties to the idealized or physiological geometries in these FE models.\cite{23-25} We believe that knowledge of the AAA regional properties can help provide greater insight into AAA rupture behavior and lead to more accurate methods of predicting rupture risk.

One of the shortcomings of many stress analyses involving patient-specific vascular structures is the common assumption that the reconstructed in vivo configuration is stress free, although the structures are in a prestressed state (i.e., there is pre-existing tensile stress). Many investigators have addressed the importance of removing this assumption of a stress-free configuration from CT scans.\cite{12,13,26-32} We submit that this assumption can be obviated using an approach that also takes into account the patient-specific blood pressure, thus increasing the accuracy of patient-specific stress estimates.

The purpose of this study was to examine the use of regional variations in mechanical properties in FE reconstruction to assist in the assessment of AAA rupture risk. This study utilized patient-specific local properties and strain data obtained from ECG-gated CT scans and related them to the local strength to determine the risk of rupture. The approach may be clinically useful in improving AAA diagnostic methods.

**METHODS**

**CT Data Acquisition**

Scans from 3 male patients (ages 81, 79, and 78 years) with known infrarenal AAA were obtained from colleagues at the University Hospital Heidelberg, Germany. The scans were acquired using a 4-detector row CT system (SOMATOM Volume Zoom; Siemens Medical Solutions, Erlangen, Germany) and a standardized protocol for ECG gating at 2 surgically relevant locations: above the infrarenal aorta and at the level of maximum aneurysm diameter (Fig. 1A). An automatic pneumatic sphygmomanometer (Maglifeme C; Schiller, Wissensbourg, France) with a measurement accuracy of 2% was used to record blood pressure during the scans. The recorded blood pressures were 115/30 mmHg for patient 1, 160/95 for patient 2, and 133/81 for patient 3, respectively.

The DICOM image of each scan was imported into commercial software (Mimics version 12.0; Materialise Ltd., Leuven, Belgium). A
Thresholding technique was applied to the grayscale DICOM image to calculate the area of the aorta. A best fit curve was applied to the boundary of the wall area and exported to Matlab r2009a (Mathworks, Natick, MA, USA) as a 2-dimensional series of points that could be summed to calculate the circumference. Inasmuch as both strain and pressure peak occur nearly simultaneously in the cardiac cycle, all measurements were made at peak systole and end diastole. The time series with maximum area was referred to as systole and minimal area as diastole (Fig. 1B). Each aortic image (Fig. 2) was sectioned into quadrants: anterior (A), posterior (P), right lateral (RL), and left lateral (LL). The circumferential lengths of these segments were tracked from diastole to systole using local anatomical markers (Fig. 3A), such as calcifications in the wall, intraluminal thrombus (ILT), etc.

Elasticity Quantification

The elastic properties of the aortic wall were characterized at the healthy neck and the maximum diameter using the following equations applied to the entire aneurysm and to the 4 individual segments for each of the 3 patients. Circumferential cyclic strain:

\[ E_{\text{circ}} = \frac{1}{2} \left[ \frac{L_s^2}{L_d^2} - 1 \right] \]  

Compliance:

\[ C = \frac{(\Delta L)}{|L_s(\Delta P)|} \]  

Hudetz incremental modulus:

\[ H_{\text{in}} = 2 \left[ \frac{d_{\text{out}} \times d_{\text{in}}^2}{\Delta d_{\text{out}} / \Delta P} + (P \times d_{\text{out}}^2) \right] \times \left[ \frac{1}{d_{\text{out}}^2 - d_{\text{in}}^2} \right] \]  

where \( L_s \) is the segment length at systole, \( L_d \) is the segment length at diastole, \( \Delta L = L_s - L_d \).
D
P
5
P
s
–P
d
(variables are shown in Figure 3B).

