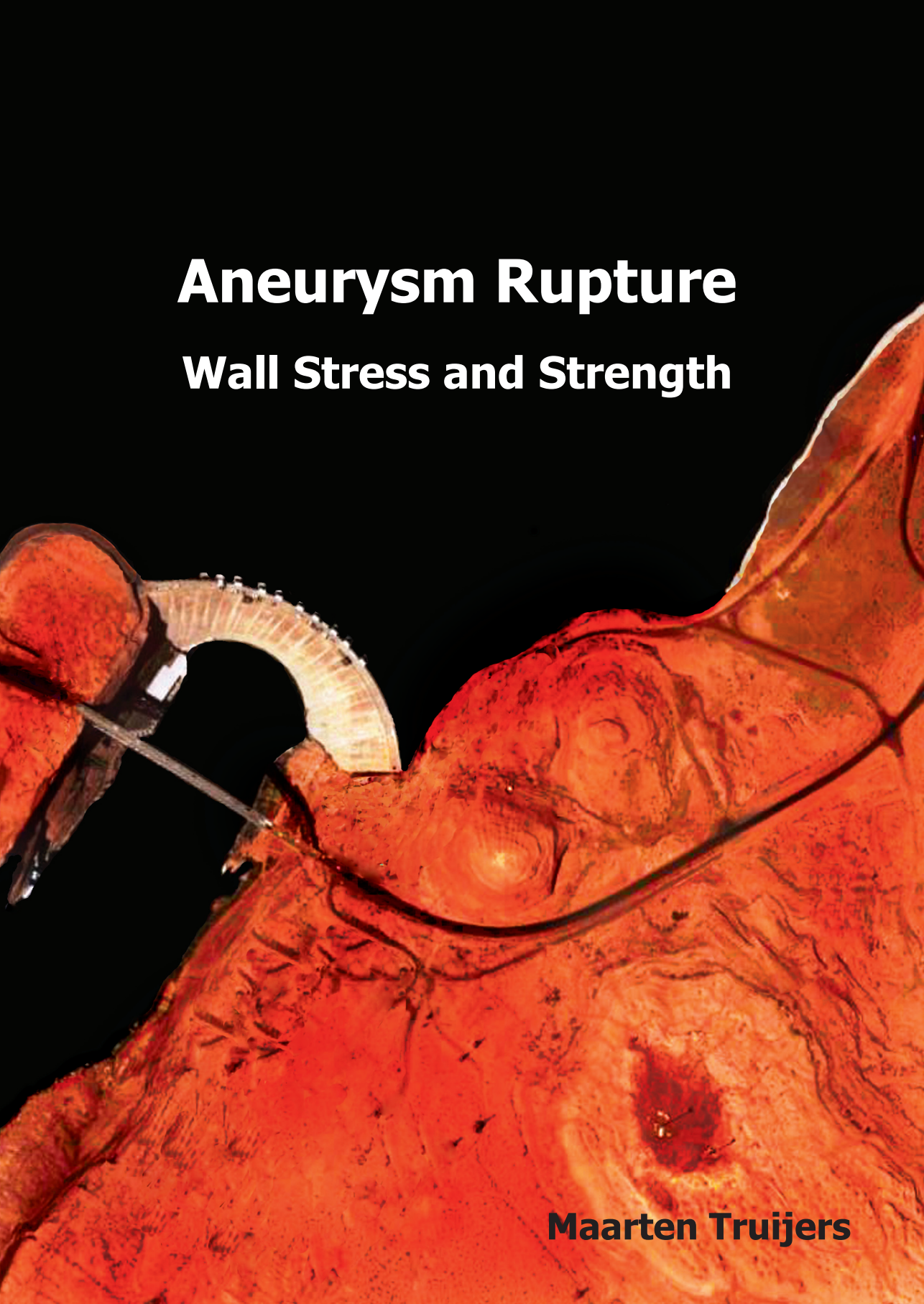
Aneurysm Rupture

Wall Stress and Strength



Maarten Truijers

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Wall Stress and Strength

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Maarten Truijers
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Promotores
Prof. dr. J.D. Blankensteijn
Prof. dr. L.J. Schultze Kool
Prof. dr. W.J.G Oyen

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General Introduction

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General introduction.

Abdominal aortic aneurysm (AAA) rupture is a common cause of death in the aging population.[1] If left untreated, nearly all aneurysms continue to enlarge until rupture; a catastrophic event that carries a high mortality.[2] Due to the high mortality associated with rupture, prophylactic surgical repair is necessary when the risk of rupture exceeds the risks of surgery.[3] The risk of mortality following conventional (open) surgical repair is approximately 4,6-8,2%.[4] Although endovascular aneurysm repair (EVAR) reduced peri-operative mortality, long term survival appears to remain unchanged.[5-7]
Since the inception of surgical aneurysm repair in the 1950s, rupture risk assessment has been based on aneurysm size.[8] Clearly, aneurysm rupture risk is associated with aneurysm size. However, while two large clinical trials have demonstrated the safety of observation of small (<5,5cm) AAA, small aneurysms do rupture.[9-12] At the same time, most aneurysm patients die with an intact aneurysm due to comorbid conditions.[4, 13] These issues illustrate the limitations of AAA diameter as the sole criterion for prophylactic aneurysm repair and warrant the need for a more accurate tool to predict aneurysm rupture.
Aneurysm rupture occurs when wall stress exceeds wall strength.[14] Information on both parameters might therefore refine rupture risk assessment and improve patient selection for prophylactic repair. The general aim of this thesis is to provide insight in aneurysm wall stress and strength.

Aneurysm wall stress.

The Law of Laplace dictates that wall tension and stress increases for larger aneurysms. The first studies on wall stress used this basic biomechanical law to determine wall stress in hypothetical AAA.[15] However, by idealizing its geometry as cylindrical or spherical this method failed to predict variations in wall stress due to local bulges or other subtle changes in aneurysm geometry.[16-18] With the use of computed tomography (CT), the reconstruction of patient specific three dimensional aneurysm models and a sophisticated mathematical technique (finite element analysis) wall stress analysis improved.[19]
The basic approach of the finite element method is to divide a complex anatomical structure (AAA) into geometrically well-defined smaller pieces or elements. The entire network of elements is called a mesh. Wall stress is determined by predicting movement of the mesh, influenced by the material properties of the aneurysm wall (e.g. stiff or elastic) and preset boundary conditions (e.g. blood pressure).[19] With the use of this technique, Fillinger et al have suggested that wall stress analysis is superior to diameter for the prediction of aneurysm rupture.[20] Although wall stress analysis seems promising for detecting patients at elevated risk of aneurysm rupture, most studied

patients had large abdominal aortic aneurysms and the potential of wall stress analysis for the identification of small AAA at risk of rupture is unclear.
A possible limitation of the currently used wall stress model is the lack of information on the biomechanical importance of intra-luminal thrombus. The effect of thrombus on aneurysm rupture risk is controversial. Some investigators have observed focal aneurysm wall hypoxia and subsequent wall weakening in the presence of thrombus.[21] Others have suggested a reduction in aneurysm rupture risk related to a possible thrombus 'cushioning effect' decreasing pressure transmission.[22, 23] Schurink et al, however, measured in vivo mean arterial and pulse pressure near the aneurysm wall and found no reduction in pressure transmission in the presence of thrombus.[24] The question therefore remains whether thrombus increases, decreases, or has no effect on wall stress and aneurysm rupture risk.

Aneurysm wall strength.

The most important structural components of the aortic wall are elastin and collagen. During aneurysm formation, the elastin content decreases, reducing the ability of the aneurysm wall to withstand cyclic strain.[25, 26] To compensate for this loss in elastic properties and prevent aortic dilatation, collagen synthesis is increased.[27] Once this mechanism fails, most likely due to persistent elastin and collagen degradation, the aneurysm wall weakens and ultimately ruptures.[27]
The involvement of matrix metalloproteinase (MMP) in aneurysm disease and aneurysm wall remodelling is well established.[28] Especially, MMP-2 and -9 appear to play an important, yet different role in AAA formation, progression, and rupture.[26, 27] Results from clinical investigations suggest an association between MMP-2 activity and early aneurysm dilatation, whereas elevated levels of MMP-9 predisposed larger AAA to aneurysm rupture.[27, 29, 30] Because of this relation between MMP-2 and MMP-9 expression and aneurysm progression, it was postulated that "hot spots" of increased MMP-2 and -9 activity may lead to focal wall weakening and even rupture.[31, 32]
Previous studies using immunohistochemical analysis and in situ hybridization identified macrophages and neutrophiles as the main source of matrix metalloproteinases.[33] This finding could have important consequences for new imaging techniques such as functional magnetic resonance (MR) imaging and 18-fluorodeoxyglucose enhanced positron emission tomography (FDG-PET). Both techniques allow the non-invasively identification of inflammation and could therefore provide information on aneurysm disease and ultimately wall strength.
The introduction of a new contrast agent for magnetic resonance (MR) imaging in the early 1990s resulted in a potentially useful technique for the non-invasive identification of aneurysm wall inflammation. The contrast is composed of ultrasmall superparamagnetic particles of iron oxide (USPIO). Due to the magnetic properties of

the contrast, accumulation results in marked signal loss (blackening) on iron-sensitive MR sequences (T2*). After intravenous injection, the particles slowly migrate from vascular to interstitial space to be internalized by macrophages.[34] Because of this cell-specificity for macrophages and the central role of macrophages in atherosclerosis, USPIO-MR has been studied extensively for the detection of vulnerable atherosclerotic plaques.[35] A pilot study by Kooi et al showed USPIO uptake in atherosclerotic plaques of the carotid artery and Howarth et al focused on the differential uptake of USPIO in symptomatic and asymptomatic atherosclerotic plaques.[36, 37] Like rupture prone vulnerable atherosclerotic plaques, aneurysm rupture is characterized by extensive inflammation of the arterial wall.[27] However, in spite of the potential of USPIO-MR as a possible selection tool for prophylactic aneurysm repair, current literature on USPIO uptake in the aortic wall is limited to a single case report.[38]
A second technique for the non-invasive detection of inflammation is FDG-PET. FDG-PET relies on the increased uptake of radioactive labelled glucose (FDG) in metabolically active (inflammatory) cells. After intracellular accumulation, FDG disintegrates resulting in positron and gamma ray emission easily detected by cameras surrounding the patient. By combining and fusing images of positron emission and computer tomography (FDG-PET/CT), the exact location of increased metabolic activity is depicted.[39] This could result in the identification of focal hotspots of aneurysm wall inflammation and decreased wall strength.

Main objective and questions to be answered

The main objective of this thesis is to provide insight in aneurysm wall stress and strength. To this end we performed several studies, designed to answer the following questions:

1. What is the current status of cross-sectional imaging?
2. Has CTA based wall stress analysis the potential to detect small aneurysms at risk of rupture?
3. What is the effect of thrombus on the forces (stress) exerted on the aneurysm wall?
4. Is aneurysm wall strength related to inflammation induced matrix metalloproteinase (MMP) activity?
5. Is it possible to non-invasively identify macrophages infiltrated in the aneurysm wall using utrasmall particles of iron oxide and magnetic resonance imaging (USPIO-MR)?
6. Is it possible to non-invasively identify aneurysm wall inflammation using integrated positron emission and computed tomography (FDG-PET/CT)?

Outline of the thesis

In **chapter 2**, current imaging techniques for the preoperative assessment of abdominal aortic aneurysm morphology are described. With the introduction of endovascular aneurysm repair, computed tomography angiography (CTA) developed as the modality of choice for imaging abdominal aortic aneurysms. One of the biggest advantages of CTA is the ability to reconstruct raw data in various ways which resulted in new and promising CTA applications.

One of the new CTA applications is aneurysm wall stress analysis. By combining geometrical CTA information, blood pressure data and computational biomechanics, the forces on the aneurysm wall (wall stress) are computed. The potential of this technique for the identification of small AAA (<5,5cm) at risk of rupture is evaluated in **chapter 3.**

A limitation of wall stress analysis the lack of data on the effect of thrombus dynamics on aneurysm wall stress. Using a second CTA post-processing tool (dynamic EKG-gated CTA), the potential effect of intraluminal thrombus on pressure transmission to the aneurysm wall is described in **chapter 4**.

In **chapter 5**, we studied the correlation between MMP activity and aneurysm wall strength.

As aneurysm wall strength is associated with MMP secretion by infiltrated macrophages and neutrophiles, the non-invasive identification of these inflammatory cells could provide valuable information on aneurysm disease. We studied the use of both MRI (**chapter 6**) and PET/CT (**chapter 7**) for the non-invasive identification of aneurysm wall inflammation.

Chapter 8, contains the general discussion, including future prospectives and conclusions.

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Assessment and imaging of abdominal aneurysms (comparison of modalities and selection of patients for endovascular repair)

2

M. Truijers
L. J. Schultze Kool
J. D. Blankensteijn

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Introduction

Endovascular aneurysm repair (EVAR) has emerged as a valuable alternative to conventional open aneurysm repair. In contrast to open repair, the success of EVAR largely depends on an accurate preoperative assessment of aneurysm morphology. The use of EVAR in patients considered anatomically unsuitable increases the risk for adverse outcome, including endoleak, stent migration and aneurysm rupture.[1] Several imaging modalities have been proposed to facilitate the preoperative assessment of aortic morphology. The ideal modality should be non-invasive and still provide all information needed for EVAR. This includes information on the dimensions and quality of the arterial access site, aneurysm and proximal and distal sealing zones.[2]

Imaging modalities

The imaging modalities discussed in this chapter are trans-abdominal ultrasound (US), intravascular ultrasound (IVUS), digital subtraction angiography (DSA), computed tomography angiography (CTA) and magnetic resonance angiography (MRA). All these modalities have been proposed for the preoperative assessment of aneurysm morphology and have their distinct advantages and pitfalls.

Trans/abdominal ultrasouns (US)
Trans-abdominal ultrasound is the method of choice to detect aortic aneurysms; it is non-invasive, generally available and allows accurate diameter measurements. US, however, fails to visualize comprehensively the orifices of aortic side branches, tortuous vessels and infrarenal dimensions. Because of these disadvantages US is insufficient for the preoperative planning of EVAR.

Intravascular ultrasound (IVUS)
Intravascular ultrasound (IVUS) is a catheter based invasive imaging modality. IVUS catheters are advanced through the femoral and iliac arteries into the aneurysm and infrarenal neck. This produces real-time information on vascular anatomy and vessel wall morphology. Because of this real-time imaging some authors advocate the use of IVUS intra-operatively during endograft deployment.[3, 4] They postulate that the use of IVUS before complete endograft deployment could result in final adjustments to the endograft position. This could improve the accuracy of endograft placement leading to possibly less graft migration or type I and II endoleak. Preoperatively, IVUS produces detailed axial images. An automated vessel analysis protocol is used to generate longitudinal reconstructions. These reconstructions facilitate the anatomical characterization of the proximal sealing zone and provide comprehensive insight in the relation of side branches to the aorta.[5]

IVUS however has limitations as the measurement of vessel diameter and length depend on the position of the catheter. Unfortunately, the catheter does not always follow true vessel centreline. This results in less accurate length measurements and elliptical-shaped artefacts, compromising diameter assessment.[6] Although IVUS provides quantitative and qualitative information on the extent and composition of atherosclerotic plaques, heavily calcified plaques produce severe shadowing, complicating image interpretation.
In conclusion, IVUS potentially delivers valuable information during endograft deployment. However due to the invasive character, inaccurate diameter and length measurements, additional costs and procedure time the use of IVUS as sole imaging modality for aneurysm morphology assessment is limited.

Digital substraction angiography (DSA)
The introduction of digital subtraction angiography significantly reduced examination time, contrast material load and patient discomfort compared to conventional angiography.[7] Magnification artefacts caused by divergence of the x-ray beam are reduced by using calibrated catheters. Although this improves aortic length and angulation measurements superstiff guidewires are needed to reduce length underestimation in tortuous vessels and length overestimation in saccular aneurysms (figure 1). DSA allows the accurate assessment of aortic sidebranch patency, this is particularly important for the construction of tailor-made branched or fenestrated endografts for complex aneurysms (figure 2).[8] DSA also facilitates adjunctive endovascular procedures in patients with adverse aneurysm or access artery morphology. Arterial access is improved by balloon angioplasty of focal iliac artery narrowing and aorto-iliac aneurysms often require fluoroscopy controlled coil embolization of the internal iliac artery to allow safe endograft coverage of the internal iliac artery orifice.
The main limitation of DSA is that it fails to visualize mural thrombus, compromising diameter measurement and landing zone assessment. To overcome this shortcoming DSA has to be combined with axial computed tomography (CT) or magnetic resonance (MR) imaging for preoperative EVAR planning.[9] With the ongoing development of non-invasive imaging modalities like CT and MR and their image post-processing tools the preoperative use of DSA is limited, especially since DSA is still associated with a small but definite risk of complications.[10]

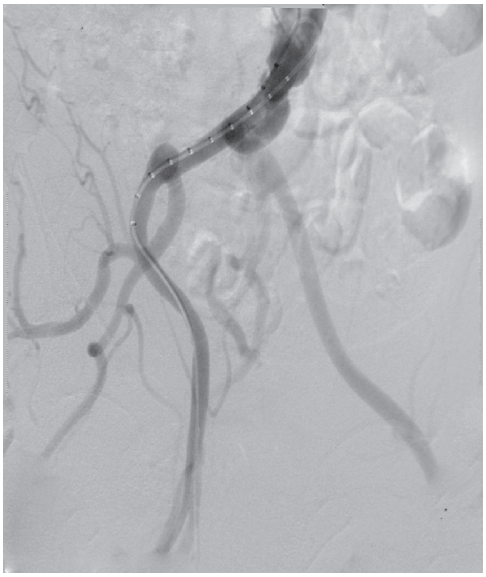

Figure 1. DSA using calibrated catheter. The calibrated catheter does not follow true vessel centreline.

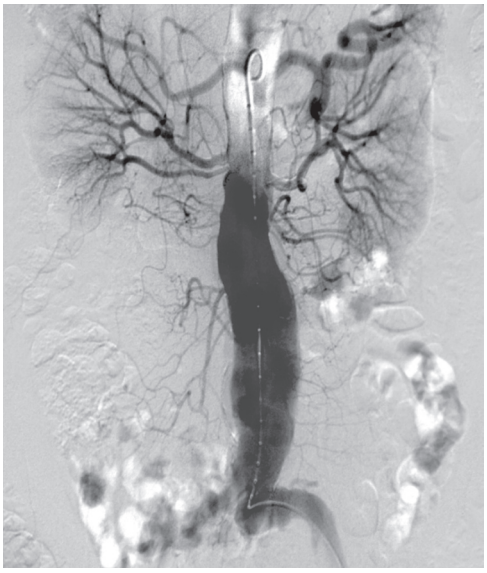

Figure 2. DSA with measuring pigtail. Double renal artery on the right.

Computed tomography angiography (CTA)

In helical or spiral computed tomography the x-ray tube and detector (gantry) rotate continuously as the patient moves through the scanner. The result is a raw dataset, representing the helical path of the x-ray beam through the scanned volume. From this primary raw data, images can be reconstructed (post-processed) in several planes and even into three-dimensional models (figure 3). By the additional infusion of intravenous contrast, spiral CTA potentially combines the advantages of conventional slices-by-slice computed tomography and angiography. The diagnostic performance of spiral CTA however depends on the appropriate choice of acquisition parameters.[11] The most important acquisition parameters are table feed per gantry rotation (TF) and slice thickness or collimation (SC). Both TF and SC are determined by overall scan range and data acquisition time. CTA of the abdominal aorta starts above the celiac artery and includes the external iliac artery and preferably the femoral bifurcation, resulting in a large scan range. In an attempt to keep scanning time, subsequent tube heating and motion artefacts limited the patient has to be moved through the scanner at high table speeds, leading to an increase in slice collimation and suboptimal spatial resolution. This inverse relation between scan range and slice collimation has been overcome by the introduction of Multi-Slice spiral Computed Tomography (MSCT).[12] MSCT allows the simultaneous acquisition of multiple slices during one gantry rotation. The effect of the number of slices on scanning time and resolution is explained by the following example.

