ABDOMINAL AORTIC ANEURYSMS

Clinical insights and outcome after endovascular repair

Herman J.A. Zandvoort

ABDOMINAL AORTIC ANEURYSMS
Clinical insights and outcome after endovascular repair

Thesis, Utrecht University, The Netherlands

The work presented in this thesis was supported by an unrestricted grant from Association Leatare, which is gratefully acknowledged.

Publication of this thesis was additionally supported by Chirurgisch Fonds Universitair Medisch Centrum Utrecht.

ISBN/EAN 9789461085450

Cover design: Jeroen de Ruijter I jeroenderuijter.nl
Lay-out: Wendy Schoneveld I wenziD.nl
Printed by: Gildeprint drukkerijen, Enschede

ABDOMINAL AORTIC ANEURYSMS

Clinical insights and outcome after endovascular repair

ANEURYSMATA VAN DE ABDOMINALE AORTA

Klinische inzichten en uitkomst na endovasculaire behandeling

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
dinsdag 10 december 2013 des middags te 4.15 uur

door

Herman Jan Albert Zandvoort

geboren op 30 januari 1986 te Alphen aan den Rijn

Promotor: Prof.dr. F.L. Moll

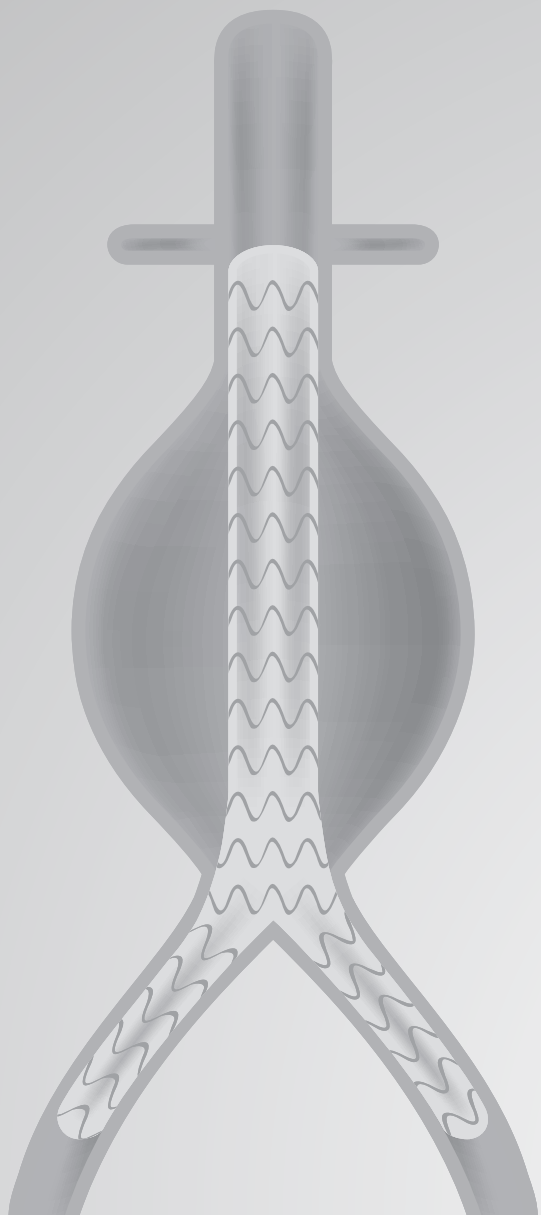
Co-promotor: Dr. J.A. van Herwaarden

CONTENTS

PART THREE **Clinical outcome after EVAR**

PART FOUR **Summary, general discussion and future perspectives**

APPENDICES



CHAPTER 1

General introduction and outline of the thesis

GENERAL INTRODUCTION

Abdominal aortic aneurysm (AAA), which comes from the ancient Greek word ἀνεύρυσμα (for widening), is a focal dilatation of the abdominal aorta.[1] The most accepted definition of an AAA is based on the diameter of the abdominal aorta, and an abdominal aortic diameter of 3 cm is considered to be aneurysmatic.[1] Another often used definition is a dilatation of at least 50% greater than the normal diameter of the aorta.[2]

The pathophysiology of AAA is a complex multifactorial process, and much is still unknown. Key events involved in aneurysm formation and dilatation are proteolysis, inflammation, smooth muscle cell apoptosis, and degradation of elastin in the medial layer of the aortic wall.[3, 4]

Large population screening studies provide insight into the prevalence of AAA, and reported prevalence rates vary between 4% and 7%.[5-7] The most important risk factors for AAA are advanced age, male gender, and smoking. Other factors associated with the development of AAA include a positive family history, history of other aneurysms, hypertension, and atherosclerosis.[8] Most aneurysms develop asymptomatically, and after progressive dilatation, an AAA may finally rupture, which is associated with significant morbidity and mortality.[1, 9] About half of the patients with an aneurysm rupture die before they reach the hospital, and for patients who reach the hospital alive, the mortality rate for emergency treatment is 30% to 70%. This results in overall survival rates of between 15% and 35%, making AAA a potentially life-threatening disease.[10, 11]

A larger aneurysm diameter is an independent significant risk factor for AAA rupture. AAAs with diameters of 4 to 5 cm have an annual rupture risk of approximately 1%, increasing to a 30% to 33% risk of rupture per year for AAAs with diameters >7 cm.[12, 13] Smoking, hypertension, female gender, and aneurysm expansion rate are other factors associated with an increased rupture risk.[14-17]

Treatment of AAA is indicated when the risk of AAA rupture exceeds the risk associated with elective surgical repair.[1, 9] Open surgical repair, consisting of replacement of the diseased aortic segment with a tube graft or bifurcated prosthetic graft by laparotomy, was the classical treatment of AAAs for many years. However, AAA treatment has significantly changed since Volodos and Parodi introduced endovascular aneurysm repair (EVAR) in the early 1990s.[18, 19] EVAR is a minimally invasive procedure, and multicenter trials have proven that EVAR improves the perioperative mortality rate in patients fit for open repair.[20, 21] Although EVAR had superior outcomes in the short-term, EVAR has been associated with increased rates of reinterventions and graft-related complications in the long-term.[22, 23]
Advancing insight made it clear that the success of EVAR is closely related to accurate preoperative assessment of aneurysm morphology, appropriate sizing of the stent graft, and adequate follow-up. High-quality imaging is therefore essential before, during, and after EVAR.

OUTLINE OF THE THESIS

This thesis consists of 3 parts. Part 1 focuses on associations between aneurysmal wall degeneration and AAA imaging. Histologic and biochemical analysis of AAA wall characteristics contribute to a better insight in AAA pathophysiology. To make these characteristics clinically applicable, correlations with imaging features must be examined. The value of the diameter ratio, defined as the ratio between the native aortic diameter and maximum AAA diameter, is described in **Chapter 2**. We also investigated the association between aneurysm wall characteristics and the thickness of the intraluminal thrombus (ILT) on computed tomography angiography (CTA) images and present the results in **Chapter 3**.

The second part of the thesis contains studies on dedicated imaging techniques in endovascularly treated patients. Pulsatile distention during the cardiac cycle can be visualized by dynamic electrocardiogram-gated CTA.[24] Because young healthy individuals have a large pulsatile distension,[25] we examined in **Chapter 4** whether a difference in pulsatile distension between young and old AAA patients could be observed. Previous studies on pulsatile distension were not able to correct for potential through-plane movement. To assess the through-plane movement, we analyzed the movement of the aorta during the 8 phases of a dynamic electrocardiogram-gated CTA scan and have described the results in **Chapter 5**.

A common and clinically relevant complication after EVAR is the occurrence of endoleak. In **Chapter 6** we have provided a literature review on endoleak detection. This chapter analyzes studies of endoleak detection on CTA, the current gold standard for endoleak detection,[1, 9] compared with endoleak detection on magnetic resonance imaging (MRI). Because MRI was able to detect more endoleaks than CTA, the value of a weak albumin-binding contrast agent for MRI was evaluated in a prospective study on endoleak detection. The results of this study are presented in **Chapter 7**.

Part 3 of the thesis describes the clinical outcome after EVAR. Long-term results are necessary to judge the durability of EVAR. **Chapter 8** presents the 4-year follow-up of one of the current commercially available stent grafts. The use of standard endografts is not possible for the treatment of patients with juxtarenal or suprarenal aneurysms. The results of the chimney technique, which offers an opportunity for preserving the vascularization of aortic side branches in these patients, are discussed in **Chapter 9**.

Chapter 10 provides a summary, general discussion, and future perspectives.

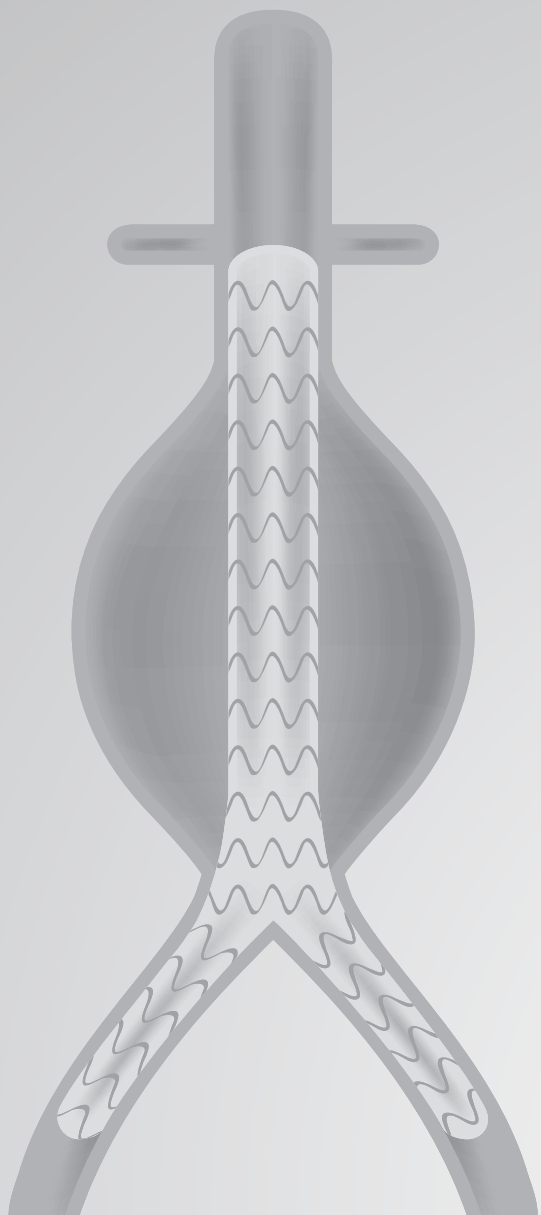
REFERENCES

1. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1-S58.
2. Johnston KW, Rutherford RB, Tilson MD, Shah DM, Hollier L, Stanley JC. Suggested standards for reporting on arterial aneurysms. Subcommittee on Reporting Standards for Arterial Aneurysms, Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery and North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg. 1991;13(3):452-8.
3. MacSweeney ST, Powell JT, Greenhalgh RM. Pathogenesis of abdominal aortic aneurysm. Br J Surg. 1994;81(7):935-41.
4. Nordon IM, Hinchliffe RJ, Loftus IM, Thompson MM. Pathophysiology and epidemiology of abdominal aortic aneurysms. Nat Rev Cardiol. 2011;8(2):92-102.
5. Ashton HA, Buxton MJ, Day NE, Kim LG, Marteau TM, Scott RA, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet. 2002;360(9345):1531-9.
6. Lindholt JS, Juul S, Fasting H, Henneberg EW. Screening for abdominal aortic aneurysms: single centre randomised controlled trial. BMJ. 2005;330(7494):750.
7. Norman PE, Jamrozik K, Lawrence-Brown MM, Le MT, Spencer CA, Tuohy RJ, et al. Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm. BMJ. 2004;329(7477):1259.
8. Lederle FA, Johnson GR, Wilson SE, Chute EP, Littooy FN, Bandyk D, et al. Prevalence and associations of abdominal aortic aneurysm detected through screening. Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Group. Ann Intern Med. 1997;126(6):441-9.
9. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg. 2009;50(4 Suppl):S2-49.
10. Bown MJ, Sutton AJ, Bell PR, Sayers RD. A meta-analysis of 50 years of ruptured abdominal aortic aneurysm repair. Br J Surg. 2002;89(6):714-30.
11. Thompson SG, Ashton HA, Gao L, Buxton MJ, Scott RA. Final follow-up of the Multicentre Aneurysm Screening Study (MASS) randomized trial of abdominal aortic aneurysm screening. Br J Surg. 2012;99(12):1649-56.
12. Scott RA, Tisi PV, Ashton HA, Allen DR. Abdominal aortic aneurysm rupture rates: a 7-year follow-up of the entire abdominal aortic aneurysm population detected by screening. J Vasc Surg. 1998;28(1):124-8.
13. Lederle FA, Johnson GR, Wilson SE, Ballard DJ, Jordan WD, Jr., Blebea J, et al. Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. JAMA. 2002;287(22):2968-72.
14. Cronenwett JL, Murphy TF, Zelenock GB, Whitehouse WM, Jr., Lindenauer SM, Graham LM, et al. Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms. Surgery. 1985;98(3):472-83.
15. Brown PM, Zelt DT, Sobolev B. The risk of rupture in untreated aneurysms: the impact of size, gender, and expansion rate. J Vasc Surg. 2003;37(2):280-4.
16. Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. Ann Surg. 1999;230(3):289-96; discussion 96-7.
17. Dalman RL, Tedesco MM, Myers J, Taylor CA. AAA disease: mechanism, stratification, and treatment. Ann N Y Acad Sci. 2006;1085:92-109.
18. Volodos NL, Karpovich IP, Troyan VI, Kalashnikova Yu V, Shekhanin VE, Ternyuk NE, et al. Clinical experience of the use of self-fixing synthetic prostheses for remote endoprosthetics of the thoracic and the abdominal aorta and iliac arteries through the femoral artery and as intraoperative endoprosthesis for aorta reconstruction. Vasa Suppl. 1991;33:93-5.

19. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg. 1991;5(6):491-9.
20. Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med. 2004;351(16):1607-18.
21. Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. Lancet. 2004;364(9437):843-8.
22. De Bruin JL, Baas AF, Buth J, Prinssen M, Verhoeven EL, Cuypers PW, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med. 2010;362(20):1881-9.
23. Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med. 2010;362(20):1863-71.
24. Muhs BE, Vincken KL, van Prehn J, Stone MK, Bartels LW, Prokop M, et al. Dynamic cine-CT angiography for the evaluation of the thoracic aorta; insight in dynamic changes with implications for thoracic endograft treatment. Eur J Vasc Endovasc Surg. 2006;32(5):532-6.
25. van Prehn J, Vincken KL, Sprinkhuizen SM, Viergever MA, van Keulen JW, van Herwaarden JA, et al. Aortic pulsatile distention in young healthy volunteers is asymmetric: analysis with ECG-gated MRI. Eur J Vasc Endovasc Surg. 2009;37(2):168-74.

PART ONE

AAA imaging and aneurysmal wall degeneration



CHAPTER 2

Aneurysm diameter ratio and absolute abdominal aortic aneurysm diameter are not associated with local wall inflammation

Submitted

H.J.A Zandvoort[1], R. Hurks[1,2], A. Vink[3], A. de Wilde[1], G. Pasterkamp[2], J.P.P.M. de Vries[4], J.A. van Herwaarden[1], F.L. Moll[1]

[1] Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Experimental Cardiology Laboratory, University Medical Center Utrecht, Utrecht, The Netherlands
[3] Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands
[4] Department of Vascular Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands

ABSTRACT

Introduction

Abdominal aortic aneurysm (AAA) disease involves inflammatory degradation of the aortic wall. The association of wall characteristics with aneurysm diameter remains unclear as previous small studies reported conflicting results. Diameter ratio, as a measure of relative aneurysm size, was never studied in this regard. The aim of this study was to analyze whether AAA diameter ratio, as compared to absolute AAA diameter, is associated with local wall characteristics.

Methods

AAA tissue of 115 patients (83% male, median age 71) was collected at the site of maximum diameter during open repair. Histological segments were analyzed for the presence of structural components and inflammatory cells in the different layers of the wall. Biochemical features (interleukin (IL) 6 and 8, matrix metalloproteinases (MMP) 2 and 9 activities, total MMP 8, osteoprotegerin (OPG) and cathepsin A,B and S levels) were measured. Pre-operative CTA scans of all patients were analyzed. Measurements were performed on slices orthogonal to a central lumen line after 3D reconstruction for maximum aneurysm diameter (A) and aortic diameter 10 mm above the most proximal renal artery (B), as a surrogate measure for the native infrarenal aorta size. Diameter ratio (A/B) and maximum AAA diameter were used for analysis.

Results

Median diameter ratio (IQR) was 2.3 (2.0 – 2.6) and AAA diameter was 60.6 mm (55.5 – 67.4). Women had smaller absolute AAA diameters than men (56.0 mm (54.0 – 61.0) and 62.0 mm (56.1 – 72.0); *P*=.006) while the diameter ratio did not differ between sexes (2.3 (2.0 – 2.6) and 2.2 (1.7 – 2.4); *P*=.106). Media elastin was inversely associated with diameter ratio (*P*= .013) but not with AAA diameter (*P*=.076). Adventitial myofibroblasts were positively associated with both diameter ratio (*P*=.001) and AAA diameter (*P*=.045). However, no associations between diameter ratio or AAA diameter and adventitial T-lymphocytes and B-lymphocytes were observed Both diameter ratio and AAA diameter were positively associated with OPG (r=.252 , *P*=.029 and r=.206 , *P*=.027). The other tested proteases and cytokines did not associate with AAA size measures.

Conclusions

AAA diameter ratio had no major advantage over absolute AAA diameter. The diameter ratio was associated with common processes of degradation and remodeling in larger AAA, which were less obvious with absolute diameter. However, no associations between either AAA diameter ratio or absolute AAA diameter and adventitial T-lymphocytes and B-lymphocytes were observed. We could not confirm that larger AAAs resemble more advanced stages of AAA disease.

INTRODUCTION

Abdominal aortic aneurysms (AAA) affect 5-8% of older men and the overall mortality rate of AAA rupture is between 65% and 85%.[1-4] Since the risk of aneurysm rupture strongly increases with diameter, decision-making for elective surgical repair is currently based on maximum aneurysm diameter.[5, 6]

However, rupture also occurs in patients with small aneurysms while other (asymptomatic) patients have large intact aneurysms, coincidentally diagnosed. Moreover, individual aneurysm growth varies over time.[7] Growth rate analysis of small AAAs in a large screening study showed that half of small AAAs remain quiescent with little aneurysm expansion, whereas the other half continued to expand, finally leading to surgical repair or rupture.[8] This suggests that aneurysm diameter alone is not enough to assess rupture risk and to determine if surgical repair is indicated. Analysis of almost 70,000 patients with no previous history of AAA and no ultrasound evidence of AAA demonstrated that age, gender, race and body size have small but significant effects on infrarenal aortic diameter.[9] Older age, male sex, white race, and increased body size were associated with a greater infrarenal aortic diameter.[9]

In addition to the aneurysm diameter as a predictor of rupture risk, several circulating markers of aneurysm wall degeneration have been investigated of which some correlated with AAA diameter and progression.[10] By investigating aortic wall specimens, small sample sized studies reported conflicting results about the correlation of histological wall characteristics and AAA diameter.[11, 12] However, the association between the diameter ratio and AAA wall characteristics has never been studied before.