Biomechanical Material Properties

The circumferential cyclic strain and the modulus calculated from the CTs were used in conjunction with Raghavan and Vorp’s average aneurysm behavior (Fig. 4) to generate a stress-strain relationship for each segment (Fig. 4A X–Y) and the entire aneurysm. The position of the regional behavior on the graph gave an indication of the prestress in the segment based on the strain and modulus calculations (Fig. 4A). The prestress was subtracted from the segmental stress-strain behavior (Fig. 4B) from X to Q. Q–Z represents the stress-strain behavior of the segment, which has been transposed to the origin. The points at X and Y are known from the tissue deformation and strain calculated in vivo. The intermediary behavior between these points is then defined by the average behavior.

\[ \Delta P = P_s - P_d \] (variables are shown in Figure 3B).

Figure 4

(A) Behaviors of 2 quadrants equated to average behavior.\(^{41}\) (B) Subtracting the prestress from the local quadrant behavior to derive a constitutive model. X–Y is the original stress-strain configuration of the segment. Q–Z is the stress-strain configuration when the stress-strain curve is returned to 00, and the prestress is removed. The points at X and Y are known from the tissue deformation and strain calculated in vivo. The intermediary behavior between these points is then defined by the average behavior.\(^{41}\)

A finite strain constitutive model was determined for the local segments and the entire aneurysm at maximum diameter for each patient. Various SEFs were examined including Marlow, Mooney-Rivlin, Ogden, and Neo-Hookean. The most applicable SEF for the wall segment stress-strain data derived from Figure 4 proved to be a reduced polynomial SEF, as it provided a good curve fit for all the data (\(r^2 > 0.999\)) and was also stable at all stresses and strains. These properties at maximum diameter were applied to a general realistic FE model using Abaqus (version 6.9.1;
Dassault Systèmes Simulia Corp., Providence, RI, USA). The FE analysis produced a detailed stress pattern on each of the aneurysm models under pressure loading. The peak stress results in each segment could be used to examine the risk of rupture in this segment based on the local properties. The effect of using segmental properties compared to homogeneous properties from the entire aneurysm was also examined.

**FE Analysis**

Using a method previously validated by our research group, a 3D reconstruction was generated from the CT scan of a 79-year-old man using Mimics (version 12.0) and Pro-Engineer Wildfire 4.0 software (Parametric Technology Corp, Meddham, MA, USA); the reconstruction was imported into Abaqus software for stress analysis. To save resources, the same 3D geometry (Fig. 5) was used in conjunction with the elastic and biomechanical material properties of each patient. Using a single geometry for each of the 3 patients was justified because the study evaluated how material properties influence the method of modeling and to demonstrate the importance of more realistic material property for prediction methods. It was not intended to actually model risk for any particular patient.

The model imported into Abaqus was segmented into 4 sections (Figure 2 shows the orientation of the segmented areas) using the partition tool. The anterior segment was easily identified by the bulge of the aneurysm sac due to the asymmetrical expansion caused primarily by the proximity to the spinal column posteriorly. This allowed local patient properties to be applied to each section based on the deformations measured from the patients’ ECG-gated CT data.

As with previous research, all models in this study omitted the iliac arteries. As the model was predominantly aneurysmal, only the properties measured at maximum diameter were used. To simulate the connection of the AAA segment to the descending aorta and the iliac bifurcation, the model was fully constrained in the proximal and distal directions. The blood pressure within the AAA acts on the sac’s inner wall; therefore, patient-specific pressures were applied to the inner surface of the computational AAA model. Aortic tissue is also known to be nearly incompressible, with a Poisson’s ratio of ~0.49.

The geometry reconstructed was at diastolic pressure; therefore, the patient-specific pressure applied was the difference between systolic and diastolic pressures recorded from the patient during the CT scan. As in previous rupture prediction methods, the anisotropy in material properties was not taken into account. The shear stress induced by blood flow was neglected in this study, although the effects of blood flow have been shown to reduce wall stress in idealized AAA models.

Once the AAA was imported into the FE software, an FE mesh was generated on the AAA model. Because wall thickness cannot be fully determined from scan data, a uniform 2-mm thickness was applied to the model based on population mean values obtained from an experimental study of excised AAA wall tissue specimens. Mesh independence was performed by increasing the number of elements in the mesh until the difference in peak von Mises stress was <2% of the result computed with the previous mesh.