The scan range from the celiac artery to the femoral bifurcation is approximately 35cm. Scanning this range using a single slice spiral CT (SSCT), with a gantry rotation time of 1 second, a collimation of 5mm and a pitch of 1 (table speed/collimation) takes 70 seconds. Scanning the same area with a 16-slice CT, using the same pitch and twice the table speed, results in a slice collimation of 0,625mm and total scanning time of only 35 seconds, increasing both resolution and scanning time. At our institution a 64-slice CT is available for elective preoperative aneurysm morphology assessment, this results in a maximal spatial resolution of 0.625mm (SC) during a total data acquisition of approximately 9 seconds (TF=40mm/s).

Besides an improvement in acquisition parameters, MSCT also allows an improvement in reconstruction parameters.[12] MSCT acquires large amounts of data. A special interpolation scheme (z-filtering) uses of all this data for the final reconstruction. The final slice thickness or spatial resolution is therefore only determined by scanner configuration (number of slices and effective detectorsize) and the selected reconstruction increment (RI). RI determines the degree of overlap between subsequent slices. At our institution we use an effective slice thickness of 1mm with an RI of 0,7 (30% overlap). This final stack of overlapping reconstructed images is used for further image post-processing. The most useful post-processing tools for the assessment of aortic morphology include, multi planar reconstruction (MPR), maximum intensity projections (MIP), volume rendering (VR) and shaded surface display (SSD).

Multi planar reconstructions are generated to visualize the aorta in axial, coronal, sagittal and orthogonal orientation. A commercially available workstation is used to scroll through the 2-dimensional stack of images (cine mode). Orthogonal images, reconstructed around the central axis (centreline) of the vessel, allow the visualization of the aorta and iliac arteries in a plane perpendicular to blood flow. The perpendicular images and centrelines are used for diameter and length measurements (figure 4).[13] Early diameter assessment using axial CT images was often inaccurate as tortuous vessels appeared elliptical, leading to an overestimation of vessel diameter. To compensate for this elliptical appearance, it has been proposed that true diameter corresponded with the smallest diameter on axial images. This however resulted in diameter underestimation for truly elliptical vessels. The use of orthogonal images has overcome this problems and renders true aneurysm diameter.[14] Centrelines are used in length measurements. Unlike IVUS or DSA catheters the virtual centreline follows the vessel lumen without bulging into an aneurysm sac or following the shorter route through tortuous vessels. Furthermore the final graft length and diameter can be calculated by manually adjusting the centreline and planar reformats to the expected endograft path. Some software applications even allow the placement of a ‘virtual graft®’ (Medical Metrx Solutions, West Lebanon, USA) within the vessel lumen.

The second useful image post-processing tool is maximum intensity projection (MIP). This tool visualizes the densest voxels for the identification of luminal contrast and wall calcifications. The result is an angiographic-like 2 dimensional image. This image can

be visualized from every desired angle which is useful for the pre-operative assessment of iliac artery calcifications or occlusions.

The final image post-processing tools, Volume Rendering (VR) and Shaded Surface Display (SSD) provide three dimensional virtual images of the aorta and relevant side branches (figure 5). Both techniques rely on the difference in voxel attenuation factor for different anatomical structures, a process called segmentation. In SSD only pixels above a certain threshold are retained for the identification of surfaces. An illusion of depth is created by displaying virtual grey scale reflections on these created surfaces. VR allows the segmentation of the entire dataset by applying color-codes to preset attenuation factors. This results in the identification of lumen, thrombus and calcification. VR produces reliable three dimensional images of tortuous vessels. By rotating the model, accurate measurements of aortic neck and iliac artery angulations can be made.

CTA has two main disadvantages. The use of ionizing radiation and the necessity for nephrotoxic contrast. With the use of MSCT, radiation exposure initially increased. In order to resolve this problem effective milliampere was introduced. This allows adjustment of radiation dose in function of slice collimation and table speed. The use of thin collimation however still requires fair amounts of ionizing radiation. At our institution we use an application called CARE Dose® (Siemens Medical Solutions, Erlangen, Germany). This application assesses the overall patient anatomy (fat, length, size) prior to actual data acquisition. The result is an estimation of individually required radiation, leading to a reduction of patient dose without compromising image quality. The second disadvantage of CTA is the use of nephrotoxic contrast. MSCT reduces the need for nephrotoxic contrast by allowing shorter data acquisition and by optimizing the delay between contrast admission and data acquisition (bolus triggering). In bolus triggering a region of interest is selected (e.g. aorta) after which the contrast is injected. When the contrast attenuation in the region of interest exceeds the preset trigger threshold (120 Houndsfeld Units) the scanner starts acquiring data reducing the need for contrast. In spite of this reduction in contrast dose prehydration is often necessary for patients with renal impairment. Furthermore even in limited dose intravenous contrast has the inherent risk for idiosyncratic reactions.

In conclusion, CTA with the use of MSCT and image post-processing, combines the advantages of conventional CT and digital subtraction angiography. CTA is the only single imaging modality that allows a thorough assessment of aortic morphology and provides all the information needed for endovascular aneurysm repair.[15-17]

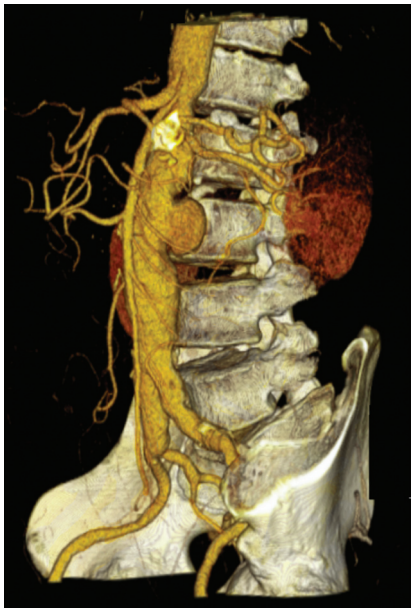

Figure 3. CTA. Three dimensional reconstruction of a saccular abdominal aortic aneurysm

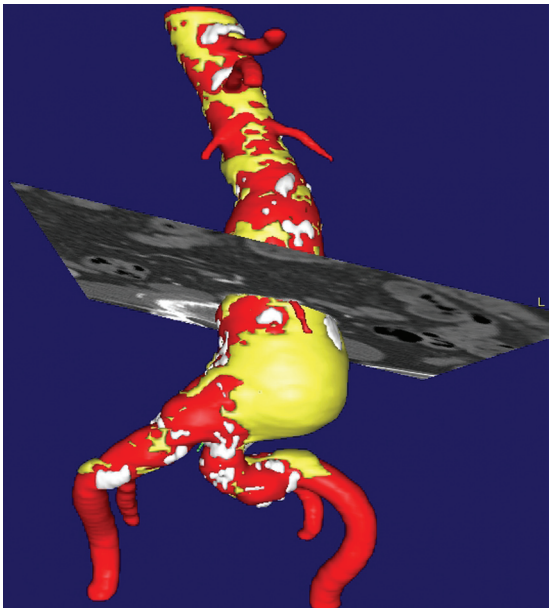

Figure 4. CTA, Slice reconstructed perpendicular to vessel centreline.

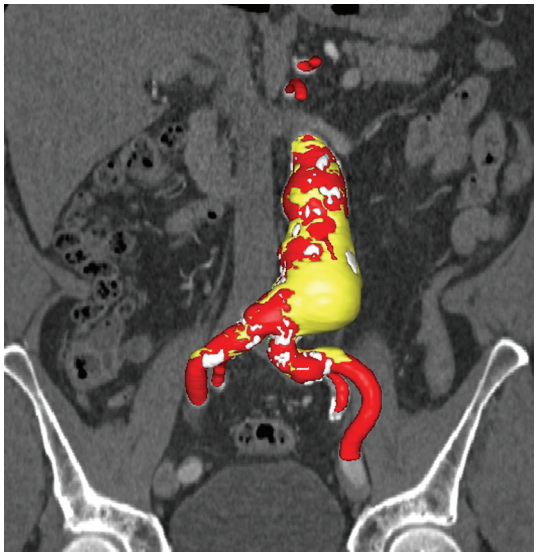

Figure 5. CTA, Volume Rendering

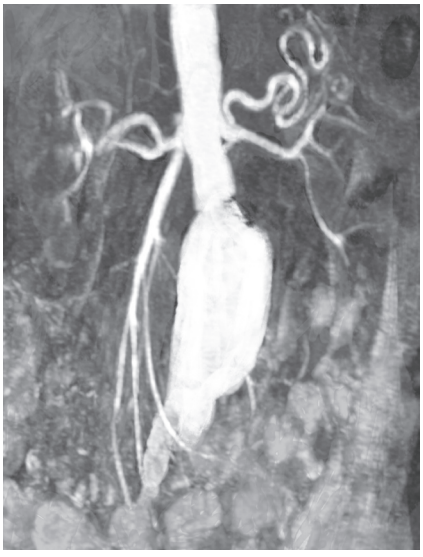

Figure 6. MRA, Maximum intensity projection (MIP)

Magnetic resonance angiography (MRA)

Since the introduction of magnetic resonance angiography several imaging protocols have been proposed. All these protocols have their distinct advantages and disadvantages. Spin-Echo (SE) MRA depends upon a signal void (black-blood) created inside the vessel lumen by flowing blood. This allows the identification of the vessel wall and intraluminal thrombus. Both spin-echo MRA and bright-blood techniques, like time-of-flight MRA, rely on the visualization of blood flow to distinguish between vessel lumen and arterial wall. Due to this flow dependency the visualization of aortic aneurysms is often limited as flow through the aneurysm is usually slow. In addition, both black- and bright-blood techniques require fairly long acquisition times which could result in motion artefacts.[18] The introduction of contrast-enhanced MRA resolved the problem of flow dependency by the application of gadolinium. Gadolinium induces a T1 shortening effect, limiting saturation problems due to slow blood flow and allowing faster data acquisition.[19] By lowering the required acquisition time new applications of MRA became feasible. In cine-MRA images are obtained during different phases of the cardiac cycle resulting in a dynamic view of the vessel wall. The potential of this technique to visualize actual vessel translation and endograft motion after EVAR has been demonstrated.[20] Besides the continuous development of MRA the main advantages of MRA remain the lack of ionizing radiation, and the ability of image post-processing. Like CTA, image post-processing of MRA includes multi planar reconstructions (MPR), maximal intensity projection (MIP, figure 6), volume rendering (VR) and shaded surface display (SSD).
MRA however has practical limitations due to poor equipment availability, associated high costs and relatively long acquisition times (up to one hour). Furthermore not all patients are eligible for MRA because of metallic implants (prosthesis, pacemaker or endograft) or claustrophobia. The main limitation of MRA however is the low sensitivity for iliac artery and sealing zone calcification this could lead to complicated arterial access and inappropriate endograft fixation. Like ionizing contrast gadolinium is nephrotoxic. MRA however still plays an important role in patients with renal impairment as the dose of gadolinium used during MRA is limited.

Morphological criteria

The technical success of EVAR, uncomplicated and complete exclusion of the aneurysm, depends on arterial access, safe and accurate device deployment and adequate fixation of the graft above and below the aneurysm.[2] Arterial access is needed for device delivery. If the iliac or femoral arteries are too small, tortuous or calcified, access is impaired possibly precluding EVAR. Safe device deployment is possible if the deployed device does not cover essential branch vessels or causes distal embolization. The main anatomical criteria that could exclude patients for EVAR however concern the dimensions and morphology of the proximal and distal aneurysm

neck. Mismatch of graft-aneurysm dimensions at one of the sealing zones could result in type I endoleak, graft migration and increase the risk for aneurysm rupture. Several criteria have been purposed to standardize and stratify the morphological risk factors associated with adverse outcome after EVAR. These criteria are summarized in table 1 and figure 7.[2, 21] Table 1 also contains the recommendations for access site and sealing zone dimensions made by three manufacturers of commercially available endografts.

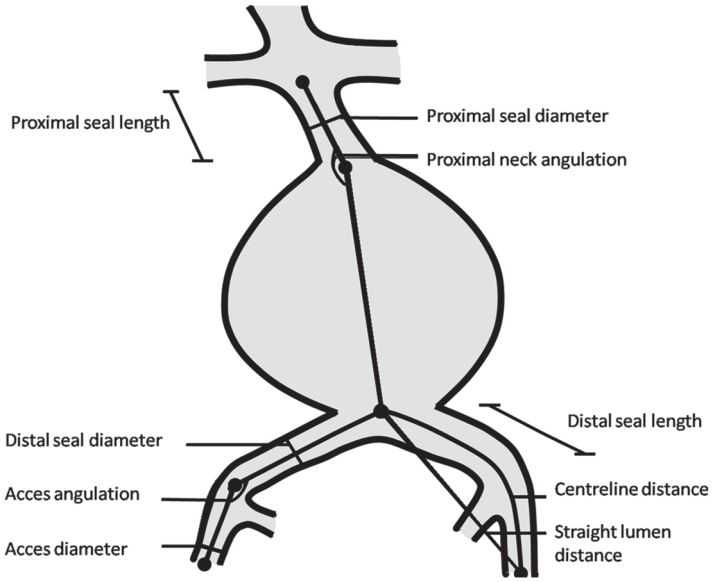

Figure 7. Summary of morphological criteria for endovascular aneurysm repair. Adapted from Chaikof et al.[23]

Arterial access

Iliac and femoral artery anatomy is an important factor for endovascular aneurysm repair. High vessel tortuosity, heavy calcifications and small arterial dimensions could complicate EVAR and preclude percutaneous access artery closure, requiring femoral artery cutdown. Unfavourable access artery dimensions are associated with an increased risk of arterial dissection, failure to deliver the endograft and distal embolization.[22] Although focal narrowing and near iliac artery occlusions can be treated by balloon angioplasty and iliac or femoral artery tortuosity can be overcome by straightening the vessels using traction, adverse access artery anatomy could lead to iliac artery damage and subsequent conversion to open or combined endovascular and open (hybrid) aneurysm repair.

Table 1. Stratification of morphological criteria.

Morphology	None	Mild	Moderate	Severe	Aneurx®	Zenith®	Excluder®
Arterial access							
diameter	>10	<10mm	<8mm	<7mm	>7mm	>7.5mm	>6mm
stenosis	absent	Diameter >7mm Lenght <3cm	Diameter <7mm Lenght <3cm	Diameter <7mm Lenght >3cm			
calcification	Absent	<25% vessel length	<50% vessel length	>50% vessel length			
Tortuosity [a]	<1.25	<1.5	<1.6	>1.6			
Angulation [b]	>160°	>120°	>90°	<90°			
Deployment							
Aneurysm							
Angulation [c]	>160°	>140°	>120°	<120°			
Tortuosity [a]	<1.05	<1.15	<1.2	>1.2			
Thrombus [d]	Absent	25% CSA	<50% CSA	>50% CSA			
Side Branches							
Aortic branches	None	1 vessel	2 vessels	2 vessels and IMA >4mm			
Hypogastric Artery	Patent	1 occluded	1 occluded 1 >50% stenosis	2 occluded			
Sealing zone							
Proximal neck							
Length	>25mm	>15mm	>10mm	<10mm	>10mm	>15mm	>15mm
Diameter	<24mm	<26mm	<28mm	>28mm	<26mm	<28mm	<26mm
Angulation [e]	>150°	<150°	<135°	<120°	>135	>120°	>120°
Calcification - thrombus	<25% circumference	<50% circumference	<75% circumference	>75% circumference			<25% circumference
Distal neck							
Length	>30mm	<30mm	<20mm	<10mm	>10mm	>10mm	>10mm
Diameter	<12.5mm	<14.5mm	<17mm	>17mm	<15mm	<20mm	<13.5mm

[a] Tortuosity = centerline distance/straight lumen distance

[b] Access site angulation= Angle between common femoral artery and aortic bifurcation

[c] Aortic angulation = most acute angle in the pathway between the lowest renal artery and the aortic bifurcation

[d] CSA= cross-sectional area

[e] Proximal neck angulation = angle between the axis of the proximal neck and the axis of the aneurysm

Adapted from Chaikof et al and Hellinger et al. [2,21]

Device deployment

Safe device deployed is possible if the device does not cover essential sidebranches or causes distal embolization. Consequently, the anatomy of the aneurysm and potentially related side branches should be assessed before deployment. The assessment of aneurysm morphology includes aneurysm diameter and length measurement, estimation of tortuosity and calculation of luminal thrombus load. Although no absolute contraindication for EVAR, large aneurysms (>6cm) often have more complex anatomical characteristics and are associated with a significant longer operation time and more proximal endograft migration.[23] Length assessment of the infrarenal aorta (lowest renal artery to aortic bifurcation) is important before deployment of modular bifurcated endografts. These endografts are comprised of two components, the main body with ipsilateral iliac limb and the contralateral iliac limb. Fixation and deployment of the contralateral limb within the main body requires catheterization of the main body from the contralateral access artery. This is only possible when the bifurcation of the selected main body is located above the aortic bifurcation. Aneurysm thrombus load and tortuosity should be assessed as the risk of embolization during EVAR is determined by the amount of intraluminal thrombus and the severity of tortuosity of the entire deployment pathway.[2]

The identification of patent aortic side branches is essential before deployment of the endograft. Accessory renal arteries are present in 15-30%, failure to identify these aberrant vessels, could lead to coverage and subsequent renal impairment or type II endoleak (back bleed). The inferior mesenteric arteries are generally excluded from the circulation after deployment. Although this rarely causes complications, patients with (near) occlusions of both the superior mesenteric artery and celiac artery could suffer from bowel ischemia.

Proximal and distal sealing zone

Complete and durable aneurysm exclusion demands an adequate seal between the endograft and the arterial wall. Failure to achieve adequate seal results in type I endoleak, graft migration and persistent increased rupture risk. Seal quality is largely determined by the morphology of the proximal and distal landing zone or ‘aneurysm neck’. The proximal neck is defined as the distance between the most caudal renal artery and the beginning of the aneurysm. Most commercially available endografts require a minimal proximal neck length of 15mm and a maximum neck diameter of 30mm. Other morphological factors related to proximal endograft fixation include the amount of thrombus and calcium within the proximal neck, the angle between the axis of the infrarenal neck and aneurysm and the shape of the proximal neck (e.g. tapered, reverse tapered, straight or bell shaped).[24, 25] In absence of a suitable infrarenal landing zone, several commercially available endografts allow suprarenal fixation with bare wire struts. Whether suprarenal fixation protects against proximal migration and is safe in regard to renal artery patency, remains to be investigated.[26]

The distal sealing zone or neck determines the type of endograft used. Since the introduction of EVAR several different endograft designs have been proposed. The first straight or tube endografts were used in patients with aneurysms confined to the aorta. These grafts required a distal sealing zone, between the aneurysm and the aortic bifurcation, with a length of at least 20mm and a diameter no larger than 25mm. Because only few patients met these anatomical criteria the need for endografts passing the aorta bifurcation was established. This has lead to the development of modular bifurcated endografts and aorto-uni-iliac devices with contralateral iliac occlusion and femoral crossover bypass. These devices are anchored distally in the common or external iliac artery. Fixation in the external iliac artery however, requires adjunctive coil embolization of the internal iliac artery to prevent type II endoleak. The morphological criteria for the distal sealing zone vary for the different commercially available endografts. Generally the distal sealing zone should be at least 10mm long and maximum 20mm wide. Like for the proximal aortic neck, assessment of the distal aortic neck includes the amount of thrombus and calcium and the degree of vessel tortuosity.
Although the number of patients eligible for EVAR is often limited by adverse proximal and distal sealing zone anatomy, new developments in endograft design and operative procedures render more patients suitable for EVAR. Scalloped, fenestrated, and even branched endografts have been developed. These endografts allow a suprarenal fixation while visceral sidebranches like the renal, mesenteric and even celiac artery remain patent.[27] Furthermore complex aneurysm and vascular anatomy can be modified by adjunctive endovascular or surgical (hybrid) procedures.[28]

Conclusion

Since the introduction of modular bifurcated endografts more patients are considered suitable for EVAR. These devices allow the distal sealing zone to be chosen almost arbitrarily between the common iliac and femoral artery. Although the development of new endovascular devices allows more flexibility, the dimensions and quality of the proximal and distal sealing zone, access site and aneurysm side branches still determine the success of EVAR. The selection of patients based on morphological criteria requires accurate preoperative and preferably non-invasive imaging.
Multi-slice CTA is the only single source imaging modality that provides all necessary information for the preoperative assessment of aortic morphology. Raw scan data are acquired in a single breath hold and transferred to an image post-processing workstation for multi planar reconstructions (MPR), maximal intensity projections (MIP), three dimensional shaded surface display (SSD) and volume rendering (VR). MPR and MIP allow the accurate assessment of thrombus, calcium, diameter and length, while iliac artery and infra renal neck tortuosity and angulation are assessed with VR and SSD reconstructions. Although CTA has disadvantages (nephrotoxic contrast and ionizing

radiation), CTA is the method of choice for patient selection based upon morphological criteria.
MRA has been introduced as a possible replacement for CTA. However, in spite of recent developments in image post-processing and contrast enhanced scanning protocols, CTA remains the primary single source imaging modality for EVAR planning. This is mainly due to practical considerations and the low sensitivity of MRA for intravascular calcium.