For intracranial aneurysms it was found that the ratio between aneurysm size and the parent artery diameter correlates with intracranial aneurysm rupture status (ruptured versus unruptured) and might be a better predictor of rupture.[13]

Possibly, this diameter ratio is also of interest for AAAs by comparing infrarenal AAA size with suprarenal aortic diameter. An AAA of 5 cm, for example, has grown more when the native aortic diameter was 1.8 cm as compared to a native diameter of 2.7 cm. It therefore appears relevant to also use the diameter ratio as a clinical determinant, as the first example might show a more distinct AAA wall degeneration compared to the second. The aim of the present study was to analyze whether AAA diameter ratio, as compared to absolute AAA diameter, is associated with local histological and biochemical parameters inside the AAA wall.

METHODS

Patients and materials

This study consisted of patients undergoing open repair of asymptomatic AAA who were included in the Aneurysm-Express Biobank. The Aneurysm-Express Biobank is an ongoing prospective cohort study including biomaterials of all patients undergoing open AAA repair in two Dutch hospitals.[14] During open surgical repair ventral AAA biopsy specimens were obtained at the site of maximal diameter. Demographic data, cardiovascular risk factors, medical history

and medication use were recorded at baseline. The Medical Ethics Committee of both hospitals approved the study, and participants provided written informed consent.
All data in the Aneurysm-Express Biobank are prospectively collected, however detailed analysis of computed tomography angiography (CTA) scans is not part of the original study protocol. All preoperative CTA scans were retrospectively collected and included based on quality of the CTA: The suprarenal part of the aorta had to be scanned at least as proximal as the celiac artery and imaging quality had to be sufficient for 3D reconstruction. In order to obtain representative diameter ratios we included only patients with infrarenal and juxtarenal aneurysms. Patients with suprarenal, saccular and para-anastomotic aneurysms were excluded.

Diameter measurements
All CTA scans were acquired on a 16- or 256-slice CT scanner (Philips Medical Systems, Best, The Netherlands) with a standardized acquisition protocol (scan parameters: 1.5- to 3.0-mm slice thickness, 0.7-mm increment). After administration of a nonionic contrast agent, scanning was started using bolus-triggering software with a threshold of 100 HU over baseline. The acquired datasets were transferred to a workstation (3mensio Vascular 4.3; 3mensio Medical Imaging B.V., Bilthoven, The Netherlands).
Subsequently, a three-dimensional (3D) reconstruction of the aorta was created. A start point was placed in the aortic lumen well above the celiac artery and an endpoint was placed below the native bifurcation. The center lumen line was automatically calculated and was adjusted manually, if needed, to the center of the aorta. After definition of the centerline, a reconstructed stretch view of the aorta was generated. On orthogonal slices, maximum diameters were measured at the site of the maximum aneurysm diameter (A) and additionally 1 cm above the most proximal renal artery (B), as a surrogate measure for the native infrarenal aortic diameter. Diameter ratio was calculated by dividing maximum AAA diameter by the suprarenal diameter (A/B).

Histologic and biologic assessment of AAA biopsy specimens
For an extensive description of AAA tissue processing and histologic assessments, we refer to the previously published study design of the Aneurysm-Express Biobank.[14] Briefly, AAA specimens were dissected into 5-mm cross-sectional segments. One segment was fixed in 4% formaldehyde, decalcified in ethylenediaminetetraacetic acid, and embedded in paraffin. AAA specimens were stained for macrophages (CD68), vascular smooth muscle cells (VSMCs; α-smooth muscle actin), elastin (van Gieson), collagen (Picrosirius red), T-lymphocytes (CD3), B-lymphocytes (CD20), macrophages (CD68) and plasma cells (CD138). The different stains were semi-quantitatively scored as (1) no to minor or (2) moderate to heavy staining in intima, media, and adventitia. Elastin degradation was scored as the estimated percentage of disruption of elastin fibers.[14] Other segments were snap-frozen in liquid nitrogen, ground, and dissolved in 1.5 mL of 40 mmol Tris-HCl.
Total amounts of interleukin-6 (IL-6), IL-8, matrix metalloproteinase (MMP) 8, cathepsin A, B and S, and osteoprotegerin (OPG) were determined via the Bio-Plex system using Luminex multianalyte profiling technology, as described previously.[15] MMP-2 and MMP-9 concentrations were measured using Biotrak activity assays (Amersham Biosciences, GE Healthcare, Hertfordshire, U.K.).

Statistical analysis

Discrete variables are shown as number and percentages. Continuous variables are shown as median with interquartile range (IQR). The Mann-Whitney U test was conducted to compare baseline characteristics and continuous data were transformed to dichotomous variables creating groups based on the median value (age) or based on reference values (creatinine).

Analyses involving histological and biochemical characteristics were adjusted for age, sex and all baseline variables showing a relevant association ($P < .10$) with diameter ratio or AAA diameter separately, using multiple linear or logistic regression analysis. Natural log-transformation was used to normalize the distributions and to improve linearity for multiple regression. All tests were two-sided and values of $P<.05$ were considered significant. All analyses were performed with SPSS statistics (version 20; IBM, Armonk, NY).

RESULTS

Diameter ratio and baseline characteristics

There were 130 patients with a good quality preoperative CTA scan. After exclusion of patients with a suprarenal (n=3), saccular (n=11) or para-anastomotic (n=1) aneurysm 115 patients (95 men) remained for analysis. Median age was 71 years (65 – 76) and median creatinine level was 89 µmol/L (76-101). Histology was available in 85 patients and biochemistry in 84.

Median suprarenal aortic diameter, measured 1 cm above the most proximal renal artery was 26.9 mm (24.8 – 29.4), and did not differ between men and women (26.9 mm (24.9 – 29.3) versus 27.2 mm (23.6 – 31.6), *P*=.759). Median diameter ratio (IQR) was 2.3 (2.0 – 2.6) and AAA diameter was 60.6 mm (55.5 – 67.4).

The baseline characteristics of the population in relation to diameter ratio or maximal AAA diameter are listed in Table 1. AAA diameter was larger in male patients (median (IQR), 62.0 mm (56.1 – 72.0)) in comparison with female patients (56.0 mm (54.0 – 61.0), *P*=.006). For diameter ratio, no differences were found between male and female patients (2.3 (2.0 – 2.6) and 2.2 (1.7 – 2.4) respectively, *P*=.106). AAA diameter showed a borderline significance for the presence of COPD (*P*=.090) as diameter ratio did not differ (*P*=.243).

Histology

Table 2 shows data of the diameter ratio and AAA diameter in association with histological parameters of the AAA wall. Diameter ratio was inversely associated with the amount of medial elastin fibers (r = -.252, *P*=.013) whereas AAA diameter was not associated with the amount of medial elastin fibers (r = -.147, *P*=.076). Median (IQR) aneurysm ratios were 2.4 (2.1 – 2.8) and 2.2 (1.8 – 2.5) in AAA specimens with no/minor and moderate/heavy amount of elastin in the media respectively.

A positive association was found for both diameter ratio and AAA diameter with the amount of adventitial myofibroblasts (r =.352, *P*=.001 and r =.217, P=.045, respectively). Median aneurysm ratios were 2.2 (1.9 – 2.5) and 2.6 (2.2 – 2.8) in AAA specimens with no/minor and moderate/heavy staining for adventitial myofibroblasts.

Table 1. Diameter ratio and maximal AAA diameter grouped on baseline characteristics.

Variables	%	Diameter ratio median (IQR)	P-value	AAA diameter (mm) median (IQR)	P-value
Age					
< Median (71 years)	50.0%	2.2 (1.9 – 2.6)		59.3 (54.8 – 65.4)	
> Median (71 years)	50.0%	2.3 (2.0 – 2.7)	.284	61.2 (55.8 – 71.3)	.183
Sex					
Male	82.6%	2.3 (2.0 – 2.6)		62.0 (56.1 – 72.0)	
Female	17.4%	2.2 (1.7 – 2.4)	.106	56.0 (54.0 – 61.0)	.006
Diabetes					
No	86.0%	2.3 (2.0 – 2.6)		61.0 (55.7 – 69.3)	
Yes	14.0%	2.3 (2.0 – 2.6)	.928	59.0 (54.8 – 64.9)	.491
Hypertension					
No	24.8%	2.4 (2.1 – 2.7)		62.6 (56.4 – 69.4)	
Yes	75.2%	2.3 (1.9 – 2.6)	.278	60.4 (55.1 – 67.1)	.523
Hypercholesterolemia					
No	34.2%	2.6 (1.9 – 2.7)		60.7 (55.2 – 69.2)	
Yes	65.8%	2.3 (2.1 – 2.6)	.912	60.6 (55.8 – 67.1)	.898
History of MI or AP					
No	63.1%	2.3 (1.9 – 2.6)		59.6 (55.2 – 68.4)	
Yes	36.9%	2.3 (2.1 – 2.6)	.486	64.2 (56.1 – 69.6)	.225
COPD					
No	76.0%	2.2 (1.9 – 2.6)		60.1 (55.1 – 66.7)	
Yes	24.0%	2.5 (2.2 – 2.6)	.243	64.9 (58.3 – 72.1)	.090
Smoking					
No	56.3%	2.3 (2.0 – 2.7)		60.6 (55.2 – 69.4)	
Yes	43.7%	2.2 (1.9 – 2.6)	.420	61.1 (55.7 – 66.3)	.571
Creatinine					
< 90 µmol/L	53.5%	2.3 (2.0 – 2.6)		59.5 (55.3 – 65.8)	
> 90 µmol/L	46.5%	2.2 (1.9 – 2.6)	.549	63.5 (56.6 – 72.5)	.140
Statin use					
No	32.4%	2.3 (1.9 – 2.7)		60.7 (56.0 – 70.4)	
Yes	67.6%	2.2 (2.0 – 2.6)	.676	59.2 (54.9 – 65.9)	.360
ACE-inhibitor use					
No	62.7%	2.2 (1.9 – 2.7)		59.1 (55.6 – 69.1)	
Yes	37.3%	2.3 (2.0 – 2.6)	.994	60.5 (55.1 – 67.2)	.771

Abbreviations: *AAA*, Abdominal aortic aneurysm; *ACE*, Angiotensin-converting enzyme; *MI*, Myocardial infarction; *AP*, Angina Pectoris; *COPD*, Chronic obstructive pulmonary disease.
Data are presented as the median (interquartile range) or as number of patients positive (%) for the variable in each group. *P*-values compare differences in diameter ratio or AAA diameter between groups for dichotomous variables.

Furthermore, an inverse association was observed between diameter ratio and the amount of intimal calcifications (r = -.219, P=.025). There was no association between AAA diameter and the amount of calcifications in the intima (r = -.079, *P*=.127).
A positive association was observed between AAA diameter and the amount of macrophages in the adventitia. Median AAA diameters were 60.7 mm (55.3 – 67.8) and 65.8 mm (60.0 – 77.6) in AAA specimens with no/minor and moderate/heavy adventitial macrophages (r =.194, *P*=.025). Furthermore, no associations between diameter ratio or AAA diameter and adventitial T-lymphocytes and B-lymphocytes were observed.

Markers of proteolysis and inflammation
Both diameter ratio and AAA diameter were positively associated with OPG (r=.252 , *P*=.029 and r=.206 , *P*=.027). There was a trend towards a positive association between diameter ratio and Il-8 (r=.299 , *P*=.068). The remaining markers of proteolysis and inflammation were indifferent along the AAA size measures (Table 3).

DISCUSSION

This study found that diameter ratio was inversely related to the amount of medial elastin fibers and intimal calcifications and positively associated with adventitial myofibroblasts. AAA diameter showed a positive association with adventitial myofibroblasts as well and also the amount of adventitial macrophages was positively associated with the AAA diameter. Diameter ratio and AAA diameter were both positively associated with OPG. No other associations were observed. To our knowledge, this is the first study to examine whether diameter ratio is reflected in histological and biochemical characteristics of the aneurysm wall. Diameter ratio represents the proportional dilation of an aneurysmatic aorta and is in the current study defined as the ratio between the maximum AAA diameter and the suprarenal diameter.
It is known that diameter of the normal aorta varies between individuals. Women tend to have smaller aortic diameters[9, 16] and also age, race and body size have statistically significant but small effects on infrarenal aortic diameter.[9] Data from large screening studies found that mean infrarenal aortic diameter was much smaller than the observed suprarenal diameters in this study. The Tromsø study reported a mean infrarenal aortic diameter of 22.5 mm (±5.4 mm) for men and 19.1 mm (±3.3 mm) in women[3] whereas Lederle et al. in the ADAM cohort found a mean infrarenal aortic diameter of 20 mm (±3 mm) and 18 mm (±3 mm) for men and women respectively.[9] For our ratio, we measured aortic diameters 1 cm above the most proximal renal artery as a surrogate measure for the native aorta. The values in literature differ from our diameter for men, median 27.0 mm (25.0 – 29.3), and women, median 26.4 mm (23.3 – 31.4) (*P*=.850). This might suggest that the suprarenal aorta was dilated in our group of patients with advanced stage AAA disease as compared to the general population. However, it should be noted that diameters from the screening studies were both obtained by ultrasound measurements. Ultrasound measurements were found to underestimate AAA diameters when compared to central lumen line measurements on CTA.[17]

Table 2. Relationships between AAA vessel wall histology and diameter ratio and AAA diameter.

	Diameter ratio per staining category					AAA diameter in mm per staining category				
Variables	**n**	**No / Minor**	**n**	**Moderate / Heavy**	***P-value***	**n**	**No / Minor**	**n**	**Moderate / Heavy**	***#P-value***
Intimal layer										
Calcifications	51	2.4 (2.2 – 2.8)	34	2.2 (1.8 – 2.5)	.025	51	64.9 (56.1 – 73.0)	34	59.8 (55.0 – 65.7)	.127
Collagen	60	2.3 (2.0 – 2.7)	25	2.3 (2.0 – 2.7)	.464	60	62.6 (56.2 – 72.8)	25	60.7 (55.2 – 66.0)	.167
Medial layer										
VSMCs	56	2.3 (2.0 – 2.7)	29	2.3 (1.9 – 2.6)	.668	56	61.4 (55.2 – 70.8)	29	63.8 (56.3 – 70.7)	.985
Elastin	59	2.4 (2.1 – 2.8)	26	2.2 (1.8 – 2.5)	.013	59	62.0 (56.1 – 72.3)	26	62.0 (55.5 – 66.6)	.076
Collagen	82	2.3 (2.0 – 2.7)	3	2.1 (2.0 – 2.4)	.321	82	62.0 (55.8 – 71.5)	3	63.8 (59.3 – 64.2)	.503
Adventitial layer										
Myofibroblasts	54	2.2 (1.9 – 2.5)	31	2.6 (2.2 – 2.8)	.001	54	60.1 (54.7 – 69.1)	31	64.9 (58.0 – 71.3)	.045
Collagen	28	2.2 (2.0 – 2.5)	57	2.4 (2.1 – 2.8)	.091	28	62.4 (55.2 – 66.6)	57	62.0 (56.1 – 71.7)	.224
Macrophages	69	2.3 (2.0 – 2.6)	16	2.5 (2.1 – 2.8)	.077	69	60.7 (55.3 – 67.8)	16	65.8 (60.0 – 77.6)	.025
T lymphocytes	52	2.3 (2.0 – 2.6)	33	2.5 (2.0 – 2.7)	.427	52	62.0 (55.2 – 71.0)	33	64.5 (56.2 – 70.4)	.481
B lymphocytes	34	2.3 (2.1 – 2.6)	51	2.3 (2.0 – 2.7)	.729	34	61.6 (54.4 – 72.5)	51	62.0 (56.3 – 69.2)	.460
Plasma cells	57	2.2 (2.0 – 2.7)	28	2.5 (2.2 – 2.6)	.559	57	61.1 (54.9 – 72.6)	28	64.9 (57.3 – 68.7)	.601

VSMC, vascular smooth muscle cell.
AAA specimens were scored as no / minor or moderate / heavy staining for each histological parameter. n represents the number of histological slides for each group. The values given under no / minor and moderate / heavy staining are the median diameter ratios or AAA diameters with (interquartile range) for each staining category.
*P-value is corrected for age and sex by logistic regression. #P-value is corrected for age, sex and COPD by logistic regression

Table 3. Correlation between proteolysis and inflammation markers and AAA ratio and AAA diameter.

	Diameter ratio		AAA diameter	
Variables	***r***	****P***	***r***	***#P***
MMP-2[a]	.148	.406	.249	.126
MMP-8	-.047	.252	-.040	.271
MMP-9[a]	.153	.911	.089	.857
Cathepsin A	.037	.512	.002	.668
Cathepsin B	.148	.381	.168	.631
Cathepsin S	.086	.899	.128	.788
IL-6	.375	.289	.312	.207
IL-8	.299	.068	.275	.102
Osteoprotegerin	.252	.029	.206	.027

MMP, Matrix metalloproteinase; *IL*, interleukin; *r* is the correlation efficient. * *P*-value is corrected for age and sex by multiple linear regression analysis. # *P*-value is corrected for age, sex and COPD by multiple linear regression analysis. [a] Measured by activity assays. Logistic regression analysis was used to calculate the adjusted P-value for MMP-2, 9 and Cathepsin A because the data were not normally distributed

For intracranial aneurysms was shown that the ratio between aneurysm size and parent artery diameter correlated with intracranial aneurysm status (ruptured versus unruptured).[10] In AAAs, Fillinger et al. found that diameter ratios of AAAs were larger for ruptured patients compared to electively treated patients in univariate analysis.[18] However, after taking age, gender and AAA diameter into account by matching the ruptured and elective group of patients this significant difference disappeared.[18]

This study had as its primary goal to examine if there was a relationship between the diameter ratio and aneurysm wall characteristics. It might be interesting to further evaluate the role of diameter ratio in a clinical setting to investigate the relationship between diameter ratio and the risk of rupture. In contrast to suprarenal diameter, median maximum aortic diameter was different for men and women in this study. AAA diameter was greater in male patients (62.0 mm (56.1 – 72.0)) compared to female patients (56.0 mm (54.0 – 61.0), *P*=.006) while diameter ratio did not significantly differ between men and women. Women were operated for smaller diameter AAAs, which is in line with current international guidelines[19, 20], and the comparable ratio between both genders suggests similar relative dilatation when compared to their suprarenal aortic measurements.

Previous small studies reported that elastin concentration, presented as % of defatted dry weight of full thickness infrarenal aortic wall specimens, was inversely correlated to AAA diameter while collagen concentration demonstrated a significant positive correlation with diameter in 30 patients.[13] These results are difficult to compare with the current study, as the previously reported values represent the amount of elastin and collagen in the entire aortic wall and no distinction was made between the different layers of the vessel wall, although the majority of collagen is found in the adventitial layer of the aortic wall.