**Prestress Inclusion in FE Analysis**

Unrelated to the patient-specific properties study, an investigative model was studied to establish the need to include prestress. Despite the fact that there are prestresses
present in the aneurysm at the moment of image acquisition, it has not been widely taken into account in previous FE studies. Commonly used nonlinear material properties in AAA modeling have been taken from Raghavan and Vorp's SEF. The materials were assumed to be incompressible and hyperelastic; therefore, the strain energy functions took the form:

$$ W = \sum_{i=1}^{N} C_{i0}(I_1 - 3)^i $$

where $I_1$ is the first invariant and $C$ is the material constant.

To justify the inclusion of prestress in FE modeling studies, SEFs were developed from commonly used properties ($C_{10} = 0.174, C_{20} = 1.881$), which were pressurized to 120 mmHg, as is typical for many studies, while the prestress models were pressurized to 40 mmHg, reflecting the difference between systolic and diastolic values in a “normal” patient with 120/80 mmHg blood pressure. Therefore, the prestress accounted for pressure <80 mmHg, so the model required only an additional 40 mmHg to bring it to maximum pressure. The newly developed SEFs applied a 5%, 10%, 15%, 20%, and 25% prestress to the properties (Table 1). After application of these properties to an FE model, the peak and prestress were summed to calculate the total stress on the aneurysm wall and determine the importance of inclusion of this prestress in the calculations. The total stress recorded using the traditional properties was compared to the total stress recorded when prestress was included. The total pressure results were then examined to establish the various levels of error that would be inherent when prestress was disregarded.

### Rupture Risk

The regional prestress rupture index (RPRI) was based on the engineering principle that a material will fail when the total stress acting on the wall exceeds the strength of the material. The prestress was based on the position of the segmental stress-strain curve on Raghavan and Vorp’s average behavior curve.

$$ \text{RPRI}_R = \frac{(\text{peak stress}_R + \text{prestress}_R)}{\text{wall strength}_R} $$

where “prestress” refers to the segmental prestress calculated using Figure 4 and “peak stress” to that measured from FE simulations. $R$ refers to the local mechanical property circumferential region, which can be ≥1 (dependent on the number of local regional property calculations on the aneurysm). In these experiments, the 4 local mechanical property regions of the aneurysm (posterior, anterior, left lateral, and right lateral) were directly compared to a single mechanical property, which represented the complete aneurysm surface. The peak stress was taken from a simulation of patient-specific pressure applied to the geometry, and the wall strengths were derived from experimental uniaxial testing of 149 AAA tissue specimens. These wall strengths had been combined and averaged (anterior: 0.7744 MPa, posterior: 0.8658 MPa, left lateral: 0.9221 MPa, right lateral: 0.9187 MPa) in a previous study to collate the specific region strength. Equation 5 returns a numerical value, where 0 indicates a very low rupture risk and larger ratios represent a greater rupture risk.

### TABLE 1

<table>
<thead>
<tr>
<th>Prestress</th>
<th>0%</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
<th>25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficients, MPa</td>
<td>$C_{10} = 0.174$</td>
<td>$C_{10} = 0.161$</td>
<td>$C_{10} = 0.320$</td>
<td>$C_{10} = 0.615$</td>
<td>$C_{10} = 0.871$</td>
<td>$C_{10} = 0.03$</td>
</tr>
<tr>
<td></td>
<td>$C_{20} = 1.881$</td>
<td>$C_{20} = 2.837$</td>
<td>$C_{20} = 3.057$</td>
<td>$C_{20} = 3.417$</td>
<td>$C_{20} = 2.963$</td>
<td>$C_{20} = 0.015$</td>
</tr>
<tr>
<td></td>
<td>$C_{30} = 4.118$</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

0% is based on the traditional properties devised by Raghavan and Vorp. The coefficients were derived from Equation 4, in which $C_{i0}$ is the material constant ($1\leq i \geq n$). As this is a 2nd or 3rd order polynomial equation, there are up to 3 material constants: $C_{10}$, $C_{20}$, and $C_{30}$.
RESULTS

