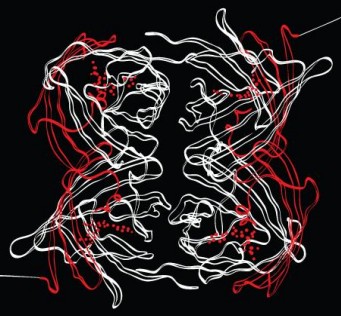

MASTER THESIS:

TOWARDS PATIENT SPECIFIC BIOMECHANICAL INDICES FOR ABDOMINAL AORTIC ANEURYSM RUPTURE RISK ASSESSMENT

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Technical Medicine

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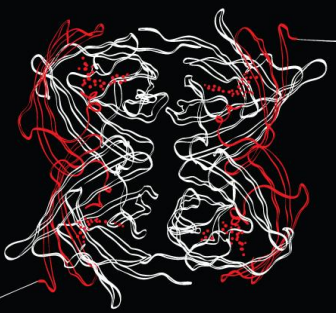

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Master Thesis: Towards Patient Specific Biomechanical Indices for Abdominal Aortic Aneurysm Rupture Risk Assessment

PREFACE

About one year ago I started this project full of enthusiasm and with many ideas. The evolving aneurysms from physiological and pathological perspectives along with the physical perspective have definitely interested me: 'Magical' forces (or just blood flow) interact with human nature to a tipping point (i.e. the rupture). I worked with cool technologies to optimize diagnosis, risk assessment and treatment. This research and its interpretation surely gave me much to reflect on.

This year has not been easy. Besides the set-backs and challenges during the research, the passing of my partner's brother gave us the most difficult challenge ever. However, somehow I managed finalizing this thesis. During this year I have learned and experienced much, not only about aneurysms but also about life. Both lessons I will remember.

This thesis marks the completion of my master Technical Medicine: Imaging and Intervention. It wasn't possible without the help of my supportive supervisors, prof. C.J.A. M. Zeebregts, dr. T.P.Willems, prof. dr. ir. C. H. Slump and drs. N.S. Cramer Bornemann. Hereby, I would like to thank them for their guidance, ideas and contributions. I would also like to thank J.K. Visscher for his enthusiastic support during the elastography experiments. Sometimes I really felt the 'nerdy technologist' surrounded by physicians but this combination continuously inspired and I very much appreciate that those physicians taught me all the necessary clinical ins and outs. I would also like to thank my partner Tim for his support, ideas and warm hugs. At last, thanks to you, reader, for your interest in my research.

CONTENTS

SUMMARY

Rupture of an abdominal aortic aneurysm (AAA) is well known for its high mortality rate. Prevention of growth and rupture is the primary treatment goal. Options consist of surveillance, pharmacologic administration, life style management, and surgery. The latter, more invasive open or endovascular repair is considered with high estimated rupture risk.

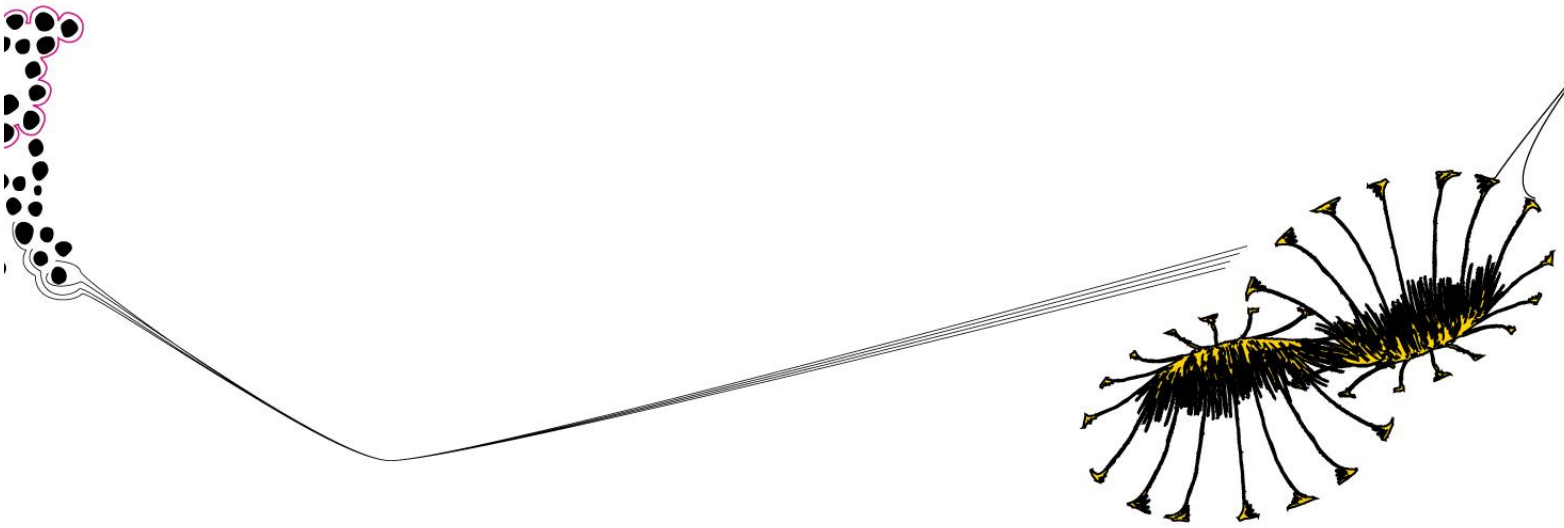
Currently only the maximum AAA diameter is validated as clinically relevant rupture risk predictor. In general, small and slowly expanding aneurysms are less likely to rupture. However, this estimated rupture risk is based on large trials and therefore not patient-specific, resulting in unnecessary treatment or death. Therefore new patient-specific diagnostic indices must be found. These indices should be able to predict when an aneurysm ruptures and when to treat this specific patient.

To develop such indices several patient specific measures based on biomechanical criteria are introduced. Biomechanical criteria describe the basic principles of material failure: an aneurysm ruptures when mural stresses exceed wall strength. This study first aimed to evaluate the feasibility of biomechanical modelling to predict AAA rupture and, second, to clarify the additional clinical role of biomechanical indices based on diagnostic imaging in the rupture risk assessment of AAA patients compared to the maximum diameter.

This study showed that biomechanical analysis supports a patient specific, individualized AAA rupture risk assessment. However, no clear improvements in risk assessment compared to the maximum AAA diameter are seen. Nevertheless, combination of the maximum AAA diameter and biomechanical indices will likely give a full overview of the patient's specific risk, especially in small to medium sized aneurysms.

In conclusion, although challenges remain, biomechanical analysis is promising in the assessment of AAA rupture risk as it incorporates the major factors, such as geometries, tissue properties and patient specific risks.

PART 1: INTRODUCTION



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1 BACKGROUND

This section focuses on the medical background of my thesis. It starts with the definition of abdominal aortic aneurysms. Subsequently the histology, pathology epidemiology and current treatment options are discussed.

1.1 Definition

An aneurysm is a localized bulge of the vessel wall. Aneurysms are classified by their location in the vessel system and their shape (fusiform (involves the total circumference) or saccular (involves a part of the circumference)). Most frequently the infrarenal abdominal aorta is involved. An aneurysm in this region is called abdominal aortic aneurysm (AAA).

The general definition for an aneurysm is “Permanent localized artery dilation with at least a 50% increase in diameter compared to the normal diameter of the artery in question”.[1] Therefore, knowledge of the normal vessel diameter is important. For the abdominal aorta this diameter is 20mm which slightly changes with gender, age and body surface area. For instance, women have smaller aortic dimensions in all segments compared to men.[2] However, most guidelines define an abdominal aortic diameter above 30mm as an AAA in both men and women.[1,3,4]

1.2 The normal arterial wall

Arteries consist of three layers (see Figure 1): the tunica intima, media and adventitia.[5] The tunica intima, the innermost layer, is in contact with the vessel lumen. This layer consists of a single layer of endothelium and a sub endothelial layer of connective tissue. The central layer or tunica media is the thickest layer and consists of smooth muscle cells secreting elastin to form the internal and external elastic membrane. The outermost layer is known as the tunica adventitia or t. externa. The layer mostly consists of collagen fibres but also contains some elastic fibres, fibroblasts and macrophages. During systole the collagen prevents the artery from stretching beyond the physiological limits. The adventitia also contains small vessels, vasa vasorum, supplying the adventitia and outer media.

The composition of the arterial wall differs between arteries. The aorta is an elastic artery, where elastic fibres dominate the smooth muscle cells in the tunica media. This vessel is able to stretch in response to each heart beat and hereby maintain a relatively constant blood pressure.

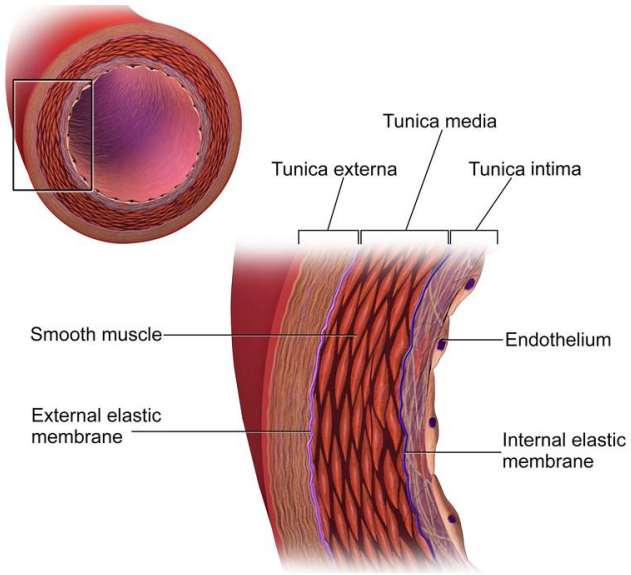

FIGURE 1. THE NORMAL ARTERIAL WALL.

1.3 Pathogenesis

Patients with AAA often also experience other artery related problems, such as peripheral occlusive artery disease due to atherosclerosis. The risk profiles of both diseases are similar.[6] In both diseases inflammation plays a major role. However, atherosclerosis affects the intima resulting in occlusive vessel disease, whereas aneurysms mainly involve the media and adventitia of the vessel wall. Aneurysm development and progression is an ongoing disease process. The pathogenesis is complex and still not fully understood. Histopathological analysis clearly shows transmural infiltration of lymfocytes and macrophages, loss of smooth muscle cells and elastin and collagen degradation.[7] Thus three key processes likely contribute to the pathogenesis: inflammation, smooth muscle cell apoptosis and destruction of the extracellular matrix.

The trigger for this inflammation and subsequently infiltration by macrophages and lymfocytes is unclear. Activated macrophages secrete cytokines leading to the matrix metalloproteinase (MMP) secretion by smooth muscle cells. These MMPs and other proteolytic enzymes degrade elastin and collagen in the extracellular matrix. Hereby, the vessel wall weakens and this is crucial in the formation of AAA. In addition, the smooth muscle cells thinning and apoptosis occur. To conclude a combinations of poorly known factors activate a complex immunologic mechanism. This results in inflammatory cell activation, chemokines and cytokines release and MMPs and protease activation. Consequently the aortic wall strength decreases, an aneurysms occurs and rupture risk increases.

1.4 Epidemiology, prevalence and risk factors

Each year approximately 50.000 patients worldwide are diagnosed with AAA.[4] With aging an increasing amount of people develop an AAA. Prevalence rates are 1.3-8.9% and 1.0-2.2% for men and women respectively.[8] Several risk factors are associated with the development of AAA: smoking, hypertension, hyperlipidemia, a positive family history and ethnics.[1,7–9]

1.5 Intervention

Most aneurysms are found incidentally during physical examination or radiological imaging.[8] Some cases present pain in the hypogastria or lower back. However, most cases are asymptomatic until rupture occurs, resulting in a sudden onset of abdominal pain, the presence of a pulsatile abdominal mass, shock and death.[8]

The primary treatment goal is prevention of growth and rupture, starting with (yearly) surveillance through diagnostic imaging, pharmacologic administration[10] and life style management.[11] Pharmacologic administration consists of antiplatelet therapy, statin treatment, beta-blockers or ACE inhibitors to minimize the risk profile of cardiovascular diseases. Life style management also focuses on reducing the risk profile by advising smoking cessation and exercise.

