Abdominal aortic aneurysms

The quest for meaningful biomarkers and opportunities to improve surgical care

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INTRODUCTION

Abdominal Aortic Aneurysm

Abdominal aortic aneurysm (AAA) is a widening of the abdominal aorta that mostly occurs in the elderly.[1, 2] The prevalence of AAA is 1.3 - 2.2% in men of 65 years old.[3, 4] AAAs generally do not cause symptoms but they can rupture when reaching larger diameters.[5] Rupture of AAA is a fatal condition that needs urgent surgical repair, with a postoperative survival rate of around 75%.[6]

To prevent death by rupture of AAA, many patients with AAA undergo prophylactic (elective) surgery. Randomized controlled trials (RCTs) have previously demonstrated that there is no benefit of elective open or endovascular repair in patients with an AAA < 5.5 cm.[7, 8] As a consequence, European and American guidelines recommend to consider elective repair once the AAA has reached a diameter of 5.5 cm.[1, 2] As long as AAAs are smaller than 5.5 cm, patients undergo active surveillance of AAA progression by means of repeated ultrasound imaging, with shorter intervals at a larger diameter.

Although the AAA diameter is the main determinant of patient management, it is not an accurate predictor of rupture. Some AAAs rupture below the threshold diameter whereas others rupture at very large diameters, or do not rupture at all. Therefore, better predictors of AAA rupture are needed to accurately identify patients at increased risk of rupture, which in turn enables to operate the patients at risk selectively.

AAA repair

Surgical treatment of AAA has changed substantially in the last decades. Throughout the majority of the 20th century, AAAs were operated via open repair (OR). OR is performed by making a large incision in the abdomen, opening of the aneurysm sac, and placement of a synthetic graft inside the abdominal aorta. In the 1990s, a new and less invasive method was introduced that radically changed AAA surgical practice: endovascular aneurysm repair (EVAR). This alternative to OR involves the placement of a stent graft in the abdominal aorta without opening of either the abdomen or the aorta. A stent is introduced through the femoral or iliac arteries, and is deployed inside the aneurysm sac. The stent prevents blood flow into the aneurysm sac by sealing along the aortic wall. The introduction of EVAR has considerably improved the short-term outcomes of patients after elective AAA surgery.[9] Because of the lower short-term mortality and complication rates after EVAR, many hospitals and guidelines now follow an EVAR-first policy when considering elective AAA repair. However, the early benefits of EVAR are lost during long-term follow-up as mortality equals that of open repair, and EVAR is followed by more complications and reinterventions in the long term.[1]

Several RCTs demonstrated that EVAR can also be performed safely for ruptured AAA (RAAA) repair.[10] The first of these trials, the AJAX trial from the Netherlands, also demonstrated that the centralization of care resulted in an improved survival after rupture.[6] Despite all improvements in care, many patients still suffer from postoperative complications after RAAA repair. Some short- and long-term complications include acute kidney injury, bowel ischemia, and incisional hernia. These complications can have substantial impact on the quality of life of patients. Patients with acute kidney injury could require dialysis, patients with severe bowel ischemia often undergo bowel resection with colostomy placement, and patients with incisional hernias sometimes require reoperation.

AAA pathophysiology

Previous studies have demonstrated that elderly patients who are male, smoke tobacco, and have an elevated blood pressure are at increased risk of developing AAA.[11, 12] Despite these known risk factors, the exact pathophysiology of AAA is insufficiently understood. Histopathological studies have revealed chronic inflammation in the AAA wall with infiltration by inflammatory cells, extracellular matrix remodeling with collagen destruction and loss of smooth muscle cells.[13] Until recently, inflammation was widely considered to be a driver of AAA formation. Results from recent trials have challenged this theory.[14] It is subject of debate whether inflammation is a driver of AAA formation or a response to other processes.[15] Our current knowledge is unfortunately limited by the fact that human AAA tissues have all been obtained during OR or autopsy, and therefore reflect late stages of AAA disease. Early determinants and drivers of AAA formation are largely unidentified due to the unavailability of AAA tissue from an early stage of the disease.