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Wall stress analysis in small asymptomatic, symptomatic and ruptured abdominal aortic aneurysms

3

M. Truijers
J. A. Pol
L. J. Schultze Kool
S. M. van Sterkenburg
M. F. Fillinger
J. D. Blankensteijn

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Abstract

Objectives
To evaluate the potential of wall stress analysis for the identification of abdominal aortic aneurysm (AAA) at elevated risk of rupture in spite of small diameter.

Materials and methods
Thirty patients with small AAA, 10 asymptomatic, 10 symptomatic and 10 ruptured, were included. Demographic data and results from physical examinations were recorded in a retrospective fashion. After CT-evaluation and the creation of a patient specific 3D model, wall stress was calculated using the finite element method.

Results
No differences were observed in diameter between asymptomatic, symptomatic or ruptured aneurysms (5.1 ± 0.2cm vs. 5.1 ± 0.2cm vs. 5.3 ± 0.2cm respectively; p=0.57). Peak aortic wall stress at maximal systolic blood pressure is significantly higher in ruptured than asymptomatic aneurysms (51.7 ± 2.4N/cm^2 vs. 39.7 ± 3.3N/cm^2 respectively; p=0.04). Wall stress analysis at uniform blood pressure, performed to correct for higher blood pressure in the symptomatic and rupture group did not result in significant differences in peak wall stress (asymptomatic 31.7 ± 2.3N/cm^2; symptomatic 30.5 ± 1.3N/cm^2; rupture 36.7 ± 4.0N/cm^2; p=0.261).

Conclusions
Wall stress analysis at maximal systolic blood pressure is a promising technique to detect aneurysms at elevated aneurysm rupture risk. Since no significant differences were found at uniform blood pressure, the need for adequate blood pressure control in aneurysm patients is reiterated.

Introduction

The prevalence of Abdominal Aortic Aneurysm (AAA) is estimated between 4.1% and 14.2% in men over the age of 60.[1] Although prevalent, 88-99% of all aneurysms detected at screening are small (<5.5cm).[2-5] The clinical relevance and optimal management strategy for these small aortic aneurysms have long been the subject of controversy. Results from two randomized controlled trials have shown the safety of surveillance in AAA smaller than 5.5cm.[6-8] These results were supported by the low annual rupture risk (0.6-1%) observed in the surveillance groups. However, since these low rupture rates are partly explained by meticulous follow-up and a high surgical intervention rate (over 60%), they do not seem to reflect the natural history of small abdominal aneurysms.[9] Results from autopsy studies show that 10-24% of all ruptured AAA have an aneurysm diameter less than 5.5cm.[10, 11] The simple observation, that even small aneurysms rupture questions the use of maximum diameter as the single threshold for surgical intervention and focuses the attention to other patient, or aneurysm specific variables likely to affect aneurysm rupture risk.

AAA rupture occurs when the stress (force per unit area) on the aneurysm wall exceeds wall strength. The first studies on aortic wall stress could not demonstrate local variations in wall stress due to the use of hypothetical, symmetrical geometrical models.[12-14] Recent advancements in Computed Tomography (CT) and image post-processing allow the reconstruction of patient specific three dimensional aneurysm models. The use of these models created in vivo and the availability of a sophisticated mathematical technique, Finite Element Analysis (FEA), have improved wall stress analysis and its clinical applicability.[15] With the use of this technique, Fillinger and others have shown that peak wall stress is significantly higher in ruptured than electively repaired AAA.[16, 17] In another series, 103 patients under observation had wall stress analysis. All 22 patients presenting with symptoms of pending aneurysm rupture or actual rupture, including 5 patients with small AAA (<5.5cm), were found to have significantly higher peak wall stresses well in advance of aneurysm rupture. The authors therefore postulated that wall stress analysis has the potential to detect small aneurysms that cannot be observed safely because of high rupture risk.[18] The purpose of this study is to evaluate the potential of wall stress analysis to detect patients at elevated risk of aneurysm rupture in spite of small aneurysm diameter.

Materials and methods

Patient population.

The study included thirty patients with small AAA, 10 asymptomatic, 10 symptomatic and 10 ruptured. After a review of medical records from two institutions 20 patients with a CT scan evaluation of a small ruptured (n=10) or symptomatic aneurysm (n=10)

were identified. Two patients in both the rupture and symptomatic group had a CT evaluation while asymptomatic but experienced rupture or symptoms (e.g. severe back pain) within the following 6 months. All patients evaluated at the time of acute aneurysm related symptoms or aneurysm rupture had stable conditions.
Patients in the asymptomatic group (n=10) had a CT evaluation for elective aneurysm repair and remained asymptomatic for at least 6 months; until the end of the study in march 2006 or until elective repair (3/10). All CT scans were performed during routine care between January 2003 and March 2006 and no CT scan was obtained for the purpose of performing stress analysis.
Patients medical records were reviewed for demographics, medical history and blood pressure data. For all patients in the asymptomatic group and most patients in the ruptured and symptomatic group blood pressure was recorded from the year prior to CT evaluation. For 3 patients in the ruptured group and 2 patients in the symptomatic group this data was unavailable and blood pressure was recorded at the time of CT evaluation. All data acquisition was performed after approval by the local ethics committee.

AAA morphology and patient body habitus
Overall indices of patient body habitus (e.g. body mass index) are recorded from medical records. Possible or known indices of AAA geometry related to aneurysm rupture, like AAA diameter, diameter asymmetry and the diameter of the body of vertebra L3 are measured and calculated from CT data. Aneurysm diameter asymmetry is defined as the difference between major and minor axis diameter.

Wall stress analysis.
In vivo aneurysm wall stress is computed by using the Finite Element Method (FEM). The basic approach of the finite element method is to divide a complex geometrical structure (AAA) into smaller pieces or elements. These elements are connected by nodes. The entire network of elements and nodes is called a mesh. Wall stress is determined by predicting movement of the nodes which are influenced by the material properties of the aneurysm wall (e.g. stiff or elastic) and preset boundary conditions (e.g. blood pressure). Wall stress analysis therefore requires three main components: the in vivo three dimensional aneurysm model to create the mesh, the boundary conditions and a material model that describes the mechanical properties of the aneurysm wall.
AAA geometry is derived from contrast enhanced spiral CT data. For all patients, including those who experienced rupture, the aneurysm outer wall could be identified and depicted by image post-processing (segmentation of bloodflow, thrombus and calcified plaques). This resulted in a patient specific three dimensional in vivo aneurysm model. From these models the mesh is created by using a previously described semi-automated process.[17, 18] In brief; dividing the original model into large amounts of elements (the mesh), results in highly accurate stress analysis. However,

by using large amounts of elements computation time is long. Our typical meshes currently contain approximately 35 000-45 000 elements. This results in accurate measurements with acceptable computation time (up to 60 minutes). Increasing the number of elements beyond this number changes computed wall stress less than 2%, but significantly augments computational time. Besides the number of elements the element shape is important. Odd shaped elements (e.g. severe angles) might result in computational errors. To eliminate these elements a refinement algorithm, based upon multiple iterations, was designed. Ultimately, this refinement was incorporated into the initial mesh generation, and this new method was validated using prior datasets before using it in this study. Finally, the refined mesh is entered into a commercially available software program for finite element analysis (ABAQUS v.6.5, Hibbit, Karlsson and Sorensen, Inc, Pawtucket, RI).

The material model is a set of equations that characterize the relation of aneurysm wall movement and the forces acting on the wall. Forces acting on the aneurysm wall result in large deformations or strains. To account for these large strains we use a previously described and validated isotropic hyperelastic nonlinear model. This model is based upon the mechanical properties of abdominal aortic aneurysms in a series of 69 patients.[19]

The FEM boundary conditions consist of the mechanical load on the wall (e.g. blood pressure) and possible physiological constraints (e.g. iliac and renal arteries) to wall movement. Bloodflow creates shear stress on the lumen surface, these shear stresses are however negligible compared to the stresses due to blood pressure. Therefore peak wall stresses reported in this study are all at systolic blood pressure. An additional analysis at uniform blood pressure (120mmHg) is performed to rule out possible differences in maximal systolic blood pressure between groups and to evaluate the effects of blood pressure on wall stress analysis.

Statistical analysis

The three groups (asymptomatic, symptomatic non-ruptured and ruptured) were compared by using SPSS v12.0.1, Chicago, ill. Continuous variables were compared with analysis of variance (ANOVA) with post hoc analysis. Nominal data was analyzed using contingency table analysis and Chi-square or Fischer exact tests. All continuous data is reported as mean ± SE.

Results.

Demographics

No statistical significant differences were found between the three groups with respect to age, hypertension (treated or >140mmHg systolic), diabetes (treated with insulin, oral medication or diet adjustment), chronic obstructive pulmonary disease (treated

or not), stroke (TIA or CVA), use of cardiovascular and anti-inflammatory medication, peripheral vascular disease or current smoking (Table 1). The only two variables that reached significance are the use of statin for hypercholesterolemia (asymptomatic 7/10, symptomatic 1/10 and rupture 2/10; p=0.01) and the use of diuretics; less frequent in the symptomatic group (asymptomatic 7/10, symptomatic 1/10 and rupture 6/10; p=0.02). There was a trend towards more ischemic heart disease in the asymptomatic group but this did not result in statistically significant differences (p=0,054)
Gender differences were noted but did not reach significance between groups nor after combining the ruptured and symptomatic group (asymptomatic 1/10 female vs. rupture/ symptomatic 6/20 female; p=0.23).

Table 1. Demographics and use of medication.

	Asymptomatic N=10	Symptomatic N=10	Rupture N=10	P- value
Age (years)	72 ± 2	75 ± 3	70 ± 2	.44
Gender (M/F)	9/1	7/3	7/3	.48
CAD[a]	7	2	3	.05
CHF[b]	1	2	2	.79
Hypertension	7	10	8	.19
Diabetes	1	3	1	.38
COPD[c]	3	4	2	.62
Stroke	2	0	2	.32
ABI[d]	4	2	2	.51
Smoking (current)	4	3	4	.87
Aspirin	5	4	4	.87
Betablocker	6	5	2	.17
Calcium antagonist	0	1	2	.33
Diuretics	7	1	6	.02
Statin	7	1	2	.01
Steroid	1	0	2	.33

[a] CAD, Coronary Artery Disease
[b] CHF, Chronic Heart Failure
[c] COPD, Chronic Obstructive Pulmonary Disease
[d] ABI, Ankle Brachial Index (<1.0)

AAA morphology and patient body habitus
Maximal (major axis) aortic diameter is not significantly different between the three groups (asymptomatic 5.1 ± 0.2cm; symptomatic 5.1 ± 0.2cm; rupture 5.3 ± 0.2cm; p=0.57). The only variable of body habitus and aneurysm dimension reaching marginal significance is aneurysm diameter asymmetry showing more asymmetry in the asymptomatic group. Variables of aneurysm and patient morphology are listed in table 2.

Peak wall stress and blood pressure.

Peak aortic wall stress at maximum systolic blood pressure is significantly different between the asymptomatic and rupture group (39.7 ± 3.3N/cm^2 vs. 51.7 ± 2.4N/cm^2 p=0.04). Peak wall stress in the symptomatic group was also higher compared to the asymptomatic group although this did not reach significance (table 3). Figure 1 shows the result from wall stress analysis for a ruptured aneurysm. Note the resemblance in location of aneurysm rupture and peak wall stress.

Maximum systolic blood pressure is significantly higher in the symptomatic group (asymptomatic 147 ± 5mmHg; symptomatic 181 ± 7mmHg; rupture 165 ± 7mmHg; p=0.004). The additional analysis of wall stress at uniform blood pressure (120mmHg), performed to compensate for these difference in maximal systolic blood pressure, did not result in statistical significant differences in aneurysm wall stress between the three groups. (asymptomatic 31.7 ± 2.3N/cm^2; symptomatic 30.5 ± 1.3N/cm^2; rupture 36.7±4.0N/cm^2; p=0.261).

Table 2. AAA morphology and patient habitus.

	Asymptomatic N=10	Symptomatic N=10	Rupture N=10	P-value
AAA diameter (cm)	5.1 ± 0.2	5.1 ± 0.2	5.3 ± 0.2	.57
Asymmetry[a]	0.6 ± 0.1	0.5 ± 0.1	0.3 ± 0.1*	.09
AAA/TC[b]	1.8 ± 0.1	1.7 ± 0.1	1.9 ± 0.1	.15
AAA/L3[c]	0.9 ± 0.8	0.9 ± 0.8	1.1 ± 0.9	.16
BMI[d]	23.0 ± 1.5	24.6 ± 0.7	23.9 ± 0.9	.61

* AAA in rupture group less asymmetric (p=0.05)

[a] Asymmetry, major axis diameter minus minor axis diameter.

[b] AAA/TC, major axis AAA diameter/aorta diameter at level of Truncus Coeliacus.

[c] AAA/L3, major axis AAA diameter/diameter corpus vertebra L3.

[d] BMI, Body Mass Index; Weight (kg)/Length2 (cm).

Table 3. Wall stress and blood pressure

	Asymptomatic N=10	Symptomatic N=10	Rupture N=10	P-value
Peak stress (N/cm^2)	39.7 ± 3.3	47.6 ± 2.7	51.7 ± 2.4[a]	.11
Stress (120 mmHg)	31.7 ± 2.3	30.5 ± 1.3	36.7 ± 4.0	.26[c]
Max. systolic BP	147 ± 5	181 ± 7[d]	165 ± 7	.004

[a] Peak wall stress in ruptured AAA significantly higher than in asymptomatic AAA (p=0.04).

[b] BP, Blood Pressure.

[c] For all three groups (p=0.26). Asymptomatic vs. ruptured (p=0.21)

[d] Max. systolic BP significantly higher for symptomatic vs. asymptomatic patients (p=0.001).

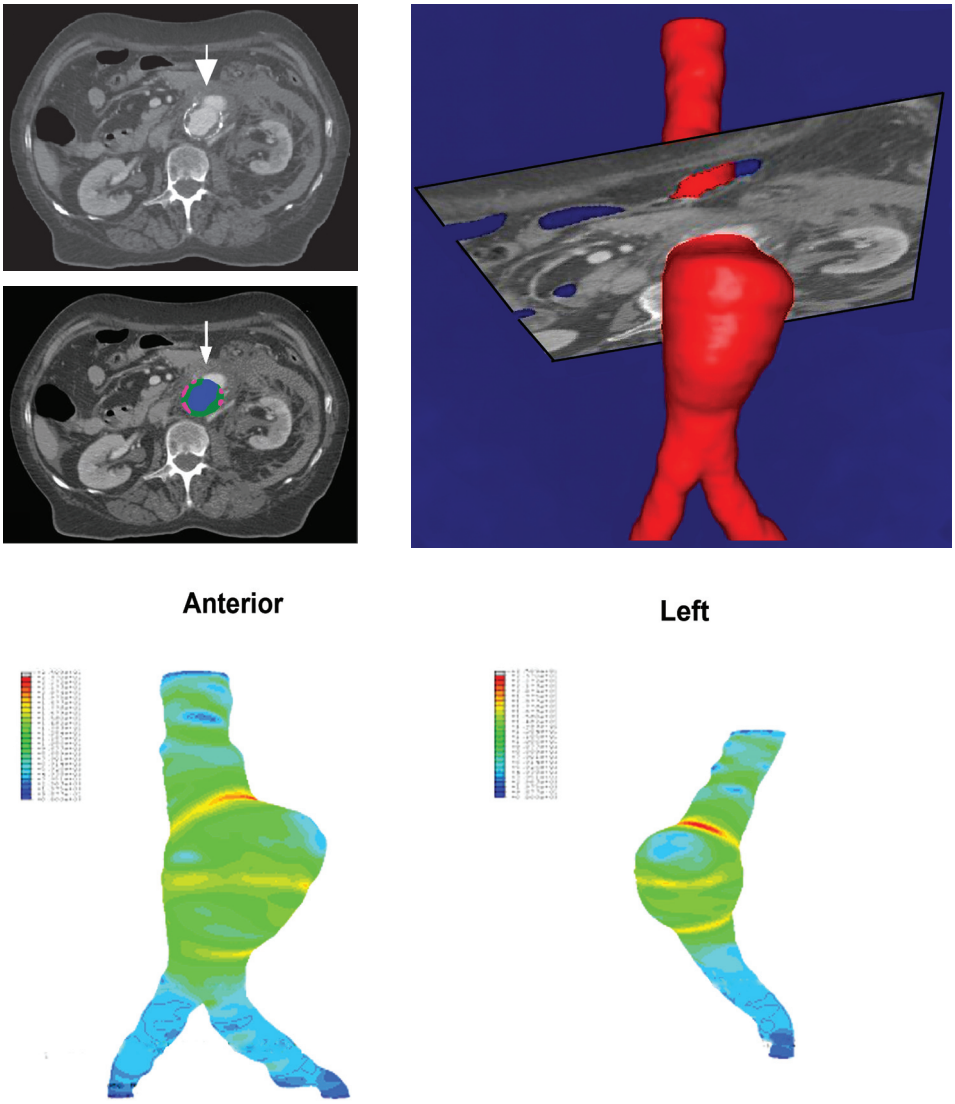

Figure 1. Wall stress analysis. Top left, aneurysm rupture (left anterior). Middle left, result from segmentation process (the hematoma is not included in the segmentation). Top right, corresponding slice within 3D model. Bottom, result from wall stress analysis. High stress (red) corresponds with site of rupture.

Discussion

Observation of small asymptomatic (<5.5cm) infrarenal aortic aneurysms is considered safe in the general population. Some small aneurysms however do rupture. Wall stress analysis has been proposed to identify patients with elevated risk of aneurysm rupture in spite of small diameter. This is the first study directly comparing aortic wall stress in small asymptomatic, symptomatic and ruptured aneurysms. Results from this study show that peak wall stress at maximal systolic blood pressure is different for asymptomatic and ruptured small aortic aneurysms. These results therefore seem to confirm the observation by Fillinger, that the use of peak aortic wall stress could improve the selection of patients for aneurysm repair and the timing of surgical intervention.[17, 18] Although this is an important finding, there is a remarkable difference between the previous studies on wall stress analysis and the present work. In contrast with previous work, significant differences in peak wall stress did not persist after analysis at uniform blood pressure. This has important consequences and requires explanation.