Surgical repair is considered with higher estimated rupture risks.[12] This repair can be done during an open or an endovascular procedure. Both procedures are expensive and risky. However, the endovascular procedure has lower operative mortality but no differences were seen in long

survival.[13] Procedure selection is therefore based on aneurysm morphology, vessel tortuosity and physician experience.

1.6 Decision to treat

Once a rupture occurs, the success rate of surgery is much lower compared to elective surgery. Elective surgery always comes with a risk. Therefore, the risk of repair must be balanced against the risk of rupture. This decision is based on three main factors:

- Rupture risk and development of symptoms
- Surgical risk
- Expectations patient (life expectancy, quality of life)

1.6.1 Rupture risk

The risk of rupture is estimated based on diagnostic imaging. Analysis of these images results in indices such as the maximum diameter, volume and growth rate. The maximum aneurysm diameter is currently the mostly used predictor of rupture. In general small aneurysms are less likely to rupture (see Table 1). This risk assessment is based on several follow up studies in patients not planned for intervention or patients who refused intervention.[14,15] Therefore smaller aneurysms are kept under surveillance. A diameter of 55mm is generally considered as an indication for elective repair. In addition, women have a much higher rupture risk than men, even with smaller diameters.[16] Therefore the threshold for repair of 50 mm in women is used.

Aneurysms slowly grow until a rupture occurs. Growth rates are therefore associated with the rupture risks: larger expansion rates are more likely to rupture. Average annual expansion rates are between 2 to 4mm per year.[17,18] However, these rates vary substantially as several conditions influence the growth rate, such as diameter, smoking, age and gender.[17–19]

In symptomatic patients, often presenting with back or abdominal pain, treatment is more urgent as their symptoms may indicate rupture. Furthermore an increased rupture risk is seen in symptomatic patient.[20] Outcomes in ruptured cases are significantly worse. Stable cases should undergo computer tomography angiography (CTa) to immediately assess treatment possibilities.

TABLE 1. ANNUAL ESTIMATED RUPTURE RISK BY DIAMETER

Diameter (mm)	***Rupture risk (%)***
30-39	0
40-49	1
50-59	1-11
60-69	10-22
>70	30-33

1.6.2 Surgical risk

As mentioned, aneurysms can be repaired with open or endovascular repair. The overall surgical risk depends on the patient's general state of health and increases with age. Open surgery is a major procedure, which requires general anaesthesia and several catheters for monitoring. Consequently, patients are admitted in the hospital for four to seven days. Endovascular repair uses a small incision or percutaneous entry and thus the hospital stay is shorter.

More in detail, open repair has several complications: lower extremity ischemia (1-5%), renal dysfunction (5-10%), bowel ischemia (0.6-13% and 7-27% for elective and acute repair respectively) and death (1-5%).[21] The cause of death for most patients is multisystem organ failure. Other complications, such as pneumonia, are similar to other major surgical procedures. Late complications include incisional hernia (<1%), sexual dysfunction (<10%), graft infection (<1%) and anastomotic aneurysm (<1%).[1,22]

The endovascular procedure has an overall complication rate of approximately 10%, or more specific lower extremity ischemia (<1 %), renal dysfunction (1-2%), bowel ischemia (1%) and death (1-2%).[21] The procedure uses intravenous contrast which could cause an allergic response or nephropathy. Device complications such as kinking, migration and endoleaks can occur in the long term.[23] This requires carefully monitoring and in some cases these complications require re-intervention. Several studies showed that endovascular repair is only superior to open repair in the short term.[21,24] The two to five year survival was similar in both groups. Thus the initial reduction in mortality was eliminated in the long term.

1.6.3 Expectations patient

The third factor to take into account is the (live) expectation of the patient. Some patients experience severe co-morbidities, increasing operative risk and decreasing life expectation. As AAA-repair is a preventative measure and therefore the benefits of intervention in patients with a limited life expectancy remains unsure. In these patients watchful waiting is recommended.

Most patients experience an initial dip of quality of life after surgery due to the impact on their general condition.[25] After one year the quality returned to baseline. The final decision to perform surgery lies with the patient. It is important to fully inform the patient about the possibilities and risks. Patients are informed in several ways: face-to-face, brochures and online information (websites and patient-experiences). Hereby, the patient becomes empowered with the skills and knowledge to actively participate in their health and thus to make an informed decision.

2 AIMS OF THE THESIS

2.1 Rationale

The rupture risk assessment based on the aneurysm diameter is extracted using prospective trials in large groups. This measure therefore allows for assessment of the relative rupture risk but not the individual risk for each patient. Hereby, two problems arise. First, some small aneurysms can rupture leading to death that could have been prevented. In addition other large aneurysms remain stable leading to unnecessary risky treatments and higher healthcare costs. Thus a need exists for patient specific decision-making with patient specific measures. Consequently new diagnostic measures must be found. These measures should be patient-specific and able to predict when an individual aneurysm ruptures and when to treat this specific patient.

To solve this need, several patient specific measures based on biomechanical criteria are introduced and gaining scientific popularity. These criteria are based on the general principle that an aneurysm ruptures when wall stress (i.e. force per unit area) exceeds wall strength at a single site. Several software programs are available to predict rupture of an individual AAA derived from diagnostic images. The outcomes include: peak wall stress, estimated wall strength, and estimated rupture index.

However, in daily decision making these measures are not used due to several reasons. Primary because these measures require a technical background to understand and implement correctly. Especially when compared to the diameter which is an easy, fast available, measure and has a clear threshold to treat.

2.2 Study objective

This study aims to clarify the additional clinical role of biomechanical indices based on diagnostic imaging in the rupture risk assessment of patients with AAA compared to role of the maximum diameter. In addition the feasibility of biomechanical modelling with a dedicated tool (A4research, VASCOPS, Graz Austria) to estimate the rupture risk in AAA is examined.

2.3 Research questions

The main research question addresses if biomechanical modelling could contribute to the rupture risk assessment and surgical decision making in patients with AAA? This question is further detailed in the following sub-questions:

- Do patients with ruptured or symptomatic aneurysms have significant different biomechanical indices compared to patients with asymptomatic intact aneurysms?
- Are the biomechanical indices able accurate predict rupture?
- How do biomechanical indices contribute to the surgical decision making process?
  - Is selection of a threshold to treat based on the biomechanical indices possible?

2.4 Structure of the thesis

This thesis will start with a short introduction on biomechanics of the aortic wall. Second, the contemporary literature on biomechanical indices is systematically reviewed. Subsequently biomechanical data from patients at the University Medical Centre Groningen (UMCG) is presented in Chapters 5 to 7. The thesis ends with recommendations for implementation and future research based on its main finding that biomechanical analysis is promising in the assessment of AAA rupture risks.

3 BIOMECHANCICAL BASICS

The first biomechanical studies described the aortic wall stress with the Law of Laplace[26], as displayed in Equation 1. In words, larger vessel radius (R) requires a larger wall tension (T) to withstand a given internal fluid pressure (P).

$$T = P * R \qquad \text{Equation 1}$$

However, AAA biomechanics are more complex. Raghavan et al.[27,28] showed that stresses acting on an aneurysm are not evenly distributed. More precisely, these stresses highly depend on the aneurysm's exact shape. Therefore, the Law of Laplace, which is strictly only valid for perfect cylindrical tubes, cannot be used. To solve this problem some basic concepts are used. When a spring is stretched a certain force (F) is needed to extend it over a certain distance (∆L) (see Equation 2). The exact force needed depends on the stiffness (k) or compliance of the string.

$$F = k\,\Delta L \qquad \text{Equation 2}$$

For vessels a similar principle is applicable. A piece of material (e.g. the continuum body) stretches when a stress (force per area (F/A)) is applied. The amount of stretch, called strain ($\frac{\Delta L}{L}$), depends on the stiffness of the material (E), equation 3. This stiffness characteristic E is called the Young's modulus.

$$\frac{F}{A} = E\,\frac{\Delta L}{L} \qquad \text{Equation 3}$$

This equation can be simplified were σ is the stress, and ε the strain, see Equation 4.Stress is usually reported in MPa (= 1 N mm^{-2}) or N cm^{-2}.

$$\sigma = E\varepsilon \qquad \text{Equation 4}$$

However, blood vessels are submitted to multiaxial loading; simultaneous loads along three directions ($\sigma_x, \sigma_y, \sigma_z$; longitudinal, circumferential and radial; see Figure 2). Therefore three directions of tensile stress and six directions of shear act on a blood vessel. Von Mises[29] devised a single scalar value (σ_{vm}) that determines the given loading conditions. This stress criterion combines not only the individual tensile stresses but also the shear stresses (also in three directions; see Equation 5).

$$\sigma_{vm} = \sqrt{\frac{(\sigma_x-\sigma_y)^2+(\sigma_y-\sigma_z)^2+(\sigma_x-\sigma_z)^2}{2}} \qquad \text{Equation 5}$$

However, when a material is stretched in one direction it usually shrinks in the two directions perpendicular to the stress: the Poisson's effect. Therefore, the Poisson's ratio (v) is needed to totally define the basic mechanical behaviour of a material. It is defined as the ratio of transversal strain ($\frac{t-t'}{t}$ or $\frac{h-h'}{h}$) to the strain along the stretched direction ($\frac{\Delta L}{L}$) (Equation 6).

$$v = \frac{\frac{t-t'}{t}}{\Delta L/L} = \frac{\frac{h-h'}{h}}{\Delta L/L}$$ Equation 6

Biomechanical analysis incorporates these basic principles into large computational models to extract wall stress and strain of the complex AAA geometry. Chapter 4 will further elaborate on the clinical use of biomechanical analysis. However, the exact mathematical background of this analysis is beyond the scope of this thesis.

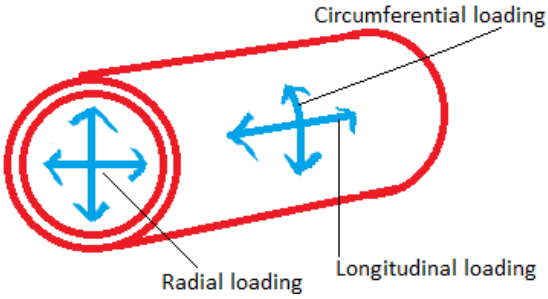

FIGURE 2. STRESS DIRECTIONS IN A VESSEL

4 SYSTEMATIC REVIEW AND META-ANALYSIS

Rupture of an AAA is well known for its high mortality rate. Currently only the aneurysm diameter is validated as clinically relevant risk factor for AAA rupture. However, biomechanical analysis of AAA is gaining popularity, but their clinical applicability and the additional value of these indices in surgical decision making (for instance wall stress (PWS), peak wall rupture index (PWRI) and rupture risk equivalent diameter (RRED)) compared to the maximum aneurysm diameter is unsure. This chapter reviews the current literature on biomechanical indices for the estimation of AAA rupture risk. First, an overview is given, emphasizing the use of model inputs. Second, a meta-analysis is done to combine the results from studies that measured biomechanics in patients with asymptomatic, symptomatic or ruptured AAAs. Hereby, the current evidence supporting biomechanics in a clinical setting is reviewed.