AAA biomarkers

Because of the difficulty to identify AAAs at increased risk of rupture, many investigators have searched for biomarkers of AAA progression. Promising circulating biomarkers associated with AAA progression include markers of matrix turnover (matrix metalloproteinases), markers of inflammation (interleukins and C-reactive protein) and markers of lipid metabolism (lipoproteins).[16-18] Yet, none of these biomarkers have found their way to clinical practice until today, mainly because of their low prognostic and clinical value. The maximal anteroposterior diameter of the AAA, as measured with ultrasound or computed tomography (CT), has remained the prime biomarker used in clinical practice. The introduction of new imaging techniques and post-processing methods has resulted in the development of novel imaging biomarkers. Researchers have investigated the value of inflammatory imaging biomarkers such as ^{18}F-fluoro-deoxy-

glucose (^{18}F-FDG) and ultrasmall superparamagnetic iron oxide particles (USPIOs), and biomechanical imaging biomarkers such as peak wall stress and wall shear stress.[19-22] Despite the promising results of these imaging biomarkers, it is unknown whether they are ready for application in daily clinical practice.

OUTLINE OF THIS THESIS

This thesis consists of three parts. The first part focuses on imaging biomarkers of AAA progression. It aims to assess the clinical value of current AAA imaging biomarkers and aims to develop new imaging biomarkers of AAA progression. The second part investigates the clinical outcome after AAA repair in order to find opportunities to improve surgical care. This part mostly deals with the prevention, diagnosis, and consequences of postoperative complications after RAAA repair. The third part presents new research infrastructures and methods which could facilitate and enhance future AAA research.

PART I
IMAGING BIOMARKERS OF AAA PROGRESSION

In recent years, a large amount of new computational methods have been developed that enable advanced analyses with CT and magnetic resonance (MR) images. As a consequence of this development, new imaging biomarkers have been introduced into AAA research, and some have been proposed as prediction tools for AAA growth or rupture. In **chapter 1**, we carried out a systematic review to assess which inflammatory imaging biomarkers are associated with either AAA growth or rupture. Several studies had previously investigated inflammatory imaging biomarkers such as ^{18}F-FDG and USPIO but it was unknown whether these markers were of value in current clinical practice. We collected the available evidence from literature to determine whether these inflammatory imaging biomarkers are ready to be used as AAA rupture prediction tools in clinical practice.

Biomechanical imaging biomarkers were investigated in **Chapter 2**. Previous studies using finite element analysis suggested that biomechanical imaging biomarkers such as peak wall stress (PWS) and rupture risk equivalent diameter (RRED) could differentiate between high and low AAA rupture risk. PWS represents the maximal stress on the AAA wall and RRED is a new biomarker that expresses rupture risk in mm. The latter is suggested to be a more intuitive biomarker because it enables an easy comparison of rupture risk with the actual diameter. For example, an AAA with an actual diameter of 66 mm could have a RRED of 82 mm when its estimated rupture risk corresponds to the

rupture risk of an AAA of 82 mm. One limitation of previous studies was that results and recommendations were predominantly based on case-control studies rather than on longitudinal studies. Therefore we carried out this study to estimate PWS and RRED in patients who experienced later rupture after CT imaging. We evaluated whether RRED was superior to the actual AAA diameter in estimating future rupture risk. In addition, we compared the pre-rupture and post-rupture AAA geometry to assess whether post-rupture geometry and biomechanics were representative of the pre-rupture state. This was done because some studies had questionably used post-rupture models for rupture risk estimations without knowing the influence of the rupture itself on AAA geometry.

In the search for new biomarkers of AAA progression, we initiated a prospective MRI study titled 'Advanced MRI in AAA'. Several new sequences of inflammatory and biomechanical imaging biomarkers were assessed in this explorative study. This MRI study aimed to determine whether advanced MRI sequences can provide robust and clinically relevant information about AAA. The sequences included 4D flow MRI, dynamic contrast-enhanced MRI, and T1 and T2 mapping. **Chapter 3** presents the preliminary results of T1 mapping of intraluminal thrombus (ILT). We know from histopathological studies that ILTs have layered aspects and that ILTs might be dynamic and biologically active structures. Yet, the role of ILT in AAA progression is largely unknown. It is not entirely clear whether ILT presence bears any relation to the risk of AAA rupture. In this chapter, we carried out T1 mapping of ILT to establish the feasibility and reproducibility of the T1 mapping technique to visualize and quantify ILT composition and heterogeneity. If feasible and reproducible, T1 mapping could be a valuable method for future longitudinal studies that monitor the natural course of ILT and AAA progression. In addition to establishing the feasibility and reproducibility, this chapter assessed whether T1 times and the variability of T1 times within ILT were associated with AAA diameter or ILT thickness.