A more recent study, including 39 patients demonstrated histological characteristics typical for AAA including decreased elastin content, distorted elastin configuration, increased collagen content and diminished number of SMCs. However, no relationship between any of the histological features

and AAA diameter was observed, suggesting that wall composition on a histological level was similar between different AAAs, irrespective of AAA diameter.[12] The results of the current study support this suggestion partially as only a few associations were found between AAA diameter and histological wall characteristics. Diameter ratio was inversely related to the amount of medial elastin fibers whereas AAA diameter alone was not. This finding might suggest that a certain relative increase of the aortic diameter, more than an increase to a certain absolute diameter, is necessary to cause a distinct degradation of elastin in the medial layer of the aortic wall.
Furthermore, AAA is also characterized by an inflammatory response in the adventitial layer of the aortic wall, primarily composed of lymphocytes.[21, 22] However, no associations between diameter ratio or AAA diameter and adventitial T-lymphocytes, B-lymphocytes were observed. Although there was a positive weak association between AAA diameter and adventitial macrophages, this difference appears less relevant given the dominant presence and role of lymphocytes in AAA.[21]
OPG, a glycoproteine which has a central role in bone remodeling, tumorigenesis, inflammation, innate immunity and vascular disease, showed a significant association with diameter ratio and AAA diameter, which is in line with our previous study in a larger cohort of patients. We showed in 329 patients that OPG was correlated to AAA diameter (r=.196, adjusted P=.001) and to several proteolytic enzymes suggesting a role for OPG in AAA pathogenesis.[23]
Many cytokines and proteases have been linked to AAA formation and growth, including prominent factors such as MMP-2, MMP-9 and IL-8.[24]
Except for the association between OPG and diameter ratio and AAA diameter no other significant associations between proteolytic enzymes and diameter ratio and AAA diameter were found. This is in line with previous results. Analysis of the anterior aneurysm wall of 55 non-ruptured AAAs by Wilson et al. showed no significant correlations between AAA diameter and proteolytic enzyme concentrations.[25] The lack of associations between AAA diameter and proteolytic factors suggest that there is not a general elevation in proteolysis in the AAA wall with increasing aneurysm size. We previously showed that the amount of AAA wall inflammation varies at different sites within the AAA.[26] It could rather be a local process that induces rupture as MMP-8 and MMP-9 levels are increased at the site of abdominal aortic rupture.[25, 26]
As for limitations, analysis of diameters was only possible for patients with advanced staged AAA disease with generally large aneurysm diameters, after exceeding the cut-off for surgical repair. This study likely lacks power to detect correlations between diameter ratio and wall characteristics. Given the subtle differences in suprarenal diameter, a larger cohort of patients could aid in answering the hypothesis.

No associations between diameter ratio or AAA diameter and adventitial T-lymphocytes and B-lymphocytes were observed. For the proteolytic enzymes, only OPG showed an association with both diameter ratio and absolute AAA diameter. Additionally, AAA diameter ratio was, in contrast to absolute diameter, associated with degraded elastin in the media and both AAA ratio and diameter showed a positive association with myofibroblasts in the adventitia. Although we could not convincingly demonstrate that larger diameter ratios resemble more advanced stages of AAA disease, it might be interesting to further evaluate the role of diameter ratio in a clinical setting and investigate the relationship between diameter ratio and the risk of rupture.

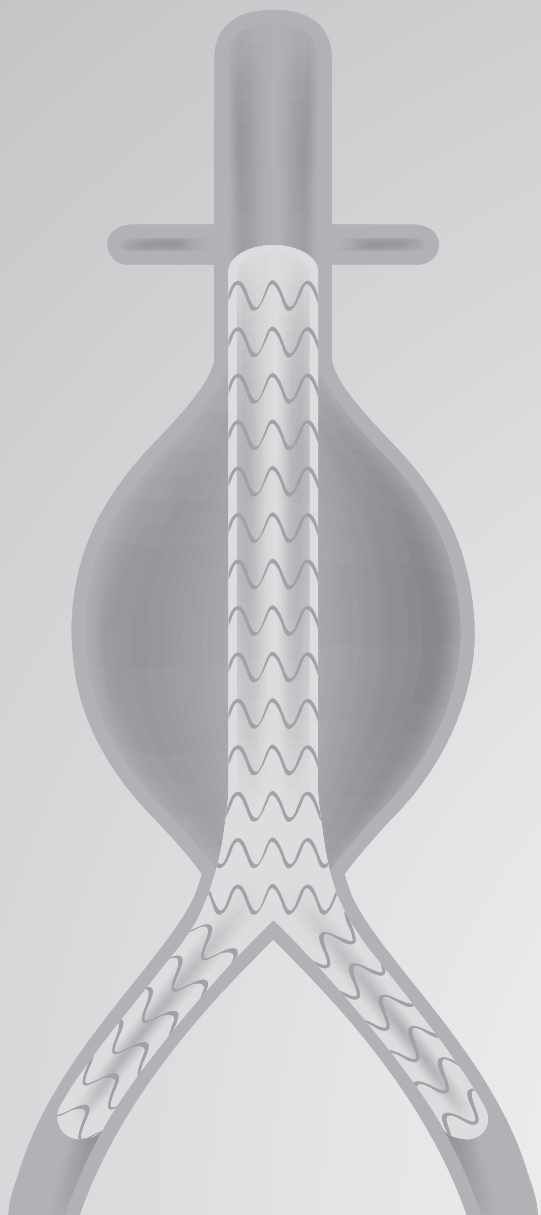
REFERENCES

1. Boll AP, Verbeek AL, van de Lisdonk EH, van der Vliet JA. High prevalence of abdominal aortic aneurysm in a primary care screening programme. Br J Surg. 1998;85(8):1090-4.
2. Lederle FA, Johnson GR, Wilson SE, Chute EP, Hye RJ, Makaroun MS, et al. The aneurysm detection and management study screening program: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. Arch Intern Med. 2000;160(10):1425-30.
3. Singh K, Bonaa KH, Jacobsen BK, Bjork L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study : The Tromso Study. Am J Epidemiol. 2001;154(3):236-44.
4. Ashton HA, Buxton MJ, Day NE, Kim LG, Marteau TM, Scott RA, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet. 2002;360(9345):1531-9.
5. Brewster DC, Cronenwett JL, Hallett JW, Jr., Johnston KW, Krupski WC, Matsumura JS. Guidelines for the treatment of abdominal aortic aneurysms. Report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. J Vasc Surg. 2003;37(5):1106-17.
6. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. J Vasc Surg. 2009;50(4):880-96.
7. Kurvers H, Veith FJ, Lipsitz EC, Ohki T, Gargiulo NJ, Cayne NS, et al. Discontinuous, staccato growth of abdominal aortic aneurysms. J Am Coll Surg. 2004;199(5):709-15.
8. Thompson AR, Cooper JA, Ashton HA, Hafez H. Growth rates of small abdominal aortic aneurysms correlate with clinical events. Br J Surg. 2010;97(1):37-44.
9. Lederle FA, Johnson GR, Wilson SE, Gordon IL, Chute EP, Littooy FN, et al. Relationship of age, gender, race, and body size to infrarenal aortic diameter. The Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Investigators. J Vasc Surg. 1997;26(4):595-601.
10. Hellenthal FA, Buurman WA, Wodzig WK, Schurink GW. Biomarkers of AAA progression. Part 1: extracellular matrix degeneration. Nat Rev Cardiol. 2009;6(7):464-74.
11. Hellenthal FA, Geenen IL, Teijink JA, Heeneman S, Schurink GW. Histological features of human abdominal aortic aneurysm are not related to clinical characteristics. Cardiovasc Pathol. 2009;18(5):286-93.
12. Sakalihasan N, Heyeres A, Nusgens BV, Limet R, Lapiere CM. Modifications of the extracellular matrix of aneurysmal abdominal aortas as a function of their size. Eur J Vasc Surg. 1993;7(6):633-7.
13. Rahman M, Smietana J, Hauck E, Hoh B, Hopkins N, Siddiqui A, et al. Size ratio correlates with intracranial aneurysm rupture status: a prospective study. Stroke. 2010;41(5):916-20.
14. Hurks R, Hoefer IE, Vink A, de Vries JP, Heijmen RH, Schoneveld AH, et al. Aneurysm-express: human abdominal aortic aneurysm wall expression in relation to heterogeneity and vascular events - rationale and design. Eur Surg Res. 2010;45(1):34-40.
15. de Jager W, te Velthuis H, Prakken BJ, Kuis W, Rijkers GT. Simultaneous detection of 15 human cytokines in a single sample of stimulated peripheral blood mononuclear cells. Clin Diagn Lab Immunol. 2003;10(1):133-9.
16. Solberg S, Forsdahl SH, Singh K, Jacobsen BK. Diameter of the infrarenal aorta as a risk factor for abdominal aortic aneurysm: the Tromso Study, 1994-2001. Eur J Vasc Endovasc Surg. 2010;39(3):280-4.
17. Manning BJ, Kristmundsson T, Sonesson B, Resch T. Abdominal aortic aneurysm diameter: a comparison of ultrasound measurements with those from standard and three-dimensional computed tomography reconstruction. J Vasc Surg. 2009;50(2):263-8.
18. Fillinger MF, Racusin J, Baker RK, Cronenwett JL, Teutelink A, Schermerhorn ML, et al. Anatomic characteristics of ruptured abdominal aortic aneurysm on conventional CT scans: Implications for rupture risk. J Vasc Surg. 2004;39(6):1243-52.

19. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg. 2009;50(4 Suppl):S2-49.
20. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1-S58.
21. Koch AE, Haines GK, Rizzo RJ, Radosevich JA, Pope RM, Robinson PG, et al. Human abdominal aortic aneurysms. Immunophenotypic analysis suggesting an immune-mediated response. Am J Pathol. 1990;137(5):1199-213.
22. Maiellaro K, Taylor WR. The role of the adventitia in vascular inflammation. Cardiovasc Res. 2007;75(4):640-8.
23. Koole D, Hurks R, Schoneveld A, Vink A, Golledge J, Moran CS, et al. Osteoprotegerin is associated with aneurysm diameter and proteolysis in abdominal aortic aneurysm disease. Arterioscler Thromb Vasc Biol. 2012;32(6):1497-504.
24. Freestone T, Turner RJ, Coady A, Higman DJ, Greenhalgh RM, Powell JT. Inflammation and matrix metalloproteinases in the enlarging abdominal aortic aneurysm. Arterioscler Thromb Vasc Biol. 1995;15(8):1145-51.
25. Wilson WR, Anderton M, Schwalbe EC, Jones JL, Furness PN, Bell PR, et al. Matrix metalloproteinase-8 and -9 are increased at the site of abdominal aortic aneurysm rupture. Circulation. 2006;113(3):438-45.
26. Hurks R, Pasterkamp G, Vink A, Hoefer IE, Bots ML, van de Pavoordt HD, et al. Circumferential heterogeneity in the abdominal aortic aneurysm wall composition suggests lateral sides to be more rupture prone. J Vasc Surg. 2012;55(1):203-9.

PART ONE

AAA imaging and aneurysmal wall degeneration



CHAPTER 3

Intraluminal thrombus is associated with disruption of wall integrity

J Vasc Surg. 2013 Jan;57(1):77-83

H.J.A. Zandvoort[1]*, D. Koole[1,2]*, A. Schoneveld[2,3], A. Vink[4], J.A. Vos[5], L.L. van den Hoogen[1], J.P.P.M. de Vries[6], G. Pasterkamp[2], F.L. Moll[1], J.A. van Herwaarden[1]

**Both authors contributed equally to this manuscript*

[1] Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Laboratory of Experimental Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands
[3] Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands
[4] Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands
[5] Department of Radiology, St. Antonius Hospital, Nieuwegein, The Netherlands
[6] Department of Vascular Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands

ABSTRACT

Objective

It has been suggested that the intraluminal thrombus (ILT) is associated with abdominal aortic aneurysm (AAA) growth. Prior *in vitro* experiments have demonstrated that aneurysm-associated thrombus may secrete proteolytic enzymes, and may develop local hypoxia which might lead to the formation of tissue-damaging reactive oxygen species.

Methods

Ventral AAA tissue was collected from asymptomatic patients at the site of maximal diameter during open aneurysm repair. Segments were divided, one part for biochemical measurements and one part for histologic analyses. We measured total cathepsin B, cathepsin S levels and matrix metalloproteinase (MMP)-2 and MMP-9 activities. Myeloperoxidase (MPO) and thiobarbituric acid reactive substances (T-BARS) were determined as measures of lipid oxidation. Histologic segments were analyzed semi-quantitatively for the presence of collagen, elastin, vascular smooth muscle cells (VSMCs), and inflammatory cells. Preoperative computed tomography angiography scans of 83 consecutive patients were analyzed. A 3-dimensional reconstruction was obtained, and a center lumen line of the aorta was constructed. Ventral ILT thickness was measured in the anteroposterior direction at the level of maximal aneurysm diameter on the orthogonal slices.

Results

Ventral ILT thickness was positively correlated with aortic diameter ($r = 0.25$, $P = .02$) and with MMP-2 levels ($r = 0.27$, $P = .02$). No biochemical correlations were observed with MMP-9 activity or cathepsin B and S expression. No correlation between ventral ILT thickness and MPO or T-BARS was observed. Ventral ILT thickness was negatively correlated with VSMCs (no/minor staining, 17.8 (11.0-22.1) mm; moderate/heavy, 12.5 (4.3-16.7) mm; P = .01) and the amount of elastin (no/minor staining, 18.0 (10.8-22.5) mm; moderate/heavy, 11.7 (1.0-15.4) mm; P = .01) in the medial aortic layer.

Conclusion

ILT thickness appeared to be associated with VSMCs apoptosis and elastin degradation. Furthermore, ILT thickness was positively associated with MMP-2 concentrations in the underlying wall. This suggest that ILT thickness affect AAA wall stability, and might contribute to AAA growth and rupture. ILT thickness had no correlation with markers of lipid oxidation.

INTRODUCTION

Abdominal aortic aneurysm (AAA) growth and maximal diameter are important determinants for AAA rupture. It has been suggested that the intraluminal thrombus (ILT) is associated with AAA growth.[1, 2] Furthermore, most aneurysms associated with rupture contain an ILT,[3-5] and the presence of blood in the ILT is associated with AAA rupture.[6, 7] The precise mechanism of AAA rupture is unclear, but elastin degradation and collagen integrity are thought to play an important role in this phenomenon. AAA wall that is covered with thrombus has decreased tensile strength, which might increase the risk of rupture.[8] In addition, histologic analysis of the aneurysm wall covered with a thrombus demonstrated a thinner underlying AAA vessel wall that contained a decreased amount of vascular smooth muscle cells (VSMCs) and elastin fibers. Elastin fibers were more fragmented, and VSMCs were more apoptotic.[9]

In vitro studies showed active secretion of proteolytic factors from cultured human thrombi.[10-13] These results suggest that ILT is a biologically active laminated structure with capabilities to influence proteolysis in the underlying AAA vessel wall. However, protease activity in the ILT is predominantly located in the luminal layer, whereas proteases in the thrombus layers more towards the AAA wall (abluminal thrombus layer) layer are mostly inactive.[10] Other theories suggest that the ILT has an indirect effect on AAA vessel wall weakening. Thrombus thickness has been associated with local hypoxia in the AAA vessel wall.[14] Local hypoxia might induce angiogenesis, accompanied with an influx of inflammatory cells, and upregulate markers of lipid oxidation to damage subjacent tissue. The three objectives in the present study were to (1) investigate the association between intraluminal thrombus thickness and medial degeneration in AAA biopsies, (2) assess the association of AAA thrombus thickness with markers of proteolysis in the AAA wall, and (3) investigate whether ILT thickness was associated with markers of lipid oxidation in the underlying AAA vessel wall.

METHODS

Aneurysm-Express Biobank

Ventral AAA biopsy specimens were obtained at the site of maximal diameter from AAA patients undergoing surgery in two Dutch hospitals participating in the Aneurysm-Express Biobank. This ongoing biobank includes all patients undergoing open AAA repair at these two hospitals.[15] The Medical Ethics Committee of both hospitals approved the study, and participants provided written informed consent.

Patient inclusion

The study included patients undergoing open repair of asymptomatic AAA. The indications for intervention were based on current guidelines.[16] Patients with a preoperative computed tomography angiography (CTA) scan with a slice thickness of more than 3.0 mm were excluded from the study because of potential inaccuracy of measurements. In total, twenty CT-examinations (19.4%) were excluded due to a slice thickness of more than 3.0 mm.

Baseline characteristics

Demographic data, cardiovascular risk factors, and medication use were retrieved from questionnaires and clinical records. Hypertension was defined as systolic blood pressure >140 mm Hg or use of blood pressure-lowering drugs; hypercholesterolemia was recorded based on statin use and clinical records or questionnaires; diabetes was defined as use of insulin or oral hypoglycemic agents, and smoking was defined by whether patients had smoked during the last weeks before AAA surgery.

Intraluminal thrombus measurements

All CTA scans were acquired on a 16- or 256-slice CT scanner (Philips Medical Systems, Best, The Netherlands) with a standardized acquisition protocol (scan parameters: 1.5- to 3.0-mm slice thickness, 0.7-mm increment). After administration of a nonionic contrast agent, scanning was started using bolus-triggering software with a threshold of 100 HU over baseline. The acquired datasets were transferred to a workstation (3mensio Vascular 4.3; 3mensio Medical Imaging B.V., Bilthoven, The Netherlands).

Subsequently, a three-dimensional (3D) reconstruction of the aorta was created. A start point was placed in the center of the aorta above the most proximal renal artery and an endpoint was placed below the native bifurcation. The center line was automatically calculated and was adjusted manually to the center of the aorta, if needed. After definition of the centerline, a reconstructed stretch view of the aorta was generated. Because a part of the ventral AAA wall was excised at the site of the maximal diameter, ILT thickness was measured at the level of the maximal diameter. The location of the maximal diameter was determined at visual sight in the reconstructed stretch view and in case of doubt, several measurements were performed to provide one conclusive location. ILT thickness was defined as the distance from the aneurysm wall to the aortic lumen in the anteroposterior (AP) direction on the orthogonal slices (Figure 1). Intraoperatively, the surgeons clinical judgment (eyeballing) was used to confirm the site of maximal diameter.