First, it stresses the importance of blood pressure control. Hypertension is a well known risk factor for aneurysm rupture and seems equally important in wall stress analysis. Eight patients in both the symptomatic and rupture group had a CT evaluation while experiencing rupture or symptoms of pending aneurysm rupture. Calculating wall stress using blood pressure data from the time of CT evaluation could therefore lead to falsely lower wall stress in the rupture group due to hemodynamic impairment. Conversely, wall stress calculations using elevated blood pressure at the time of symptoms increases wall stress due to pain and distress. To correct for this selection bias we used blood pressure data from the year prior to CT evaluation. Since some patients presenting with adverse outcome were never evaluated before, this data was unavailable for 3 patients in the ruptured and 2 patients in the symptomatic group. For these patients wall stress was calculated using blood pressure from the time of CT evaluation. The effect of this bias seems however limited as wall stress is elevated for ruptured AAA and not significantly higher for patients experiencing symptoms.

More complex is the effect of this blood pressure related bias on wall stress analysis at uniform (120mmHg) blood pressure. Including patients with ruptured AAA and subsequent low blood pressure (<120mmHg) could lead to an increase of wall stress computed at uniform blood pressure, increasing the probability of finding significant differences between ruptured and non-ruptured AAAs. However, in the current analysis all patients with ruptured AAA presented with blood pressures over 120mmHg. This does not explain the difference between the present and previous studies on wall stress as Fillinger also analyzed patients in stable conditions only, but it does reemphasize the importance of blood pressure in wall stress analysis.[17]

Second, if blood pressure is uniform, differences in computed wall stress are based upon variations in aneurysm geometry. Since no significant differences in wall stress were found between asymptomatic, symptomatic and ruptured aneurysms at uniform

blood pressure, AAA geometry has to be relatively uniform. This might be due to the fact that we studied small aortic aneurysms. During aortic dilatation the aneurysm is remodelled, elastin fibres are degraded, and collagen is synthesized. If dilatation is more prominent (larger aneurysms) this remodelling might cause more dramatic shape changes possibly leading to larger differences in peak wall stress. Previously, diameter asymmetry has been associated with elevated rupture risk and increased wall stress.[20, 21] Remarkably, our ruptured aneurysms showed less diameter asymmetry. A possible explanation for this finding is the high portion of ruptured aneurysms (8/10) at the time of CT-evaluation. Aneurysm rupture could result in the formation of hematoma, distorting the original geometry (asymmetry) and obscuring subtle anatomical characteristics known to affect aneurysm rupture risk, like blebs and blisters.[22]

Besides these limitations related to study design, several opportunities exist to refine the material model. Currently, the model is based upon several assumptions (material isotropy and homogeneity) and does not account for intra-luminal thrombus (ILT) or calcification. The effect of ILT on aneurysm rupture and wall weakening is controversial.[23] Some investigators have observed focal aneurysm wall hypoxia and subsequent wall weakening in the presence of ILT.[24] Others have suggested a reduction in aneurysm rupture risk related to a possible ILT 'cushioning effect' decreasing pressure transmission.[25, 26] Schurink however, measured in vivo mean arterial and pulse pressure near the aneurysm wall and found no reduction in pressure transmission to the aneurysm wall in the presence of thrombus.[27] Therefore, the effects of thrombus on wall stress seem limited and the main limitations of the current material model are the assumptions made at initial development; aneurysm wall isotropy and material homogeneity.[19]

Materials are called isotropic when the physical properties are identical for any given direction. This is probably not true for the aneurysm wall as recent experiments have shown preferential stiffening in the circumferential direction (anisotropy).[28, 29] Although the introduction of aneurysm wall anisotropy could result in more accurate stress reports the effect of this new finding on the finite element assessment of aneurysm rupture risk remains to be investigated. The assumption of material homogeneity includes, uniform wall thickness and identical material properties for every aneurysm. Several authors have addressed this phenomenon and investigated the effect of variations in wall thickness and changed material properties on computed wall stress and aneurysm rupture risk. [30-32]Local alternations in wall thickness could result in increased wall stress and variations in material properties like aneurysm tensile strength (maximal stress before aneurysm rupture).[30]

Since aneurysm rupture occurs when wall stress exceeds wall strength, future material models should include patient specific information on aneurysm wall strength. Although this will substantially refine rupture risk assessment, wall stress analysis using the current material model is already superior to diameter in differentiating patients at elevated risk of rupture.[18]

Conclusion

Wall stress at maximal systolic blood pressure is significantly higher for ruptured compared to asymptomatic aneurysms. This confirms the potential of wall stress analysis as a promising technique to detect small aneurysms at elevated risk of rupture. Analysis at uniform blood pressure resulted in less pronounced and non-significant differences in wall stress between asymptomatic and ruptured small aneurysms. This reiterates the need for strict blood pressure control to reduce peak aortic wall stress and aneurysm rupture risk. Larger prospective follow-up programmes will be needed to confirm our findings and to investigate the effect aneurysm growth and blood pressure change over time on aortic wall stress.

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In vivo imaging of changes in abdominal aortic aneurysm thrombus volume during the cardiac cycle

4

M. Truijers
M. F. Fillinger
W. K. J. Renema
S. P. Marra
L. J. Oostveen
H. A. J. M. Kurvers
L. J. Schultze Kool
J. D. Blankensteijn

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Abstract

Purpose
Although present in the majority of aneurysms, the biomechanical importance of intraluminal thrombus is controversial. Objective of the present study was to evaluate in vivo thrombus compressibility in abdominal aortic aneurysms.

Methods
Dynamic EKG gated CTA was performed in 17 aneurysm patients, 11 patients scheduled for surgical repair and 6 patients kept under routine surveillance. Intraluminal thrombus, lumen and, total aneurysm volume were quantified for each phase of the cardiac cycle. Thrombus compressibility was defined as the percent change in thrombus volume between diastole and peak systole. Continuous data is presented using medians and interquartile ranges (IQR).

Results
A substantial inter-patient variability was observed in thrombus compressibility, ranging from 0.4 to 43.6% (0.2 to 13.5ml, respectively). Both thrombus and lumen volume varied substantially during the cardiac cycle. As lumen volume increased (5.2%, IQR 2.8-8.8%), thrombus volume decreased (3.0%, IQR 1.0-4.6%). Total aneurysm volume remained relatively constant (1.3%, IQR 0.4-1.9%). Changes in lumen volume were inversely correlated with changes in thrombus volume (r=-0.73; p=0.001).

Conclusions
In vivo thrombus compressibility varies from patient to patient and this variation is irrespective of aneurysm size, pulse pressure, and thrombus volume. This suggests that thrombus might act as a biomechanical buffer in some, while it has virtually no effect in others. Whether differences in thrombus compressibility alter the risk of rupture will be the focus of future research.

Introduction

Elective aneurysm repair aims at the prevention of aneurysm rupture and is considered when the risk of rupture exceeds the risks of repair.[1] In general, large abdominal aortic aneurysms (AAA) are repaired whereas small AAA (<5.5cm) are kept under surveillance. The commonly used 5.5cm threshold for intervention was confirmed in two large clinical trials that showed a low annual rupture risk (0.6-1%) in small AAA.[2-4] However, as 60% of all patients in the observation groups underwent elective repair for rapid expansion or symptoms, it is questionable whether these data accurately reflect the natural history of AAA.[5] The simple observation that even small aneurysms rupture questions the validity of maximum diameter as the single criterion for surgical intervention.[1, 6, 7]
To differentiate rupture prone from "stable" aneurysms, several investigators have focused on the biomechanical properties of associated intraluminal thrombus and suggested that thrombus could act as a potential mechanical buffer or cushion.[8-10] Results from these studies were however, based upon two dimensional testing of relatively well organized thrombus and little is known about the biomechanical role of thrombus in vivo. We used dynamic EKG gated CTA and volumetric analysis to quantify changes in thrombus volume (compressibility) during the cardiac.

Methods

Data acquisition.
Dynamic EKG gated CTA was performed in 17 aneurysm patients, 11 patients scheduled for surgical repair and 6 patients during routine follow-up. All patients were scanned using a 64 slice CT scanner (Siemens Somatom Sensation™, Erlangen, Germany) and simultaneous EKG reading.
Data acquisition started after intravenous administration of 100ml contrast (Xenetix 350™, Guerbet, Paris, France). Scanning parameters included a tube voltage of 120kV. Pitch was set at 0.34. Reconstruction of the raw data resulted in 1mm slice thickness with 0.75mm overlap. Blood pressure was recorded, before and directly after CT data acquisition, using a standard cuff. Systemic pulse pressure was calculated by subtracting diastolic from systolic blood pressure. Patient medical history and use of medication were prospectively collected. The protocol was approved by the local ethics committee and informed consent was obtained in all patients.

Image post-processing.
Simultaneous EKG reading and an algorithm for retrospective EKG gating allowed the reconstruction of ten datasets per patient. Each dataset represented one tenth of the cardiac cycle (R-R interval). Based upon these reconstructions, 170 three-dimensional aneurysm models were created (figure 1). Ten per patient, one for each part of the R-R interval.

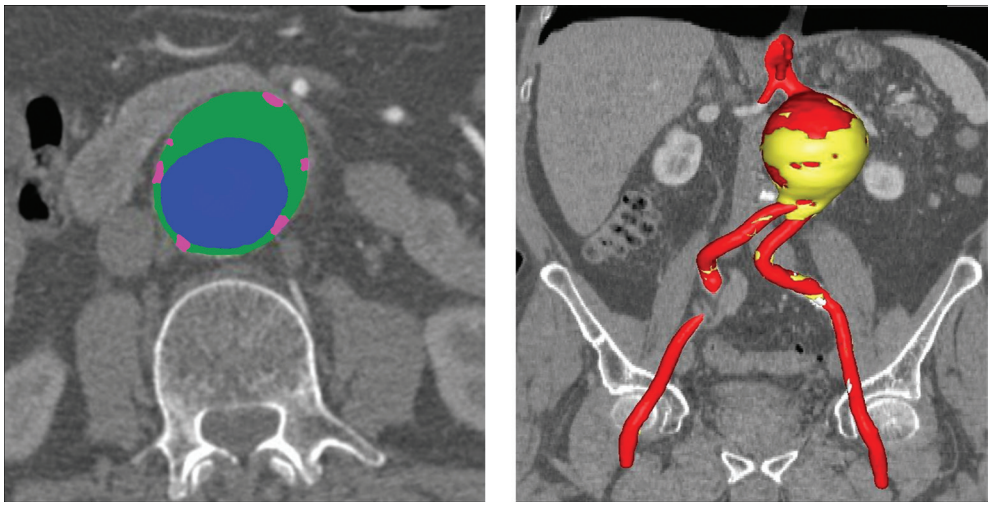

Figure 1. Image post-processing. Segmentation results in the identification of the aneurysm's lumen (blue), thrombus (green) and calcified plaque (pink). Based upon the segmentation a 3-dimensional aneurysm model was created. This model was used to calculated thrombus, lumen and total aneurysm volume.

Volumetric analysis.
Thrombus, lumen and total aneurysm volume were quantified from the distal renal artery to the iliac bifurcation. The models with maximal and minimal lumen volume were considered to represent peak systole and minimal diastole. Thrombus compressibility was defined as the difference in thrombus volume between peak systole and minimal diastole and is expressed as the relative or percent change in thrombus volume. Image post-processing and volumetric analysis was performed using validated proprietary software (M2S, Inc. West Lebanon NH, USA).

Statistical analysis.
Continuous data is reported as median with interquartile range (IQR); $p<0.05$ was considered significant. Changes in intraluminal thrombus, lumen, and total aneurysm volume were analyzed using the Wilcoxon signed rank test for paired non-parametric data. Spearman's correlation coefficient was determined to asses the correlation between changes in thrombus, lumen, and total aneurysm volume. The relation between changes in thrombus volume and aneurysm size, pulse pressure, and total intraluminal thrombus volume was determined by means of Spearman's correlation test. Statistical analysis was performed using SPSS 14.0 (SPSS Inc. Chicago, Illinois, USA).

Results

Patient demographics
Patient characteristics and demographics are presented in table 1.

Table 1. Patient demographics

	Patients (N=17)
Age (years)	73 (69-76)
Gender (Male)	15 (88%)
Hypertension[1]	13 (77%)
Hypercholesterolemia[2]	12 (71%)
Diabetes Mellitus[3]	1 (6,0%)
CAD[4]	5 (29%)
COPD[5]	3 (18%)
Stroke[6]	5 (29%)
PAOD[7]	5 (29%)
Smoking[8]	12 (71%)
Anti-coagulant therapy[9]	15 (88%)
Lipid lowering therapy	11 (65%)
Anti-hypertensive therapy	10 (59%)

[1]Hypertension, use of antihypertensive medication or recorded systolic blood pressure over 140mmHg,
[2]Hypercholesterolemia, use of lipid lowering therapy (e.g. statin) or increased levels of LDL cholesterol (>240 mg/dl),
[3]Diabetes Mellitus, use of oral anti-diabetic medication or insulin,
[4]CAD, coronary artery disease, history of angina pectoris of prior myocardial infarction,
[5]COPD, chronic obstructive pulmonary disease,
[6]Stroke, history of transient ischemic attack or cerebrovascular disease
[7]PAOD, Peripheral arterial occlusive disease
[8]Smoking, current smoking.
[9]Anti-coagulant therapy, aspirin or coumadin derivates

Volumetric analysis.
A substantial inter-patient variability was observed in thrombus compressibility ranging from 0.4 to 43.6% (0.2 to 13.5ml, respectively). Both thrombus and lumen volume changed considerably during the cardiac cycle ($p<0.001$). As lumen volume increased (5.2%, IQR 2.8-8.8%), thrombus volume decreased (3.0%, IQR 1.0-4.6%). Total aneurysm volume remained relatively constant (1.3%, IQR 0.4-1.9%). Figure 2, shows the changes in lumen, thrombus, and total aneurysm volume for each individual patient.
Changes in lumen volume were inversely correlated with changes in thrombus volume ($r=-0.73$; $p=0.001$; figure 3). Changes in lumen volume were not significantly correlated to changes in total aneurysm volume ($r=0.01$; $p=0.97$).

AAA size and pulse pressure.
Median aneurysm diameter was 5.3 cm (IQR 4.5-5.7). Thrombus volume was positively correlated with aneurysm size ($r=0.74$; $p=0.001$). Thrombus compressibility was not correlated with aneurysm size ($r=0.07$; $p=0.8$), total thrombus volume ($r=0.21$; $p=0.4$), or pulse pressure ($r=0.1$; $p=0.7$).

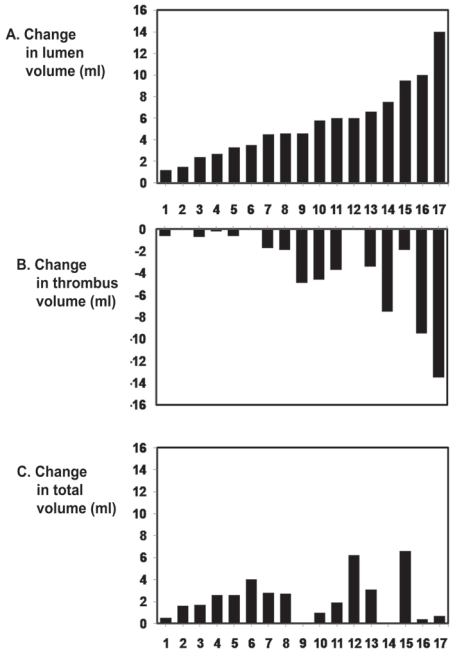

Figure 2. Changes in lumen (A), thrombus (B) and total AAA (C) volume during the cardiac cycle. The X-axis represents the 17 individual aneurysm patients. The Y-axis represents the volume changes in ml.

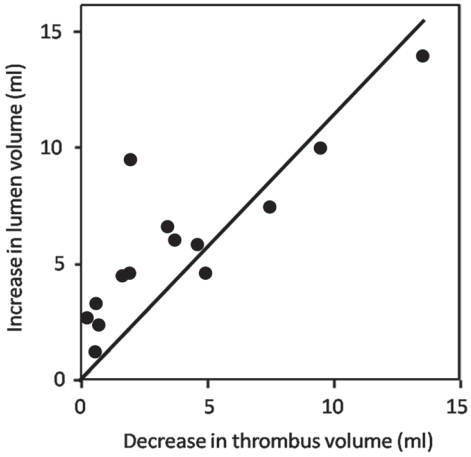

Figure 3. Correlation between changes in thrombus and lumen volume during the cardiac cycle. On the X-axis the decrease in thrombus volume, on the Y-axis the increase in lumen volume (both in ml).

Discussion.

During the cardiac cycle, changes in thrombus volume are inversely correlated to changes in lumen volume. As lumen volume increases, thrombus volume decreases. This compensatory volume effect of thrombus was, however, not observed in all patients. Which strongly suggests that thrombus could act as a biomechanical buffer in some, while it has little to no effect in others. The observed differences in thrombus compressibility are not correlated with aneurysm size. This is of particular interest as it shows that EKG gated CTA has the potential to quantify differences in thrombus compressibility for equally sized AAA. Future studies will have to focus on the possible effect of differences in thrombus compressibility on aneurysm risk. The effect of thrombus on rupture risk is controversial. Previous imaging studies showed increased thrombus volume in expanding and ruptured AAA.[11, 12] This, however, could merely result from the fact that large aneurysms have an increased risk of rupture and also contain more thrombus.[13-15] A later study confirmed this theory, showing no difference in thrombus volume between diameter-matched intact and ruptured AAA.[16] Results from the present study support these findings, as large AAA contained more thrombus. Interestingly, thrombus compressibility was not related to thrombus volume or pulse pressure and therefore most likely results from intrinsic biomechanical properties of thrombus.

The development of intraluminal thrombus is a complex and dynamic process. Near the luminal surface, fibrin is deposited by penetrating platelets resulting in a dense luminal layer. At the abluminal surface, thrombus contains fewer viable cells and shows increased fibrin degradation.[17] This remodelling process results in different biomechanical properties for different thrombi and even for different layers within the same thrombus.[9] The net effect of this rather heterogeneous material on pressure transmission and aneurysm rupture risk, has been studied extensively. Based upon in vitro studies it was postulated that aneurysm wall stress and thus rupture risk is reduced in the presence of thrombus.[10, 18-20] Although this is an important finding it results from in vitro testing of excised well structured thrombus. Because of the limitations related to in vitro biomechanical testing, extrapolating experimental data to in vivo thrombus dynamics might be inappropriate. The present study using dynamic EKG gated CTA describes the distinct in vivo response of different thrombi, in three dimensions.

A possible limitation of the current study is that the data does not provide information on the biomechanical properties of the aneurysm wall. If we assume a completely rigid aneurysm wall lined with an extremely compliant thrombus, it requires little force to compress the thrombus. The remaining force will still be exerted to the rigid aneurysm wall leaving total aneurysm volume unchanged. However, even in this rather hypothetical situation, thrombus deforms and thus absorbs energy. In addition, our results confirm a previous dynamic imaging study using ultrasound in eight patients which suggested that thrombus acts as a biomechanical buffer.[21] Conversely, we observed larger variations in thrombus compressibility (ranging from 0.1 to 43.6%) and therefore assume that thrombus could act as a biomechanical buffer in some, while it has virtually no effect in others.

Conclusion

In vivo thrombus compressibility varies considerably from patient to patient and this variation is irrespective of aneurysm size, pulse pressure, and thrombus volume. This suggests that intraluminal thrombus might act as a biomechanical buffer in some, while it has virtually no effect in others. Whether differences in thrombus compressibility alter the risk of rupture will be the focus of future research.

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Focal reduction in aneurysm wall strength is associated with matrix metalloproteinase-9 activity.

5

M. Truijers
J. A. Pol
M. E. N Pierie
S. M. van Sterkenburg
R. M. L. M. Lomme
T. Hendriks
J. D. Blankensteijn

Submitted

Abstract

Objective

There is an association between matrix metalloproteinase (MMP) expression and abdominal aortic aneurysm (AAA) progression. This has lead to the hypothesis that "hot spots" of increased MMP activity may lead to focal aneurysm wall weakening and even rupture. The objective of the present study was to study this hypothesis by investigating the correlation between aneurysm wall strength and MMP-2 and MMP-9 activity.