4.1 Methods

4.1.1 Literature search

A search strategy was devised according to the 2009 Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) Statement.[30] The Medline and Scopus databases were searched on the 7th of June 2015. To identify all relevant studies the following search terms were used: abdominal aortic aneurysm (AAA), biomechanical analysis, peak wall stress (PWS), peak wall shear stress (PWSS) and strain. Reference lists were screened to increase the yield of relevant publications. No limitations were selected with regards to language, publication status and article type or publication year. All titles and abstracts were screened for relevance and subsequently all full texts were assessed for eligibility. The following exclusion criteria were used:

- Case reports
- In case only ex vivo methods were used
- If there is no reference to diagnostic imaging, AAA or biomechanical indices
- Studies done in thoracic or repaired aneurysms

4.1.2 Data extraction

One researcher extracted the data from the selected studies using the above criteria. The data were subsequently recorded in a tabular format. The following data were recorded: study type, aim of the study, imaging method, analysis method, analysis software, population (asymptomatic intact AAA, symptomatic AAA, ruptured AAA), smoking status, gender, blood pressure (BP), inclusion of calcification and intra luminal thrombus (ILT) and biomedical indices (diameter, PWS, PWSS, PWRI, wall stiffness, wall strain).

Methodology quality of the studies included in the quantitative analysis was assessed using the Newcastle-Ottawa tool.[31] Quality measures include description of patient characteristics and inclusion, control for aneurysm diameter, the used sample size and the reported risk factors. Quality

was scored in three categories: selection, comparability and exposure/outcome. Per category a study could get 4, 2 and 3 points respectively.

4.1.3 Statistical analysis

A statistical analysis is done to compare the outcomes of asymptomatic intact cases and symptomatic or rupture cases. Statistical analysis is done using Review Manager 5.3 (The Cochrane collaboration, the Nordic Cochrane centre, Copenhagen, Denmark). Data is reported as mean and standard deviation. Some studies represented their data as mean and standard error. These values were converted by the software to standard deviation. For each included study a separate comparison was done using a two-sample t-test. Standard mean differences (SMDs) were calculated for each study. Studies were combined using an inverse variance random-effect model to reduce the effect of heterogeneity in FEA methods on the summary statistics. The inter-study heterogeneity was assessed by means of the I^2 index. A sub-analysis evaluated the results in the diameter controlled groups.

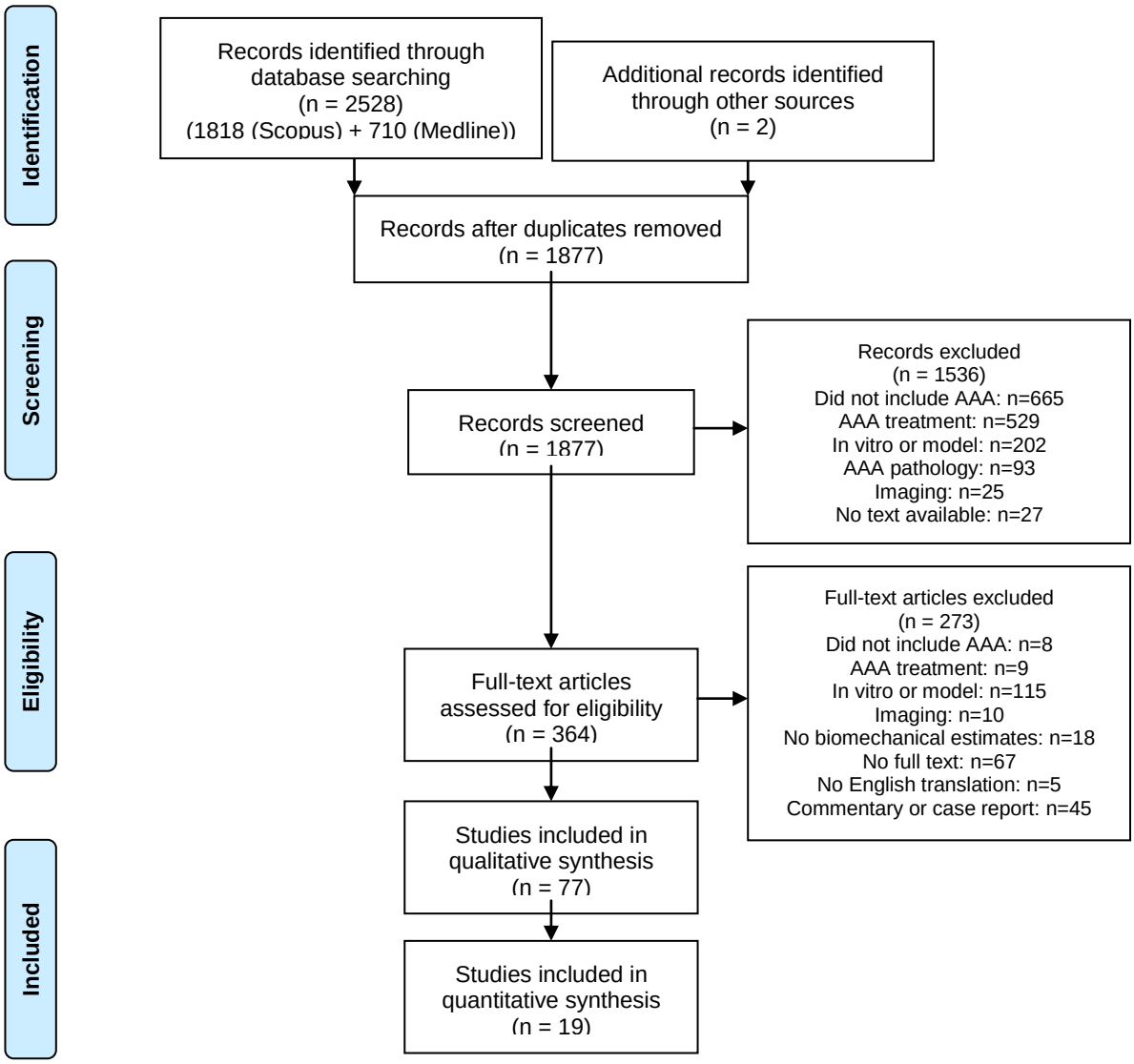

FIGURE 3. PRISMA FLOW DIAGRAM

4.2 Results

4.2.1 Study selection

The initial database searches yielded 1877 studies (see Figure 3). Most studies were excluded based on title and abstract. The main reason for exclusion was the lack of AAA or studies done regarding AAA treatment. 77 studies are included in the qualitative synthesis. Three main groups of biomechanical indices could be differentiated: PWS trough finite element analysis (FEA) (n = 46), PWSS trough computational fluid dynamics (CFD) (n = 17) and strain measurements using ultrasound (n = 14).

4.2.2 Literature on biomechanical analysis

Biomechanical analysis has two major routes: assessing mural stresses or mural strength. Wall stress is assessed using computational models, while wall strength studies examine wall movement and strain. Mural stresses are examined with two types of computational models; FEA and CFD or fluid structure interaction (FSI).[32,33] The majority of the studies use FEA, for which several software packages are available. Recently an innovative dedicated user-friendly software package (A4research, VASCOPS, Gaz, Austria) became available. FEA cuts the mathematical problem into smaller solvable equations. Subsequently the AAA geometry is divided into elements connected with nodes (the mesh). Application of the equations on the nodes results in a solvable problem.

FSI studies determine the interaction of a fluid with the surrounding; the blood flow with the arterial wall. Movement of the blood along the vessel causes a shear stress that is parallel to the wall. This stress results in movement of the wall: a local deformation or rigid body motion. The arterial blood flow is unique as the pulse propagation is governed by interaction with the elastic arterial wall, increasing the model complexity. However, the model is solved with an iterative approach but only a few studies assess AAA with FSI. This makes clinical implementation of the model difficult.

GEOMETRY

The dimensions and shape of the AAA influence the wall mechanics and the stress distribution and thus the rupture risk. Consequently, computational analysis starts with segmenting the three dimensional (3D) geometry from CT or magnetic resonance (MR) images. In addition ILT and calcifications could be segmented. Image segmentation is often semi-automatic. Manual input is required to start the segmentation and correct the automated part. The accuracy, inter-observer variability and relative volume errors of this step depends on the selected method, image contrast and spatial resolution. Several methods are available, applied in 2D (slice to slice) or 3D (surface extraction). These include: manual segmentation, thresholding, level set methods[34–36] and active shape models[37]. In addition methods can be combined to optimize results.[36] Figure 4 shows an example of such segmentation.

Based on the segmentation a digital mesh is created. The mesh reflects the geometry of interest using basis element and significantly influences the stability, quality and topology of the

computational model.[38] Tetrahedron and hexahedron elements are mostly used. A hexahedral mesh increases the complexity but has several advantages: less elements are needed resulting in faster computations and more precise stresses are calculated.[39] The current challenge in mesh development is generating high quality meshes of more complex aneurysms, extending above the renal arteries and including ILT and calcifications.

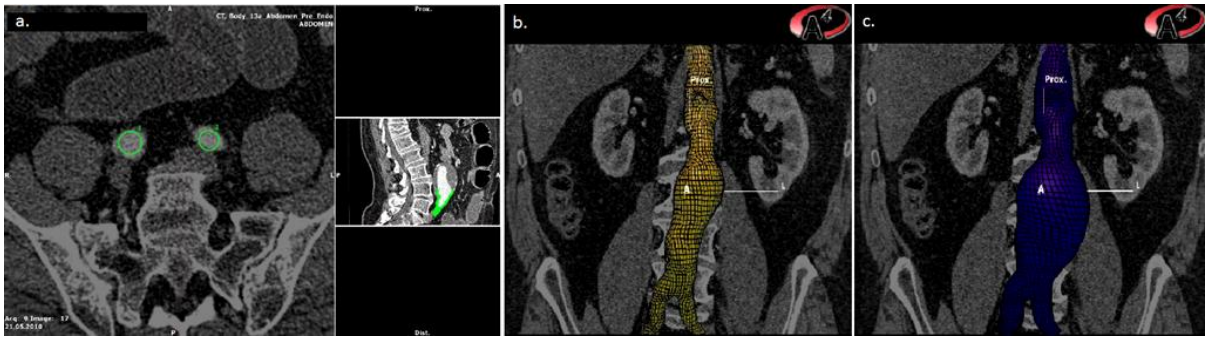

FIGURE 4. GEOMETRY RECONSTRUCTION AND MESH GENERATION BY A4RESEARCH (VASCOPS). A. INITIALISATION BY MANUALLY SELECTING THE ILIAC ARTERIES AND EVOLUTION OF THE ACTIVE SHAPE. B. LUMEN SEGMENTATION C. EXTERNAL SEGMENTATION. THE BLOCKS REPRESENT THE MESH ELEMENTS.

MATERIAL PROPERTIES

During development and progression of an AAA the tissue wall changes and this influences the tissue properties, such as stiffness, strength and, consequently, the rupture risk. To incorporate these changes into the model, mostly in vitro quantification of the AAA tensile strength is done.[40–42] In vivo modelling of the material properties often uses US speckle tracking to evaluate wall strain and compliance to differentiate between cases.[43–47] As US is mostly 2D, integration in the computational models is difficult. However new possibilities with electrocardiography-gated (ECG-gated) CT, MR or positron emission tomography (PET) arise.[48–52] These new methods create 3D maps which are easy to implement into the model. Subsequently, the measured material properties are assigned to the mesh elements.