To analyze the interobserver and intraobserver variability, two investigators (H.Z. and L.H.) performed ILT thickness measurements for 25 randomly chosen patients independently and in a random order. For determination of the intraobserver variability, the first observer measured each scan twice, with an interval of 2 weeks between measurements. To assess interobserver variability, measurements of observer 2 were compared with the first measurement of observer 1. Interobserver and intraobserver variability for ILT thickness measurements were calculated using the Bland-Altman difference against the mean analysis.[17]

Histologic and biologic assessment of AAA biopsy specimens

AAA specimens were dissected into 5-mm cross-sectional segments. One segment was fixed in 4% formaldehyde, decalcified in ethylenediaminetetraacetic acid, and embedded in paraffin. Consecutive slides were stained with hematoxylin and eosin (H&E), elastin von Gieson (EvG), picrosirius red, and antibodies against α-actin, macrophages (CD68), T-lymphocytes (CD3), B-lymphocytes (CD20), and plasma cells (CD138). Extracellular matrix components were semiquantitatively scored as (1) minor or (2) moderate to heavy staining in intima, media, and adventitia separately for collagen (picrosirius red) and smooth muscle cells (SMCs; α-actin).

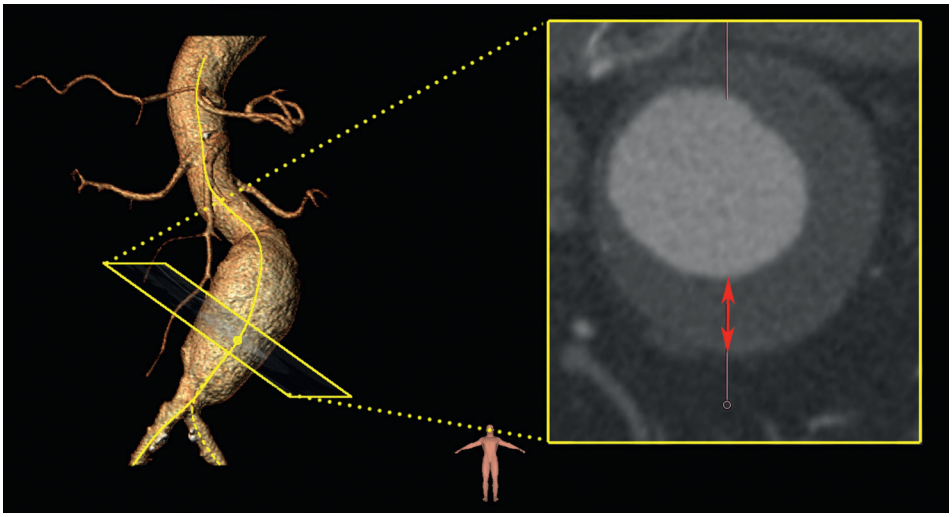


Figure 1. ILT thickness (red arrow) is defined as the distance from the ventral aneurysm wall to the aortic lumen in the anteroposterior direction on the orthogonal slices.

Different components of the inflammatory infiltrate were scored as (1) minor or (2) moderate to heavy staining in the adventitia. Minor staining was defined as fewer than 100 positively stained cells per representative high power field at x100 magnification, and moderate to heavy staining was defined as more than 100 positively stained cells meeting the same conditions. This was performed for macrophages (CD68), T-lymphocytes (CD3), B-lymphocytes (CD20), and plasma cells (CD138).

Other segments were snap-frozen in liquid nitrogen, ground, and dissolved in 1.5 mL of 40 mmol Tris-HCl. Total protein of every sample was quantified by using a bicinchoninic acid protein measurement method (Pierce Biotechnology, Rockford, Ill). A Bio-Plex system (Bio-Rad, Hercules, Calif) was used to measure osteoprotegerin (OPG), interleukin-6 (IL-6), IL-8, cathepsin B and cathepsin S.[18, 19] MMP-2 and MMP-9 were measured using Biotrak activity assays (Amersham Biosciences, GE Healthcare, Hertfordshire, U.K.). The assays used recognizes the pro and active forms of MMPs. It does not cross react with other MMPs or TIMPs. Inter-assay coefficient of variation was <10% for MMP-2 and MMP-9 with a detection limit of 190 pg/ml, and 125 pg/ml respectively. Concentrations of myeloperoxidase (Human MPO, Hycult Biotech, the Netherlands) and thiobarbituric acid reactive substances (T-BARS) (Oxiselect, Cell Biolabs, San Diego, Calif) were determined by enzyme-linked immunosorbent assays. Measured concentrations were related to the protein concentrate of every sample.

Statistical analysis

Discrete variables are reported as number and percentages. Continuous variables are reported as median with interquartile range (IQR) or as mean and the standard deviation. Spearman correlation analysis, Mann-Whitney *U* test, and the Kruskal-Wallis test were conducted where appropriate. Multiple linear or logistic regression analysis was used to assess independent

associations. The natural log-transform was used to normalize the distributions and to improve linearity for multiple regression. All *P*-values were adjusted for age, sex, hypertension, hypercholesterolemia, diabetes, smoking, and AAA diameter. Only the P-values calculated for differences in baseline characteristics were not adjusted. All tests were two-sided, with $P < .05$ considered statistically significant. Statistical analyses were performed with SPSS 15.0 software (SPSS Inc, Chicago, Ill).

RESULTS

Baseline characteristics

The study cohort consisted of 83 asymptomatic AAA patients. The study cohort consisted of 65 men (78.3%) with a median age of 71 years (IQR, 66-76 years). The median AAA diameter was 56.6 mm (IQR, 51.4-64.0 mm). In total, 43 patients (51.8%) used antiplatelet drugs, 14 (16.9%) used anticoagulant drugs, and no patients used heparin derivatives. Table 1 summarizes the differences in baseline characteristics between patients with an ILT thickness below or above the median value. AAA diameter and the percentage of men were significantly increased in the group with an ILT thickness above the median. In addition, ventral ILT thickness was positively correlated with aortic diameter ($r = 0.25, P = .02$). No differences were observed in antiplatelet or anticoagulant drug use.

Table 1. Baseline characteristics of the study population.

	ILT thickness		
	< 15.0 mm	**> 15.0 mm**	
Variables	**n=41**	**n=42**	**P-value**
Age, yrs, median (IQR)	72 (66-77)	71 (66-76)	.71
AAA diameter, mm, median (IQR)	55 (48.6-60.2)	58 (53.4-67.6)	.02
Creatinine, µmol/L, median (IQR)	94 (80.0-113.0)	86 (76.0-101.3)	.17
Male gender	28 (68.3%)	37 (88.1%)	.03
Hypertension	33 (80.5%)	30 (71.4%)	.34
Hypercholesterolemia	27 (65.9%)	26 (61.9%)	.71
Diabetes	6 (14.6%)	11 (26.2%)	.18
Current smoker	15 (36.6%)	21 (50.0%)	.40
Antiplatelet drug use	20 (48.8%)	23 (54.8%)	.67
Anticoagulant drug use	7 (17.1%)	7 (16.7%)	.92
ACE-inhibitor use	11 (26.8%)	17 (40.5%)	.25
Statin use	28 (68.3%)	29 (69.0%)	.92

This table shows baseline characteristics between patients with an ILT thickness below or above the median thickness (15.0 mm). n represents the number of patients in each group. Data are presented as number of patients positive for the variable in each group with (%) or as median (IQR). Abbreviations: *AAA*, Abdominal aortic aneurysm; *ACE*, angiotensin converting enzyme; *ILT*, intraluminal thrombus.

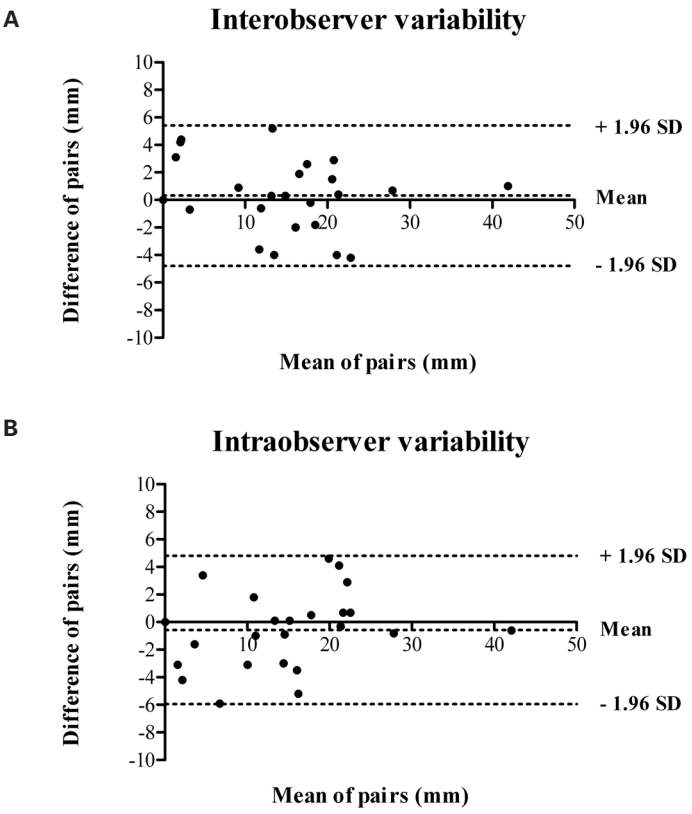


Figure 2. Bland and Altman plots of interobserver (A) and intraobserver (B) variability for the intraluminal thrombus thickness measurements. The mean of pairs is plotted against the difference of pairs. The mean difference is close to zero, and the limits of agreement (1.96 standard deviations) are acceptable.

Interobserver and intraobserver variability

For observer 1, the mean ILT thickness was 14.5 ± 9.5 mm for the first measurement and 14.0 ± 9.8 mm for the second measurement. For observer 2, the mean ILT thickness was 14.2 ± 10.1 mm. The differences of measurements plotted against the mean of measurements for the interobserver and intraobserver variability are shown in Figure 2. The interobserver mean difference for ILT thickness was 0.3 mm, with a repeatability coefficient of 5.1 mm. The intra-observer mean difference for ILT thickness was –0.6 mm, with a repeatability coefficient of 5.4 mm. All measurement differences were within the limits of agreement. No significant differences were observed between the two observers.

The association between ILT thickness and medial degeneration in AAA specimens

A negative correlation between ILT thickness and the amount of elastin fibers was observed (r = -0.30, P = 0.01). ILT thickness measurements for the amount of elastin fibers were 18.0 (10.8-22.5) mm and 11.7 (1.0-15.4) mm in AAA specimens with no/minor and moderate/heavy staining for elastin fibers, respectively (P = .01; Table 2).

A trend towards ILT thickness and elastin fragmentation was observed (r = -0.199, P = .071). Furthermore, a significant negative correlation was observed between medial VSMCs and ILT thickness (r = –0.27, P = .01). Median (IQR) ILT thickness measurements were 17.8 (11.0-22.1) mm and 12.5 (4.3-16.7) mm in AAA specimens with no/minor and moderate/heavy staining for VSMCs in the medial layer, respectively (P = .01; Table 2). Although thicker thrombus measurements were observed in patients with a high number of inflammatory cells, this was not significant after adjustment for age, sex, AAA diameter, smoking, diabetes, hypertension, and hypercholesterolemia (Table 2).

The association of ILT thickness with markers of proteolysis in AAA specimens

Ventral ILT thickness was positively correlated with MMP-2 concentrations in the underlying vessel wall (r = 0.27, P = .02). However, no significant associations were found between ventral thrombus ILT thickness and MMP-9 concentrations in the underlying vessel wall. ILT thickness measurements were not correlated with cathepsin B and S concentrations in AAA specimens (Table 3). Furthermore, no significant correlation between OPG, IL-6, or IL-8 concentrations and ILT thickness measurements were observed (Table 3).

Table 2. Relationships between AAA vessel wall histology and intraluminal thrombus thickness.

	ILT thickness in mm per staining category				
Variables	**n**	**No / Minor**	**n**	**Moderate / Heavy**	**[a]P**
Intimal layer					
Calcifications	53	14.8 (10.0-22.5)	30	17.2 (8.6-21.7)	.44
Collagen	63	16.1 (8.7-21.7)	20	14.5 (10.8-21.8)	.84
Medial layer					
VSMCs	60	17.8 (11.0-22.1)	23	12.5 (4.3-16.7)	.01
Elastin	65	18.0 (10.8-22.5)	18	11.7 (1.0-15.4)	.01
Collagen	82	15.3 (10.0-21.7)	1	…	.64
Adventitial layer					
Myofibroblasts	53	14.9 (10.4-21.7)	30	18.1 (8.9-26.2)	.75
Collagen	22	16.1 (11.6-21.6)	61	15.2 (8.8-21.8)	.94
Macrophages	68	15.1 (8.5-21.7)	15	17.6 (11.3-25.4)	.27
T-lymphocytes	54	14.7 (9.0-21.3)	29	18.3 (10.9-21.9)	.73
B-lymphocytes	36	15.1 (8.3-21.6)	47	17.0 (10.6-21.7)	.46
Plasma cells	55	14.8 (10.0-21.7)	28	18.0 (9.1-21.7)	.99

A total of 83 histologic AAA slides were scored as no/minor or moderate/heavy staining for each histological parameter. n represents the number of histologic slides for each group, which is defined as no/minor and moderate/heavy staining. The values given under no/minor and moderate/heavy staining are the median ILT thickness measurements with (interquartile range) for each staining category. [a]P value adjusted for age, gender, hypertension, hypercholesterolemia, diabetes, smoking, and AAA diameter by logistic regression analysis.

The association of ILT thickness with markers of lipid oxidation in AAA specimens

Different markers for oxidative stress were measured. Our study observed no correlation between ventral ILT thickness and measured T-BARS concentrations in AAA specimens ($r = 0.10$, $P = .55$). MPO, a catalyst for lipoprotein oxidation, was also quantified in AAA homogenates. No correlation was observed between MPO and ventral ILT thickness ($r = -0.02$, $P = .76$; Table 3).

Table 3. Correlations of ILT thickness with proteases, cytokines, and lipid oxidation in the AAA vessel wall.

Variables	r	[a]P
MMP-2	0.27	.02
MMP-9	0.10	.61
Cathepsin B	0.00	.40
Cathepsin S	-0.06	.42
IL-6	0.11	.62
IL-8	0.15	.54
Osteoprotegerin	0.05	.31
T-BARS	0.10	.55
Myeloperoxidase	-0.02	.76

All analyzed markers were measured in all 83 patients. *MMP*, matrix metalloproteinase; *T-BARS*, thiobarbituric acid reactive substances. [a]P Adjusted for age, sex, hypertension, hypercholesterolemia, diabetes, smoking, and AAA diameter by multiple linear regression analysis. Logistic regression analysis was used to calculate the adjusted *P* value for MMP-2, MMP-9, and T-BARS because these data were not normally distributed.

DISCUSSION

Previous studies suggested that the ILT is associated with AAA growth.[1, 2] Furthermore, most aneurysms associated with rupture contain an ILT,[3-5] and the presence of blood in the ILT is associated with AAA rupture.[6, 7] The present study investigated associations between ILT thickness and AAA wall pathophysiology.

This study showed that aneurysm walls covered with a thick thrombus contained fewer elastin fibers and VSMCs, which is in line with the result of another study.[9] These results remained significant after multivariable correction. ILT thickness was not correlated with the amount of inflammatory cells after multivariable analysis. MMP-2 concentrations in the aortic wall were positively associated with ILT thickness. These results are in line with Coutard et al, who showed that MMP-2 concentrations in the aneurysmal wall of rat models were positively associated with ILT weight.[13] In addition, ILT thickness was significantly correlated with AAA diameter. These observations suggests that ILT thickness influences the AAA wall stability, and might contribute to AAA growth and rupture. However, no relationship between MMP-9 concentrations in the aortic wall and ILT thickness was observed. Furthermore, no correlations between ILT thickness and T-BARS or MPO concentrations were observed.

Several studies have demonstrated that the ILT actively secretes MMP-9 and various serine proteases.[10-13] Most of these enzymes are secreted by trapped neutrophils or platelets that are located in the luminal layer of the ILT. Release of MMP-9 and neutrophil elastase was demonstrated to be significantly higher from the luminal layer than from the thrombus layers more towards the AAA wall.[10, 12] Moreover, release of protease inhibitors was elevated in the thrombus layers more towards the AAA wall of the ILT compared with the luminal layer.[10, 11] These previous results suggest that MMP-9 and the investigated serine proteases from the ILT may reach the underlying aortic wall in relatively low concentrations. This study supports this concept, because no association between ILT thickness and MMP-9 concentrations in the aortic wall was found.

There are, however, theories that suggest an indirect effect of the ILT on the underlying aortic wall.[10, 14] A previous study showed that AAA walls covered with thick thrombi demonstrated signs of localized hypoxia.[14] It has been demonstrated that chronic hypoxia induces an oxidant/antioxidant imbalance, which might result in increased oxidative stress levels.[20] Furthermore, the ILT is considered as a privileged site for reactive oxygen species formation by MPO-catalyzed or by Fe^{2+}-catalyzed conversion of H_2O_2.[21, 22] Therefore, we investigated MPO and T-BARS as measures of lipid oxidation; however, no correlations were found with the ILT. This suggests that the ILT does not influence the lipid oxidation (directly or indirectly via hypoxia) in the AAA vessel wall, and does not contribute to the AAA stability via this pathway.

Several studies have shown that chronic hypoxia also influences the bioreactivity of inflammatory and vascular cells.[23-25] Erdozain et al. showed that VSMCs under hypoxic conditions secrete more MMP-2 than normoxic VSMCs.[23] In addition, apoptosis of VSMCs under hypoxic conditions occurs at an increased rate. ILT thickness induced hypoxia of VSMCs might explain the correlations of MMP-2 in the AAA vessel wall with ILT in our study and in aneurysmal rats.[13] A thicker thrombus creates more hypoxia in the underlying aortic wall,[14] and thereby enhances VSMCs apoptosis, increases MMP-2 secretion, and damages the elastin fibers. In addition, it was shown that elastin and collagen synthesis are impaired under hypoxic conditions.[26] These processes might weaken the structural integrity of an AAA vessel wall covered with a thick thrombus. Proteolytic enzymes in the luminal layer of the ILT may exacerbate this situation by causing fissures in the ILT. Fissures in the ILT increase the mechanical stress in the underlying wall,[27] and this could possibly cause AAA rupture in a hypoxic weakened AAA vessel wall.[28] Via this hypoxic pathway the ILT might cause VSMCs apoptosis, elastin degradation, and upregulate MMP-2 in the vessel wall. These alterations influences the AAA wall stability, and might contribute to AAA growth and rupture. Studies that investigate therapies to reduce the ILT thickness are warranted to evaluate the effect on AAA growth and rupture.

This study observed no association of MMP-9 with ILT thickness. However, an association of measured MMP-2 in AAA biopsies with ILT thickness was observed. Although MMP-9 is secreted by VMSCs, macrophages are the predominant cells that secrete MMP-9.[29] In advanced AAA biopsies almost no macrophages were observed. Furthermore, it was shown that MMP-9 from neutrophils in the luminal thrombus layer did not penetrate into the thrombus layers more towards the AAA vessel wall.[10] These observations might explain why MMP-9 concentrations were not associated with ILT thickness. MMP-2 on the other hand is predominately secreted by (hypoxic) VSMCs, and could also originate from activated platelets in the ILT or underlying

vessel wall.[30] This might explain the observed association of ILT thickness with MMP-2.
Several limitations in our study need to be addressed. There is heterogeneity concerning inflammatory or histologic processes in the AAA vessel wall that might bias the results.[31] However, the study consisted of relatively large numbers, and our results confirmed the histologic findings from another study.[9] Furthermore, the study design hampered our ability to investigate whether the ILT is causally related with AAA progression.