Elasticity Quantification

The patients’ circumferential cyclic strains for both locations are displayed in Table 2 for both the homogeneous and segmental models. Assuming the properties of the entire aneurysm are homogeneous, the average circumferential cyclic strain of the aorta decreased by 68% from the neck to the level of the maximum diameter on the model. In like fashion, the compliance values of each quadrant displayed an average decrease of 63% going from the neck to the maximum diameter of the aneurysm (Fig. 6). The incremental moduli of the aorta calculated at both the neck and maximum diameter (Fig. 7) reflected a >5-fold increase between the healthy neck and the aneurysmal aorta, as well as between local regions at the same area. In addition to the average 68% reduction in circumferential cyclic strain, 63% reduction in compliance, and large differences in incremental modulus between the healthy and aneurysmal locations, there were also regional variations in all elastic properties in each individual patient.

FE Analysis

Inclusion of prestress. In the typical wall stress analyses, the geometry obtained from a CT scan is presumed to be unstressed, but at levels of prestress up to 20% (Table 3), total stress can be significantly overestimated if prestress is neglected. As the prestress increases toward 25%, the difference changes to an underestimation in the total stress.

Patient reconstructions. The SEF coefficients for each patient, both segmental and treating the entire aneurysm as a homogeneous material, are listed in Table 4 and the contours for each patient are shown in Figure 8. There was great disparity in the magnitudes of peak stress and contours between models with homogeneous properties and the segmented properties for each patient. For example, for patient 2, the peak stress in the homogeneous model was 0.54 MPa on the anterior surface, with an elevated stress on the posterior wall of 0.45 MPa. The segmented model peak stress was 0.596 MPa on the anterior surface; an area of elevated stress of 0.489 MPa was evident on the posterior surface. The average difference in total stress in the different models after inclusion of prestress was 59%, 67%, and 15%, respectively, for the 3 patients. There was an average circumferential cyclic strain difference between the homogeneous and segmented FE models of 5.17%. Comparison of the strain from FE models with the in

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### TABLE 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Posterior</th>
<th>Left Lateral</th>
<th>Anterior</th>
<th>Right Lateral</th>
<th>Entire Aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>0.5%</td>
<td>22%</td>
<td>21%</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>1.8%</td>
<td>1.7%</td>
<td>1.8%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Neck</td>
<td>7.4%</td>
<td>20.9%</td>
<td>19.4%</td>
<td>6.9%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>5.0%</td>
<td>10%</td>
<td>11%</td>
<td>5.2%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Neck</td>
<td>20%</td>
<td>11.2%</td>
<td>11.9%</td>
<td>31.9%</td>
<td>17.3%</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>5.6%</td>
<td>1.1%</td>
<td>4.6%</td>
<td>0.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Average</td>
<td>Neck</td>
<td>9.3%</td>
<td>18.4%</td>
<td>17.8%</td>
<td>15.1%</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>4.2%</td>
<td>4.5%</td>
<td>6.1%</td>
<td>4.4%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

The percentage cyclic strain represents behavior between the points X and Y in Figure 4.
The RPRI values (Fig. 9) were calculated from the data on peak stresses, locations of peak stress, and corresponding prestress values for each patient using the homogeneous and segmented modeling methods. An indication of the possible rupture risk using the index based on the local material properties can be determined. Using Equation 5, an example calculation of the risk for patient 2 (79-year-old man with a 160/95 mmHg pressure), using homogeneous properties, the peak stress (0.54 MPa) in the anterior region, and a prestress value of 0.05 MPa, would return: \( \text{RPRI}_R = (0.54+0.05)/0.7744 = 0.76 \).

### DISCUSSION

Many previous studies have investigated the FE modeling of AAAs to predict rupture risk. An important aspect of any FEA study should be the inclusion of accurate material properties. These material inputs should be as similar to the patient-specific properties as possible if the results are to fully depict the state of health and behavior of the aneurysm. However, to date, to the best of our knowledge, FE investigations have not been undertaken using the regional variation of the aneurysm mechanical response. To address this, we examined the hypothesis that the inhomogeneity and regional variation of aneurysm properties should be integral to constructing FE models to assess rupture risk.