During recent years more studies include ILT and/or calcifications in the computational model. Inclusion of ILT reduces maximum wall stress and estimated rupture risk.[53–61] In addition the ability to differentiate between ruptured and non-ruptured cases improves.[62] Higher calcification amounts showed a significant lower expansion rate in small AAA in men[63] as calcifications showed to decrease the compliance and elasticity of the vessel wall.[64] Therefore, calcifications probably have a protective role.[63,65] However, stresses increase up to 22% at local calcification sites[64,66] and stress concentrates at the interface of calcium deposits with softer plaque components, inducing compliance mismatches and mechanical failure.[67]

BOUNDARY CONDITIONS

Finally, a set of boundary conditions are selected. These conditions could be described as assumptions made to simplify the model. The first set of assumptions regard the wall properties, the second regard the aneurysm configuration. Often the wall is assumed to be isotropic and react

linear to applied stress. Studies with a non-linear material model reported both higher and lower wall stress.[68,69] Biaxial tests show relative low anisotropy but when anisotropy is taken into account higher stresses were obtained.[70] However, these effects might be interchangeable and therefore difficult to distinguish.[71]

The contact of the aneurysm with the surrounding tissue may also influence the biomechanical outcomes.[72] However, almost all models neglect the surrounding tissue and focus on the stress caused by the blood flow and the normal aneurysm configuration. During FEA the geometry is often assumed to be pressure free or subjected to a uniform pressure. However, the normal blood flow applies a pulsatile pressure. Several studies propose a method to calculate a zero pressure configuration to improve the accuracy.[73–77] Nevertheless, using such zero-pressure geometry only slightly improves the results (reported differences of 0.7% to 2.7%). FSI applies incorporates a pulsatile pressure but could also be improved using patient specific flow conditions.[72,78–80]

REPORTED INDICES

With the computational modelling a 3D stress map is created and subsequently the resulting indices are derived: the PWS and peak WSS. In addition, wall strain and compliance could be derived from imaging. To simplify clinical implementation new, easily understandable parameters are sought. Doyle et al.[81] were the first to propose a FEA rupture index (FEARI), hereby creating a basis for clinical implementation. This simple measure divides the calculated wall stress trough the wall strength. However, the strength is based on the previously described tensile tests and thus not patient-specific. Strength assessment is improved by patient specific measures, such as ILT thickness, age, smoking status, family history and gender.[82,83] With incorporation of these factors a new rupture index is created: the peak wall rupture index (PWRI).

During a large retrospective trial Gasser et al.[84] showed that PWS increases linearly and PWRI increases exponentially with diameter. With this relation the RRED is also introduced. This value denotes the diameter of an average patient with the same PWRI (see Figure 5).[84] This interpretation increases clinical simplicity but the exact threshold for repair is still unsure and should be discussed.

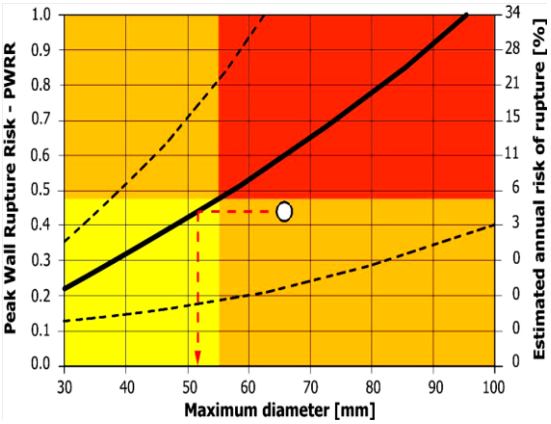

FIGURE 5. DETERMINATION OF THE RUPTURE EQUIVALENT DIAMETER. THE DOT REPRESENTS A SPECIFIC PATIENT, COMPARING THIS PATIENT TO THE AVERAGE POPULATION (BLACK LINE) RESULTS IN THE RRED (AS POINTED BY THE ARROW. FIGURE CREATED WITH A4 RESEARCH (VASCOPS)

4.2.3 Meta-Analysis

In the quantitative analysis, the three main groups in biomechanical analysis (FEA, CFD and wall strength) are also present (14, 3 and 2 studies are respectively included). Study characteristics and quality scores are displayed in Table 2. These studies mainly examine populations from the USA and Europe. The measured age was similar in the ruptured or symptomatic group and the asymptomatic intact group (range: 49-96 year old). All studies included more males but often the fraction of females in the ruptured group was higher compared to the asymptomatic intact group. The percentage smokers was reported in six studies[85–89] and was equally distributed between groups.

All FEA and FSI studies use CT to acquire the AAA geometry. The wall strength studies all use US. The biomechanical index was measured before the onset of rupture in seven cases[43,44,70,82,89–91] and after in eight cases[86,88,92–95], for three studies[96–98] the acquisition moment was unclear. Five FEA studies and three FSI studies reported the PWS and WSS controlled for the diameter. Sample size in the studies ranged from 3 to 282 in the intact (AAA), 1 to 40 in the ruptured (RAAA) and 0 to 15 in the symptomatic (SAAA) group. The AAA group compared to the RAAA group in the combined analysis.

TABLE 2. OVERVIEW SELECTED STUDIES

Study	Year	Software	ILT	Ca	Patients			Newcastle Ottawa Score		
					AAA	RAAA	SAAA	S	C	O
Finite element analysis										
Fillinger et al.[85]	2002	ABAQUS	N	N	48	10	8	3	2	3
Fillinger et al.[89]	2003	ABAQUS	N	N	42	14	8	3	1	3
Venkatasub. et al.[86]	2004	ANSYS	N	N	15	12	-	2	2	3
Raghavan et al.[90]	2005	ANSYS	N	N	14	17	-	2	1	2
Truijers et al.[96]	2006	ABAQUS	N	N	10	10	10	3	1	3
Vande Geest et al.[82]	2006	ABAQUS	N	N	5	8	-	3	0	2
Vande Geest et al.[70]	2008	ABAQUS	N	N	5	9	-	3	0	2
Heng et al.[97]	2008	ANSYS	N	N	40	30		3	1	3
Reeps et al.[55]	2010	HARPOON	Y	Y	3	1	-	2	0	2
Maier et al.[99]	2010	HARPOON	Y	N	30	14	9	3	1	3
Gasser et al.[92]	2010	VASCOPS	Y	N	30	20	-	3	2	3
Doyle et al.[98]	2010	ABAQUS	Y	N	42	17	-	2	1	2
Gasser et al.[84]	2014	VASCOPS	Y	N	203	40	-	3	1	2
Erhart et al.[88]	2015	VASCOPS	Y	N	30	15	15	3	0	2
Fluid structure interaction										
Xenos et al.[100]	2010	Adina	Y	Y	8	2	-	2	1	1
Xenos et al.[101]	2010	Adina	Y	Y	1	2	-	2	1	1
Xenos et al.[95]	2014	Adina	Y	Y	8	8	-	2	1	2
Wall strain										
Sonesson et al.[43]	1999	US	n.a.		121	11	-	3	0	1
Wilson et al. [44]	2003	US			282	28	-	4	2	2

S = selection (maximum = 4), C = comparability (maximum = 2) O=outcome/exposure (maximum = 3)

PWS: The PWS is reported in N/cm^2, which required conversion from MPa or kPa in five studies. The analysis of 14 studies contains 247 ruptures or symptomatic and 503 asymptomatic intact AAA. Two of the included studies reported an insignificant difference in PWS between the ruptured group

and the intact AAA group (p=0.524[82] and p=0.535[70]). A combined analysis showed a significant higher PWS in the symptomatic/ruptured group with a SMD of 1.11 (95 CI 0.93 to 1.26, p < 0.001), see Figure 6. Analysis suggested low heterogeneity between the study (I^2 = 9%).

A sub analysis of PWS in the diameter controlled groups contains four studies as the fifth study[92] did not report exact data. These studies examined 55 patients in the ruptured group and 61 patients in the asymptomatic intact group. One study showed an insignificant difference (p=0.056[98]).The sub-analysis also showed a significant higher PWS in the ruptured group with a SMD of 0.85 (CI 0.46-1.23, p < 0.001) as displayed in Figure 7. Heterogeneity between the studies in the sub analysis was low (I^2 = 0%).

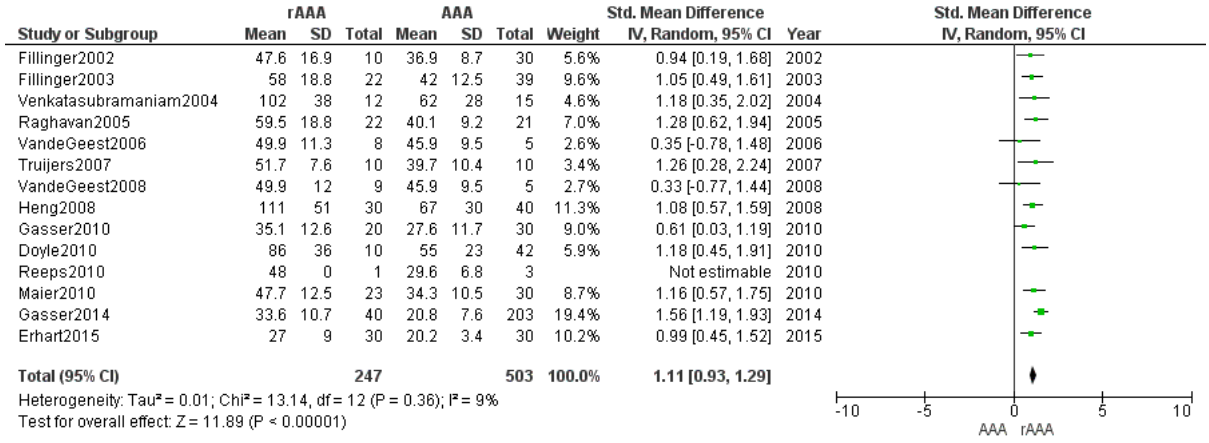

FIGURE 6, FORREST PLOT FOR THE PEAK WALL STRESS (N/CM^2)

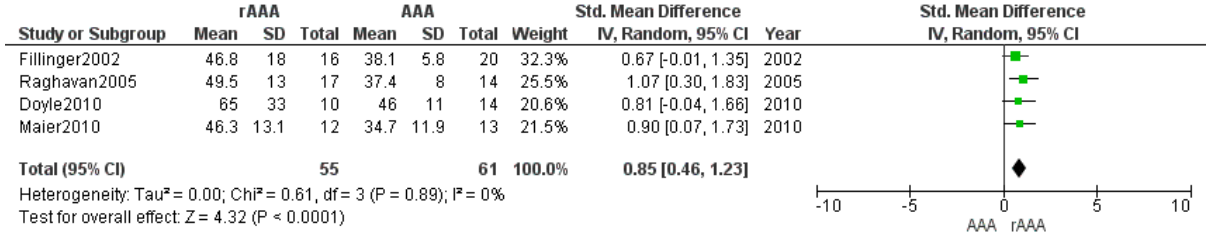

FIGURE 7, FORREST PLOT FOR THE DIAMETER MATCHED PEAK WALL STRESS (N/CM^2)

PWRI: Eight studies assessed a rupture index (FEARI (n=1)[98], PWRI (n=3)[88,92,102] or the rupture potential index (RPI) (n=4) [82,95,100,101]). Three studies used FSI to calculate the RPI.[95,100,101] but no exact data was reported. The remaining studies all used FEA. Analysis of the studies assessing PWRI with FEA contained 90 rupture cases and 263 asymptomatic intact AAA. One of the studies showed no significant differences between groups (p=0.06[92]). The combined analysis showed a significant higher PWRI in the ruptured or symptomatic group with a SMD of 1.15 (95 CI 0.30 to 2.01 p = 0.008) (Figure 8). Analysis suggested considerable heterogeneity between the studies (I^2 = 89).