CONCLUSIONS

ILT thickness appeared to be associated with VSMCs apoptosis and elastin degradation. Furthermore, ILT thickness was positively associated with MMP-2 concentrations in the underlying wall. This suggest that ILT thickness affect AAA wall stability, and might contribute to AAA growth and rupture. ILT thickness had no correlation with markers of lipid oxidation.

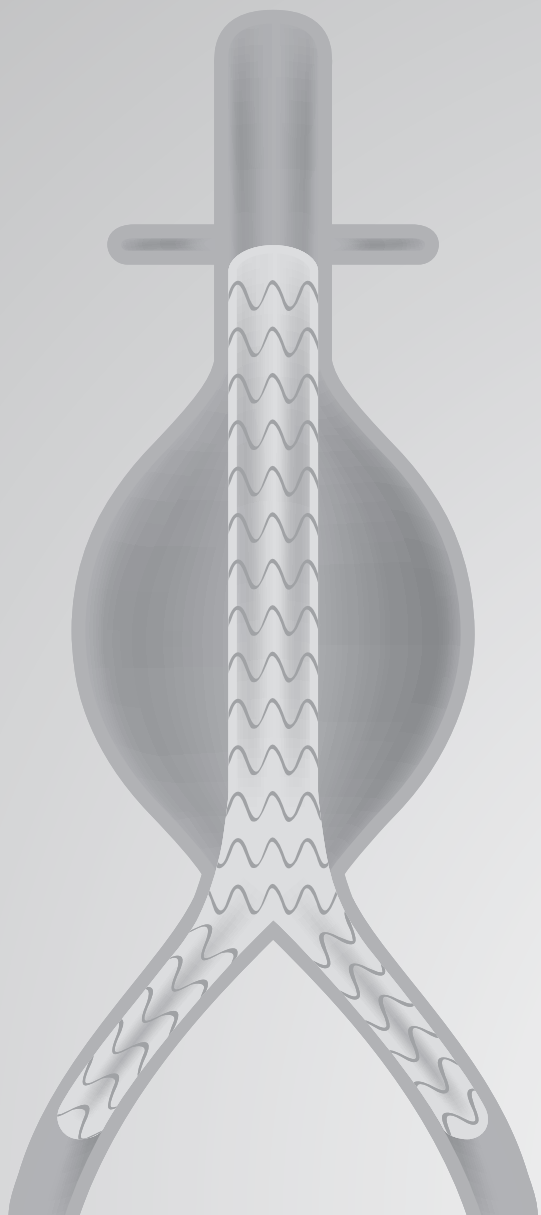
REFERENCES

1. Parr A, McCann M, Bradshaw B, Shahzad A, Buttner P, Golledge J. Thrombus volume is associated with cardiovascular events and aneurysm growth in patients who have abdominal aortic aneurysms. J Vasc Surg. 2011;53(1):28-35.
2. Wolf YG, Thomas WS, Brennan FJ, Goff WG, Sise MJ, Bernstein EF. Computed tomography scanning findings associated with rapid expansion of abdominal aortic aneurysms. J Vasc Surg. 1994;20(4):529-35; discussion 35-8.
3. Hans SS, Jareunpoon O, Balasubramaniam M, Zelenock GB. Size and location of thrombus in intact and ruptured abdominal aortic aneurysms. J Vasc Surg. 2005;41(4):584-8.
4. Stenbaek J, Kalin B, Swedenborg J. Growth of thrombus may be a better predictor of rupture than diameter in patients with abdominal aortic aneurysms. Eur J Vasc Endovasc Surg. 2000;20(5):466-9.
5. Satta J, Laara E, Juvonen T. Intraluminal thrombus predicts rupture of an abdominal aortic aneurysm. J Vasc Surg. 1996;23(4):737-9.
6. Roy J, Labruto F, Beckman MO, Danielson J, Johansson G, Swedenborg J. Bleeding into the intraluminal thrombus in abdominal aortic aneurysms is associated with rupture. J Vasc Surg. 2008;48(5):1108-13.
7. Arita T, Matsunaga N, Takano K, Nagaoka S, Nakamura H, Katayama S, et al. Abdominal aortic aneurysm: rupture associated with the high-attenuating crescent sign. Radiology. 1997;204(3):765-8.
8. Vorp DA, Vande Geest JP. Biomechanical determinants of abdominal aortic aneurysm rupture. Arterioscler Thromb Vasc Biol. 2005;25(8):1558-66.
9. Kazi M, Thyberg J, Religa P, Roy J, Eriksson P, Hedin U, et al. Influence of intraluminal thrombus on structural and cellular composition of abdominal aortic aneurysm wall. J Vasc Surg. 2003;38(6):1283-92.
10. Folkesson M, Silveira A, Eriksson P, Swedenborg J. Protease activity in the multi-layered intraluminal thrombus of abdominal aortic aneurysms. Atherosclerosis. 2011;218(2):294-9.
11. Houard X, Rouzet F, Touat Z, Philippe M, Dominguez M, Fontaine V, et al. Topology of the fibrinolytic system within the mural thrombus of human abdominal aortic aneurysms. J Pathol. 2007;212(1):20-8.
12. Fontaine V, Jacob MP, Houard X, Rossignol P, Plissonnier D, Angles-Cano E, et al. Involvement of the mural thrombus as a site of protease release and activation in human aortic aneurysms. Am J Pathol. 2002;161(5):1701-10.
13. Coutard M, Touat Z, Houard X, Leclercq A, Michel JB. Thrombus versus wall biological activities in experimental aortic aneurysms. J Vasc Res. 2010;47(4):355-66.
14. Vorp DA, Lee PC, Wang DH, Makaroun MS, Nemoto EM, Ogawa S, et al. Association of intraluminal thrombus in abdominal aortic aneurysm with local hypoxia and wall weakening. J Vasc Surg. 2001;34(2):291-9.
15. Hurks R, Hoefer IE, Vink A, de Vries JP, Heijmen RH, Schoneveld AH, et al. Aneurysm-express: human abdominal aortic aneurysm wall expression in relation to heterogeneity and vascular events - rationale and design. Eur Surg Res. 2010;45(1):34-40.
16. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1-S58.
17. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307-10.
18. de Jager W, te Velthuis H, Prakken BJ, Kuis W, Rijkers GT. Simultaneous detection of 15 human cytokines in a single sample of stimulated peripheral blood mononuclear cells. Clin Diagn Lab Immunol. 2003;10(1):133-9.
19. Vignali DA. Multiplexed particle-based flow cytometric assays. J Immunol Methods. 2000;243(1-2):243-55.

20. Hartney T, Birari R, Venkataraman S, Villegas L, Martinez M, Black SM, et al. Xanthine oxidase-derived ROS upregulate Egr-1 via ERK1/2 in PA smooth muscle cells; model to test impact of extracellular ROS in chronic hypoxia. PLoS One. 2011;6(11):e27531.
21. Ramos-Mozo P, Madrigal-Matute J, Martinez-Pinna R, Blanco-Colio LM, Lopez JA, Camafeita E, et al. Proteomic analysis of polymorphonuclear neutrophils identifies catalase as a novel biomarker of abdominal aortic aneurysm: potential implication of oxidative stress in abdominal aortic aneurysm progression. Arterioscler Thromb Vasc Biol. 2011;31(12):3011-9.
22. Michel JB, Martin-Ventura JL, Egido J, Sakalihasan N, Treska V, Lindholt J, et al. Novel aspects of the pathogenesis of aneurysms of the abdominal aorta in humans. Cardiovasc Res. 2011;90(1):18-27.
23. Erdozain OJ, Pegrum S, Winrow VR, Horrocks M, Stevens CR. Hypoxia in abdominal aortic aneurysm supports a role for HIF-1alpha and Ets-1 as drivers of matrix metalloproteinase upregulation in human aortic smooth muscle cells. J Vasc Res. 2011;48(2):163-70.
24. Albina JE, Henry WL, Jr., Mastrofrancesco B, Martin BA, Reichner JS. Macrophage activation by culture in an anoxic environment. J Immunol. 1995;155(9):4391-6.
25. Campbell EJ, Wald MS. Hypoxic injury to human alveolar macrophages accelerates release of previously bound neutrophil elastase. Implications for lung connective tissue injury including pulmonary emphysema. Am Rev Respir Dis. 1983;127(5):631-5.
26. Herrick SE, Ireland GW, Simon D, McCollum CN, Ferguson MW. Venous ulcer fibroblasts compared with normal fibroblasts show differences in collagen but not fibronectin production under both normal and hypoxic conditions. J Invest Dermatol. 1996;106(1):187-93.
27. Polzer S, Gasser TC, Swedenborg J, Bursa J. The impact of intraluminal thrombus failure on the mechanical stress in the wall of abdominal aortic aneurysms. Eur J Vasc Endovasc Surg. 2011;41(4):467-73.
28. Gasser TC, Gorgulu G, Folkesson M, Swedenborg J. Failure properties of intraluminal thrombus in abdominal aortic aneurysm under static and pulsating mechanical loads. J Vasc Surg. 2008;48(1):179-88.
29. Newby AC. Dual role of matrix metalloproteinases (matrixins) in intimal thickening and atherosclerotic plaque rupture. Physiol Rev. 2005;85(1):1-31.
30. Falcinelli E, Giannini S, Boschetti E, Gresele P. Platelets release active matrix metalloproteinase-2 in vivo in humans at a site of vascular injury: lack of inhibition by aspirin. Br J Haematol. 2007;138(2):221-30.
31. Hurks R, Pasterkamp G, Vink A, Hoefer IE, Bots ML, van de Pavoordt HD, et al. Circumferential heterogeneity in the abdominal aortic aneurysm wall composition suggests lateral sides to be more rupture prone. J Vasc Surg. 2012;55(1):203-9.

PART TWO

Dedicated imaging studies in EVAR patients



CHAPTER 4

Preoperative infra- and suprarenal aortic pulsatile distension is comparable between relatively young and older patients with an abdominal aortic aneurysm

Ann Vasc Surg. 2013 Oct 27. Epub ahead of print

H.J.A. Zandvoort[1], F.L. Moll[1], A. Domanian[1], J.W. van Keulen[1] , E.P.A. Vonken[2], J.A. van Herwaarden[1]

[1] Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT

Background

Young healthy individuals have a large aortic pulsatile distension during the cardiac cycle. In patients with an abdominal aortic aneurysm (AAA), aortic distension during the cardiac cycle is associated with stent graft migration. However, whether the pulsatile distension is larger in relatively young patients with an AAA compared with older AAA patients is unknown. This study investigated whether preoperative pulsatile aneurysm neck distension is related to age.

Methods

From our database of endovascular aneurysm repair (EVAR), we selected 25 consecutive male patients aged 65 years or younger (group 1) and 25 consecutive patients older than 65 (group 2). All had a preoperative electrocardiogram-triggered computed tomography angiography scan consisting of eight phases. Aortic area and diameter changes per heartbeat were measured at two levels: (A) 3 cm above and (B) 1 cm below the most distal renal artery.

Results

In group 1 compared with group 2, distension during the cardiac cycle at level A was 1.6 ± 0.4 vs. 1.5 ± 0.4 mm (P = .62) and the aortic area increase was 45.4 ± 19.6 vs. 41.7 ± 20.8 mm^2 (P = .52). Aortic distension at level B was 1.4 ± 0.3 vs. 1.5 ± 0.4 mm (P = .79), and the area increase was 35.5 ± 12.0 vs. 35.0 ± 15.5 mm^2 (P = .90).

Conclusions

Preoperative pulsatile aneurysm neck distension did not differ between younger and older patients; therefore, we do not expect young patients to have more pulsatile distension-related complications after EVAR.

INTRODUCTION

Randomized controlled trials have showed that endovascular aneurysm repair (EVAR) is a minimally invasive procedure with a reduction in perioperative mortality and morbidity compared with open aneurysm repair. However, EVAR is still associated with increased rates of reinterventions and graft-related complications.[1, 2] Most of these complications, such as type Ia endoleaks and stent graft migration, are caused by insufficient proximal sealing and fixation.[3-5]
Dynamic electrocardiogram (ECG)-triggered studies have reported that the proximal aneurysm neck diameter changes significantly during the cardiac cycle.[5, 6] Preoperative distension in the aneurysm neck is significantly associated with stent graft migration after 3 years and is significantly higher in patients with stent graft migration than in patients without stent graft migration.[7] This is interesting, because it has recently been suggested that young patients especially benefit from EVAR.[8] Although young healthy individuals do have a significant aortic pulsatile distension,[9] it is unknown whether young AAA patients have a larger pulsatile distension than older AAA patients.
This study investigated whether there is a difference in preoperative infra- and suprarenal aortic pulsatile distension between young and old AAA patients.

METHODS

Patients
From our EVAR database, we selected 25 consecutive patients aged 65 years or younger (group 1) and 25 consecutive patients older than 65 years (group 2) between January 2008 and December 2010. All patients had a preoperative ECG-triggered computed tomography angiography (CTA) scan and an asymptomatic aneurysm that was eligible for endovascular aneurysm repair.

Imaging
The dynamic preoperative CTA scans were performed on a 64-slice or 256-slice CT scanner (Philips Medical Systems, Best, The Netherlands; values for the 256-slice scanner stated between parentheses) with a standardized acquisition protocol. Scan parameters were: slice thickness, 0.9 mm (0.9 mm); increment, 0.7 mm (0.7 mm); collimation, 64 × 0.625 mm (256 × 0.625 mm); and pitch, 0.25 (0.2). Field of view was 250 × 250 mm (250 × 250 mm), and the reconstructed matrix size was 512 × 512 (512 × 512), resulting in a voxel size of 0.5 × 0.5 × 0.9 mm (0.5 × 0.5 ×0.9 mm). Radiation exposure parameters were 120 kVp (120 kVp) and 300 mAs (250 mAs), resulting in a CT dose index (CTDIvol) of 17.6 mGy (16.5 mGy). An intravenous injection of 120 mL nonionic contrast (Iopromide, Bayer Healthcare, Berlin, Germany) was followed by a 60-mL saline chaser bolus at a rate of 6 mL/s. Before contrast administration heart rate and blood pressure were measured (Table 1).
The scan was started using bolus-triggering software with a threshold of 100 HU over baseline. Retrospectively, ECG-gated reconstructions were made at eight equidistant intervals covering the cardiac cycle on the CTAs. All scans were acquired during a single breath-hold. The CTA data

sets were transferred to a 3 Surgery 4.0 workstation (3Mensio Medical Imaging B.V., Bilthoven, The Netherlands) for analysis. The dynamic images were analyzed using a custom-designed dynamic extension tool for this software.

Table 1. Measurements before contrast administration.

	Group 1 (age ≤65 years)	**Group 2 (age >65 years)**	***P* value**
Blood pressure before contrast administration (mm Hg)			
Systolic	148 ± 27	166 ± 29	*<.05*
Diastolic	88 ± 22	88 ± 10	*.8*
Pulse pressure before contrast administration	61 ± 23	78 ± 25	*<.01*
Heart rate before contrast administration (beats/minute)	71 ± 15	75 ± 21	*.5*

Dynamic CTA analysis

Analysis was performed according to a previously described process [7, 9, 10] and included the following steps: After semiautomatic segmentation of the aortic lumen, an aortic center lumen line (CLL) was automatically constructed by placement of a proximal start and distal endpoint in the aortic lumen. Aortic CLL spline points were manually checked and corrected, if necessary. Multiplanar reconstructions were made perpendicular to the aortic CLL at two levels: 3 cm above the most distal renal artery (level A) and 1 cm below the most distal renal artery (level B). Semiautomatic segmentation of the aortic lumen of the eight images per cardiac cycle was performed at those two levels. A seeding point was placed manually inside the aortic lumen, and a region-growing algorithm was applied to automatically segment the aorta. The segmentations were reviewed, and minor corrections were made manually, if necessary. After segmentation of the aortic lumen, areas and minimum/maximum diameters were calculated.
Diameter measurements were performed through the center of mass of the aortic lumen over 180 axes (with an angular increment of 1°) in all eight images. The distension was defined as the difference between the minimum and maximum area and average minimum and maximum diameter over 180 axes. Maximum AAA diameters were also measured perpendicular to the CLL. Measurements were performed by two observers (HZ and AD) who were blinded to each other's measurements.

Statistical analysis

Changes in diameter and area are presented as mean ± standard deviation and range. Statistical analysis (SPSS, Inc., Chicago, IL) was performed using the t test for unpaired data, considering a *P* value of < .05 as significant. Analysis of covariance (ANCOVA) was used to control for potential confounding variables. Any post-hoc analysis was carried out with Bonferroni correction. Chi-square analysis was used to compare between age group and other nominal variables.
Inter- and intraobserver variability of diameter and area changes were calculated according to the Bland and Altman method. All measurements were performed blinded from age category and from the other measurements.[11]

RESULTS

The study included two groups of 25 AAA patients with the following baseline characteristics: mean maximal aneurysm diameter, 59 ± 12 mm (range, 30-98 mm); mean aneurysm neck length, 35 ± 17 mm (range, 9-71 mm); mean suprarenal angulation, 26° ± 13° (range, 0°-74°); and mean infrarenal angulation, 43° ± 16° (range, 6°-75°). All patients were men and the mean age in group 1 (age ≤65 years) was 60.9 years (±4.5, range 50.6-65.8). The mean age of group 2 (age >65 years) was 76.3 years (±4.9, range 66.5-85.9). Baseline characteristics are summarized in Table 2. Continuous values are presented as the mean and discrete values as numbers (percentage). The differences in aneurysm and patient characteristics between the two groups were not significant.

Change in mean aortic diameter

In the patients aged 65 years or younger (group 1), the mean change in aortic diameter at level A (3 cm above the most distal renal artery) was 6.39% ± 1.85% (range, 3.08%-9.87%) and at level B (1 cm beneath the most distal renal artery) was 6.23% ± 1.41% (range, 4.26%-9.22%).

Table 2. Baseline characteristics of patients in both groups.