Methods

A prospective clinical trial was conducted. Aneurysm wall strips were collected during elective (N=16) or urgent aneurysm repair (N=9) in consecutive patients. Aortic control specimens were obtained from the redundant aortic patch of 9 post-mortem kidneys. All strips were divided into multiple samples and subjected to biomechanical testing and matrix metalloprotease (MMP) assay. Continuous data is reported using medians and interquartile ranges (IQR).

Results

Breaking strength varied substantially for different sites of the same aneurysm. Based upon the lowest recorded breaking strength per specimen, wall strength was higher in control-subjects than in aneurysm patients (0.98N/mm; IQR 0.91-1.53N/mm for control-subjects vs. 0.52N/mm; IQR 0.33-0.71N/mm for asymptomatic AAA and 0.61N/mm; IQR 0.53-1.04N/mm for ruptured AAA; P=0.006). Local reductions in aortic and aneurysm wall strength were significantly correlated with both active and latent MMP-9 activity (r=-0.39; P=0.02, for both active and latent MMP-9).

Conclusions

Aortic wall strength varies substantially between control-subjects and aneurysm patients and there is a marked spatial variability in each individual aneurysm. In aneurysm patients, wall strength is focally reduced and this local reduction in wall strength is associated with high levels of both latent and active MMP-9. This could have important clinical consequences as it provides the rationale for proteinase inhibiting medical therapy to prevent aneurysm rupture.

Introduction

Abdominal aortic aneurysm (AAA) formation and progression is a multifactorial process, characterized by extensive remodeling of the extracellular matrix (ECM) of the aneurysm wall.[1, 2] The most important structural components of the aortic wall are elastin and collagen fibers. During aneurysm formation, the elastin content decreases, reducing the ability of the aneurysm wall to withstand cyclic strain. To compensate for this loss in elastic properties and prevent aortic dilatation, collagen synthesis is increased.[3] Based upon this theory of tissue remodeling, it was postulated that once this mechanism fails, most likely due to persistent elastin and collagen degradation, the aneurysm wall weakens and ultimately ruptures.[3]
Although the exact mechanisms leading to aneurysm formation and progression are unknown, the involvement of matrix metalloproteinases (MMPs) is well established.[4] Especially, MMP-2 and -9 appear to play an important, yet different role in AAA formation, progression, and rupture.[2, 3] Results from clinical investigations suggest an association between MMP-2 activity and early aneurysm dilatation, whereas elevated levels of MMP-9 predisposed larger AAA to aneurysm rupture.[3, 5, 6] Because of this relation between MMP-2 and MMP-9 expression and aneurysm progression, it was postulated that “Hot spots” of increased MMP-2 and -9 activity may lead to focal wall weakening and even rupture.[7, 8] The present study was designed to study this hypothesis by investigating the correlation between aneurysm wall strength and MMP-2 and MMP-9 activity.

Methods.

Patients
Between June 2007 and August 2008, rectangular aneurysm wall specimens were collected during elective (N=16) and urgent (N=9) aneurysm repair in consecutive patients. Urgent repair was performed because of aneurysm rupture (N=8) or symptoms considered to indicate pending aneurysm rupture (N=1). Informed consent was obtained in all patients and the procedures were approved by the institutional ethical review board. Control specimens were obtained from the redundant abdominal aortic patch of 9 post-mortem kidneys, all meeting the criteria for donation.

Biomechanical testing
After removal of adherent tissue, the specimens were placed in 0.9% NaCl to prevent dehydration during processing. If possible, depending on sample size, the specimens were divided into four equally large pieces (proximal, anterior, posterior and distal). For biomechanical testing (tensile strength) these pieces were further divided into longitudinally and circumferentially orientated strips (figure 1).

Before placing the strips in a tensile testing system, the width was measured using an analog clipper. The force, applied to each strip was continuously increased and recorded until material failure (rupture). Breaking strength was defined as the peak value on the load-displacement curve (N). The results were discarded if the material slipped from the clamps or the aneurysm wall dissected before rupture. To correct for possible differences in tissue sample size, breaking strength was calculated per millimeter (mm) tissue width.

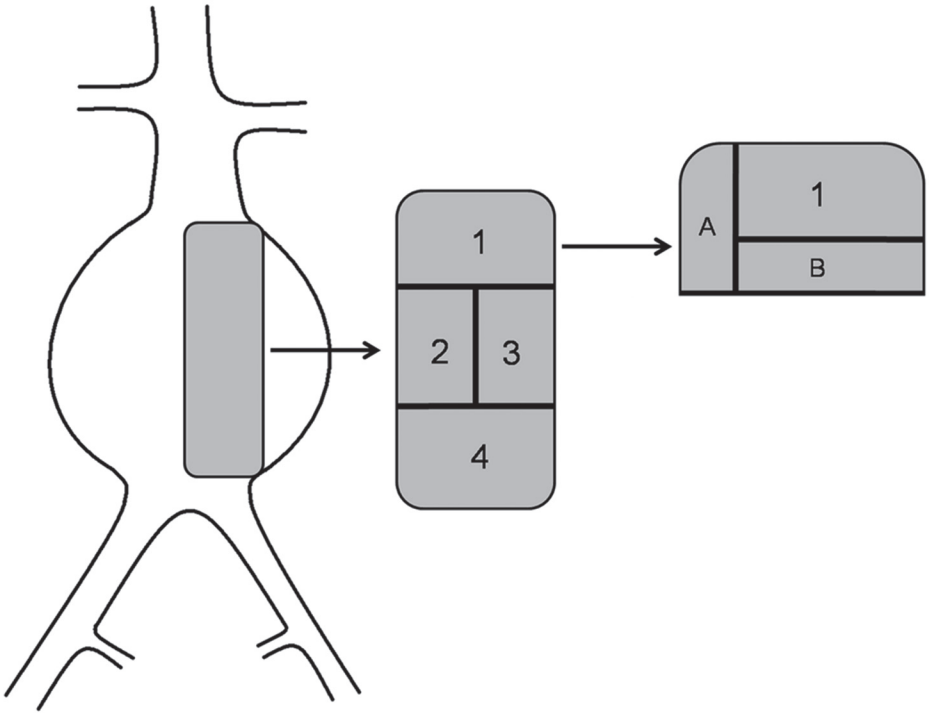

Figure 1. Specimens were collected during conventional aneurysm repair. Depending upon sample size, the specimen was divided into a proximal (1), anterior (2), posterior (3), and distal (4) piece. These pieces were further processed into longitudinally (A) and circumferentially (B) orientated strips. No biopsies were taken from the site of rupture.

MMP assay by quantitative zymography

After biomechanical testing the disrupted tissue was instantly freezed in liquid nitrogen and processed for MMP assay. Gelatin zymography was performed to quantify the presence of both active (aMMP) and latent (pMMP) forms of the gelatinases MMP-2 and MMP-9. The presence of the MMP-9 heterodimer (hMMP-9; 135-kDA) was also assessed. MMP activity is expressed as arbitrary units (AU) per mg extracted tissue.

MMP activity is quantified by using a previously validated and described method (quantitative zymography).[9] In brief, the samples were pulverized using a Micro-Dismembrator (Braun® Melsungen A.G, Germany) and the enzymes were extracted by freeze thawing the material twice (40ml/mg tissue). After centrifugation the supernatant was dialyzed and heated at 60 °C for 20 min. 5 µl aliquots were loaded on a 7.5% (w/v) standard lamella containing 2mg/ml gelatin as a substrate. Gels were electrophorezed until the bromophenol blue stained front reached the bottom of the gel. Collagenase was electrophorezed on each gel as an internal standard. After electrophoresis, the gels were washed and incubated overnight (37 °C). The zymograms were stained using Coomassie Brilliant Blue R250. Proteolytic activity resulted in clear zones against a dark blue background indicating lyses of gelatin. Proteinase activity was quantified based upon the size of the lyzed area and staining intensity (Imagemaster ID software; Amersham Pharmacia Biotech, Uppsala, Sweden). The internal standard, present on each gel was used to allow in-between comparison of MMP activity between the different gels.

Statistical analysis.

Kruskall-wallis and Mann-Whitney U tests, were used to compare the difference in MMP expression and breaking strength between the different groups (control, elective, and urgent). The correlation between breaking strength and MMP activity was analyzed for significance using Spearman's Correlation test.

All comparisons were performed using average breaking strength and average MMP activity per patient/control-subject. However, as aneurysm rupture is most likely at the site of low wall strength an additional analysis was performed using the tissue strip with lowest recorded breaking strength per control-subject and aneurysm patient.

Differences in breaking strength between circumferentially and longitudinally orientated strips were analyzed for significance using Wilcoxon signed rank tests (paired for patient and location).

All statistical analysis were performed using SPSS v16.0.1 (SPSS inc. Chicago, ill, USA). In all cases a $P<0.05$ was considered significant. Continuous data is presented using median and interquartile range (IQR)

Results.

Aneurysm wall strength.

A total of 209 aneurysm and aortic wall strips were subjected to biomechanical testing. Breaking strength was successfully determined in 183 strips (87.6%), 93 obtained during elective repair, 63 following urgent repair and 27 control specimens. Twenty-six strips (4 control, 21 elective and 1 urgent) slipped from the grips or dissected before rupture.

Based upon average breaking strength per specimen, wall strength was similar between control-subjects and aneurysm patients (table 1). However, the additional analysis using the lowest recorded breaking strength per specimen, showed that wall strength was higher in control-subjects than in elective aneurysm patients (0.98N/mm; IQR 0.91-1.53N/mm vs. 0.52; IQR 0.33-0.71, respectively P=0.002). Breaking strength was not significantly different between elective and urgent AAA specimens (0.61N/mm; IQR 0.53-1.04N/mm; figure 2).

Aneurysm wall strength was higher in circumferentially than longitudinally orientated strips (1.12N/mm; IQR 0.81-1.70N/mm vs. 1.10N/mm; IQR 0.73-1.61N/mm, respectively; P=0.049). Although wall strength was not different for the proximal, anterior, posterior or distal part of the specimen, large differences in breaking strength were found for different locations of the same aneurysm. The largest intra-patient variation was observed in an asymptomatic, electively repaired aneurysm. In this patient the anterior part of the aneurysm was weaker that the proximal part and wall strength varied from 0.24N to 3.80N/mm.

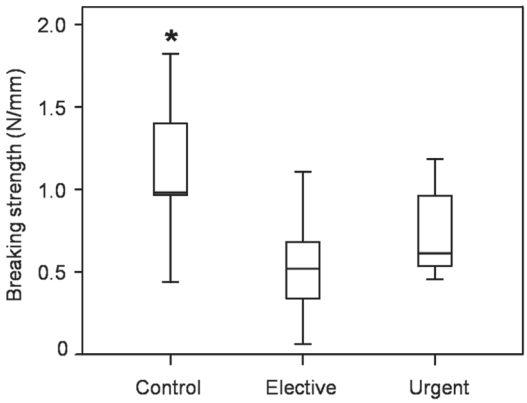

Figure 2. Lowest recorded breaking strength per patient/control-subject. Median (horizontal bars) values for the control (N=9), elective (N=16) and urgent (N=9) group. Boxes represent interquartile range (25th to 75th percentile), vertical bars 10th and 90th percentiles. Aneurysm wall strength is significantly* ($p<0.05$) higher in control subjects than aneurysm patients.

MMP assay

Based upon average MMP activity per patient, pMMP-2 and aMMP-2 activity was not significantly different between the control and both aneurysm groups. However, compared to the control group, both aneurysm groups showed significantly higher levels of hMMP-9, pMMP-9 and aMMP-9 levels. Active MMP-9 activity was negligible in the control group. MMP-9 expression was not different between the urgent and elective group (table 1).

Table 1. Average breaking strength and MMP activity per patient/control-subject.

	Controls N=9	Elective AAA N=16	Urgent AAA N=9	P-value
BS[a] (n/mm)	1.2 (1.0-1.6)	1.2(0.8-1.5)	1.42(1.0-1.6)	0.56
pMMP-2[b]	41.9 (33.4-103.2)	40.7 (20.6-63.3)	52.8 (31.2-74.2)	0.47
aMMP-2	1.7 (1.0-6.2)	3.3 (2.3-7.3)	6.5 (3.3-9.8)	0.21
hMMP-9	2.7 (1.2-5.8)	9.2 (3.1-15.5)*	12.5 (6.4-35.3)*	0.01
pMMP-9	13.2 (5.1-27.6)	60.3 (20.9-81.7)*	57.1 (22.4-168.1)*	0.01
aMMP-9	0.2 (0-0.3)	2.12 (1.1-6.4)*	1.2(1.1-4.4)*	<0.01

Compared to the control group both aneurysm groups show significantly* higher levels of hMMP-9, pMMP-9 and aMMP-9.

[a]BS: Breaking Strength. (N/mm)

[b]MMP: Matrix Metalloproteinase (Au/mg)

Aneurysm wall strength and MMP expression

Based upon average breaking strength per patient, aneurysm wall strength was not correlated to either MMP-2 or MMP-9 activity. However, the additional analysis using the weakest strip per control-subject or aneurysm patient, yielded a significant inverse correlation between wall strength and hMMP-9, pMMP-9 and aMMP-9 activity. Figure 3 shows the corresponding scatter plots. Weakest aneurysm wall strength was not correlated to pMMP-2 or aMMP-2 activity (r=-0.04; P=0.82 and r=-0.23; P=0.18 respectively).

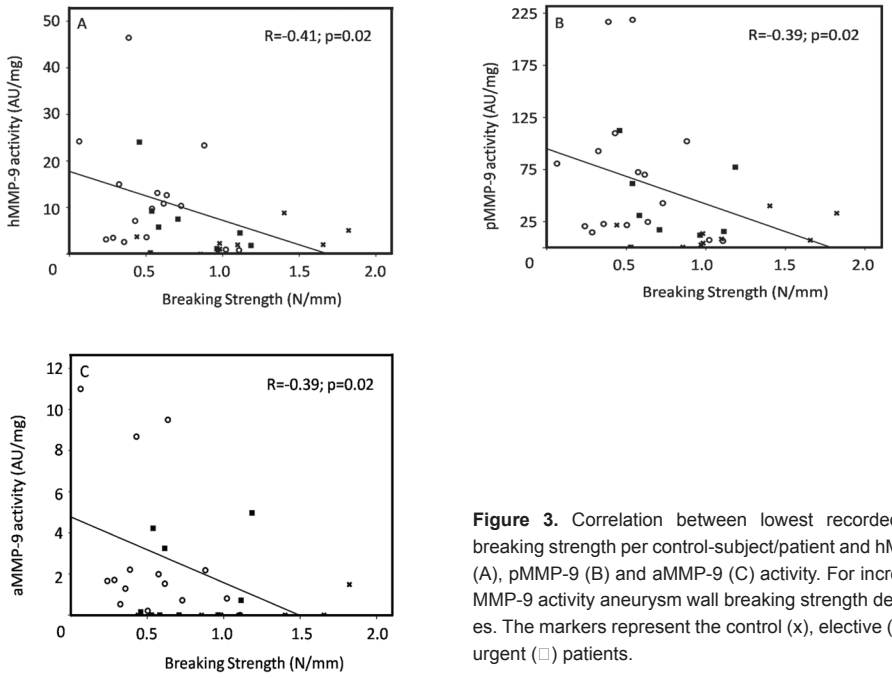

Figure 3. Correlation between lowest recorded wall breaking strength per control-subject/patient and hMMP-9 (A), pMMP-9 (B) and aMMP-9 (C) activity. For increasing MMP-9 activity aneurysm wall breaking strength decreases. The markers represent the control (x), elective (o) and urgent (□) patients.

Discussion

Aneurysm formation, progression, and rupture are characterized by extensive inflammation, increased proteolytic activity, and subsequent damage to the arterial wall.[3, 9] This structural damage is likely to cause diminished aneurysm wall strength.[10, 11] Based upon multiple samples per patient, we showed large differences in aneurysm wall strength for different locations of the same aneurysm. Average wall strength was not significantly lower for asymptomatic or ruptured AAA. However, by analyzing the weakest strip per patient/control-subject we did find reduced wall strength in AAA and showed that this local reduction in tensile strength was correlated with focally increased MMP-9 activity.

In addition to differences in breaking strength for different patient groups, we found lower wall strength in longitudinally orientated wall strips. Although differences were small, the observed aortic wall anisotropy is confirmed by others using biaxial tensile strength testing devices.[12] The use of the uniaxial testing system is a possible drawback of the present study. However, we subjected both circumferentially and longitudinally orientated strips (derived from the same location and aneurysm) to biomechanical testing.

The involvement of various MMPs in the pathogenesis of abdominal aortic aneurysms

is widely acknowledged.[4] Due to their capacity to degrade both elastin and collagen, the gelatinases A (MMP-2) and B (MMP-9) have been studied extensively.[13] Although experimental work has shown that both MMP-2 and MMP-9 work in concert to produce aortic aneurysms, MMP-2 and MMP-9 might have a different role in human AAA development.[4, 14] Studies on the relationship between MMP expression and aneurysm size and rupture risk showed increased levels of MMP-2 in small growing AAA, whereas MMP-9 levels were increased in large and ruptured AAA.[3] Results from the present study seem to support these findings as hMMP-9, pMMP-9 and aMMP-9 activity was elevated in AAA requiring repair because of size or rupture.

The possible correlation between MMP expression and wall strength was first considered by Vallabhaneni et al.[7] Their results, however, did not show a significant correlation between wall strength and MMP-9 activity, most likely due to the marked spatial variation in both, and the use of different specimens for biomechanical testing and zymography.[3] By using the same specimen for both assays we did find a negative correlation between MMP-9 activity and aneurysm wall strength. Our results therefore support the hypothesis of focally increased MMP-9 activity and locally decreased aneurysm wall strength. Because of this focal nature of aneurysm wall degradation, we question the use of MMP-9 serum levels as a biomarker for aneurysm wall strength and rupture risk.[15] It seems unlikely that serum levels of MMP-9 provide information on locally increased MMP-9 activity and focally reduced wall strength.

Previous studies using immunohistochemical analysis and in situ hybridization identified macrophages and neutrophiles as the main source of MMP-9.[16] This finding could have important consequences for new imaging techniques such as 18-fluorodeoxyglucose enhanced positron emission tomography (FDG-PET), which have the potential to non-invasively identify aneurysm wall inflammation.[17] in addition, increased FDG uptake in the AAA wall is associated with histopathologic characteristics of aneurysm wall instability and clinical symptoms.[18] Future studies should be directed at the possible correlation between FDG uptake and MMP activity as this could potentially lead to a new tool for the identification of hot spots of MMP expression and diminished wall strength.

In addition to the implications for aneurysm rupture risk, the findings of the present study provide the rationale for protease inhibiting medical therapy. For years doxycyxline has been proposed as a promising strategy to inhibit in vivo MMP activity and small randomized trials have indeed shown reduced aneurysm expansion rate in patients taking doxycycline.[19] Although promising, these studies are hindered by small sample size and short follow-up. In contrast to doxycycline, the effect of HMG CoA Reductase inhibitors (statins) on MMP expression and aneurysm growth has been studied to a larger extent. Statins did not only reduce MMP-9 tissue levels but also reduced aneurysm growth.[20, 21] Whether these medical intervention strategies could also reduce focal aneurysm wall weakening and thus aneurysm rupture risk will be the focus of future research.

Conclusion

Aortic wall strength varies substantially between control-subjects and aneurysm patients and there is a marked spatial variability in each individual aneurysm. In aneurysm patients, wall strength is focally reduced and this local reduction in wall strength is associated with high levels of both latent and active MMP-9.

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In vivo imaging of the aneurysm wall using MR and a macrophage specific contrast agent (USPIO)

6

M. Truijers
J. J. Fütterer
S. Takahashi
R. A. Heesakkers
J. D. Blankensteijn
J. O. Barentsz

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Abstract

Background
Aneurysm growth and rupture are associated with extensive inflammation. The non-invasive identification of arterial wall inflammation could therefore identify patients at increased risk of disease progression. Since recent studies have shown the potential of ultrasmall superparamagnetic particles of iron oxide (USPIO) enhanced magnetic resonance (MR) imaging to detect inflammation in vulnerable atherosclerotic plaques, we studied USPIO uptake in the wall of both aneurysms and normal sized aortas.