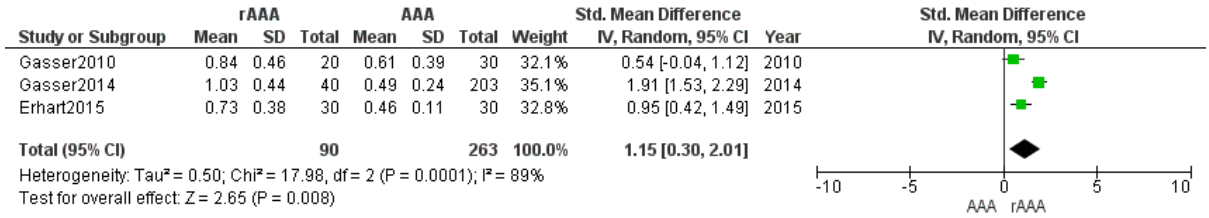

FIGURE 8, FORREST PLOT FOR THE PEAK WALL RUPTURE INDEX

PWSS: Three studies reported the PWSS for asymptomatic and ruptured cases.[95,100,101] The results showed a trend toward a higher PWSS in ruptured aneurysms. However, the studies have a low amount of patients and only in one study the exact data was reported. Therefore a combined analysis couldn't be done.

Wall stiffness: Two studies assessed the wall stiffness. However, only median and range were reported, thus a combined analysis isn't done. The results showed no significant difference in wall stiffness between the asymptomatic and ruptured group.[43] However, a decrease of stiffness over time was significantly correlated with rupture.[44]

4.3 Discussion

Over the past decades biomechanical analysis for estimating AAA rupture risk has gained (scientific) popularity. This resulted in several biomechanical indices. This systematic review showed that the inputs of the computational model are likely to influence the results. Therefore careful and consistent selection is needed to get the most accurate and clinical valuable results. However, patient specific biomechanical profiling seems to be reliable to predict AAA rupture risk and should be included in the risk assessment.

FEA showed to be the most popular method. However, the popularity and possibilities of flow and strain measurements are increasing as more complicated imaging methods become available. Due to the limited amount of data available the quantitative analysis could only assess two biomechanical indices: PWS and PWRI. Both indices were significant higher in ruptured cases compared to asymptomatic cases. The diameter controlled groups also showed a significant difference. However, a large overlap between groups could be seen.

These results must be viewed in the context of their limitations. First, the participant selection, imaging moment and model conditions differ between studies. In some cases these conditions weren't carefully[103] reported. Therefore heterogeneity between the studies exists. This study used a random-effects model to calculate the SMD for each index between ruptured and asymptomatic intact AAA. With this model the influence of the heterogeneity was minimized. However, a significant and large statistical heterogeneity between the PWRI studies was still present.

Second, most studies retrospective selected asymptomatic, symptomatic and ruptured AAA cases. This has drawbacks as the (elective) AAA patient in the non-ruptured group might rupture without repair. Earlier repair of the ruptured case could alternate groups as well. A prospective trial with

sufficient sample sizes is needed to truly assess the effect. In addition, an interest exists in following the aneurysm development and accompanying stress over time.

Another concern is the variability of the available software. However recent studies showed that the observer variability of A4research (Vascops, Graz, Austria) was low and a large observer agreement was present.[97,104,105] Most other models are not tested for observer variability, limiting the confidence of the index measured with these models.

Finally, the clinical applicability in addition to diameter is still unsure. Fillinger et al. showed that PWS was superior to diameter in predicting rupture.[89] However, often a large overlap between groups could be seen. Only few studies examine a threshold treat but receiver operating characteristics (ROC) curves for predicting rupture showed a high sensitivity and specificity and accuracy (94%, 81% and 85% respectively) at a threshold of 44N cm^{-2}. Such a threshold for repair simplifies the clinical implementation but needs further verification.

4.4 Conclusion

This chapter reviewed the biomechanical assessment of AAA rupture risk. Although challenges remain biomechanical analysis showed to be a promising tool in the assessment of AAA rupture risk as it incorporates several factors: geometry, tissue properties and patient specific risk factors. However, the lack of standardization limits the translation of this technique to clinical practice. Combining the biomechanical indices with the diameter and the surgical risk should finally result in more effective patient specific decision making.

PART 2: CLINICAL DATA

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5 PREDICTION OF AAA RUPTURE: PEAK WALL STRESS VERSUS DIAMETER

This study used patient-specific AAA geometry and FEA to examine the use and clinical value of PWS, PWRI and RRED in asymptomatic intact, ruptured and symptomatic AAA. It also assesses the potential of these biomechanical indices to identify AAAs that may have higher risk compared to other similar sized aneurysms.

5.1 Methods

This study included all patients electively planned for endovascular repair between 2009 and 2014. In addition all acute repaired AAAs between 2002 and 2014 are included. Acute repair was done in case of rupture or symptoms. Patients were retrospectively collected from the central patient database at the Department of Surgery (Division of Vascular Surgery) at the UMCG. A total of 600 patients underwent endovascular aneurysm repair between 2002 and 2014. All patients with a suitable preoperative CTa scan were included. The aorta must be visible from the renal arteries to the iliac bifurcation, with a sufficient amount of contrast. The aneurysm must be infrarenal but a mild extension to the iliac arteries is accepted. Only scans with a slice thickness below 10mm were included.

This resulted in the inclusion of 179 asymptomatic intact AAA, 11 SAAA and 60 RAAA cases. The symptomatic group contains patients who showed acute signs of rupture but no signs of rupture on the CTa. The ruptured group contains patients who presented with acute signs of rupture and the rupture was confirmed on the CTa. Therefore the used CTa scans for this group are post-rupture. In four asymptomatic intact AAA and thirteen RAAA FEA was not possible due to complex geometry and consequently these cases were excluded.

The following risk factors and co-morbidities were registered: gender, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), smoking, family history and hypercholesterolemia. Patients were classified as a smoker when they smoked at least one cigarette per day within one year prior to the AAA repair. The following clinical variables were collected from the database: age, blood pressure (systolic, diastolic and mean arterial pressure (MAP; 1/3 systolic pressure + 2/3 diastolic pressure) and body mass index (BMI). Data was collected from the last non-critical measurement within one year before intervention. These criteria were not met in some ruptured patients and their data could thus not be collected.

5.1.1 Biomechanical analysis

All biomechanical analyses were done using the commercially available AAA dedicated FEA software A4 research (VASCOPS, Gaz, Austria). First the AAA geometry was reconstructed, segmenting the luminal and ILT volume, and the vessel wall. Second a mesh was generated and

the FEA is executed. The exact analysis method for geometry reconstruction, mesh generation and FEA is explained in the following sections.

Geometry reconstruction: Segmentation was semi-automatic using deformable snake and balloon models for the 2D and 3D segmentation respectively. These are objects that deform within the image until they stop at the boundary of a structure (lumen or vessel). The evolution of the object depended on a set of reconstruction parameters and contrast differences. First, a snake model to pre-segment the luminal surface was initialized by manually placing an initialization circle in the lumen of the iliac arteries. Subsequently the luminal service was perfected using a balloon model and the exterior surface is segmented with a second balloon starting from the luminal surface. Segmented volumes were manually corrected with enriching image data and control polygons. The amount of user interaction depended on the image quality and the complexity of the aneurysm. In general ruptured aneurysms required more manual correction. Finally the external vessel wall and ILT were automatically segmented by the software.

Mesh generation and FEA analysis: After the geometry reconstruction a mesh was created of the 3D volume using hexahedral elements. Details are presented elsewere.[38] The FEA region was set from the renal arteries to just after the iliac bifurcation. The model was pressurized at the MAP. In case the BP was not reported a set BP of 140 over 80 was used (n= 8, 12, 2 for asymptomatic, symptomatic and ruptured cases respectively). An isotropic constitutive model was used for the ILT and aneurysm wall. The wall strength model uses the position of the ILT, gender, family history and the relation between the local diameter and the calculated normal aortic diameter.

Parameter calculation: Several geometric (maximum diameter, volume) and biomechanical parameters (PWS, PWRI, RRED) were extracted. All parameters were calculated automatically. The maximum diameter was based on the centreline. The software produced coloured overlays to provide information of the distribution of wall stress and rupture risk (see Figure 9). The maximum diameter as determined by an experienced radiologist was also extracted from the patient file to assess the differences with current clinical practice.

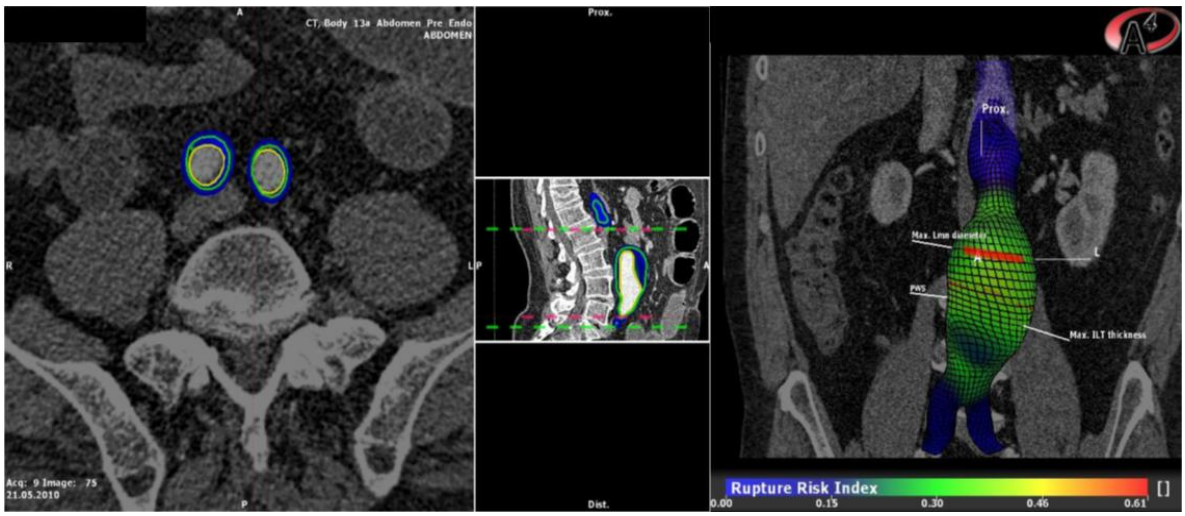


FIGURE 9. VASCOPS OUTCOME SCREENSHOT

5.1.2 Statistical analysis

All statistical analyses were performed using SPSS statistics 23 (IBM, New York, United States). Statistics were expressed as mean ± standard deviation. Percentages were given for nominal variables. Comparison between scans or groups was done using a Student t-test in case of normal distribution. Mann-Whitney U tests were performed to compare skewed variables. Nominal variables were compared using the chi square test. Missing values were pair wise excluded. Maximum diameter as measured by a radiologist and software were compared using a Wilcoxin signed rank rest. Rank order diagrams are created to assess the predictive capability of different indicators. In addition to the rank order plots, an ROC-curve is created to examine the discrimination between groups under varying thresholds.

5.1.3 Diameter matching

A significant difference was seen between the maximum diameter of the asymptomatic and ruptured groups. Therefore a comparison with only size-matched subjects is also executed. Hereby, providing a more stringent analysis of whether the biomechanical outcomes could differentiate the ruptured AAA. The diameters as measured by VASCOPS are matched using SPSS Case-Control matching. Match tolerances were set at 5mm. This resulted in zero exact matches and 31 matches within the tolerance rate.

5.2 Results

5.2.1 Patient characteristics

Both groups show similar characteristics (see Table 3). No significant differences were observed ($p > 0.05$). However, a trend could be seen towards a lower or higher frequency of cardiovascular disease in the ruptured and symptomatic group respectively ($p=0.146$). Familial AAA incidence was missing in most patients, but the known incidences were not significant different. No significant differences were seen between the asymptomatic and ruptured group after diameter matching.

5.2.2 Evaluation biomechanical indices and diameter

Maximum diameter measurements of the radiologist and the software were significantly different ($p = 0.001$). However, a large positive correlation between both diameter measurements was seen (Kendall's tau $\beta = 0.739$, $p = 0.001$; see also Figure 10). In most cases the software maximum diameter was larger ($n = 181$). Five cases show a software based diameter of more than 1.5 times the diameter measured by the radiologist. In these cases a software measurement error is present, mostly due to a highly tortuous AAA. However, after exclusion of these cases the measurement difference remained significant ($p = 0.001$). The differences also remained significant after exclusion of ruptured cases ($p = 0.002$).