The use of multidetector CT scans to acquire patient data is a noninvasive method to extract distensibility and elasticity properties of an aneurysm as described by the circumferential cyclic strain, compliance, and incremental modulus. Our study used a novel method to relate the patient-specific elasticity properties to average behavior, generating finite strain constitutive relationships for use in FE modeling. These calculations will help to fully understand the dynamics of the aortic environment and lead to an improved understanding of the native environment.

Understanding and quantifying differences in elasticity properties during aneurysmal development is vital to gain insight into the...
pathogenesis and progression of the disease and changes in vessel wall properties. Our study demonstrated the differences in noninvasively measured elastic properties between the aneurysm site and the healthy proximal aorta. The healthy neck circumferential cyclic strain calculations (13%–17.3%) in our study agree with previously published estimates of strain in healthy human vessels (13.2%–17.8%).

There is an average decrease in segmental compliance of 64%±15% going from the more elastic neck to the diseased aneurysm bulge. Also, the increased incremental modulus values at the aneurysm site further highlight the increased stiffness due to aneurysm formation. These elasticity studies provide insight into the distension of the abdominal aorta. The wall motion and strain may explain aneurysm pathogenesis and may also have some relevance for the design of stent-grafts.

From our evaluation of the need to include prestress in modeling, we found that the effect of prestress is significant and should be considered. The use of common properties can lead to significant under- or overestimation of

### TABLE 3
Differences in Total Stress to Support Including Prestress in the Investigative Model

<table>
<thead>
<tr>
<th>Prestress</th>
<th>0%</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
<th>25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prestress based on normal curve (representing 80 mmHg), MPa</td>
<td>—</td>
<td>0.02</td>
<td>0.08</td>
<td>0.19</td>
<td>0.38</td>
<td>0.65</td>
</tr>
<tr>
<td>Stress from FE model on test material, MPa</td>
<td>—</td>
<td>0.338</td>
<td>0.308</td>
<td>0.305</td>
<td>0.318</td>
<td>0.39</td>
</tr>
<tr>
<td>Pressure applied to model, mmHg*</td>
<td>120</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Total stress prediction, MPa</td>
<td>0.99</td>
<td>0.358</td>
<td>0.388</td>
<td>0.495</td>
<td>0.698</td>
<td>1.04</td>
</tr>
<tr>
<td>Difference, %</td>
<td>−63.84</td>
<td>−60.81</td>
<td>−50.0</td>
<td>−29.5</td>
<td>5.05</td>
<td></td>
</tr>
</tbody>
</table>

0% represents the traditional properties. The 5% to 25% values of prestress from Table 1 were used to account for pressures of 0 to 80 mmHg.

* This study was not related to the patient-specific properties study.

FE: finite element.

### TABLE 4
Patient-Specific SEF Coefficients for Each Patient at Maximum Diameter From the ECG-Gated CT Scans

<table>
<thead>
<tr>
<th></th>
<th>Posterior</th>
<th>Left Lateral</th>
<th>Anterior</th>
<th>Right Lateral</th>
<th>Entire Aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=1.2117 C&lt;sub&gt;20&lt;/sub&gt;=0.5131</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=1.3266 C&lt;sub&gt;20&lt;/sub&gt;=1.5362</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=1.2117 C&lt;sub&gt;20&lt;/sub&gt;=0.5131</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=0.4241 C&lt;sub&gt;20&lt;/sub&gt;=3.2789</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=0.8393</td>
</tr>
<tr>
<td>Patient 2</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=0.3793 C&lt;sub&gt;20&lt;/sub&gt;=8.5193</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=0.1758 C&lt;sub&gt;20&lt;/sub&gt;=6.9218</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=0.1758 C&lt;sub&gt;20&lt;/sub&gt;=6.9218</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=0.3793 C&lt;sub&gt;20&lt;/sub&gt;=8.5193</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=0.2120</td>
</tr>
<tr>
<td>Patient 3</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=0.4656 C&lt;sub&gt;20&lt;/sub&gt;=4.0749</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=1.5920 C&lt;sub&gt;20&lt;/sub&gt;=4.1887</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=0.5302 C&lt;sub&gt;20&lt;/sub&gt;=4.0749</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=1.4884 C&lt;sub&gt;20&lt;/sub&gt;=4.0749</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;=0.6540</td>
</tr>
</tbody>
</table>
stress, which could have an implication for patient care and diagnostic decisions. Several previous studies have also proposed various methods to correct for the inclusion of the prestress present during data acquisition. All studies recommended including prestress in future FE analyses because it improves wall displacement accuracy.