	Group 1 (age ≤65 years)	**Group 2 (age >65 years)**	***P* value**
Patients, n (%)	25 (50%)	25 (50%)	
Age, mean years	60.9 (±4.5)	76.3 (±4.9)	
AAA variables			
-Max diameter (mm)	57.3 (±6.9)	60.1 (±14.6)	*.4*
-Neck length (mm)	31.3 (±16,5)	31.0 (±17.6)	*.9*
Angulation,			
-Suprarenal (°)	29.3 (±14.5	28.8 (±17.2)	*.9*
-Infrarenal (°)	44.0 (±17.1)	46.0 (±20.1)	*.7*
ASA classification > 3, n (%)	5 (20%)	9 (36%)	*.3*
Smoking, n (%)	8 (32%)	9 (36%)	*.9*
Diabetes mellitus, n (%)	3 (12%)	5 (20%)	*.7*
Body mass index (kg/m^2)	28.3 (±4.6)	26.3 (±3.6)	*.1*
Hypertension	17 (68%)	20 (80%)	*.5*
Beta-blocker use	13 (52%)	17 (68%)	*.3*
Statin use	14 (56%)	12 (48%)	*.6*
History of cardiac disease	9 (36%)	13 (52%)	*.3*
History of peripheral arterial disease	2 (8%)	8 (32%)	*<.05*
History of cerebral vascular disease	1 (4%)	5 (20%)	*.1*

Data are the means ± standard deviations or absolute numbers including percentage (%) .
Abbreviations: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists;

In group 2 (age older than 65), the mean aortic diameter change at level A was 6.10% ± 1.74% (range, 3.52%-11.19%), and at level B was 6.43% ± 1.69% (range, 4.13%-10.49%). Coherent absolute values can be found in Table 3. The interobserver repeatability for diameter changes was 0.5mm and the intraobserver repeatability was 0.5mm as well.

Change in aortic area

The mean change in aortic area in group 1 was 9.17% ± 4.12% (range, 3.02%-17.44%) at level A, and 8.22% ± 2.99% (range: 3.67-15.11%) at level B. In group 2 the change in area was 8.20% ± 3.92% (2.53%-18.88%) at level A and 8.19% ± 3.15 (3.00%-14.41%) at level B. The absolute values can be found in Table 4. Repeatability coefficients for area changes were 36.4mm^2 for interobserver repeatability and 28.7mm^2 for intraobserver variability.

After adjustment for parameters that were significant in univariate analysis (history of peripheral disease and pulse pressure), multivariate analysis demonstrated that there was no significant

Table 3. The absolute values of the change in mean aortic diameter (mm).

	Group 1 (age ≤65 years)	**Group 2 (age >65 years)**	***P* value**
Suprarenal			
Diameter change	1.6 ± 0.4	1.5 ± 0.4	*.6*
Minimum diameter	25.2 ± 3.0	25.4 ± 4.1	*.8*
Maximum diameter	26.8 ± 3.0	27.0 ± 4.2	*.9*
Infrarenal			
Diameter change	1.4 ± 0.3	1.5 ± 0.4	*.8*
Minimum diameter	23.5 ± 3.4	23.1 ± 3.8	*.7*
Maximum diameter	24.9 ± 3.5	24.6 ± 3.9	*.8*

Table 4. The absolute values of mean aortic area change (mm^2).

	Group 1 (age ≤65 years)	**Group 2 (age >65 years)**	***P* value**
Suprarenal			
Area change	45.4 ± 19.6	41.7 ± 20.8	*.5*
Minimum area	515.5 ± 126.9	532.9 ± 192.6	*.7*
Maximum area	560.8 ± 132.2	574.7 ± 200.4	*.8*
Infrarenal			
Area change	35.5 ± 12.0	35.0 ± 15.5	*.9*
Minimum area	450.8 ± 130.7	443.2 ± 142.5	*.9*
Maximum area	486.3 ± 136.2	478.3 ± 149.0	*.8*

difference in pulsatile diameter changes during the cardiac cycle between young and old patients. Adjusted p-values were .8 for suprarenal diameter change, .6 for infrarenal diameter change and .9 and .2 for suprarenal area change and infrarenal area change respectively.

DISCUSSION

This study showed that preoperative pulsatile aneurysm neck distension does not significantly differ at the suprarenal and infrarenal level between younger and older AAA patients. A previous study demonstrated that the aortic diameter change of the nonpathologic aorta in young healthy volunteers ranged from 14% to 41% over the major axis during the cardiac cycle. Mean changes of 30% suprarenal and 25% infrarenal were reported over the major axis.[9] Another study analyzing preoperative pulsatile aneurysm neck distension showed that AAA patients (median age, 73; range, 50-82 years) had less pulsatile distension, but the diameter still increased during the cardiac cycle from 4.8% to 11.8%. The reported mean aortic diameter change 3 cm above the most distal renal artery was 8.3% in the group with stent graft migration and 7.3% in the group without migration, and at the infrarenal level the percentages, respectively, were 8.4% and 6.9%.[7]

As far as we know, this is the first study to investigate the differences in aneurysm neck dynamics between younger and older AAA patients. Iezzi et al.[6] investigated aortic pulsatility in 40 AAA patients with a mean age of 78.9 years (range, 75-89 years). In their discussion, they suggested that it would be interesting to study pulsatile distension in younger AAA patients because aortic pulsatility may be age-dependent. This is important in the on-going EVAR debate about the inclusion criteria for endovascular treatment of AAAs. Recent results of the large EVAR trials and registry studies suggest that young patients especially benefit from EVAR.

Data from the Medicare population by Schermerhorn et al.[8] showed a benefit for EVAR in young patients. Perioperative mortality was 1.2% in the EVAR group and 4.8% after open repair (relative risk for open repair, 4.00; 95% CI, 3.51-4.56; $P < .001$). After stratification according to age, patients aged 67 to 69 years showed a mortality of 0.4% after EVAR vs. 2.5% after open repair (relative risk, 6.21; 95% CI, 4.98-7.73; $P < .001$).[8] Because this study demonstrates favorable mortality rates in young patients, one may conclude that especially young patients with an AAA benefit from EVAR. However, durability is still a concern after EVAR and especially important in younger patients.

Although young healthy volunteers showed a large increase in aneurysm neck diameters during the cardiac cycle, this study demonstrated that relatively young AAA patients had not this great increase in diameter and showed no differences compared with older AAA patients. However, most AAA patients also have generalized atherosclerosis, and AAA risk factors are comparable with traditional atherosclerotic risk factors.[12] Baseline characteristics in this study population are, therefore, comparable between young and old patients regarding atherosclerotic risk factors except the smaller number of young patients with a history of peripheral arterial disease. So if a younger patient has an AAA that is large enough to consider treatment, their aortic wall proximal to the aneurysm is probably more affected by atherosclerosis than an individual of the same age without an AAA.

In addition, the presence of atherosclerosis is strongly associated with an increased aortic stiffness and also increased age results in decreased arterial compliance.[13,14] Although we do not have pulse wave velocity measurements to assess arterial stiffness we observed a significant difference in pulse pressure between the young and old patient group (61 vs. 78 mm Hg). However, after correction for pulse pressure and other possible confounding factors there was still no difference in pulsatile diameter changes during the cardiac cycle between the group with young and old patients.

In this study, we analyzed whether there was a difference in preoperative pulsatile aneurysm neck distension between younger an older AAA patients. Although we examined a relatively small number of patients, we assume that our results are representative for a larger population. The *P* values for comparison of pulsatile distension between both groups were by far not significant in this study, which makes it unlikely that the results were influenced by underpowering.

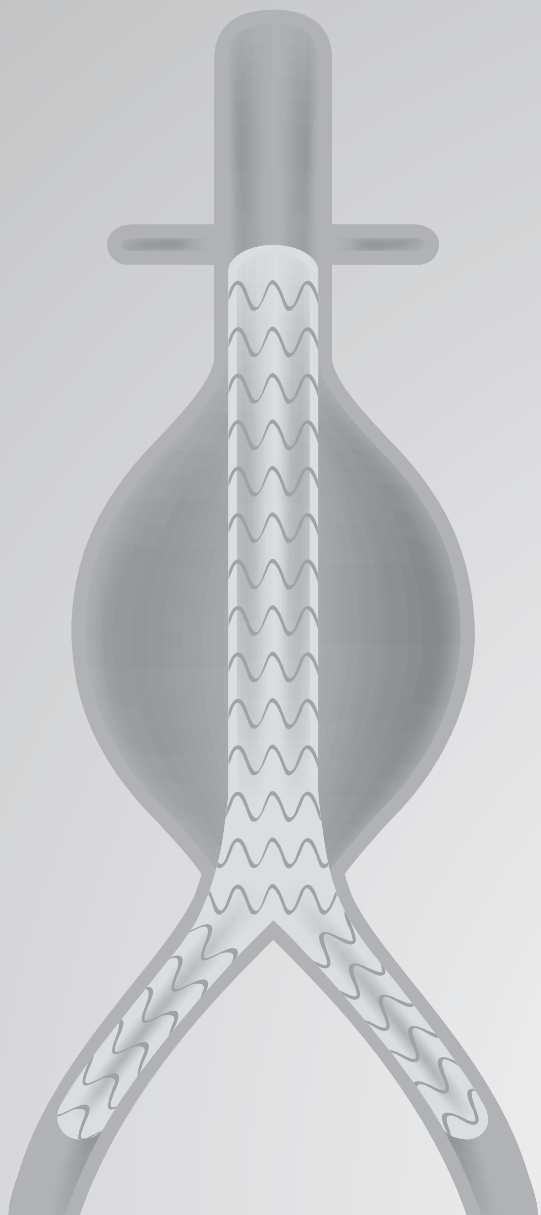
In conclusion, this study showed no relation between preoperative pulsatile aneurysm neck distension and age. Therefore, we do not expect that young patients will have more pulsatile distension-related complications after EVAR.

REFERENCES

1. De Bruin JL, Baas AF, Buth J, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med. 2010;362(20):1881-9.
2. Greenhalgh RM, Brown LC, Powell JT, et al. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med. 2010;362(20):1863-71.
3. Alric P, Hinchliffe RJ, Wenham PW, et al. Lessons learned from the long-term follow-up of a first-generation aortic stent graft. J Vasc Surg. 2003;37(2):367-73.
4. Zarins CK, Bloch DA, Crabtree T, et al. Stent graft migration after endovascular aneurysm repair: importance of proximal fixation. J Vasc Surg. 2003;38(6):1264-72; discussion 72.
5. van Herwaarden JA, Bartels LW, Muhs BE, et al. Dynamic magnetic resonance angiography of the aneurysm neck: conformational changes during the cardiac cycle with possible consequences for endograft sizing and future design. J Vasc Surg. 2006;44(1):22-8.
6. Iezzi R, Di Stasi C, Dattesi R, et al. Proximal aneurysmal neck: dynamic ECG-gated CT angiography--conformational pulsatile changes with possible consequences for endograft sizing. Radiology. 2011;260(2):591-8.
7. van Keulen JW, Moll FL, Barwegen GK, et al. Pulsatile distension of the proximal aneurysm neck is larger in patients with stent graft migration. Eur J Vasc Endovasc Surg. 2010;40(3):326-31.
8. Schermerhorn ML, O'Malley AJ, Jhaveri A, et al. Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. N Engl J Med. 2008;358(5):464-74.
9. van Prehn J, Vincken KL, Sprinkhuizen SM, et al. Aortic pulsatile distention in young healthy volunteers is asymmetric: analysis with ECG-gated MRI. Eur J Vasc Endovasc Surg. 2009;37(2):168-74.
10. van Prehn J, van Herwaarden JA, Vincken KL, et al. Asymmetric aortic expansion of the aneurysm neck: analysis and visualization of shape changes with electrocardiogram-gated magnetic resonance imaging. J Vasc Surg. 2009;49(6):1395-402.
11. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of c linical measurement. Lancet 1986; 1(8476): 307-10.
12. Nordon IM, Hinchliffe RJ, Loftus IM, et al. Pathophysiology and epidemiology of abdominal aortic aneurysms. Nature reviews Cardiology. 2011;8(2):92-102.
13. van Popele NM, Grobbee DE, Bots ML, et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. Stroke. 2001;32(2):454-60.
14. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J. 2010;31(19):2338-50

PART TWO

Dedicated imaging studies in EVAR patients



CHAPTER 5

Preoperative through-plane movement on dynamic computed tomography angiography is limited in patients with an abdominal aortic aneurysm

Submitted

J. de Jonge[1], H.J.A. Zandvoort[1], E.P.A. Vonken[2], F.L. Moll[1], J.A. van Herwaarden[1]

[1] Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT

Purpose

The aorta expands significantly during the cardiac cycle at several levels of the abdominal and thoracic aorta. However, movement in the craniocaudal direction, the so-called through-plane movement, has not been quantified. The aim of the present study was to analyze the movement of the aorta in the craniocaudal direction during the cardiac cycle at several levels.

Methods

From our database of endovascular aneurysm repair (EVAR), we randomly selected 30 patients. All had a preoperative electrocardiogram-gated computed tomography angiography scan consisting of 8 phases. After semiautomatic segmentation, a 3-dimensional location probe was placed in the center of the aorta (center point) on the orthogonal slices. This was performed at 12 different levels along the aorta and iliac arteries and for all 8 phases. Movement of the center point during the cardiac cycle was analyzed for each level.

Results

The study population consisted of 30 patients (27 men), with a median age 73.0 of years (interquartile range [IQR], 65.7–78.7 years). The median through-plane movement of all levels was 3.0 mm (IQR, 2.8–3.2 mm) and appeared to be lower in the region of the celiac and renal arteries (2.6 mm; IQR, 1.7–3.1 mm) at 3 cm proximal to the most distal renal artery and 2.4 mm (IQR, 1.9–2.9 cm) at 1 cm distal to the most distal renal artery, respectively. The thoracic part of the aorta showed largest through-plane motion, 4.1 mm (IQR, 2.7–4.6 mm).

Conclusions

This study suggests that the through-plane motion in the craniocaudal direction is limited. Findings of several studies investigating pulsatile distension of the aorta seem to be representative because the need for correction for through-plane motion is marginal.

INTRODUCTION

Endovascular aneurysm repair (EVAR) has become the preferred treatment in most patients with an abdominal aortic aneurysm (AAA) and a suitable anatomy.[1] To achieve optimal results after EVAR, adequate fixation and sealing of the endovascular stent graft are of utmost importance.[2] Factors undermining proximal fixation and sealing of the stent graft could contribute to reduced sustainability and a higher complication rate, such as endoleaks and migration of the stent graft.[2,3]

Preoperative assessment of aneurysm neck and sac morphology is an important part of EVAR planning and mostly takes place on computed tomography angiography (CTA) imaging, which usually produces static images depicting vascular anatomy during a single time point. Previously, when CT-scanners had longer rotation times, these images showed the average situation throughout the cardiac cycle, with possible blurring as a result. Current scanners, however, are so fast that the images represent a small interval somewhere within the cardiac cycle. This could originate at any moment in the cardiac cycle.

Reports indicate that the aorta expands significantly during the cardiac cycle at several levels of the abdominal aorta.[4-11] Some of these levels are especially important for EVAR fixation and sealing, such as the suprarenal, infrarenal, and iliac levels of the aorta. Because static CT images do not reflect these shape changes, decisions regarding the size and type of the stent graft for endovascular repair might be compromised. Consequently, aortic pulsatility, in combination with the potentially inaccurate stent sizing and selection, might increase the chance of complications such as stent graft migration and endoleaks.

This was supported in a study by van Keulen et al[11] showing a higher preoperative pulsatile distension in patients with stent graft migration compared with patients without migration. However, apart from distension in the orthogonal plane, resulting in diameter and area changes, the aorta could also move in the craniocaudal direction, the so called through-plane movement. We therefore studied the movement of the aorta at several levels relevant for endovascular repair during the cardiac cycle, with special attention to the movement in craniocaudal direction at the suprarenal and infrarenal level.

METHODS

Patients

From our prospectively collected EVAR database, we randomly selected 30 patients with an infrarenal AAA and a preoperative electrocardiogram (ECG)-gated CTA. The scans were performed before endovascular repair between 2006 and 2010.

CTA imaging

All scans were performed on a 64- or 256-slice CT scanner (Philips Medical Systems, Best, The Netherlands) using a standardized acquisition protocol. Scan parameters were (256 slice CT parameters in parentheses): collimation, 64 × 0.625 (128 × 0.625) mm; pitch 0.25 (0.2) and rotation time 0.4 (0.33) seconds. Field of view was 250 × 250 (250 × 250) mm, and the

reconstructed voxel size was 0.5 × 0.5 × 0.9 (0.5 × 0.5 × 0.9) mm. Radiation exposure parameters were 120 (120) kVp and 300 (250) mAs. A total of 150 (100) mL intravenous nonionic contrast (Ultravist-300, Bayer Schering Pharma, Berlin, Germany), followed by a 60-mL saline chaser bolus, was injected at a rate of 6 mL/s. The scan was started using bolus-triggering software with a threshold of 100 HU over baseline. The CTA covered the thoracic and abdominal aorta and the iliac arteries. ECG-gated reconstructions were retrospectively made at 8 equidistant time points covering the entire cardiac cycle. All scans were acquired during a single breath-hold.

CTA Analysis

All preoperative CTA data sets were loaded into a separate workstation (3mensio Medical Imaging B.V., Bilthoven, The Netherlands), and a 3D reconstruction was created. Analysis for each of the 8 phases of the cardiac cycle started with semiautomatic segmentation of the aortic lumen, and an aortic central lumen line (CLL) was automatically constructed. Aortic CLL spline points were manually checked and corrected, if necessary. Multiplanar reconstructions were made perpendicular to the aortic CLL.

Next, 12 levels of interest were defined at each individual phase (Figure 1). These levels were: (A) 3 cm proximal to the left subclavian artery, (B) 1 cm distal to the left subclavian artery, (C) 3 cm distal to the left subclavian artery, (D) 3 cm proximal to the celiac trunk, (E) 3 cm proximal to the most distal renal artery, (F) 1 cm distal to the most distal renal artery, 5 mm distal to the aortic bifurcation both in the left (G) and right (J) common iliac artery, halfway to both the left (H) and right (K) common iliac artery, and finally, 5 mm before the iliac bifurcation of both the left (I) and right (L) common iliac artery.

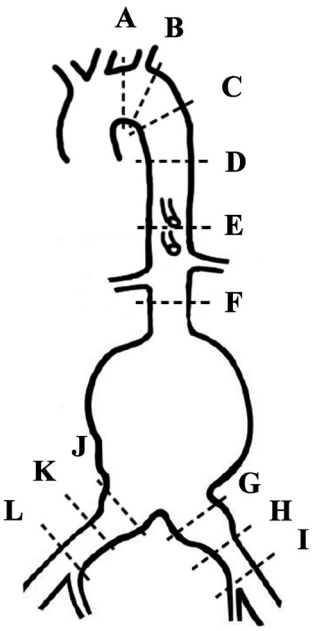


Figure 1. Measurement levels

Measurements, at the orthogonal plane perpendicular to the central lumen line, were performed on the following levels: (A) 3 cm proximal to the left subclavian artery, (B) 1 cm distal to the left subclavian artery, (C) 3 cm distal to the left subclavian artery, (D) 3 cm proximal to the celiac trunk, (E) 3 cm proximal to the most distal renal artery, (F) 1 cm distal to the most distal renal artery, 5 mm distal to the aortic bifurcation both in the left (G) and right (J) common iliac artery, halfway to both the left (H) and right (K) common iliac artery, and finally, 5 mm before the iliac bifurcation of both the left (I) and right (L) common iliac artery.

The center of the aorta (center point) was determined at each mentioned level in all 8 phases. Five different location probes were placed in the orthogonal plane. Each location probe represented a 3-dimensional coordinate, providing an X (mediolateral direction), Y (ventrodorsal direction), and Z value (craniocaudal direction).