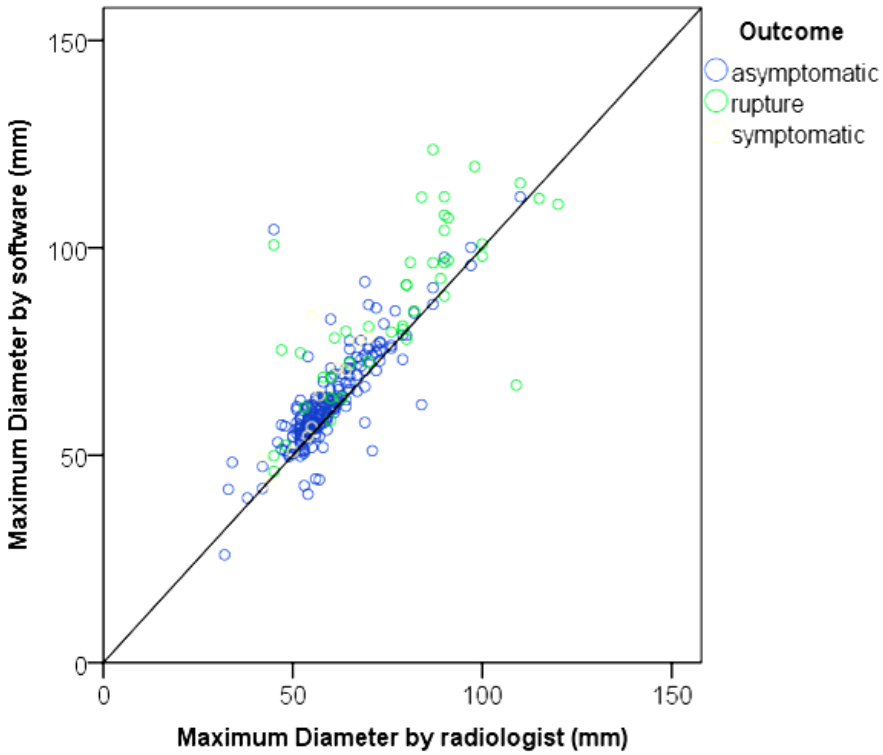


FIGURE 10. MAXIMUM DIAMETER MEASUREMENTS PER SUBGROUP. THE BLACK LINE REPRESENTS A SIMILAR MAXIMUM DIAMETER AS MEASURED BY THE RADIOLOGIST AND SOFTWARE.

The asymptomatic group showed a skewed distribution as most values were between 50 and 60mm. Aneurysms sizes differed strongly between the asymptomatic and the ruptured group for both the software and the radiologist based diameter (P=0.001; see Table 4). All other geometric variables also showed a significant difference (p=0.001). The PWS (22.0 ± 5.8 vs. 33.4 ± 15.8), PWRI (0.52 ± 0.2 vs. 1.01 ± 0.64), and RRED (65 ± 60 vs. 98 ± 51) were significantly lower in the asymptomatic group compared to the ruptured group. Although the symptomatic group did not show a significant difference in diameter compared to the asymptomatic intact group a strong trend was seen towards a higher PWS (p=0.084). The PWRI and RRED also showed a trend towards higher values in the symptomatic group (p=0.161 and 0.204 respectively). The diameter matched comparison show a contrasting outcome. No significant differences in geometric and biomechanical indices were seen within the asymptomatic and the ruptured group (p>0.05; see Table 5).

5.2.3 Predicting rupture, ROC analysis.

For the entire population the maximum diameter captures the large aneurysms very well (see Figure 12). However, such diameter fails to distinguish between small asymptomatic intact, ruptured and symptomatic aneurysms. The biomechanical indices show a similar profile. A large overlap between groups is seen and in the lower range to distinguish between groups is hard. Thus multiple ruptured cases cannot be distinguished from the asymptomatic cases based on these parameters.

The ROC-curves are displayed in Figure 11. They show, in accordance with the rank plots, for the maximum diameter, PWS, PWRI and RRED a similar area under the curve (0.843, 0.770, 0.796 and 0.778 for the maximum diameter, PWS, PWRI and RRED respectively).

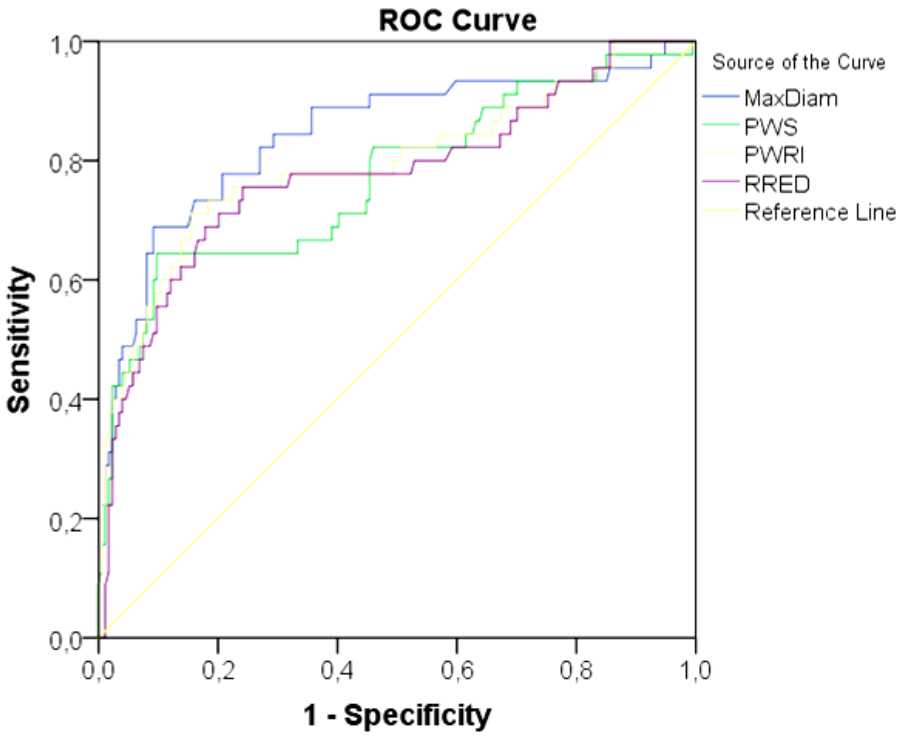


FIGURE 11, ROC-CURVE OF THE MAXIMUM DIAMETER (BLUE), PWS (GREEN), PWRI (BROWN) AND RRED (PURPLE)

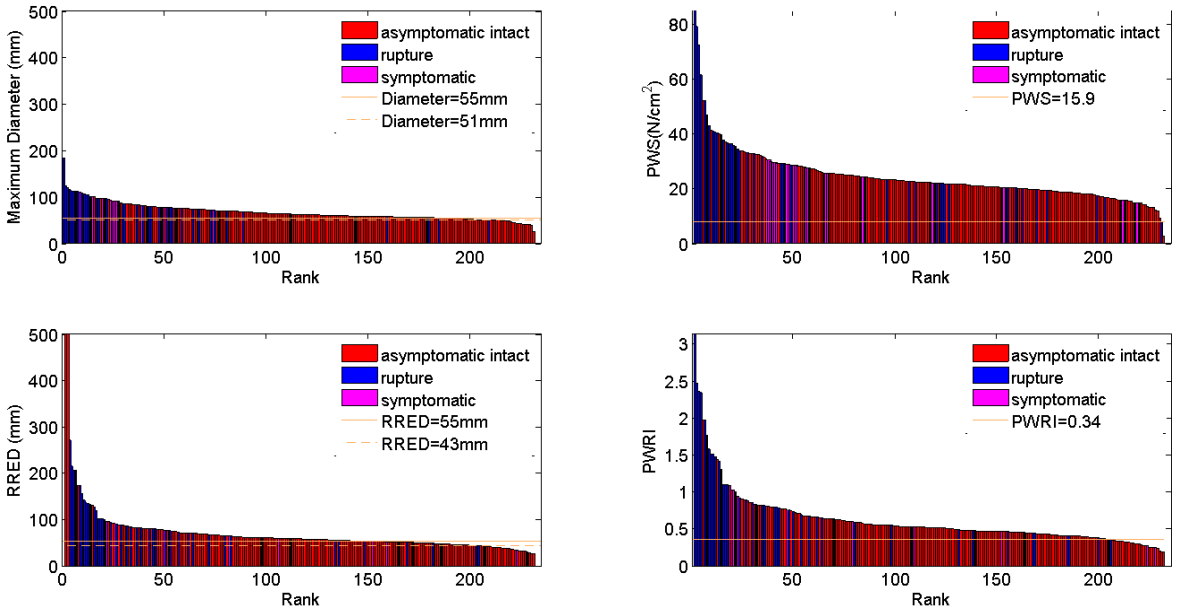


FIGURE 12, RANK ORDER PLOTS FOR MAXIMUM DIAMETER, PWS, RRED, PWRI. RANKS INDICATE THE DESCENDING ORDER OF RUPTURE RISK AS ASSESSED BY THE CORRESPONDING INDICATOR. SOLID LINES INDICATE THE LOWEST VALUE OF ALL RUPTURED AAAS, DASHED LINES INDICATE THE CURRENT TREATMENT THRESHOLD OF 55MM

TABLE 3. DEMOGRAPHICS

	Asymptomatic	Rupture	Symptomatic	P-Value
n	175	45	11	-
Age (year)	72.4 ± 8.7	73,9 ± 8.7	73,4 ± 10.4	0.304[a] / 0.706[b]
Male	156 (89%)	39 (87%)	7 (63%)	0.404 [a] / 0.303 [b]
Blood pressure (mmHg)				
Systolic	135 ± 18	140 ± 25	136 ± 13	0.288[a] / 0.791[b]
Diastolic	76 ± 12	76 ± 16	79 ± 5	0.881[a] / 0.088[b]
MAP	96 ± 13	96 ± 20	98 ± 6	0.898[a] / 0.215[b]
BMI	26.9 ± 4.2	26.6 ± 6.9	23.9 ± 3.1	0.370a / 0.202b
DM	23 (13%)	7 (15%)	1 (9%)	0.871
COPD	41 (24%)	10 (21%)	2 (18%)	0.889
CVD	107 (61%)	24 (51%)	9 (82%)	0.146
Smoking	85 (49%)	22 (47%)	3 (27%)	0.368
High cholesterol	31(18%)	10 (21%)	3 (27%)	0.309
(diagnosis/meds)	66 (38%)	11 (23%)	2 (18%)	
Family History	10 (5%)	0 (0 %)	1 (9%)	0.451
(positive/unknown)	157 (90%)	45 (96%)	10 (91%)	

a: asymptomatic compared to ruptured, b: asymptomatic compared to symptomatic. * Significant difference P<0.05

TABLE 4. FEA OUTCOMES

	Asymptomatic	Rupture	Symptomatic	P- Value
n	175	45	11	-
Maximum Diameter by radiologist (mm)	60 ± 11	77 ± 19	56 ± 9	0.001[*a] /0.371[b]
Maximum diameter by software (mm)	63 ± 13	88 ± 24	64 ± 14	0.001[*a] /0.883[b]
Total Luminal Volume (cm^2)	93 ± 49	190 ± 134	93 ± 56	0.001*[a] /0.899[b]
Total Volume (cm^2)	200 ± 102	424 ± 214	195 ± 64	0.001[*a] /0.797[b]
Total ILT Volume (cm^2)	83 ± 61	186 ± 135	65 ± 35	0.001*[a] /0.492[b]
PWS (N/cm^2)	22.0 ± 5.8	33.4 ± 15.8	24.3 ± 5.4	0.001*[a] /0.084[b]
PWRI	0.52 ± 0.20	1.01 ± 0.64	0.64 ± 0.28	0.001*[a] /0.161[b]
RRED (mm)	65 ± 60	98 ± 51	67 ± 24	0.001*[a] /0.204[b]

a: asymptomatic compared to ruptured, b: asymptomatic compared to symptomatic. * Significant difference P<0.05