The location of absolute peak stress at the inflection point was similar on both homogeneous and segmented models, as noted in other studies, although the magnitudes of peak stress and contours differed markedly between models with homogeneous properties and the segmented properties for each patient. On its own, the peak stress acting on the wall does not give a true indication of the rupture risk; it should be coupled with the local material properties. The local regional material property measurements may be more realistic and may give a better estimation of behavior than using homogeneous properties. For example, in the 79-year-old patient 2, the peak stress acted on the anterior wall, but there was elevated stress acting on the posterior wall. However, due to local wall properties, the peak stress location was determined to have a lower risk of rupture. From the 3 cases examined, all AAAs experienced peak wall stress on the anterior surface, with elevated stress on the posterior surface. Relating these high stress areas to the regional properties identified the region that has the highest ratio of total stress to strength.

In contrast to previous research that applied the “conventional” 120-mmHg blood pressure to the configuration, our study
applied a lower patient-specific pressure that reflected the pressure acting on the aneurysm. Using an elevated pressure may increase the stresses and result in false values of peak stress, which could lead to inaccurate risk results. Also, higher pressures are associated with larger deformation of the aneurysm due in part to the pressure and also to the material properties applied starting at a no load condition (low stiffness). In contrast, our modeling method accounted for the prestress on the tissue. Since the pressure was also significantly lower, this resulted in lower overall deformation, which in turn can affect stress.

Previous studies have evaluated rupture potential indices\cite{10,11,51} similar to the RPRI we studied here. Both indices use the fundamental principle that a material will fail when the total stress acting on the wall exceeds the strength of the material. The principle is based on the hypothesis that, under no load, elastin and smooth muscle cells (SMC) are connected, such that elastin sheaths and fibers are prestressed. The exact 3D configuration of the links between SMC and elastin is not exactly known; however, a section of the artery that is under a high level of prestress can only undergo a certain level of stress until rupture. Other researchers have presented several methods that use static CT data in FE analysis to aid decision making.\cite{10,11,25,44,45,52} However, if these methods are to be used to their full potential and relied upon, the most accurate material properties to characterize normal aortic motion during the cardiac cycle must be used. Our technique incorporates regional mechanical properties and initial stress in the artery in FE methods to aid clinical decision making. It takes into account patient-specific regional properties to convert the regional stress to a specific regional rupture risk, which represents a departure from the “one size fits all” criterion currently in use. To justify this new approach, the resources for incorporating gated CTs into current scanning protocols and the additional computational work would have to be weighed against the benefits of an improved FE analysis.

**Limitations**

At the time of the CT scans were acquired, they were taken only at the neck and maximum diameter of the abdominal aorta; the full geometry was not acquired. Therefore, we could not apply the patient mechanical properties to their own geometries, so we applied each patient’s mechanical properties to a single AAA geometry. Had 3 geometries been used, it would have been difficult to
extract conclusive evidence on the use of regional properties. A more comprehensive study would involve using patient-specific properties in conjunction with the patient-specific geometry to address the significance of the geometry.