Methods
Eleven patients with either an aortic (n=6) or iliac (n=5) aneurysm and 11 age matched controls were identified in a database of 239 patients evaluated for lymph node staging of prostate cancer. USPIO enhanced MR imaging and contrast enhanced Multi-Detector CT was performed in all patients. After image fusion (CT and MR) the presence of USPIO was assessed during consensus reading. USPIO uptake was quantified by counting the number of quadrants with subendothelial signal voids, related to USPIO uptake in macrophages.

Results
USPIO uptake was significantly higher in the aneurysm than in the control group, 158 (4.5%) USPIO positive quadrants in the aneurysm group and 13 (0.4%) in the control group ($p<0.001$), respectively. USPIO uptake was present in three out of eleven aneurysms and two aneurysms accounted for more than 97% (154/158) of all USPIO positive quadrants.

Conclusions
Based upon the results of this preliminary study, the aneurysm wall shows more USPIO uptake than the non-dilated arterial wall. As not all aneurysms showed USPIO uptake, USPIO-MR might have the potential to differentiate stable from growing or rupture prone aneurysms. To confirm this hypothesis, larger longitudinal studies are needed.

Introduction

An accurate assessment of aneurysm rupture risk is essential to select patients for prophylactic aneurysm repair.[1, 2] While there is strong evidence that aneurysm size is correlated with rupture risk, small aneurysms do rupture.[3, 4] Moreover, most aneurysm patients have poor life expectancy and are likely to die with an intact large aneurysm.[5] To reduce the number of unanticipated ruptures without exposing all aneurysm patients to the risks of surgery additional selection criteria are needed.
Aneurysm rupture is associated with extensive inflammation of the arterial wall.[6] Due to their capacity to secrete various cytokines and matrix metalloproteinases especially, infiltrated macrophages are considered to play a central role in aneurysm formation, progression and rupture.[6-8] Because of this important role, the non-invasive detection of macrophages could contribute to the identification of aneurysms at increased risk of growth or rupture. Although, MR imaging using a macrophage specific contrast agent (USPIO) has the potential to non-invasively identify macrophages in lymph nodes and atherosclerotic plaques, little is known on USPIO uptake in the aneurysm wall.[9-12] We studied USPIO uptake in the aortic wall of aneurysms and normal sized aortas.

Materials and methods

Patient selection
From January 2003 through September 2006, 239 prostate cancer patients were evaluated for lymph node metastasis using CT angiography and USPIO enhanced MR imaging. After retrospective review of all USPIO enhanced MR datasets, 11 patients were identified with an aortic (N=6) or iliac (N=5) aneurysm. Since age is an important risk factor for atherosclerosis and aneurysm formation, 11 age-matched controls (non-dilated artery) were identified in the same database. Data on demographics, medical history and medication use were collected from hospital medical charts.

MR Imaging protocol
MR imaging was performed using a 1.5 tesla MR unit (Sonata™, Siemens, Erlangen, Germany). Data acquisition started 24–36h after USPIO (Ferumoxtran-10, Sinerem™, Guerbet, France) infusion. USPIO is composed of ultrasmall superparamagnetic particles of iron oxide which slowly migrate from vascular to interstitial space to be phagocytised by macrophages.[13] This results in iron accumulation and marked signal voids (blackening) on iron sensitive MR-sequences (e.g. T2*-weighted images).
After initial localization with a three-dimensional T1-weighted gradient echo (GRE) sequence, T2*-weighted GRE and T1-weighted fast-spin echo (FSE) MR images were acquired. The T1-weighted and T2*-weighted MRI images were subsequently reconstructed perpendicular to the aortic and iliac central luminal line for an accurate

visualization of the abdominal aorta and both common iliac arteries. To reduce motion artefacts by bowel peristalsis, patients were injected with 1mL (20mg) of butyl scopolamine (Buscopan™; Boeringer, Ingelheim, Germany) one hour prior to MR data acquisition.

CT protocol

All CT examinations were performed the day before MR imaging using a 4-slice Multi-Detector CT scanner (Somatom Sensation™, Siemens, Forchheim, Germany). Patients were administered both oral and intravenous contrast (200ml Telebrix 300™ and 95ml Xenetix 300™ respectively; Guerbert, Germany). Data acquisition started 45sec after intravenous contrast admission. Scan range covered the area between the distal renal artery and the femoral bifurcation. Scanning parameters included 160mAs, 120kVp, 2.5mm detector collimation and a table feed of 12.5mm. Thee millimetre (3mm) thick axial slices were reconstructed at a 2mm increment.

Alignment of CT and MR data.

To differentiate USPIO induced signal voids from diminished MR signal intensity by mural calcifications, we used a commercially available software package for data fusion (Syngo Image Fusion™, Siemens, Erlangen Germany). This software allows the visual alignment of MR and CT images by adjusting translation and rotation until the MR dataset fits the CT volume.

Image interpretation

All fused and reconstructed images were analyzed during consensus reading (MT and JF). A specially designed questionnaire was used to assess the quality of the reconstructed images and to quantify USPIO uptake in the vessel wall.

The quality of the fused images was evaluated by recording the presence of flow, contrast- and motion-related artefacts on a four-point scale: absent (1), mild (2), moderate (3) and severe (4). Flow artefacts were defined by a low signal intensity of the arterial lumen compared to the signal of the Psoas muscle. Loss of signal intensity beyond the vessel wall (blooming) was considered an USPIO contrast artefact. Overall MR image quality and arterial wall visibility were rated on a five-point scale: very poor (1), poor (2), adequate (3), good (4) and very good (5). Arterial wall visibility was defined as the ability to differentiate the arterial wall from the lumen.

USPIO uptake was defined as a subendothelial lack of signal intensity (void) not attributable to calcification or intramural haematoma (figure 1). In both groups, the presence of USPIO was quantified by calculating the number of USPIO positive quadrants on each individual slice. The total number of quadrants between distal renal and iliac bifurcation was 3800 in the aneurysm (median 344 quadrants per patient; interquartile range 308-384) and 3580 in the control group (median 300 quadrants per patient; interquartile range 272-380). USPIO uptake in the associated intraluminal thrombus was recorded separately.

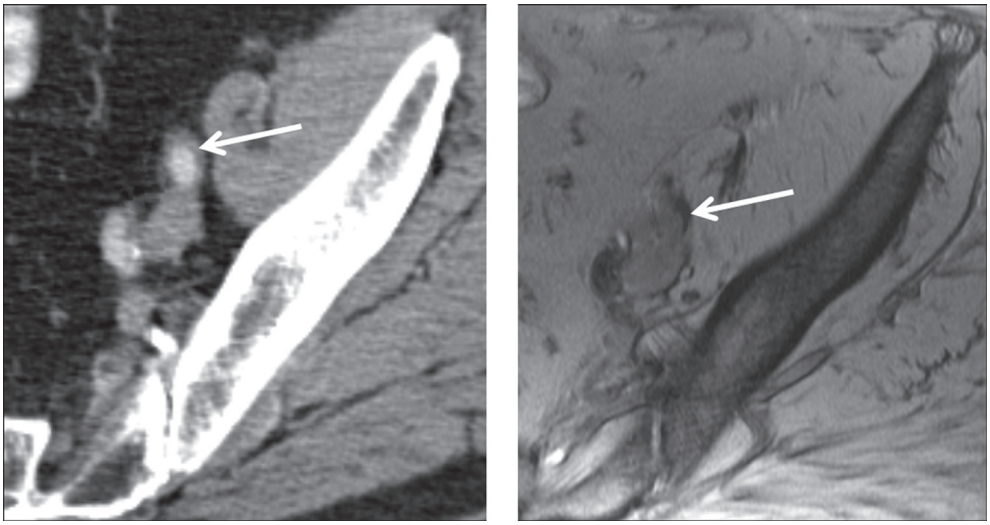

Figure 1. USPIO uptake in the wall of the left External Iliac Artery. The right panel (T2*-weighted MR sequence) shows a subendothelial signal void not attributable to calcification or intramural haematoma on CT (left). Note similar drops in signal intensity as a result of calcium in the Ilium and Sacrum.

Statistical analysis

The chi-square test was used to compare the difference in USPIO-positive quadrants between the aneurysm and control group, a two-sided P value of <0.05 was considered significant. Continuous variables were analyzed using Man-Whitney U tests for non-parametric variables. Nominal data was analyzed using contingency table analysis and Chi-square tests. All statistical analyses were performed using GraphPad Instat (version 3.06; GraphPad Software Inc, San Diego, CA, USA).

Results

Patient population

All included patients were male. Age matching resulted in a median age of 72 years in both groups. Median abdominal aortic aneurysm size was 3.4cm (interquartile range 3.2 – 4.1cm) and median iliac aneurysm size was 2.4cm (interquartile range 2.3 – 2.7cm), respectively.

More patients in the aneurysm group suffered from arterial occlusive disease (six in the aneurysm vs. one in the control group; P=0.02). Based on medical history and CTA evaluation, none of the patients was diagnosed with an “inflammatory aneurysm”. Patient characteristics are listed in table 1.

Image fusion quality

No significant differences in the presence of artefacts (contrast, flow and motion), aortic wall visibility or overall image quality were observed between the control and aneurysm group (table 2). The quality of the fused images was rated good in 10 (46%), adequate in 10 (46%), and poor in 2 (9.1%) patients, respectively. Of all 32 artefacts observed after image fusion, 15 (47%) were related to motion during CT or MR imaging.

Table 1. Patient characteristics

	Aneurysm N=11	Control N=11	P-value
Gender (Male)	11	11	NA
Age (years)	72 (69-78)	72 (69-77)	.95
Hypertension[a]	8	4	.09
Diabetes[b]	0	0	NA
AOD[c]	6	1	.02
COPD[d]	2	1	.53
Smoking[e]	4	2	.39
ASA	5	1	.06
Statin	4	1	.34

[a] Use of antihypertensive medication or a recorded systolic blood pressure (>140mmHg)

[b] Use of antidiabetic medication or history of diabetes mellitus

[c] Arterial occlusive disease (AOD), including peripheral and coronary artery disease.

[d] Chronic obstructive pulmonary disease (COPD)

[e]Smoking, current or prior.

Table 2. Qualitative assessment of the fused images in both groups.

	Aneurysm N=11[a]	Control N=11[a]	P-value
Flow artifact[b]	1.36	1.63	.48
Contrast artifact[c]	1.45	1.72	.50
Motion artifact	1.72	2.36	.17
Wall visibility	3.64	3.27	.51
Image quality	3.55	3.27	.54

[a] Mean values of visual assessment criteria in both patient groups on a scale of 1 to 4 for artifacts and on a scale of 1 to 5 for aortic wall visibility and overall image quality.

[b] Flow artifact. low signal intensity of the arterial lumen compared to the signal of the Psoas muscle.

[c] Contrast artifact, Loss of signal intensity beyond the vessel wall (blooming).

Wall visibility, the ability to differentiate the arterial wall from the lumen.

USPIO uptake

The number of USPIO positive quadrants was significantly higher in the aneurysm than in the control group, 158 (4.5%) quadrants in the aneurysm and 13 (0.4%) in the control group ($p<0.001$), respectively. Two abdominal aortic aneurysms accounted for 90% (154/171) of all USPIO positive quadrants. In both patients, USPIO was present at the level of maximal aneurysm diameter and within the wall of the aneurysm neck. In the remaining aneurysm and control patients USPIO uptake was absent or limited (1-4 quadrants per patient).

Thrombus was present in 8/22 (36%) patients, 4 patients in each group. USPIO induced signal voids were observed in the associated thrombus of one abdominal aortic aneurysm. This was one of the aneurysms showing a high number of USPIO positive quadrants (figure 2).

The patient with the largest number of USPIO positive quadrants had the largest abdominal aortic aneurysm (5.2cm). Within the first year following USPIO-MR, the aneurysm increased in size (6.2cm) and the patient was scheduled for endovascular aneurysms repair. Unfortunately he died of a myocardial infarction days before surgery. The second patient showing a high number of USPIO positive quadrants had a relatively small abdominal aortic aneurysm (3,7cm). The aneurysm has not been imaged since the study's CT and USPIO-MR. The largest iliac aneurysm (4.8cm) did not show USPIO uptake.

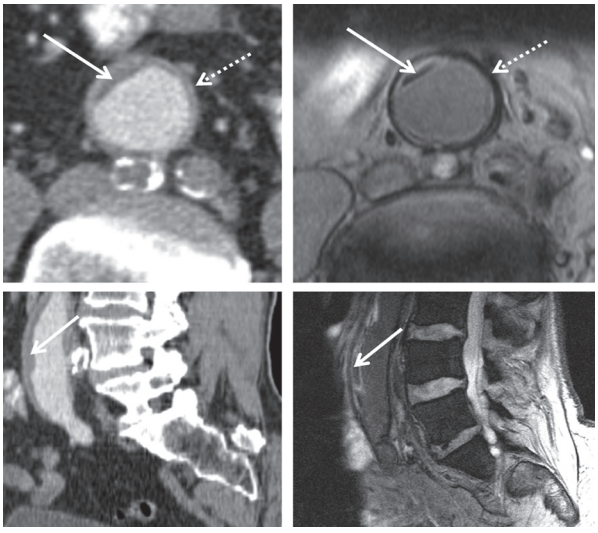

Figure 2. USPIO uptake in the wall and thrombus of a 3,7cm large abdominal aortic aneurysm. The dashed arrow shows diminished T2* signal intensity in the aneurysm wall (right panel), not related to the presence of calcified plaque on the corresponding CT (left panel). The full arrow shows USPIO uptake in the centre of the associated intraluminal thrombus. Note that the calcifications in the wall of the occluded venous aorto-iliac bypass graft result in dimished signal intensity on T2*-weigthed MR images.

Discussion

The potential of USPIO-MR for the detection and quantification of macrophage infiltration in atherosclerotic plaques was established in experimental studies, showing USPIO uptake in the aortic wall of hyperlipidemic rabbits.[14-16] Subsequent pilot studies in humans, showed USPIO uptake in carotid arteries affected by atherosclerosis.[11, 17] Howarth et al, focused on the differential uptake of USPIO in patients with symptomatic (vulnerable) and asymptomatic carotid artery stenosis. They showed more USPIO positive quadrants in patients suffering from transient ischemic attacks or stroke.[18]

Like rupture prone vulnerable atherosclerotic plaques, aneurysm rupture is characterized by extensive inflammation of the arterial wall.[6] An in vivo diagnostic technique, able to identify infiltrated macrophages, might therefore help select patients at increased risk of aneurysm growth and rupture. in spite of the potential of USPIO-MR for the detection of infiltrated macrophages, current literature on USPIO uptake in the aortic wall is limited to a single case report.[8] We studied a larger series of both iliac and abdominal aortic aneurysms and found a high number of USPIO positive quadrants in the wall of two abdominal aortic aneurysms. The arterial wall of the remaining aneurysm patients and controls showed limited or no USPIO uptake.

The observed variation in USPIO uptake between aneurysm patients might result from the fact that most included patients had a small aneurysm. Although little is known on the inflammatory activity in the wall of small aneurysms, most small aneurysms have little risk of rupture and show little increase in diameter over time. Another possible explanation is a limited sensitivity of USPIO-MR for the identification of aneurysm wall inflammation. This however, seems unlikely as both previous experimental and human pilot studies have shown a high sensitivity (>90%) for the detection of macrophages in atherosclerotic plaques.[15, 17-19] Moreover, the used T2*-weighted sequence is highly sensitive for the detection of small iron deposits.[10, 20] A clinically more intriguing explanation for the variation in USPIO uptake between aneurysm patients is the assumption that uptake is limited to aneurysms with a propensity for rupture or growth. Moreover, clinical data provide evidence for a staccato growth pattern in abdominal aortic aneurysms.[21] This suggests a dynamic process of arterial wall damage and episodes of repair.[6] Because of the dynamic nature of the disease, USPIO uptake in the aneurysm wall is likely to be transient and might precede episodes of growth. Whether USPIO uptake could actually predict aneurysm growth should be the focus of future research.

Next to uptake in the aneurysm wall, one USPIO positive abdominal aortic aneurysms, showed USPIO induced signal voids in the associated intraluminal thrombus. The remaining 7 thrombi did not show USPIO uptake. This might suggest that thrombus is impermeable could impair migration of USPIO to the arterial wall. However, the second aneurysm with USPIO uptake in the aneurysm wall, showed no uptake in the intraluminal thrombus. Moreover, results from histological studies show that thrombus

is biologically active and contains small channels that are believed to facilitate transport of leukocytes and enzymes to the aneurysm wall.[22, 23]
A potential limitation for the use of USPIO-MR in atherosclerosis is the high rate of false positive readings related to the presence of calcifications and intramural haematomas.[19] By fusing MR and CT angiography data we were able to localize calcifications on CT and reduce the number of false positive findings. Although contrast enhanced CT has a high sensitivity for the detection of intramural hematomas the CT protocol was optimized for prostate imaging and might therefore be less ideal for vascular imaging.
Patients were not matched for cancer stage and the presence of USPIO in (metastasis free) lymph nodes could have influenced results. The effect of this possible bias seems however limited as we observed a low rate of USPIO contrast or “blooming” artefacts. Furthermore, patients in the aneurysm group showed a higher risk profile for cardiovascular disease, including prior vascular disease. However, based upon the present results this did not result in a higher number of patients with USPIO uptake in the aneurysm group. Both aneurysm patients with the highest number of USPIO positive quadrants used statin. This is inconsistent with the alleged inhibitory effect of statin on inflammation in atherosclerosis and questions the use of USPIO-MR to monitor the effect of statin on inflammation of the aneurysm wall.[24]

Conclusion

USPIO uptake is limited or absent in the wall of normal sized aortas and most aneurysms. However, individual abdominal aortic aneurysms show high levels of USPIO uptake, indicative for extensive macrophage infiltration in the aneurysm wall. Future research should focus on the predictive value of USPIO uptake for aneurysm growth and rupture.

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In Vivo imaging of abdominal aortic aneurysms increased FDG uptake suggests inflammation in the aneurysm wall

7

M. Truijers
H. A. J. M. Kurvers
S. J. H. Bredie
W. J. G. Oyen
J. D. Blankensteijn

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Abstract

Objective
To study the potential of integrated positron emission tomography and computed tomography (PET/CT) to identify aneurysm wall inflammation.

Methods
The level of F18-fluorodeoxyglucose (FDG) uptake was studied in aneurysmal and normal-sized aortas of 34 male patients [17 with abdominal aortic aneurysm (AAA) and 17 age-matched controls] identified in a database of 278 consecutive patients evaluated for staging of primary lung cancer. The maximal standardized uptake value (SUV) was calculated to quantify FDG uptake in the AAA wall.

Results
AAAs showed significantly higher FDG uptake than the normal-sized aorta in age-matched controls (SUV 2.52 ± 0.52 versus 1.78 ± 0.45, respectively; $p<0.001$). The level of FDG uptake did not correlate with maximal aneurysm diameter ($r=0.09$; 95% CI 0.42 to 0.56; $p=0.7$).

Conclusion
FDG-PET/CT is a promising technique to identify inflammation of the aneurysm wall. Irrespective of aneurysm diameter, asymptomatic AAAs show more FDG uptake and more inflammatory activity in the wall than the non-dilated abdominal aorta of sex/age-matched controls. Future studies will be directed at the predictive value of increased FDG uptake for aneurysm wall strength, rupture risk, and the utility of FDG-PET/CT in assessing the effect of medical interventions.