PART II
OUTCOMES AFTER AAA REPAIR

One important complication of RAAA repair is bowel ischemia. We carried out a systematic review and meta-analysis in **chapter 4** to determine the best available estimate of the contemporary prevalence of bowel ischemia after RAAA repair. This meta-analysis was conducted because the clinical outcome after RAAA repair has improved in the last decade, but it was unknown whether this had also resulted in a reduction of bowel ischemia as a postoperative complication. In this study we assessed bowel ischemia prevalence, changes in the course of time, and differences between OR and EVAR.

Chapter 5 assessed the diagnostic value of sigmoidoscopy to detect colonic ischemia after RAAA repair. We retrospectively analyzed patients who underwent RAAA repair in the AMC, VUmc and OLVG hospitals between 2004 and 2011 (AJAX cohort). We determined the diagnostic value of sigmoidoscopy by estimating the positive and negative predictive value of sigmoidoscopy results to detect transmural colonic ischemia. The clinical course and findings at laparotomy served as the reference standard for this analysis. A logistic regression analysis was carried out to determine independent factors associated with transmural colonic ischemia.

Acute kidney injury (AKI) is another complication occurring after RAAA repair. Studies from other surgical fields have shown a negative association between AKI and long-term survival. Therefore, we investigated in **chapter 6** whether AKI after RAAA repair was also associated with a reduced long-term survival after RAAA repair. We conducted a retrospective study with patients from the AJAX cohort who were alive at discharge, and carried out Kaplan-Meier survival analyses to compare survival rates between patients in different AKI groups (no AKI, Risk, Injury, Failure). In addition, we conducted a Cox regression analysis to determine the independent association of AKI with long-term survival. We also assessed the occurrence of long-term end-stage renal disease by retrieving chronic dialysis data from the Dutch national dialysis registry Renine.

Incisional hernias are one of the main mid-term complications after open AAA repair. Because of presumed overlapping predisposing connective tissue characteristics, patients with AAA are at increased risk of developing abdominal wall hernias, affecting one in five patients. The consequences of incisional hernia can range from mild discomfort to strangulation of herniated bowel segments. In **Chapter** 7 we carried out a systematic review and meta-analysis of randomized trials to determine whether prophylactic mesh reinforcement can reduce the rate of incisional hernia in comparison to standard sutured closure. We also assessed whether prophylactic mesh reinforcement can reduce the number of reoperations for incisional hernia.

Some patients develop abdominal aneurysms distal from the aortic bifurcation in the iliac arteries. Such iliac artery aneurysms (IAAs) occur in approximately 20% of patients with AAA. IAAs can also develop without dilatation of the abdominal aorta. The 2019 guideline of the European Society for Vascular Surgery recently increased the threshold diameter for elective IAA repair from 3.0 cm to 3.5 cm. This recommendation was based on evidence of low quality. In **chapter 8** we used data from the Dutch Surgical Aneurysm Audit (DSAA) registry to compare the new threshold diameter with clinical practice in the Netherlands. We determined the diameters at time of elective IAA repair and at time of ruptured IAA repair in all Dutch patients operated between 2014 and 2018. Furthermore, we used the DSAA data to evaluate the clinical outcomes after IAA repair and to assess differences between OR and EVAR.

PART III
INFRASTRUCTURES AND METHODS FOR FUTURE AAA RESEARCH

The newly established AAA databank, biobank and imagebank (Pearl AAA) is presented in **Chapter 9**. The Pearl AAA is a joint project of the departments of Vascular Surgery of the two academic hospitals of Amsterdam UMC (AMC and VUmc) and of Leiden University Medical Center. This project is established to facilitate future research on the pathophysiology and natural history of AAA. The Pearl AAA has the following scientific aims: (1) to gain insight in the pathophysiology and natural history of AAA, (2) to gain more knowledge about the rupture risk of AAA, (3) to evaluate and improve treatment of patients with an AAA. This project is constructed in collaboration with the String of Pearls Institute which facilitates uniform biobanking in all academic hospitals in the Netherlands.

Chapter 10 presents a new method to visualize results in surgical studies: the lasagna plot. A lasagna plot is a graphical tool that can display multiple outcomes over the course of time. Previous non-surgical studies used these plots to visualize scientific outcomes but the value of these plots for surgical studies was unknown. Therefore, we created lasagna plots to demonstrate the results of the AJAX trial which randomized patients with RAAA to either OR or EVAR. In addition, lasagna plots were created to visualize the results from two other surgical trials (LAFA trial and DROP trial). We evaluated whether the lasagna plots were able to improve the visualization of results, and whether they could demonstrate new observations of the data presented in the original studies.

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