We did not include the ILT component in our simulations, but there was <8% difference (average 6.2%) between all compliance calculations, suggesting that the wall properties taken from the CT scans included the effects of ILT on deformation. There are differing opinions in the literature about the importance of ILT in rupture assessment. The studies made by Vorp et al. indicated that the presence of ILT reduces AAA wall strength. Adolph et al. claimed that ILT can play an active role in AAA pathogenesis due to inflammatory infiltration cells (macrophages and neutrophils). Stenbaek et al. showed that increasing thrombus surface area increases aneurysm rupture risk, particularly when the increase amounts to $\geq 15 \text{ mm}^2$ per year. Wolf et al. found that an increase in ILT volume was connected with the growth of the aneurysm. In contrast, Schurink et al. demonstrated that the presence of ILT does not cause any reduction in the arterial blood pressure acting on the wall, so it did not play any significant role. On the basis of comparative studies of groups of ruptured and unruptured AAAs, Hans et al. did not find statistically significant differences in the ILT to total aneurysm volume ratio between the studied groups. In their opinion, this finding disproves the usefulness of ILT for the assessment of AAA rupture probability.

This study measured motion in the transverse plane and did not address the out-of-plane motion of the aorta. Aortic motion is generally 3D, but because of the relatively small motion of the aortic wall, it is reasonable to assume that out-of-plane motion is highly limited, so the motion can be extracted from 2D image sequences. The in-plane motion of the aorta is typically $<1 \text{ mm}$ per frame. It is physiologically reasonable to expect the out-of-plane motion to be even smaller than the motion in the transverse plane, so it can be neglected.

The entire circumference of the aneurysm was sectioned into 4 segments, which were each given its individual properties. There was an abrupt transition between certain segments; although this did not present any problems for this study, it may be more accurately modeled if treated as a gradient between the segments. Published results have shown that wall thickness varies regionally and between AAAs from as low as 0.23 mm at a rupture site to 4.26 mm at a calcified site. Scotti et al. reported that an asymmetrical AAA with regional variations in wall thickness would be exposed to higher mechanical stresses and an increased risk of rupture than a more fusiform AAA with uniform wall thickness. It is difficult to accurately assess this dimension in patient-specific CT images due to calcification, thrombus, and the lack of clear image definition between the inner and outer wall surfaces. Therefore, a uniform thickness of 2 mm is typically assumed when modeling individual AAAs.

The average properties taken from RagHAVAN and Vorp, although based on 69 samples, only used uniaxial properties; biaxial data would also be necessary. The use of anisotropic properties in the material properties would yield greater accuracies in the wall stress analysis, which could lead to a more accurate rupture index. Longitudinal deformations and longitudinal strain were not taken into account for any of the computational reconstructions; previous studies have shown longitudinal strain to be in the order of 2%, which is negligible and justifies this approach. Notably, we are not facing a pure deformation problem since continuous remodeling processes are taking place in living tissue. These remodeling effects were not taken into account. The model assumed the prestress was uniform through the individual segment in the segmented model or uniform throughout in the case of the single property model.

There are conflicting opinions on the role of calcifications in AAA behavior. They may diminish tissue strength, which increases the rupture risk at those sites. Using FE simulations, Maier et al. found that calcifications exhibit significant load-bearing effects and reduce stress in the adjacent vessel wall by 9.7% to 59.2%. These calcifications are visible in CT scans, and this information could be
considered in an FE model by assigning constitutive properties for calcified tissue to finite elements representing calcified regions. The reliability, however, of such an approach would heavily depend on the quality of constitutive information, as it would be extracted from in vitro experiments of the calcified aneurysm wall.

Conclusion

We have reported the regional mechanical properties in healthy aorta, with no visible signs of aortic pathology, and at the visibly distended aneurysmal bulge. This analysis contributes to the understanding and quantification of the local regional properties in the healthy and diseased aorta. Quantifying the regional behavior will yield insight into the changes in patient-specific aneurysms and increase understanding about the progression of aneurysm disease. Ultimately, identifying the local areas of the aneurysm that have high prestress could indicate higher degradation of elastin in these regions, which may leave them susceptible to rupture. A greater understanding of the local material properties and their use in FE models is essential for greater accuracy in rupture prediction. The incorporation of additional patient-specific parameters into the FE modeling criteria may reduce the uncertainty associated with rupture prediction.

Acknowledgments: The authors wish to acknowledge Drs. Marika Ganten and Stefan Delorme, Department of Radiology, Heidelberg, Germany, for providing the CT scans.

REFERENCES


APPENDIX D
D – CONFERENCE PUBLICATIONS