Introduction

In the late 1940s, the diagnosis of an abdominal aortic aneurysm (AAA) held little to no clinical significance. Therapy was relatively ineffective, prognosis regarding time utterly uncertain, and the ultimate prognosis for life hopeless.[1] Although the introduction of surgical repair improved life expectancy, it raised an important question. Should vascular surgeons repair all aneurysms or is life expectancy limited by comorbidity or associated operative risks?[2] In 1955, Crane[1] introduced aneurysm diameter measurement as a potential tool to predict AAA rupture and to select patients for prophylactic repair.
Although surgical techniques and perioperative management improved dramatically over the past 50 years, patient selection is still based on measurement of aortic diameter. Some aneurysms, however, rupture at an unexpectedly small size while others grow exceptionally large and remain intact.[3, 4] To decrease the number of unanticipated ruptures while reducing the number of unnecessary AAA repairs (and associated morbidity and mortality), a more accurate method for aneurysm rupture prediction is needed. Since rupture occurs when the aneurysm wall fails to withstand the forces acting on it, in vivo data on AAA wall pathology could identify patients at risk of rupture.
End-stage aneurysm disease and especially aneurysm rupture are characterized by extensive inflammation of the arterial wall.[5] Although the stimulus for this enhanced infiltration is not known, recent insights into the pathophysiology of aneurysm formation, growth, and rupture indicate a close relationship between increased mechanical stress (hypertension) and the activation of infiltrated lymphocytes and macrophages.[5-8] This increased inflammatory activity results in the progressive breakdown of the aortic wall, aneurysm dilatation, and, ultimately, rupture.[5, 9] As inflammation is characterized by increased metabolic activity of leukocytes, F18-fluorodeoxyglucose (FDG), a glucose derivative used for positron emission tomography (PET), shows increased uptake in inflammatory tissue.[10] Using an integrated PET and CT scanner, FDG-PET/CT could have the potential to both quantify and localize inflammation of the aneurysm wall.[11-13] This could provide valuable in vivo information on the pathophysiological mechanisms leading to aneurysm formation and progression and might aid the identification of patients who benefit most from prophylactic aneurysm repair. We studied the levels of FDG uptake in AAAs compared to normal-sized aortas.

Methods

Patient Population
From February 2006 through September 2007, 278 patients were evaluated using FDG-PET/CT for staging of primary lung cancer. After reviewing the 278 FDG-PET/CT scans, 17 male patients (mean age 71 years) with an asymptomatic AAA (abdominal

aortic diameter >3cm) were identified by an investigator blinded to the results of the FDG-PET scans. The same physician chose 17 sex/age-matched controls with a normal abdominal aortic diameter (<3cm) from the same dataset. Medical records were reviewed for demographics and medical history.

Integrated PET/CT and Image Analysis
In all included patients, simultaneous FDG-PET and CT imaging was performed using an integrated PET/CT scanner (Biograph Duo; Siemens Medical Solutions, Knoxville TN, USA). Data acquisition started 60 minutes after intravenous administration of 250 MBq of F18-FDG (Covidien, Petten, The Netherlands). The entire CT dataset was fused with the 3-dimensional PET images using an integrated software interface (Syngo Image Fusion; Siemens Erlangen, Germany) to create anatomical image superimposed with FDG uptake in the arterial wall (figure 1).
After image fusion, a volume of interest (VOI) was placed over the entire abdominal aorta (figure 2). Within this VOI, FDG uptake was quantified by calculating the maximal standardized uptake value (SUV), which was defined as the maximal concentration of FDG in the VOI divided by the injected dose and body weight.

Statistical Analysis
Continuous data are reported as mean ± standard deviation. Possible differences in FDG uptake between AAA and normal-sized aortas were evaluated for significance using an independent sample t test. The correlation between maximal aneurysm diameter and FDG uptake was evaluated by calculating the Spearman's rank correlation coefficient (r) and 95% confidence interval (CI). Nominal data were analyzed using contingency table analysis and chi-square tests. All statistical analyses were performed using GraphPad Instat (version 3.06; GraphPad Software Inc, San Diego, CA, USA).

Results

No statistically significant differences were observed between AAA patients and sex/age-matched controls with respect to blood pressure, diabetes, chronic obstructive pulmonary disease, stroke, medication use, or smoking habits (table 1). Statins were used more frequently in the AAA group (n=7, 41%) than in the controls (n=2, 12%; p=0.05).
AAAs showed significantly higher FDG uptake (figure 3) than normal-sized aortas in age-matched controls (SUV 2.52 ± 0.52 versus 1.78 ± 0.45, respectively; p<0.001). No significant correlation was found between advanced age and FDG uptake (r=0.12; p=0.5).
The use of statins did not result in reduced FDG uptake in AAA patients: the SUV was 2.47 ± 0.71 in AAA patients taking statins versus 2.55±0.38 in AAA patients not taking

statins (p=0.96). Two patients in the AAA group used steroids; one showed low FDG uptake and the other had a higher than average SUV (1.60 and 3.23, respectively).
The mean diameter in the AAA group was 4.0 ± 1.0cm (range 3.2 – 6.2). In the control group, the diameter of the abdominal aorta was <3cm by definition (mean diameter 2.1 ± 0.3). No significant correlation was observed between maximal AAA diameter and the level of FDG uptake in the AAA group (r=0.09, 95% CI –0.42 to 0.56; p=0.7). The patient with the largest aneurysm (6.2cm) showed low FDG uptake (SUV 1.9). In this patient, surgery was deferred because of severe pulmonary comorbidity, and he was discharged from active follow-up. High FDG uptake (SUV >3.23) was observed in 3 patients with relatively small AAAs (3.4, 4.4, and 4.5cm). Two of these patients died within 1 year of follow-up, both with intact aneurysms. In the third patient, aneurysm size increased from 3.4 to 3.8cm at 7 months after initial PET/CT imaging; he is still in active follow-up.

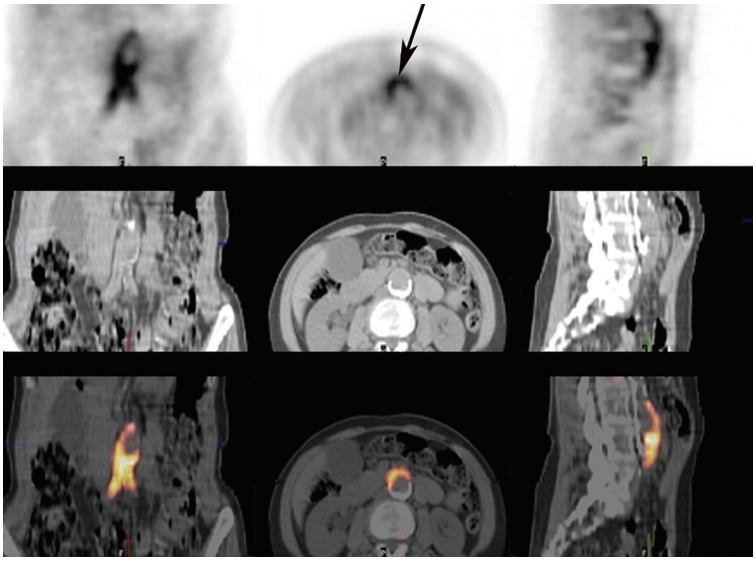

Figure 1. Fusion of FDG-PET and CT data. The top row shows FDG-PET data in the coronal, transverse, and sagittal planes (left to right). The middle row depicts the corresponding location on CT. Fusion of both datasets provides detailed anatomical and functional information (bottom row). On the axial images, FDG uptake is located within the anterior aneurysm wall. No FDG uptake is observed in the heavily calcified posterior aneurysm wall.

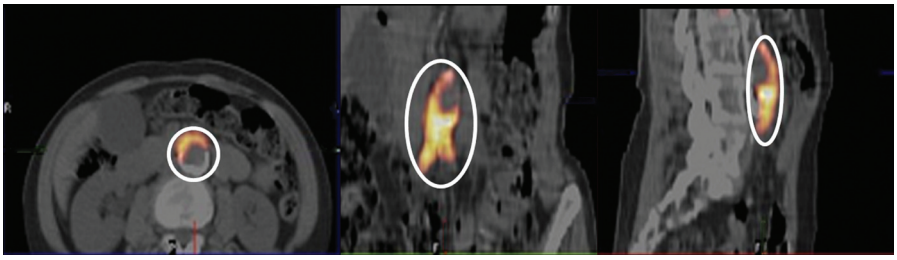

Figure 2. Quantification of FDG uptake. A volume of interest (VOI) was created by placing a marker around the site of maximal FDG uptake in all 3 dimensions. Subsequently, standardized uptake value was calculated by determining the maximal FDG concentration in this well defined volume.

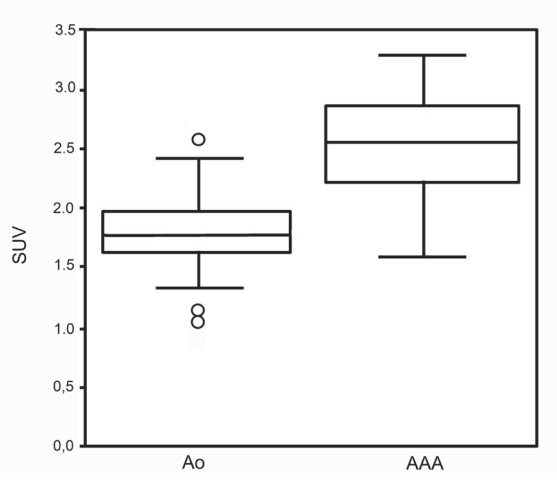

Figure 3. The box plot shows that FDG uptake is significantly higher ($p<0.001$) in aneurysmal versus normal sized aortas (Ao). Rectangles represent the 25th to 75th percentiles, the horizontal bars within rectangles are the means, the short horizontal bars outside the rectangles are the 10th and 90th percentiles, and the solid circles are outliers (below the 10th or above the 90th percentile).

Dicussion

The results of this study support the important role of inflammation in the natural history of AAA. While FDG-PET has been studied extensively for the detection of vulnerable atherosclerotic plaques, little is known about FDG uptake in AAA.[14-18] Like atherosclerosis in general, aneurysm formation, growth, and rupture are associated with extensive inflammation of the arterial wall[5]; in 2005, Defawe et al.[13] reported increased FDG uptake in an AAA, corresponding to an inflammatory infiltrate in the aortic wall. These findings provide the pathophysiological basis for the enhanced FDG uptake in AAA observed in this study.

To our knowledge, no one has quantified FDG uptake in the AAA wall. Sakalihasan et al.[19] reported a possible association between increased FDG uptake and AAA rupture. Ten of their 26 AAA patients showed increased FDG uptake. Among these 10 patients, 9 needed surgery due to rupture, aneurysm-related symptoms, or rapid expansion. Because Sakalihasan studied AAA patients only and most AAAs were large (mean AAA diameter 6.3cm) or symptomatic, it remained unclear whether FDG uptake in small, asymptomatic AAAs is increased compared to the non-dilated aorta. In the present study, we observed increased uptake of FDG in asymptomatic AAAs compared to the non-dilated aorta of age-matched controls. This confirms the potential of FDG-PET imaging for noninvasive detection of aneurysm wall inflammation and, possibly, disease progression.

Limitations

A potential limitation of this study is the inability to discriminate between FDG uptake in malignant lesions and focal areas of infection or inflammation on FDG-PET. Since we studied lung cancer patients, this could have resulted in false positive readings in the abdominal aortic area. However, by using integrated PET/CT, the interpretation of the PET images was improved, reducing the number of false positive findings.[20] Furthermore, none of the enrolled patients had clinical evidence of active vasculitis or aortitis.[21]

Because age is a major risk factor for the development of atherosclerosis, both the intensity and prevalence of FDG uptake in the wall of affected arteries increases with aging.[22] By matching for age, we minimized the effect of this confounding factor. The only difference between both groups that approximated significance was the use of statins, which were used more frequently in the AAA group. Besides lowering cholesterol, statin use has been demonstrated to reduce proteolytic activity within the aneurysm wall and to attenuate aneurysm growth.[23, 24] Recently, Tahara et al.[25] reported decreased FDG uptake in atherosclerotic plaques of patients using statins. Although the effects of this potential bias seem limited due to the small difference in statin use between groups, the relatively more frequent use of statins in the AAA group could have resulted in an underestimation of FDG uptake in the wall of the aneurysm.

Like atherosclerosis in general, aneurysm disease is a dynamic process characterized by damage of the arterial wall due to inflammation and repair.[5] Because of the dynamic nature of the disease, FDG uptake in atherosclerosis is transient and only present at the time of active inflammation.[26] Combined with the small changes in FDG uptake over a short period of time and the excellent inter- and intraobserver agreement observed by Rudd et al.,[16] FDG-PET could be a useful tool to assess the effect of anti-inflammatory medication on aneurysm growth and rupture.[18, 26]

Conclusion

FDG-PET/CT is a promising technique to identify inflammation of the aneurysm wall. Irrespective of aneurysm diameter, asymptomatic AAAs show more FDG uptake and thus inflammatory activity in the wall than the non-dilated abdominal aorta of age-matched controls. Future studies will be directed toward the predictive value of increased FDG uptake for aneurysm wall strength, rupture risk, and the use of FDG-PET/CT to assess the effect of medical interventions.

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8 General discussion

General discussion

Elective aneurysm repair aims at the prevention of aneurysm rupture and is considered when the risk of rupture exceeds the risks of repair. In general, large abdominal aortic aneurysms (AAA) are repaired whereas small AAA (<5.5cm) are kept under surveillance.[1] The commonly used 5.5cm threshold for intervention was confirmed in two large clinical trials that showed a low annual rupture risk (0.6-1%) in small AAA.[2, 3] However, as 60% of all patients in the observation groups underwent elective repair for rapid expansion or symptoms, it is questionable whether these data accurately reflect the natural history of small AAA.[1] Results from observational studies show that small aneurysms do rupture.[4-6] At the same time, most aneurysm patients die with an intact aneurysm due to comorbid conditions.[7, 8] A more accurate assessment of aneurysm rupture risk could therefore reduce the incidence of rupture in small AAA and prevent unnecessary aneurysm repair in patients with large stable AAA.
Like any material, the aneurysm wall ruptures when the forces (stress) acting on the wall exceed wall strength.[9] To contribute to the development of a more accurate tool for predicting rupture, we focused on the non-invasive assessment of both wall stress and strength.

Aneurysm wall stress

Wall stress analysis is potentially superior to aneurysm diameter for the prediction of rupture.[10] However, most studies to date included large AAA and the potential of wall stress analysis for the detection of small AAA at increased risk of rupture remains unclear. By fusing CTA with blood pressure data we studied wall stress in 30 patients with a small AAA (10 asymptomatic, 10 symptomatic and 10 ruptured). Results from this study showed that wall stress at maximal systolic blood pressure is significantly higher for ruptured than asymptomatic aneurysms. This confirms the potential of wall stress analysis as a promising technique to detect small aneurysms at elevated risk of rupture. Analysis at uniform blood pressure resulted in less pronounced and non-significant differences in wall stress between asymptomatic and ruptured small aneurysms. This reiterates the need for strict blood pressure control to reduce peak aortic wall stress and aneurysm rupture risk. Larger prospective follow-up programmes will be needed to confirm our findings and to investigate the effect of strict blood pressure control on aortic wall stress and rupture risk.
Although promising, the wall stress model does not account for thrombus. Thrombus is a complex structure of fibrin and viable cells and is found in most aneurysms. The effect of thrombus on aneurysm wall stress is controversial. Some authors suggest that thrombus has no effect on pressure transmission while others found reduced stress in the presence of thrombus.[11, 12] The biomechanical properties assigned to thrombus in

these studies were all derived from in vitro testing of relatively well structured specimens and extrapolating this experimental data to in vivo three dimensional thrombus dynamics might be inappropriate.[13] To study thrombus in vivo, we used dynamic CTA and volumetric analysis and showed large variations in thrombus compressibility (volume change during the cardiac cycle) between individual patients. This suggests that thrombus acts as a biomechanical buffer in some, while it has little to no effect in others. Because of this large inter-patient variation, it seems irrational to incorporate mean thrombus material properties in a model for wall stress analysis. Future research will be directed at the development of patient specific thrombus material models. After the development of these models, research should focus on the impact of thrombus on computed wall stress analysis and the prediction of aneurysm rupture.

Aneurysm wall strength

Aneurysm progression and rupture are characterized by extensive damage to elastin and collagen fibres within the aneurysm wall.[13-15] Based upon multiple samples per patient, we showed large differences in aneurysm wall strength for different locations of the same aneurysm. Moreover, local reductions in aneurysm wall strength were found to be associated with focally increased matrix metalloproteinase activity (MMP-9). Previous studies using immunohistochemical analysis and in situ hybridization, identified macrophages and neutrophiles as the main source of MMP-9.[16] This could have important consequences for imaging techniques like USPIO-MR and FDG-PET/CT, which have the potential to non-invasively identify macrophages and leukocytes.
The potential of USPIO-MR for the detection of macrophages in vulnerable atherosclerotic plaques was established in experimental and clinical pilot studies.[17-20] Like rupture prone atherosclerotic plaques, aneurysm rupture is characterized by extensive inflammation of the arterial wall.[13] In spite of the potential of USPIO-MR as a possible selection tool for prophylactic aneurysm repair, current literature on USPIO uptake in the aortic wall is limited.[21] We studied both iliac and abdominal aortic aneurysms and found a large variation in USPIO uptake between individual aneurysm patients. This observed variation in USPIO uptake could be related to the fact that most included patients had a small aneurysm. Although little is known on the inflammatory activity in the wall of small AAA, most small aneurysms have little risk of rupture and show little increase in diameter over time.[22] A clinically more intriguing explanation for the observed variation in USPIO uptake between AAA patients is the assumption that uptake is limited to AAA with a propensity for rupture or growth. Clinical data provide evidence for a staccato growth pattern in AAA which suggests a dynamic process of arterial wall damage alternated by episodes of repair.[13, 23] Because of this dynamic nature, USPIO uptake in the aneurysm wall is likely to be transient and might precede episodes of growth. This should be the focus of future research.

Although USPIO-MR provides high anatomical detail and is both sensitive and specific for detecting macrophages in the aneurysm wall, its use in practice is limited by the availability of both MR and USPIO). These limitations focused the attention to FDG-PET/CT for the non-invasive identification of aneurysm wall inflammation. FDG is a radioactive glucose analogue produced in cyclotrons all over the world. One of the problems of FDG is the instability of the molecule. This requires fast shipping from nuclear reactors to medical centres. Fortunately, the nuclear reactor in Petten, The Netherlands, is one of the main suppliers of FDG. This means that in our institution, FDG is available in sufficient quantities for "on demand" PET/CT imaging. A second important advantage of FDG-PET/CT over USPIO-MR is the ability to calculate standardized (FDG) uptake values (SUV). This reduces observer variability and at the same time allows quantification of FDG-uptake, which is known to correspond to the level of inflammation.[24-26] To our knowledge, no quantitative studies on FDG uptake in the AAA wall have been published to date. Sakalihasan et al.[27] reported a possible association between increased FDG uptake and AAA rupture. Ten of their 26 AAA patients showed increased FDG uptake. Among these 10 patients, 9 needed surgery due to rupture, aneurysm-related symptoms, or rapid expansion. Because Sakalihasan studied AAA patients only and most AAAs were large (mean AAA diameter 6.3cm) or symptomatic, it remained unclear whether FDG uptake in small, asymptomatic AAAs is increased compared to the non-dilated aorta. In a retrospective study, we quantified FDG uptake in 17 aneurysm patients and 17 age-sex-matched controls and observed increased FDG uptake in AAA. This confirms the potential of FDG-PET imaging for noninvasive detection of aneurysm wall inflammation. Reeps et al. showed a significant correlation between FDG uptake, increased MMP expression and histopathologic characteristics of aneurysm disease progression.[28] Future studies should be directed at the predicative value of increased FDG-uptake for aneurysm wall strength and increased aneurysm rupture risk.

Questions answered and future prospectives

1. *What is the current status of cross-sectional imaging?*
   CTA and MRA data acquisition is fast and provides high anatomical detail. Sophisticated image post-processing tools allow the reconstruction of images in all three dimensions.