One location probe was located in the center of the aortic lumen, and to ensure that we precisely marked the center point, 4 other location probes were placed at the outer border of the aortic wall, at clock positions 3, 6, 9, and 12 (Figure 2). We calculated the position of the center point by averaging the value of the probe located in the center of the aortic lumen and the mean value of the location probes at the 4 clock positions. This calculation was repeated for each level and all 8 phases.

By comparing the center point X, Y, or Z values at a certain level in one phase with those at the same level of another phase, movement of the aorta at that level could be quantified in the mediolateral, ventrodorsal, or craniocaudal direction, respectively. The difference between the highest and lowest X, Y and Z value of the center points in all 8 phases per level was calculated and considered as movement of the center point in millimeters at that specific level during the cardiac cycle. Difference in the Z value, representing movement in the craniocaudal direction, was defined as through-plane movement during the cardiac cycle.

Statistical analysis

Data are presented as median with the interquartile range (IQR). The Wilcoxon signed rank test was used to test differences in X, Y, and Z values of the center point between diverse levels. Intraobserver and interobserver variability according to the Bland-Altman method[12] was performed to analyze variability and compare measurements by 2 observers. Statistical analysis was performed with SPSS 20 software (IBM, Armonk, NY).

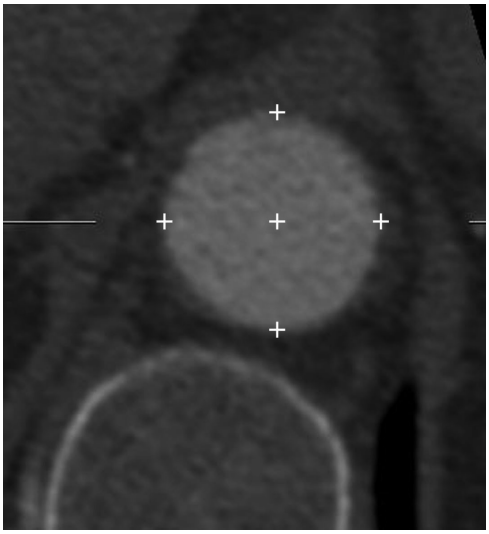


Figure 2. Placement of location probes
Orthogonal plane of the aorta displaying the location of the five location probes (white crosses).

RESULTS

The study population consisted of 30 patients (27 men) with a median age of 73.0 years (65.7–78.7 years). Overall, median through-plane movement was 3.0 mm (2.8–3.2 mm). Data of all levels are listed in Table 1. As depicted in Figure 3, there was a trend toward less movement of the center point the X, Y, and Z directions around the region of the celiac trunk and the renal arteries compared with the thoracic part of the aorta and the iliac arteries. Median through-plane movement at level E, 3 cm proximal to the most distal renal artery, was 2.6 mm (1.7–3.1 mm) and at level F, 1 cm distal to the that artery, median through-plane movement was 2.4 mm (1.9–2.9 mm). Compared with the median through-plane movement 1 cm distal to the left subclavian artery, a relevant level for thoracic endovascular repair, through-plane movement showed a significant difference at level E ($P = .02$) and level F ($P < .01$). Through-plane movement at level F was also lower compared with level I in the left ($P = .04$) and right iliac artery ($P = .02$). Intraobserver variability was 0.6, 0.9, and 0.7 mm for the X, Y, and Z values, respectively. The interobserver variability for movement of the center point was 0.7, 1.0, and 1.0 mm for the X, Y, and Z values, respectively.

Table 1. Movement of the center point during the cardiac cycle.

Level	X (mm)	Y (mm)	Z (mm)
1 cm proximal left subclavian	3.2 (2.6–4.2)	4.2 (3.5–5.2)	3.4 (3.0–4.9)
1 cm distal left subclavian	3.1 (2.0–3.7)	4.2 (2.7–5.5)	2.9 (2.3–4.0)
3 cm distal left subclavian	3.3 (2.1–4.0)	3.8 (2.8–6.2)	4.1 (2.7–4.6)
3 cm distal celiac trunk	2.3 (1.7–3.9)	2.3 (1.8–3.3)	2.2 (1.9 - 2.8)
3 cm proximal lowest renal	2.1 (1.9–2.9)	2.5 (2.1 - 3.2)	2.6 (1.7–3.1)
1 cm distal lowest renal	2.0 (1.8–3.0)	2.0 (1.6–2.8)	2.4 (1.9–2.9)
0.5 cm distal aortic bifurcation R	3.5 (2.3–5.5)	3.6 (2.7–5.5)	3.7 (2.5–4.6)
Middle part common iliac R	2.9 (2.5–4.4)	3.2 (2.5–4.6)	3.0 (2.5–4.3)
0.5 cm proximal iliac bifurcation R	3.2 (2.4–4.9)	3.2 (2.5–4.3)	3.0 (2.2–5.5)
0.5 cm distal iliac bifurcation L	2.9 (2.2–4.1)	3.2 (2.1–3.7)	3.0 (2.4–4.5)
Middle part common iliac L	3.1 (2.2–4.0)	2.7 (1.7–4.1)	3.1 (2.0–4.2)
0.5 cm proximal iliac bifurcation L	3.1 (2.0–4.8)	3.4 (2.6–4.3)	2.9 (2.3–3.9)

Data are presented as median value (interquartile range). Values for X, Y and Z represent the movement in the mediolateral, ventrodorsal and craniocaudal direction, respectively.

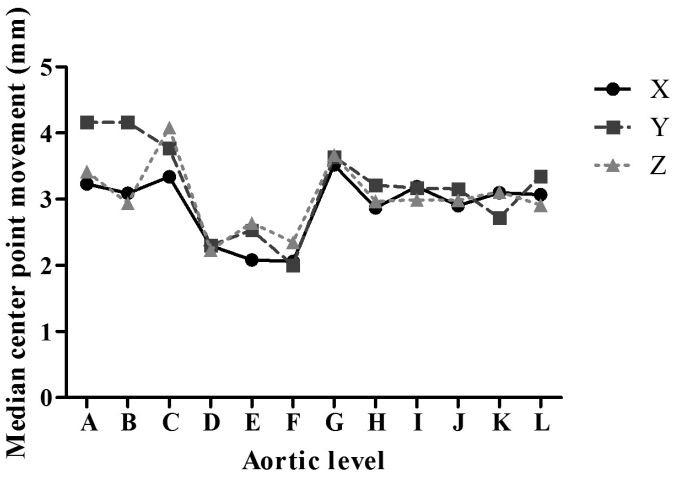


Figure 3. Movement of the center point during the cardiac cycle
Values for X, Y, and Z represent the median movement in the mediolateral, ventrodorsal, and craniocaudal direction, respectively. (A) 3 cm proximal to the left subclavian artery, (B) 1 cm distal to the left subclavian artery, (C) 3 cm distal to the left subclavian artery, (D) 3 cm proximal to the celiac trunk, (E) 3 cm proximal to the most distal renal artery, (F) 1 cm distal to the most distal renal artery, 5 mm distal to the aortic bifurcation both in the left (G) and right (J) common iliac artery, halfway to both the left (H) and right (K) common iliac artery, and finally, 5 mm before the iliac bifurcation of both the left (I) and right (L) common iliac artery.

DISCUSSION

This study demonstrates that through-plane motion is present in the both mediolateral, ventrodorsal and craniocaudal direction at the thoracic aorta, abdominal aorta, and iliac arteries. However, this motion is small and even smaller at levels relevant for fixation and sealing during EVAR.

Previous studies highlighted the preoperative diameter and area changes of the aorta at several levels relevant for EVAR implantation, particularly at suprarenal and infrarenal EVAR landing sites.[4-11] These shape changes occur as a consequence of pulsatile cardiac contraction and aortic compliance and could lead to more complications related to inadequate proximal fixation and sealing, including type Ia endoleak and stent graft migration.[3] Moreover, these changes seemed to remain after stent graft implantation. If the stent grafts were unable to adapt to the aorta, the postoperative aorta pulsatility would be expected to differ from the preoperative dynamic changes. However, it has been observed that the degree and direction of (asymmetrical) expansion is preserved after endograft implantation.[4,6,8,10] Hence, the stent grafts seem to be able to adapt to the aortic pulsatility changes.[10]

None of these studies, however, could correct for through-plane movement, which might have, on the one hand, additional effects on proximal sealing and fixation of the endograft and, on the other hand, complicates the interpretation of the results of aortic pulsatility.

In preceding studies diameter and area changes of the aorta during the cardiac cylce were analyzed at the same level in the patient's body. Because the through-plane motion of the

aorta could not be taken into account, this level was not necessarily the same level of the aorta in all 8 phases. However, in this study, we demonstrate that the through-plane movement of the aorta is limited and especially at the most important levels for suprarenal and infrarenal endograft fixation.

If a larger through-plane motion had been present, diameter and area changes from previous studies could also be interpreted as measuring a more distal or proximal part of the aorta in every phase due to the craniocaudal motion of the aorta during the heart cycle. The finding of a minimal through-plane motion proximal and distal to the lowest renal artery contributes to the accuracy and validity of previous studies measuring aortic diameter and area changes at these EVAR-specific levels.

A possible explanation for the reduced through-plane motion at the suprarenal and infrarenal level might be related to the surrounding tissue and arterial branches, which create a strong and firm environment so that the cardiac-induced pulsatile changes of the aorta at this level are being reduced.[4]

A limitation of this study was that we could only observe movement of the entire aorta during the cardiac cycle in the craniocaudal direction. Knowing whether distension of the aortic wall is also present parallel to the CLL would be of great interest and should illustrate whether the aorta elongates during the cardiac cycle in the longitudinal direction. This potential elongation of the aorta should be studied on preoperative and postoperative scans to see if there is any effect for the stent graft. Elongation and subsequent shorting of the aorta during the cardiac cycle might influence the proximal and distal sealing of the endograft.

CONCLUSIONS

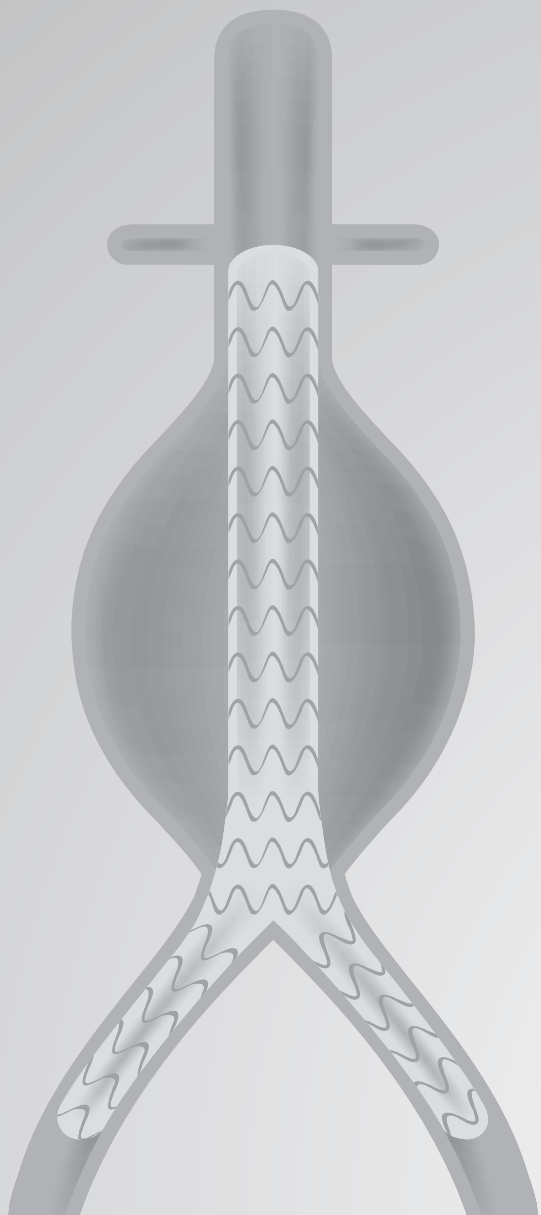
This study suggests that the through-plane motion in the craniocaudal direction of the aorta is limited. Findings of several studies investigating pulsatile distension of the aorta seem to be representative because the need for correction for through-plane motion is not needed.

REFERENCES

1. Sachs T, Schermerhorn M, Pomposelli F, Cotterill P, O'Malley J, Landon B. Resident and fellow experiences after the introduction of endovascular aneurysm repair for abdominal aortic aneurysm. J Vasc Surg. 2011;54(3):881-8.
2. van Herwaarden JA, van de Pavoordt ED, Waasdorp EJ, Albert Vos J, Overtoom TT, Kelder JC, et al. Long-term single-center results with AneuRx endografts for endovascular abdominal aortic aneurysm repair. J Endovasc Ther. 2007;14(3):307-17.
3. van Keulen JW, van Prehn J, Prokop M, Moll FL, van Herwaarden JA. Dynamics of the aorta before and after endovascular aneurysm repair: a systematic review. Eur J Vasc Endovasc Surg. 2009;38(5):586-96.
4. van Prehn J, van Herwaarden JA, Vincken KL, Verhagen HJ, Moll FL, Bartels LW. Asymmetric aortic expansion of the aneurysm neck: analysis and visualization of shape changes with electrocardiogram-gated magnetic resonance imaging. J Vasc Surg. 2009;49(6):1395-402.
5. van Keulen JW, Moll FL, Vonken EJ, Tolenaar JL, Muhs BE, van Herwaarden JA. Pulsatility in the iliac artery is significant at several levels: implications for EVAR. J Endovasc Ther. 2011;18(2):199-204.
6. Teutelink A, Muhs BE, Vincken KL, Bartels LW, Cornelissen SA, van Herwaarden JA, et al. Use of dynamic computed tomography to evaluate pre- and postoperative aortic changes in AAA patients undergoing endovascular aneurysm repair. J Endovasc Ther. 2007;14(1):44-9.
7. Teutelink A, Rutten A, Muhs BE, Olree M, van Herwaarden JA, de Vos AM, et al. Pilot study of dynamic cine CT angiography for the evaluation of abdominal aortic aneurysms: implications for endograft treatment. J Endovasc Ther. 2006;13(2):139-44.
8. van Herwaarden JA, Bartels LW, Muhs BE, Vincken KL, Lindeboom MY, Teutelink A, et al. Dynamic magnetic resonance angiography of the aneurysm neck: conformational changes during the cardiac cycle with possible consequences for endograft sizing and future design. J Vasc Surg. 2006;44(1):22-8.
9. Arko FR, Murphy EH, Davis CM, 3rd, Johnson ED, Smith ST, Zarins CK. Dynamic geometry and wall thickness of the aortic neck of abdominal aortic aneurysms with intravascular ultrasonography. J Vasc Surg. 2007;46(5):891-6; discussion 6-7.
10. van Keulen JW, Vincken KL, van Prehn J, Tolenaar JL, Bartels LW, Viergever MA, et al. The influence of different types of stent grafts on aneurysm neck dynamics after endovascular aneurysm repair. Eur J Vasc Endovasc Surg. 2010;39(2):193-9.
11. van Keulen JW, Moll FL, Barwegen GK, Vonken EP, van Herwaarden JA. Pulsatile distension of the proximal aneurysm neck is larger in patients with stent graft migration. Eur J Vasc Endovasc Surg. 2010;40(3):326-31.
12. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1(8476): 307-10.

PART TWO

Dedicated imaging studies in EVAR patients



CHAPTER 6

Magnetic resonance imaging is more sensitive than computed tomography angiography for the detection of endoleaks after endovascular abdominal aortic aneurysm repair: a systematic review

Eur J Vasc Endovasc Surg. 2013 Apr;45(4):340-50

H.J.A. Zandvoort[1]*, J. Habets[2]*, J.B. Reitsma[3], L.W. Bartels[4], F.L. Moll[1], T. Leiner[2]*, J.A. van Herwaarden[1]*

**These authors contributed equally to this manuscript*

[1] Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands
[3] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[4] Image Sciences Institute, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT

Objectives

The purpose of this systematic review was to examine whether magnetic resonance imaging (MRI) or computed tomography angiography (CTA) is more sensitive for the detection of endoleaks in patients with abdominal aortic aneurysm (AAA) after EVAR.

Materials and methods

A systematic electronic search was performed. Articles were included when post-EVAR patients were evaluated by both MRI as index test and CTA as comparison. Methodological quality was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. Primary outcome was the proportion of patients in whom MRI detected additional endoleaks, which were not seen with CTA.

Results

Eleven articles were included. The overall methodological quality of the articles was good. In total, 369 patients with 562 MRI and 562 CTA examinations were included. A total of 146 endoleaks were detected by CTA; MRI detected all but two of these endoleaks. With MRI 132 additional endoleaks were found.

Conclusions

MRI is more sensitive compared to CTA for the detection of post-EVAR endoleaks, especially for the detection of type II endoleaks. MRI should be considered in patients with continued AAA growth and negative or uncertain findings at CTA.

INTRODUCTION

The aim of endovascular aortic aneurysm repair (EVAR) is to prevent aneurysm rupture by exclusion of the aneurysm sac from the systemic circulation. A successful endovascular procedure will result in depressurisation of the aneurysm sac and arrest of abdominal aortic aneurysm (AAA) growth.[1,2] A clinically important complication after EVAR is the occurrence of endoleak. Endoleak is defined as leakage of blood into the aneurysm sac, which may result in continued aneurysm growth and, ultimately, rupture. Endoleaks are classified into different types (Table 1).[3] Correct endoleak classification is important because there are different treatment strategies for different endoleak subtypes.[3,4]

For the detection of complications after EVAR, postoperative surveillance is advised by performing computed tomography angiography (CTA) and plain radiography within 1 month.[3] If an endoleak is detected, CTA and plain radiography are advised after 6 and 12 months and yearly thereafter. If no endoleak is detected at 1 month, CTA is advised after 12 months followed by yearly abdominal duplex ultrasound and plain radiography.[4] In current guidelines digital subtraction angiography (DSA) has no diagnostic role during EVAR follow-up.[4] However, in patients with inconclusive imaging follow-up or in patients with an endoleak that requires treatment, DSA is recommended but often not performed.

Currently, tri-phasic CTA with unenhanced, arterial and delayed phases is considered to be the most appropriate method for detection of endoleaks after EVAR. Nevertheless, it is known that CTA sometimes fails to detect the presence of endoleaks.[5,6] In patients with aneurysm growth post-EVAR, it is important to detect these missed endoleaks with alternative imaging strategies because they may require treatment.[4,7,8] Because of its excellent soft-tissue contrast, magnetic resonance imaging (MRI) is of high interest for this purpose. On the other hand, it is conceivable that susceptibility artefacts associated with the stent-graft material limit assessment of post-EVAR AAA with MRI. At present, the diagnostic capabilities of MRI for the detection of endoleak after EVAR remain to be determined.

The purpose of this systematic review is to examine whether MRI is more sensitive than CTA for the detection of endoleaks in patients with AAA after EVAR.