TABLE 5. FEA OUTCOMES OF THE DIAMETER MATCHED SUBGROUP

	Asymptomatic	Rupture	P- Value
n	31	31	-
Maximum Diameter by radiologist (mm)	71 ± 15	72 ± 18	0.807
Maximum diameter by software (mm)	77 ± 16	78 ± 17	0.668
Total Luminal Volume (cm^2)	132 ± 79	132 ± 76	0.757
Total Volume (cm^2)	296 ± 150	324 ± 148	0.338
Total ILT Volume (cm^2)	129 ± 91	158 ± 117	0.314
PWS (N/cm^2)	26.1 ± 8.9	26.2 ± 7.5	0.994
PWRI	0.69 ± 0.33	0.70 ± 0.27	0.612
RRED (mm)	88 ± 89	73 ± 22	0.949

* Significant difference P<0.05

6 DISCUSSION AND CONCLUSIONS

Currently the maximum diameter is mostly used as the threshold for surgical repair as it is easy to determine. Moreover, statistics have shown that larger diameters have higher yearly rupture risks. However, this diameter measure has some well known short-comings. Small aneurysms can rupture leading to death that could have been prevented while large aneurysms remain stable leading to unnecessary risky treatments and higher healthcare costs. Therefore a patient specific rupture predictor that is accurate and easy to perform is urgently needed.

My study is one of the largest independent studies assessing biomechanics for AAA rupture risk assessment. It examined three potential parameters (PWS, PWRI, RRED) based on FEA with patient specific geometry segmented from CTa. The results in the non-diameter matched group indicate a significant different PWS, PWRI and RRED between asymptomatic and ruptured aneurysms. Which is consistent with previous studies, as described in Chapter 4.[81,82,85,86,88,92,96,106–110]. Additionally symptomatic AAAs showed a trend towards higher PWS, PWRI and RRED.

However, the diameter matched group showed no significant differences between intact asymptomatic and ruptured aneurysms. Three out of four previous studies using diameter matching did show a significant difference between groups, see Chapter 4.[81,85,99,111] This study used a true matched subject design as most ruptured aneurysms were matched to a similar sized aneurysm in the intact asymptomatic group.

However, my results should be viewed in context of its limitations. Patients were selected when endovascular repair was already planned. Therefore, the geometries included in this study are geometries suitable for endovascular repair without fenestrations; i.e. an infrarenal AAA with a proper landing zone, sufficient iliac access and low tortuosity. Retrospective inclusion of AAA repaired through surgery would represent the total AAA population better. Nonetheless, the used software is optimized for infrarenal AAA and tortuosity does not increase the rupture risk.[112] The inclusion method also resulted in a selection bias regarding the aneurysm size. Most elective repaired aneurysms are sized between 50 and 60mm and this is close to the treatment threshold, while the ruptured and symptomatic aneurysms display a normal distribution with a mean diameter of 77 and 59mm respectively. The diameter matched group corrects for this bias, as asymptomatic patients are matched to ruptured patients based on diameter. Previous studies excluded the large and small diameters to create a diameter matched group (55-75mm).[85,99] This study included 111 asymptomatic and 10 ruptured patients within this range and a trend towards a significant different PWS, PWRI and RRED were seen between both groups ($p = 0.41$, 0.18, 0.26 respectively). This study examined the use of biomechanical indices throughout the clinical range by matching also large and small diameters instead of only intermediate diameter group.

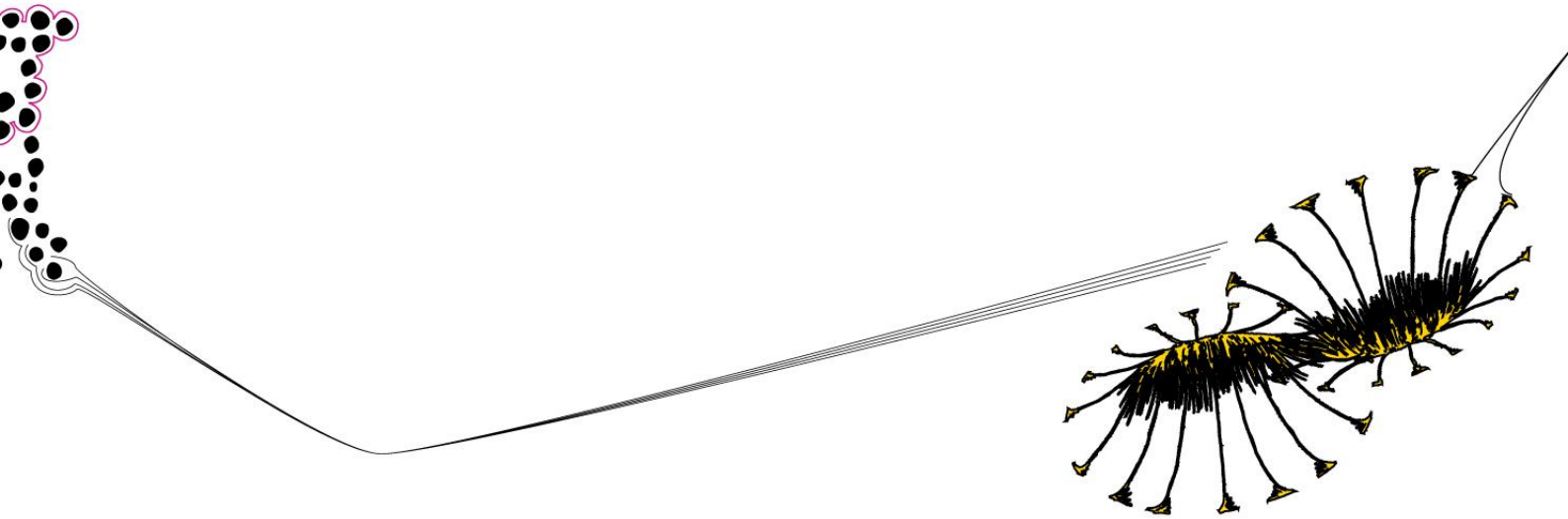
The additional value of the biomechanical indices compared to the diameter was assessed using rank plots and ROC-curve. The maximum diameter provide similar discrimination between groups as the biomechanical indices, hence the area under the ROC-curve was similar for all measures.

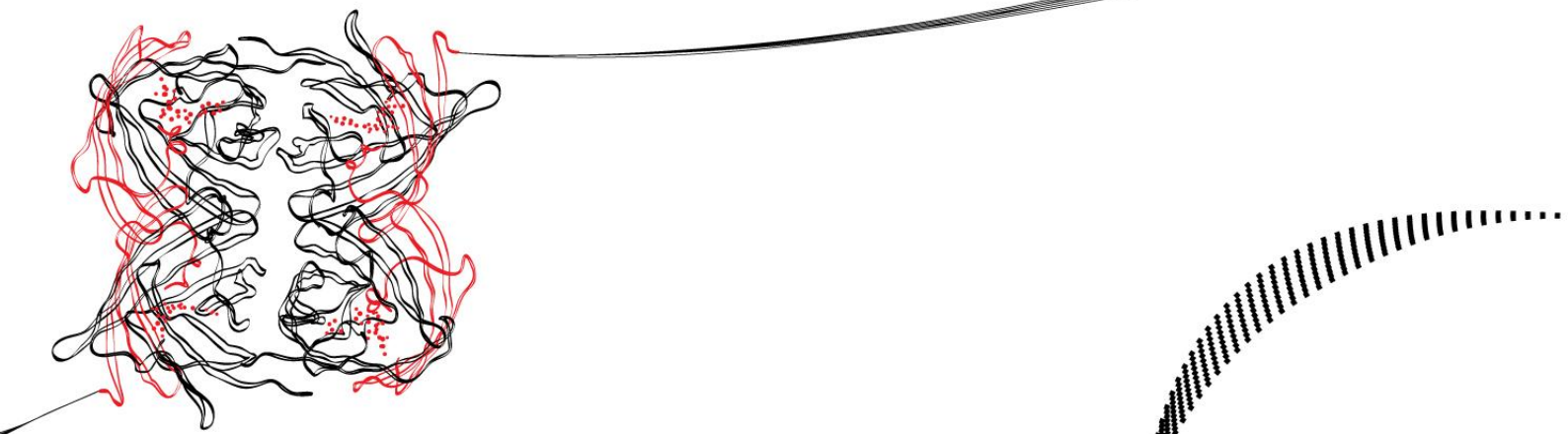
The ability of biomechanical indices to predict rupture was similar to the maximum diameter's ability. However, the design of my study was retrospective. This has drawbacks as patients could be shifting between groups as the AAA patients in the non-ruptured group might rupture without repair. Fillinger et al.[106] followed 103 patients over at least half a year and during this time 22 and 39 patients required emergency and elective repair respectively. The PWS showed better ROC-curves for predicting rupture than the maximum diameter. In contrary to Fillinger et al. my study included the ILT, which reduces wall stress[53–61] and a patient's specific blood pressure. Therefore, the used model is more accurate, but a prospective trial with this model is needed to truly evaluate the predictive capacity.

One last comment should be made; my study used the pre-operative scans of all patients. Therefore the scans of the ruptured group displayed ruptured aneurysms. These aneurysms may not accurately reflect the geometry pre-rupture as the rupture likely changes the blood flow and pressure in the aneurysm. Previous studies both use pre-rupture and post-rupture geometries (c.f. Chapter 4). Which of these representations is the most accurate biomechanical analysis remains unclear and should be resolved by future studies.

Although further research is needed to precisely asses the additional value of biomechanical analysis, my study supports a patient specific individualized AAA rupture risk assessment. No clear improvements in risk assessment compared to the established maximum diameter approach are observed. Nevertheless, combining the biomechanical criteria with the maximum diameter gives a full overview of the patient specific risk, especially in the small to medium sized aneurysms.

PART 3: IMPLEMENTATION





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7 IMPLEMENTATION AND FUTURE RESEARCH

7.1 The changing shape at rupture

As mentioned before, studies use both pre-rupture and post-rupture CTa-scans to extract the patient specific geometry. Which of those two geometries is the most accurate is still unclear. However, in a clinical setting the pre-rupture geometry is more important as this shape and the corresponding biomechanics predicts the need for surgery before rupture. In other words, to prevent rupture a physician needs to know the biomechanics before a rupture occurs.

Nevertheless, whether the AAA geometry changes during rupture is uncertain. Therefore a comparison between pre and post rupture data must be done. Eleven patients of the 78 ruptured aneurysms (i.e. 14%) examined for this study had an additional pre-rupture CTa scan. Combining the results from these scans helps to examine the possible change in shape after the rupture. To extend the database contacts with the Amsterdam Medical Centre have been established. This medical centre was part of the Amsterdam Acute Aneurysm (AJAX) trial, a large prospective study assessing the outcome of surgery after rupture.[113] Therefore a large group of known ruptured aneurysms is available. Subsequently, all pre (if available) and post rupture CT scans will be acquired and analyzed with the software.

7.2 Prospective trials

Ideally the ability of biomechanical indices to predict aneurysm rupture should be assessed during a prospective natural history (non-interventional) study of AAA. However, consensus when AAA with a large diameter should undergo surgery is available. Following a wait-and-see policy for these aneurysms would be unethical. However, a group of patients still declines surgery. Following these and other AAA patients probably tells much about AAA growth and changes in AAA biomechanics and their potential rupture risk. Alternatively a randomized controlled trial (RCT) comparing patients with a relatively small diameter and low PWS during continued surveillance or surgery could be an option. Such a trial will further clarify the clinical utility of biomechanics.