2. *Has CTA-based wall stress analysis the potential to detect small aneurysms at risk of rupture?*
   Wall stress at maximal systolic blood pressure is significantly higher for ruptured than asymptomatic small aneurysms. This shows the potential of wall stress analysis as a promising technique to detect small aneurysms at elevated risk of

rupture. Analysis at uniform blood pressure resulted in less pronounced and non-significant differences in wall stress between asymptomatic and ruptured small aneurysms. This reiterates the need for strict blood pressure control to reduce peak aortic wall stress and aneurysm rupture risk. Larger prospective follow-up programmes will be needed to confirm our findings and to investigate the effect of strict blood pressure control wall stress and rupture risk.

3. *What is the effect of thrombus on the forces (stress) exerted on the aneurysm wall?*
   Thrombus might act as a biomechanical buffer in some, while it has virtually no effect in others. This individual variation may prevent the incorporation of generalized thrombus characteristics and suggest that individual assessment of thrombus characteristics may be required. Whether the incorporation of a patient specific thrombus material model would alter the result of wall stress analysis and thus contribute to a better assessment of aneurysm rupture risk should be the focus of future research.

4. *Is aneurysm wall strength related to inflammation induced matrix metalloproteinase (MMP) activity?*
   Local reductions in aneurysm wall strength are associated with high levels of both latent and active MMP-9. Macrophages and neutrophiles have been identified as the main source of MMP-9. This could have important consequences for imaging techniques directed at the in vivo identification of aneurysm wall inflammation. Future studies should focus on the association between the non-invasive assessment of aneurysm wall inflammation and wall strength. In addition to the implications for aneurysm rupture risk, the observed correlation between aneurysm wall strength and MMP-9 activity, provides the rationale for future studies on aneurysm rupture risk and protease inhibiting medical therapy (e.g. doxycycline and statin).

5. *Is it possible to non-invasively identify macrophages infiltrated in the aneurysm wall using utrasmall particles of iron oxide and magnetic resonance imaging (USPIO-MR)?*
   Individual abdominal aortic aneurysms show high levels of USPIO uptake, indicative for extensive macrophage infiltration in the aneurysm wall. Whether USPIO uptake is limited to aneurysms with a propensity for rupture or growth will be the focus of future research. Another interesting application of USPIO-MR in aneurysm patients is the non-invasive assessment of the efficacy of medical interventions on aneurysm disease. In the near future, studies will be directed at the effect of statin on USPIO uptake in the aneurysm wall.

6. *Is it possible to non-invasively identify aneurysm wall inflammation using integrated positron emission and computed tomography (FDG-PET/CT)?*
   FDG-PET/CT is a promising technique to identify inflammation of the aneurysm wall. Irrespective of aneurysm diameter, asymptomatic AAAs show more FDG uptake than the non-dilated abdominal aorta of sex/age-matched controls. Future studies will be directed at the predictive value of increased FDG uptake for aneurysm wall strength, rupture risk, and the utility of FDG-PET/CT in assessing the effect of medical interventions.

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Summary

Summary

An abdominal aortic aneurysm (AAA) is a focal dilatation of the abdominal aorta. AAA mainly affects the aging population. Results from a Dutch aneurysm screening study showed that 8.1% of all male participants (>60yrs) had an AAA.[1] In 2005, a total of 3900 Dutch patients were admitted to the hospital because of aneurysm disease. Of these patients, 21% (815 patients) was admitted as a result of aneurysm rupture.[2] This is probably an underestimation of the incidence of aneurysm rupture as most patients experiencing rupture will not make it to the hospital alive. Moreover, autopsy is rarely performed in the Netherlands and aneurysm rupture is likely to be missed as the primary cause of death.
The risk of rupture increases with aneurysm size and because of the considerable risks associated with prophylactic surgery, aneurysm repair is only considered in patients with a large aneurysm (>5,5cm).[3, 4] Although this diameter-based threshold is widely used to select patients for prophylactic aneurysm repair, small aneurysms do rupture. At the same time, other AAA grow exceptionally large and remain intact.[5, 6] A more reliable tool to predict aneurysm rupture might reduce the number of unanticipated ruptures without exposing all AAA patients to the risks of surgery.
Aneurysm rupture occurs when the forces (wall stress) acting on the aneurysm wall exceed wall strength. A non-invasive assessment of both determinants might therefore refine rupture risk assessment and patient selection of prophylactic aneurysm repair.
In the early 1990s, a new technique was introduced for the treatment of AAA. This minimally invasive technique involves an incision in both groins to gain access to the femoral or external iliac artery. With the use of guide wires, catheters and specially designed introducer systems a prosthetic endograft is placed in the AAA to exclude it from circulation. In contrast to conventional aneurysm repair, the success of EVAR depends on an accurate preoperative assessment of aortic morphology.[7] Improved cross-sectional imaging techniques and new image post-processing tools facilitate this preoperative work-up. We studied whether these new techniques could also facilitate aneurysm wall stress and strength analysis.

Chapter 2 provides an overview of available vascular imaging techniques. Due to the development of new and faster equipment and the introduction of image post-processing tools, multislice helical CTA is the method of choice for imaging abdominal aortic aneurysms.

By using a well known civil engineering technique (finite element analysis) anatomic CTA information is used to calculate aneurysm wall stress.[8] In **chapter 3**, we studied whether wall stress analysis has the potential to identify small AAA at increased risk of rupture. Results from this study showed that wall stress analysis is significantly higher in ruptured than asymptomatic small AAA. This confirms the potential of aneurysm wall

stress analysis as a promising tool to select patients for prophylactic aneurysm repair. Although promising, the finite element model currently used lacks information on thrombus.

Thrombus exists in most AAA and is a rather complex structure of viable cells and fibrin deposits. The effect of thrombus on wall stress is controversial. Some suggest that thrombus might reduce wall stress while others showed no effect of thrombus on pressure transmission to the aneurysm wall. In **chapter 4**, we used dynamic CTA and volumetric analysis and showed large differences in thrombus compressibility between individual patients. This variation in thrombus compression most likely results from different material properties for different thombi. The effect of thrombus on aneurysm wall stress therefore varies from patient to patient. Simply adding mean thrombus material properties to the previously described finite element technique might be inappropriate for a patient specific prediction of aneurysm rupture.

Wall strength is the second determinant of aneurysm rupture. To date there is no method available to non-invasively assess aneurysm wall strength. Although, the involvement of matrix metalloproteinase (MMP) in aneurysm disease and aneurysm wall remodelling is well established the effect on aneurysm wall strength is unknown.[9] Based upon multiple aortic samples we showed a significant correlation between local reductions in aneurysm wall strength and focal MMP-9 activity (**chapter 5**). Previous studies have identified macrophages and neutrophiles as the main source of MMP-9.[10] This could have important consequences for the non-invasive assessment of aneurysm wall strength using contrast enhanced MR and integrated PET/CT.

MR imaging using a macrophage specific contrast agent (USPIO) has the potential to non-invasively identify macrophages in lymph nodes and atherosclerotic plaques.[11] USPIO is composed of ultrasmall superparamagnetic particles of iron oxide which slowly migrate from vascular to interstitial space to be phagocytised by macrophages.[12] We studied USPIO uptake in eleven patients with either an aortic (n=6) or iliac (n=5) aneurysm and 11 age matched controls (**chapter 6**). Compared to the normal sized aorta in controls, aneurysms show significantly more USPIO uptake. However, not all aneurysms show USPIO in the arterial wall. This suggests that USPIO is only present at the time of active inflammation and aneurysm progression. Whether USPIO uptake preludes aneurysm growth or rupture should be the focus of future research.

Because of the limited availability of both USPIO and MR, we focused on FDG-PET/CT for the non-invasive identification of aneurysm wall inflammation (**chapter 7**). FDG-PET/CT, relies on uptake of radioactive labeled glucose (FDG) in inflammatory tissue. After accumulation in inflammatory cells, FDG is metabolized which results in emission of photons detected by cameras surrounding the patient. Based upon a retrospective

study in 17 aneurysm and 17 age matched controls, we showed significantly higher levels of FDG in the wall of AAA. Current research is directed at the correlation between FDG uptake and aneurysm wall strength.

Conclusions

The evolution of medical imaging, from two-dimensional x-ray to advanced cross-sectional imaging has dramatically expanded the clinical use of MR and CT. These advanced techniques, combined with sophisticated image post-processing, might contribute to the identification of aneurysms at increased risk of rupture. The most promising technique is aneurysm wall stress analysis. Which has the potential to identify small AAA at risk of rupture. However, the technique does not provide information on the effect of intraluminal thrombus. This is related to the variation in thrombus compressibility between patients. Thrombus might act as biomechanical buffer in some patients, while it has little effect in others. Incorporating an average thrombus model in the used finite element technique seems irrational for the prediction of rupture in individual patients.
Aneurysm wall strength is correlated with MMP-9 activity. Inflammation induces MMP-9 activity and the non-invasive identification of aneurysm wall inflammation could therefore provide information on aneurysm wall strength. Using USPIO-MR and FDG-PET/CT it is possible to identify inflammation in the wall of AAA. Current research should focus on the correlation between USPIO or FDG uptake and aneurysm wall strength.

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Samenvatting

Samenvatting

Een abdominaal aorta aneurysma (AAA) is een lokale verwijding van de lichaamslagader (aorta) in de buik. AAA komen relatief veel voor. Tijdens een bevolkingsonderzoek in 1998 werd bij 8.1% van alle mannen ouder dan 60 jaar een AAA gevonden.[1] In 2005 werden 3900 patiënten met een AAA opgenomen in het ziekenhuis, 21% (815) van de opnamen was het gevolg van een aneurysma ruptuur (scheur).[2] Het werkelijke aantal patiënten dat een ruptuur doormaakt is waarschijnlijk veel groter. Dit heeft te maken met het feit dat veel patiënten met een ruptuur thuis of onderweg naar het ziekenhuis overlijden. Bovendien wordt in Nederland zelden een autopsie uitgevoerd bij ouderen die plotseling overlijden.
Omdat de kans op een fatale ruptuur stijgt wanneer de diameter van het aneurysma toeneemt, worden (in principe) alle AAA groter dan 5,5cm geopereerd.[3, 4] Hoewel dit logisch lijkt, kunnen ook kleine AAA scheuren.[5] Daarnaast overlijden veel patiënten met een intact groot AAA, aan andere aandoeningen zoals hartziekten (infarct) of longaandoeningen.[6] Om het aantal patiënten dat een ruptuur doormaakt te reduceren zonder iedereen met een AAA bloot te stellen aan de risico's van een operatie (complicaties) is het noodzakelijk de kans op een ruptuur beter in te schatten.
Net als alle materialen scheurt de vaatwand wanneer de krachten die erop inwerken groter zijn dan de wandsterkte. Hoewel de druk op de vaatwand gemeten kan worden met speciale katheters in het aneurysma en de wandsterkte in het lab onderzocht kan worden, zijn deze methoden te belastend (invasief). In 1990 werd een nieuwe techniek geïntroduceerd voor de behandeling van AAA.[7] Bij deze endovasculaire techniek (EVAR) wordt via de slagaders in beide liezen een prothese in het aneurysma geplaatst. In tegenstelling tot de conventionele (open) behandeling is het succes van EVAR in grote mate afhankelijk van goede preoperatieve beeldvorming.[8] De laatste jaren zijn bestaande radiologische technieken (CT en MRI) verbeterd en nieuwe toepassingen ontwikkeld. Of deze nieuwe toepassingen kunnen bijdragen aan het inschatten van de krachten op de AAA wand of de sterkte van de vaatwand is het onderwerp van dit proefschrift.

In **hoofdstuk 2** wordt een overzicht gegeven van de beschikbare technieken voor de preoperatieve beeldvorming van patiënten met een AAA. Door de ontwikkeling van nieuwe en snelle apparatuur en de manier waarop de verkregen data verwerkt kan worden is CT op dit moment de belangrijkste techniek voor het beoordelen van de anatomie van AAA.

Door het toepassen van een bestaande bouwkundige techniek (finite element analysis) kan anatomische CT informatie gebruikt worden voor het berekenen van de krachten op de vaatwand.[9] De techniek is gebaseerd op het verdelen van complexe geometrische structuren (zoals AAA) in duizenden driehoekige elementen. Door aan de elementen

mechanische eigenschappen toe te kennen en deze te koppelen aan gegevens over de bloeddruk kunnen de krachten op de vaatwand (wandstress) berekend worden. Of het met deze techniek mogelijk is kleine AAA te identificeren met een verhoogde kans op ruptuur werd onderzocht in dertig patiënten met een klein geruptureerd, symptomatisch (intact) of asymptomatisch AAA (**hoofdstuk 3**). Uit de resultaten blijkt dat het, met deze techniek, mogelijk is non-invasief de krachten op de wand (wandstress) te berekenen en dat deze significant hoger zijn voor patiënten met een geruptureerd AAA. Hoewel deze resultaten bemoedigend zijn, is de huidige techniek gebaseerd op een aantal aannames. Een mogelijke tekortkoming is het negeren van de intraluminale thrombus.

In vrijwel alle AAA zit thrombus, een complexe structuur van geklonterd bloed en fibrine. Een aantal wetenschappers stelt dat thrombus werkt als een schokbreker en de krachten op de wand neutraliseert.[10, 11] Anderen hebben juist geen enkel of zelfs een negatief effect van thrombus vastgesteld.[12, 13] Deze onduidelijkheid wordt met name veroorzaakt doordat weinig bekend is over hoe de thrombus zich in het menselijk lichaam (in vivo) gedraagt. Om dit te onderzoeken hebben we een studie uitgevoerd met dynamische CT (**hoofdstuk 4**). Dit is een nieuwe techniek waarbij CT beelden worden gereconstrueerd voor verschillende fases (systole en diastole) van de cardiale cyclus. Uit dit onderzoek blijkt dat bij sommige patiënten de thrombus gecomprimeerd wordt tijdens de cardiale cyclus terwijl dit bij anderen niet het geval is. Deze variatie is waarschijnlijk het gevolg van een andere samenstelling van de thrombus bij verschillende patiënten (meer of minder fibrine). Hierdoor is het mogelijk dat de thrombus beschermend werkt tegen de hemodynamische krachten in sommige patiënten terwijl het weining of geen effect heeft bij anderen. Het toevoegen van de thrombus aan de in hoofdstuk 2 beschreven methode voor wandstress analyse is dan ook bijzonder ingewikkeld en zal verder onderzocht moeten worden.

Hoewel het mogelijk is met CT data de krachten op de wand uit te rekenen is het nog niet mogelijk met beeldvormende technieken de wandsterkte te bepalen. Tijdens het ontstaan van AAA worden elastine vezels in de vaatwand afgebroken. Hierdoor dilateert het bloedvat en worden alle krachten opgevangen door collageen vezels. Wanneer ook deze worden afgebroken kan de vaatwand zo zwak worden dat ze scheurt.[14] Hoewel het exacte mechanisme achter deze progressieve verzwakking van de vaatwand niet bekend is, wordt verondersteld dat enzymen (matrix metalloproteinasen; MMP) een belangrijke rol spelen.[14-16] Om deze hypothese te onderzoeken hebben we van 25 AAA patiënten en 9 postmortale controles de wandsterkte en MMP activiteit onderzocht (**hoofdstuk 5**). Hieruit bleek dat de wand zwakker is, wanneer de concentratie MMP-9 in het weefsel hoger is. Omdat MMP-9 wordt geproduceerd door macrofagen en neutrofielen en deze cellen kunnen worden aangetoond met beeldvormende technieken is het in theorie mogelijk non-invasief de wandsterkte te bepalen.

Door gebruik te maken van ijzerhoudend contrast (USPIO) en MRI scans kunnen macrofagen in de vaatwand aangetoond worden.[17] Het contrast wordt ingespoten waarna het wordt opgenomen door macrofagen. Door de magnetische eigenschappen van ijzer ontstaan veranderingen in signaal intensiteit op de plaats waar zich macrofagen bevinden. Na het herbeoordelen van een groot aantal USPIO-MRI scans werd bij 11 patiënten een aneurysma gevonden (**hoofdstuk 6**). Bij deze patiënten werd significant meer USPIO in de vaatwand gezien dan bij personen zonder aneurysma. Opvallend is dat niet alle AAA, USPIO opname vertonen. Dit zou kunnen betekenen dat USPIO alleen wordt gezien in de wand van AAA met actieve ontsteking. Of dit aanleiding geeft tot een zwakkere wand en dus een verhoogd risico op ruptuur zal prospectief onderzocht moeten worden. Helaas heeft USPIO-MRI een aantal belangrijke nadelen. De beschikbaarheid van MRI scans is beperkt. Hoewel dit opgelost kan worden door in het weekend te scannen vermindert het de klinische toepasbaarheid. Daarnaast is het contrast momenteel alleen goedgekeurd voor oncologische doeleinden. Vanwege deze logistieke bezwaren is gekozen voor een alternatieve techniek.

Positron emissie tomografie (PET) is een beeldvormende techniek waarbij radioactief glucose (FDG) wordt ingespoten. Na inspuiting wordt FDG opgenomen in metabool actieve cellen (hoe actiever hoe meer opname), hierdoor vervalt het radioactief materiaal en worden positronen uitgestraald. Deze straling wordt opgevangen door een PET camera. Door PET data met CT data te fuseren kunnen de metabool actieve gebieden (inflammatie) gelokaliseerd worden. Een belangrijk voordeel van PET is de mogelijkheid om de mate van FDG opname te kwantificeren (SUV berekening). De vaatwand in AAA patiënten blijkt significant meer FDG op te nemen en dus metabool actiever te zijn dan de normale aorta wand (**hoofdstuk 7**). Of de mate van metabole activiteit voorspellend is voor de sterkte van de aneurysma wand of het optreden van aneurysma ruptuur zal prospectief onderzocht worden.

Conclusies

De ontwikkelingen op het gebied van medische beeldvorming hebben geleid tot diverse nieuwe toepassingen. Een aantal nieuwe technieken zouden in de toekomst kunnen bijdragen aan de identificatie van AAA met een verhoogde kans op ruptuur. De meest veelbelovende techniek is AAA wandstress analyse. Met deze techniek is het mogelijk kleine AAA met een verhoogde kans op ruptuur te identificeren. Desondanks, zijn er mogelijkheden het model verder te verbeteren. Het huidige model geeft bijvoorbeeld geen informatie over de intraluminale thrombus of de sterkte van de vaatwand. Vanwege de grote verschillen in thrombus eigenschappen tussen patiënten lijkt het op dit moment echter onmogelijk thrombus op te nemen in modellen voor wandstress analyse. De sterkte van de AAA wand wordt mede bepaald door de aanwezigheid van

enzymen (MMP) die instaan voor afbraak van collageen en elastine. Omdat MMPs worden geproduceerd door inflammatoire cellen zoals macrofagen en neutrofielen kan de non-invasieve detectie van inflammatie theoretisch informatie verschaffen over de sterkte van de vaatwand. Zowel met USPIO-MRI als PET/CT is het mogelijk de mate van inflammatie in de vaatwand te kwantificeren. Of het met deze technieken ook mogelijk is de sterkte van de vaatwand te voorspellen zal nader onderzocht worden.

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Curriculum Vitae

Maarten Truijers werd op 27 juni 1978 geboren. Hij groeide op in Raamsdonksveer en Druten waar hij in 1996 zijn VWO diploma behaalde. Aansluitend ging hij geneeskunde studeren aan de Universiteit van Antwerpen. In 2003 legde hij “met grote onderscheiding” zijn artsexamen af. Daarna heeft hij gedurende twee jaar in het Twee Steden Ziekenhuis gewerkt als arts-assistent chirurgie (dr. S.E. Kranendonk). Na deze leerzame periode is hij als arts-onderzoeker begonnen op de afdeling chirurgie van het Universitair Medisch Centrum St Radboud. Onder leiding van Prof. Dr. J.D. Blankensteijn heeft hij hier gedurende drie jaar aan de voltooiing van dit proefschrift gewerkt. Tijdens deze periode heeft hij een aantal maanden in de Verenigde Staten (Prof. Dr. M.F. Fillinger, Dartmouth-Hitchcock Medical Center) onderzoek verricht naar aneurysma wandstress. In 2009, is hij begonnen aan de opleiding chirurgie in het Rijnstate Ziekenhuis te Arnhem (Dr. M.M.P.J. Reijnen).