7.3 Material properties, elastography

As mentioned in my systematic literature review (Chapter 4) patient specific material properties could greatly influence and approve the accuracy of the results. However, 18F-fluorodeoxyglucose PET studies showed that areas of high PWS correlated with high metabolic activity.[51,114] Furthermore, a recent preliminary study histological compared the regions with lowest and highest PWRI. The study showed that PWRI correlates with histological degeneration of the individual AAA wall but correlation between patients was not seen.[115] Both methods indicate towards interplay between biomechanical indices and wall integrity. Therefore, FEA and FSI predictions might be accurate enough to adequately predict rupture risks.

Nonetheless, results could be improved by incorporating the calcifications in the biomechanical analysis. Currently only a few studies incorporate the calcifications.[55,66] These studies show that calcifications influence the vessel wall in multiple ways: a decrease the compliance and elasticity of a vessel,[64] stress concentration at the interface of calcium deposits with softer plaque components induces compliance mismatches and mechanical failure[67], shape and location influence wall stress[64]. During stress simulations the local stresses increases at calcifications sites, which may indicate an increased risk of rupture. In the most severe case the peak stress increases with 22%.[64,66]

Vascular elastography is a promising technique for mechanical characterization of diseased arteries. 3D methods based on ECG gated CT and MRI images could be easily incorporated into the biomechanical analysis.[48–52] 2D US based methods are more difficult to incorporate in the 3D biomechanical models but these methods are less invasive, and could be done during daily clinical practise.

Elastography aims to map the tissue stiffness by assessing the tissue strain under a constant or dynamic stress.[116] The technique is often called palpation imaging as differences variations between tissues are 'felt'. The technique already proved its feasibility in several arteries, such as the carotid. Fromageau assessed the feasibility of the proposed technique in aneurysms, which were created in the iliac artery of dogs.[117]

Dynamic elastography is preferred as static methods are observer dependent as the force is manually applied. During dynamic elastography the mechanical is short transient or oscillatory. This compression creates shear waves, which are directly related to the elastic modulus of the tissue. The compression is acquired using the ultrasound acoustic pressure, a radiation force impulse or a mechanical vibrator.[118] However, in AAA the compression could also be replaced trough following the aortic movement as a reaction to the pulsatile blood flow. Several challenges exist when applying this technique on the abdominal aorta. First, the abdominal aorta is a deep artery which requires a lower frequency probe and thus the spatial resolution is decreased. Second, the ultrasound beam propagates axially while the vessel stresses/motion occurs within the vessel wall degrading information in the transverse direction further. Hansen et al. proposed an angular compounding technique to reduce this effects in non-invasive coronary elastography.[119]

Acoustic radiation force impulse (ARFI) imaging is a relatively new image modality but already readily available on several commercial ultrasound devices. Preliminary studies on healthy subjects using the Acuson 3000 (Siemens Healthcare, Erlangen, Germany) done during this thesis indicate a great loss of quality. However, in general the strain in the direction of the probe could be assessed. The more superficial femoral artery showed a lower displacement and a higher velocity compared to its surroundings (see Figure 13). Tierney et al proved the feasibility of ARFI in an AAA case.[120] Further research, however, is needed to assess the clinical value of this technique.

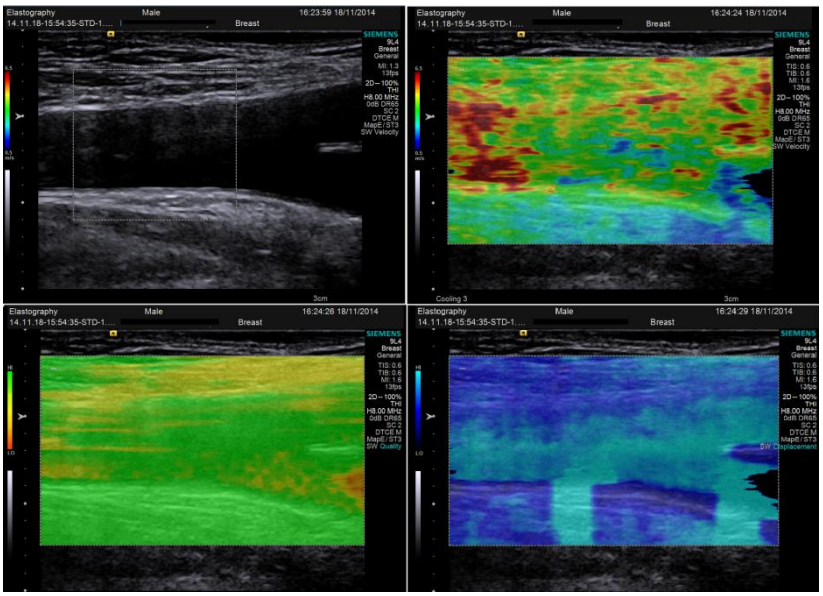

FIGURE 13. FEMORAL ARTERY OF A HEALTHY PATIENT AS IMAGED WITH ARFI-ELASTOGRAPHY. TOP LEFT: B-MODE US, TOP RIGHT: VELOCITY PROFILE, BOTTOM LEFT: QUALITY PROFILE, BOTTOM RIGHT: DISPLACEMENT PROFILE

7.4 Decision to treat

The decision to treat is based on a balance between potential benefits, harms and costs. My recommendations indicate that the inclusion of biomechanical indices likely provides a more accurate prediction of rupture risk for the individual patient compared to size alone. Thus with this information a decision for an individual patient could be made based on a patient specific rupture and surgical risks. Such risks and their perception will be further elaborated in the next sections.

7.4.1 Surgical risk

Currently multiple surgical risk calculators are available. These include American society of anaesthesiologists classification (ASA), acute physiology and chronic health evaluation (APACHE) and physiological and severity score for enumeration of mortality and morbidity (POSSUM).[121] These calculators are often based on some patient characteristics combined with statistics based on large databases. A surgical risk below the (yearly) rupture risk could justify surgery.

For the asymptomatic intact patients in our database, the surgical risk was calculated using the surgical risk calculator of the American College of Surgeons.[122] This calculator uses 22 patient characteristics (type of surgery, age, gender, smoking status, BMI etc.) to predict the outcomes for a specific patient within the first 30-days following surgery. The model is based on data of 1.4 million operations. Following the recommendations, missing patient predictors are set to the default setting (usually ‘no’).

According to Gasser et al. a PWRI of 0.5 is equal to a yearly rupture risk of approximately 6% and a PWRI of 1 equals a yearly risk of 34%.[62] Combining these risk calculations gives a higher yearly rupture risk compared to the surgical risk in 36 of the 178 electively repaired patients (20%). However, the five year rupture risk is larger than the surgical risk in 156 of the 178 patients (87%).

7.4.2 The perception of risk

Thus multiple factors, such as the rupture risk based on biomechanical indices and the diameter, the surgical risk and also the life expectancy of the patient, have to be considered. However, most important is the patient perspective as the patient is, ultimately, the one who decides. Therefore the patient's perspective is central interpreting these risks. The patient's understanding of the evidence is fundamental to acquire high value patient centred care.[123] Patients still have to face a difficult decision as both waiting and surgery could be life threatening. It is seen that patients often tend to choose surgery.

Hoffman and Del Mar[123] showed that patients overestimated benefits and underestimated harms for most interventions. Thus, a mismatch between the patient's expectations and the evidence is present. This mismatch is due to several factors: general societal bias towards more rather than less care, a good access to care and, patient's perception towards AAA. Furthermore, the risk of the surgery is chosen voluntary while the risk of rupture is not. For the patient the latter risk is involuntary and unsure. Patients experience and AAA as a 'ticking time bomb'.[124] It is seen that people perceive voluntary risks as less troublesome than involuntary risks.[125,126]

Hansson et al.[124] showed that patients with an AAA under surveillance appreciate having the knowledge but that they were also feeling anxiety, worry about the fragility and finiteness of their lives. As most AAA are asymptomatic and found incidentally during examinations, such AAA is only visible to experts. In other words, to be aware of the invisible embodied risks[127] a patient has to rely on the knowledge of experts and their expert advice and not on personal experience (which generally lead to action). Therefore, patients feel often much calmer after they talked to a physician. Regular check-ups only gave some additional insurance.[124]

A physician should guide the patient through the decision making process. The success of expert guidance depends on the patients trust in a physician. For instance, some patients worry that a physician is mainly focused on healthcare costs. Therefore, additional measures could help to guide the patient through the process. That the physician first understand the risk herself (or himself) is important. Only, then it can be effectively communicated. Statistical risks and quantitative indices must be translated into clinical knowledge and applied to individual cases. Biomechanical indices are acquired through a more complex process compared to the maximum diameter. Therefore, the results might be harder to interpret. For both physician and patient could be helped by decision boxes to facilitate the understanding of evidence. A decision box is a (one page) summary of research and diagnostic based information, stated simply and clearly. It contains a combination of numbers, graphics and narratives to facilitate optimal uptake. There are multiple key components according to Trevena et al. present the patient's tailored chance on the risk that a potential event will occur. This presents the patient specific changes in estimated outcome, conveys uncertainty, visual formats, formats for understanding outcome over time and narrative evaluation.[128] Much research is done into the design of an effective decision box as design could influence the

communication.[129] Thus before implementing a decision box, the selected box should be carefully designed.

To conclude, the decision to treat might be more complex than presented at first. A threshold to treat for biomechanical indices may aid the decision making process but also loses a part of the patient's specific risk profile. Both the physician and the patient should understand the risks to together create an optimal decision for this specific patient.

8 CONCLUSION

The aim of my thesis was evaluate the feasibility of biomechanical modelling to predict AAA rupture and to clarify the additional clinical role of biomechanical indices based on diagnostic imaging in the rupture risk assessment of patients with AAA compared to the maximum diameter. The systematic review showed a high potential for biomechanical indices. Especially the PWS and PWRI are promising as these parameters improve rupture prediction compared to the diameter. However, the presented clinical data show a different result. A significant difference of PWS, PWRI and RRED was seen between AAA and RAAA, but this change was insignificant after diameter matching. No clear improvements of the risk assessment compared to the diameter were seen, as the selected groups show a large overlap in their risk profiles and the areas under the ROC curves were similar. Nevertheless, combining the biomechanical criteria and the maximum diameter likely gives a full overview of the patient specific risk, especially in the small to medium sized aneurysms.

Although challenges remain, biomechanical analysis is promising in the assessment of AAA rupture risk as it incorporates several major factors, such as geometry, tissue properties and patient specific risk factors.

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APPENDIX

1 LIST OF ABBREVIATIONS

3D	Three dimensional
AAA	Abdominal aortic aneurysms
BMI	Body mass index
BP	Blood pressure
CFD	Computational fluid dynamics
COPD	Chronic obstructive pulmonary disease
CTa	Computer tomography angiography
CVD	Cardiovascular disease
ECG	Electrocardiography
FEA	Finite element analysis
FEARI	Finite element analysis rupture index
FSI	Fluid structure interaction
ILT	Intraluminal thrombosis
MAP	Mean arterial pressure
MMP	Matrix metalloproteinase
MR	Magnetic resonance
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PWRI	Peak wall rupture index
PWS	Peak all stress
PWSS	Peak wall shear stress
RAAA	Ruptured abdominal aortic aneurysms
ROC	Receiver operating characteristics
RRED	Rupture risk equivalent diameter
SAAA	Symptomatic abdominal aortic aneurysms
SMD	Standard mean difference
UMCG	University medical centre Groningen

2 LIST OF FIGURES

3 LIST OF TABLES