MATERIALS AND METHODS

Literature search

A systematic electronic search was performed in the PubMed and Embase databases for original articles published until 1 November 2011. The language was restricted to English articles. Key search terms were ‘magnetic resonance imaging’, ‘endoleak’, ‘endovascular treatment’ and corresponding synonyms. The exact search terms are shown in Appendix I.

Selection of publications

After removal of duplicates, two reviewers independently screened titles and abstracts of the remaining studies. Articles were included if: (1) patients after EVAR of an abdominal aortic aneurysm were studied; (2) examination during follow-up for the detection of endoleaks included

assessment with MRI; and (3) a comparison between findings at MRI and CTA was performed. Full-text versions of studies that matched the inclusion criteria were obtained. The reference lists of all included articles were scanned by the first authors for any relevant publication not identified by the electronic searches (cross-referencing); if present, these articles were included. All full-text publications were examined by two reviewers independently and in cases of disagreement consensus was reached during a consensus meeting.

Quality assessment

Information on study design characteristics, sample size and type of patient population, MRI protocol, CTA protocol as well as the number and type of endoleaks detected by MRI and CTA was collected.

Studies were assessed for quality based on the criteria as proposed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist.[9] The QUADAS items for each included study were scored as 'yes', 'no' and 'unclear' (Appendix II).

Data analysis

On MRI examinations, endoleak was defined as a high-intensity signal within the aneurysm sac on post-contrast T1-weighted images, not present on pre-contrast T1-weighted images.

The outcome in the first set of analyses was the proportion of patients in whom an endoleak was detected by MRI, which was not detected by CTA, divided by the total number of patients examined. In case a study reported results of MRI versus CTA examination during follow-up from multiple time points, we used all available data.[10] A Forest plot was generated to depict the proportion of additional endoleaks detected by MRI and corresponding 95% confidence intervals (CIs) for all studies. To evaluate if data could be pooled, we calculated I^2 and the Cochran's Q test to examine how consistent the proportion of additionally detected endoleaks by MRI was across studies. I^2 represents the percentage of variability in the estimates of additionally detected endoleaks by MRI, which is attributable to heterogeneity between studies rather than sampling error.

Furthermore, we examined the types of endoleaks that were detected by MRI, but not seen at CTA. If available, data were extracted on the five subtypes of endoleaks (Table 1).

Table 1. Endoleak classification.[3]

Endoleak type	Description
I	Attachment site leak – IA proximal, IB is distal, IC Iliac occluder
II	Branch vessel retrograde flow – IIA IMA; IIB Lumbar arteries
III	Graft Failure
IV	Graft-wall porosity
V	Endotension

IMA = Inferior Mesenteric Artery.

RESULTS

Search results

The electronic search yielded a total of 218 publications after removal of duplicates. Nineteen full-text versions of studies that matched the inclusion criteria were obtained. Six studies were excluded: two case reports, two publications that contained the same patient population, one article that did not meet the language restriction (German article) and one study that discussed thoracic EVAR (TEVAR) patients. Cross-referencing of all included articles did not yield additional articles. The final selection of articles consisted therefore of 11 studies (Figure 1). The detailed results of the quality assessment for each study are given in Appendix II.

All included studies (Table 2) reported on the detection of endoleaks in patients during follow-up after EVAR and compared MRI with CTA findings. These 11 studies included 369 patients, who underwent at least one MRI and CTA examination, with 562 MRI and 562 CTA examinations. The interval between CTA and MRI should ideally be restricted to ≤1 month. Most studies (n = 7) reported a mean time between MRI and CTA of 1 month or shorter. Two studies exceeded the 1 month mean interval time between MRI and CTA modality.[5,11] Furthermore, two studies did not explicitly report the time interval between both examinations.[10,12] The latter four studies were also included in the systematic review because of the limited number of studies providing data on this topic. One study reported similar proportions of additional endoleaks detected by MRI than the other included studies. By contrast, the other study detected relatively more additional endoleaks but this study had a limited sample size (n = 6).[11] All MRI examinations were performed on 1.5-T MRI systems, except in one study in which a 1.0-T MRI system was used in some patients.[13] All included studies performed arterial-phase imaging. Delayed-phase CTA (≥60 s after contrast administration) was performed in 8 of 11 (73%) studies (Table 2). In one study not all patients received delayed-phased imaging. Delayed-phase imaging was performed only in 13 patients (13/28; 46%) with suspected endoleaks.[14] One study did not report the time interval between contrast administration and delayed-phase imaging.[11] Finally, in one study delayed phase imaging was not performed.[12] Detailed individual information on patient characteristics and stent-graft type was inconsistently reported in the different studies. The available information is shown in Table 3. Overall, MRI detected 278 endoleaks while CTA detected 146 endoleaks. Thus, MRI detected 132 additional endoleaks compared to CTA. MRI failed to detect two type I endoleaks: one proximal type IA endoleak and one distal type IB endoleak.[10,15] In Table 4, the number of additional endoleaks detected by MRI in the different studies is presented.

Patient population

In the analysis two different study populations were distinguished: (1) an unselected patient population (n = 10) and (2) patients with no discernible endoleaks at CTA (n = 1). One study consisted of both unselected patients and patients with known endoleaks on CTA.[13] We considered pooling the extracted data of the individual studies by examining an unselected patient population. However, we refrained from pooling because of large clinical heterogeneity based on the QUADAS assessment and large statistical heterogeneity as demonstrated by the I^2 test in the unselected population – 81.1% (P value of Cochran's Q statistic < 0.001).

Therefore, only estimates from individual studies are shown in Figure 2. In the single study that included patients with non-shrinking AAA without visible endoleaks on CTA (population 2), MRI detected six endoleaks (55%) (Figure 2).[16]

Endoleak types

The proportion of additional endoleaks detected by MRI was classified into the different endoleak subtypes. In the unselected patient population MRI detected a total of 128 additional endoleaks. The study of Insko et al. detected four additional endoleaks with MRI in nine patients, but did not specify which types of endoleaks were found.[12] Therefore, 124 additional endoleaks detected

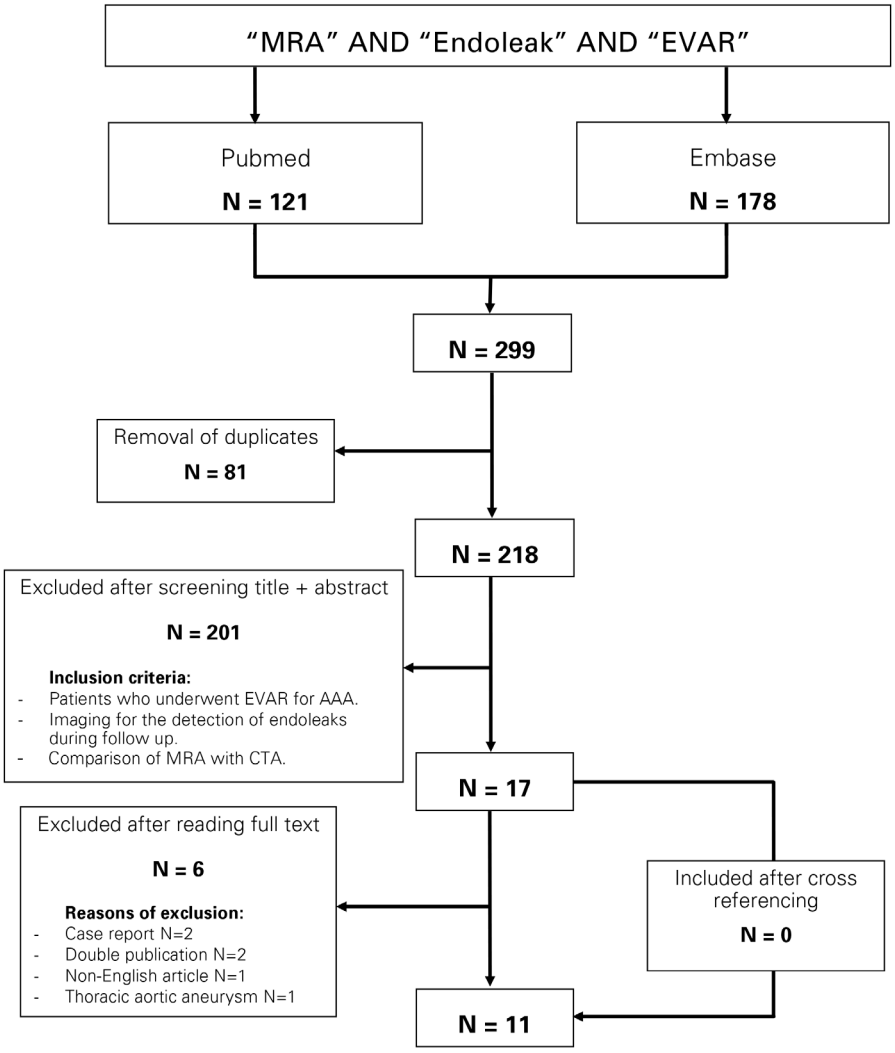


Figure 1. Flowchart demonstrating search results and number of included and excluded studies.

by MRI could be classified per endoleak type. This resulted in the following distribution of additional endoleaks detected by MRI: 86 type II (69%); 12 type III (10%) and 26 indeterminate endoleaks (21%). Data on type II subtype (IIa and IIb) were not provided in most studies and therefore not addressed in this meta-analysis. A total of two endoleaks were detected by CTA and missed by MRI. Both these leaks were type 1 endoleaks.[10,15]

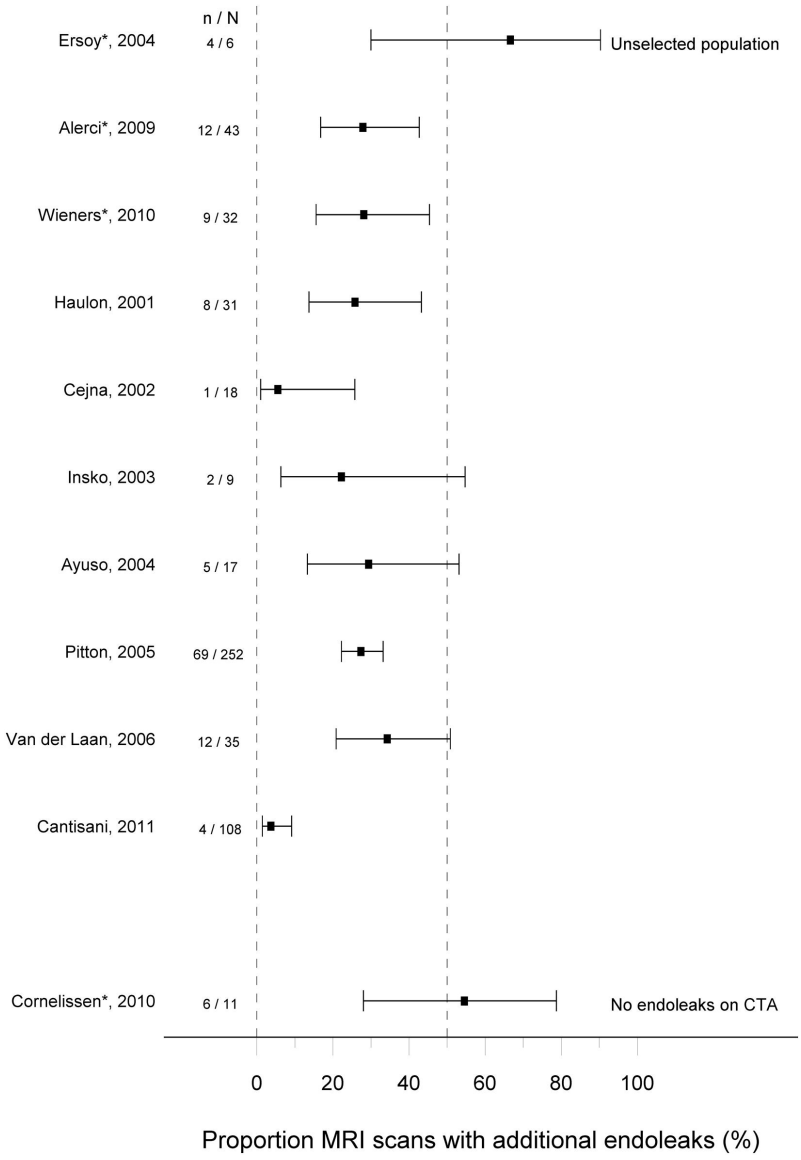


Figure 2. Proportion (%) of additional endoleaks detected by MRI. * studies with albumin-binding MRI contrast agents.

Table 2. Included studies.

Author, journal, year	Number of patients included (number of scans)	Study population	MRI	Reference modality	Delayed phase CTA (acquisition time after start contrast injection)	Mean time between MRI and CTA (range)	No. and type of endoleaks detected by MRI	No. and type of endoleaks detected by CTA
Haulon, Eur. J. Vasc. Endovasc. Surg., 2001	31 (31)	Unselected	MRI (1.5T)	DSA	Yes (60 seconds)	2.6 months (1-6 months)	Total MRA: 18 Type I:1 Type II: 17	Total CTA: 10 Type I: 1 Type II: 9
Cejna, Eur. Radiol., 2002	32 (40)	Unselected	MRI (1.0T or 1.5T)	CTA	Yes (60-70 seconds)	6.6 days (0-28 days)	Total: 18 Type I/III: 6 Type II: 12	Uniphasic (n=22 scans) Total: 7 Type I/III: 3 Type II: 4 Biphasic (n=18 scans) Total: 8 Type I/III: 3 Type II: 5
Insko, Acad. Radiol., 2003	9 (9)	Unselected	MRI (1.5T)	CTA	No	Not reported	Total:6 Type I:2 Type II:4	Total: 4 Type I: 2 Type II: 2
Ayuso, J. Magn. Reson. Imaging, 2004	27 (27)	Unselected (n=17) Endoleaks present on CTA (n=10)	MRI (1.5T)	CTA	Yes (20-30 seconds after arterial phase)	1-30 days	Total: 21 Type II: 15 Type III: 3 Indeterminate: 3	Total: 16 Type II:12 Type III 3 Indeterminate: 1
Ersoy, Eur. J. Radiol., 2004	6 (6)	Unselected	MRI (1.5T)	CTA	Yes (not reported)	90 days (5-203 days)	Total: 6	Total:2

Table 2 continued

Pitton, Am. J. Roentgenol., 2004	52 (252)	Unselected	MRI (1.5T)	Consensus reading of CTA and MRI	Yes (90 seconds)	N/A	Total MRA: 131 Type I: 7 Type II: 93 Type III: 21 Complex: 10	Total CTA:62 Type I: 8 Type II:42 Type III: 10 Complex 2
Van der Laan, Eur. J. Vasc. Endovasc. Surg., 2006	28 (35)	Unselected	MRI (1.5T)	CTA	Yes (120 and 240 seconds) in patients with suspected endoleak	Max 1 month	Total: 23 Type I:2 Type II: 6 Type III: 1 Indeterminate 14	Total:11 Type I: 2 Type II: 3 Type III: 1 Indeterminate: 5
Alerci, Eur. Radiol., 2008	43 (43)	Unselected	MRI (1.5T) CTA	Consensus reading of CTA and MRI	Yes (60 seconds)	Max 1 week	Observer 1 Total: 22 Type II: 19 Indeterminate:3 Observer 2 Total: 24 Type II:13 Indeterminate:11	Observer 1 Total: 11 Type II: 10 Type V: 1 Observer 2 Total: 12 Type I: 1 Type II: 7 Indeterminate: 4
Cornelissen, Invest. Radiol., 2010	12 (11)	No endoleaks on CTA	MRI (1.5T)	CTA	Yes (90 seconds)	23 days (13-49 days)	Total: 6 Type II: 1 Indeterminate: 5	Total: 0
Wieners, Cardiovasc. Interv. Radiol., 2010	32 (32)	Unselected	MRi (1.5T)	CTA	Yes (70 seconds)	7.5 days (1-30 days)	Total: 21 Type II: 21	Total: 12 Type II:12
Cantisani, Eur. J. Vasc. Endovasc. Surg., 2011	108 (108)	Unselected	CTA MRI (1.5T) CEUS CDUS	Consensus reading of CTA, MRI and DSA if available	Yes (120 seconds)	Max 1 week	Total: 24 Type II: 21 Type III: 3	Total: 20 Type II: 18 Type III: 2

Table 3. Included studies.

Author, journal, year	Mean max AAA diameter (range)	Stentgraft type	Male / female ratio	Mean age in years (range)	MRI contrast agent type	MRI T1 sequence type
Haulon, Eur. J. Vasc. Endovasc. Surg., 2001	49 mm	25 Vanguard; 4 AneuRx; 2 Talent	30/1	64 (47-77)	Gadolinium based extracellular	Spin echo
Cejna, Eur. Radiol., 2002	Not reported	3 Talent; 7 Excluder; 30 Stentor and Vanguard	29/3	72 (58-84)	Gadolinium based extracellular	Gradient echo
Insko, Acad. Radiol., 2003	Not reported	8 Medtronic nithinol; 1 elgiloy Guidant	Not reported	Not reported	Gadolinium based extracellular	Gradient echo
Ayuso, J. Magn. Reson. Imaging, 2004	CTA: 56.7 mm (39-93) MRA: 58.8 mm (37-96)	4 Talent; 20 Excluder; 2 Vanguard; 2 AneuRx	Not reported	Not reported	Gadolinium based extracellular	Gradient echo
Ersoy, Eur. J. Radiol., 2004	50 mm (44-65)	AneuRx; Ancure	6/1	62-83	Albumin-binding	Not reported
Pitton, Am. J. Roentgenol., 2004	Not reported	Talent; Vanguard	48/4	71.1 (55-82)	Gadolinium based extracellular	Gradient echo
Van der Laan, Eur. J. Vasc. Endovasc. Surg., 2006	Not reported	3 Excluder; 25 Ancure	26/2	72.3	Gadolinium based extracellular	Spin echo
Alerci, Eur. Radiol., 2008	58 mm(50-74)	13 Talent; 30 Excluder	41/2	Not reported	Albumin-binding	Gradient echo
Cornelissen, Invest. Radiol., 2010	60 mm (41-87)	9 Talent; 1 Excluder; 2 Guidant (1 AUI and 1 Ancure)	10/2	76.6 (62-90)	Albumin-binding	Spin echo
Wieners, Cardiovasc. Interv. Radiol., 2010	CTA: 52.5 mm (24 - 84) MRI: 52.8 mm (24 - 86)	25 Excluder; 4 Talent; 3 Anaconda	Not reported	76 (64-86)	Albumin-binding	Gradient echo
Cantisani, Eur. J. Vasc. Endovasc. Surg., 2011	54 mm (39-87)	55 Talent; 50 Excluder; 12 Powerlink; 6 Jomed	92/31	63.0	Gadolinium based extracellular	Gradient echo

Table 4. Endoleaks detected by different studies, specified by type (unselected patients).

Author	year	Patients (n)	scans (n)	MRI: total endoleaks	MRI: endoleaks by type						Reference: total endoleaks	Reference: endoleaks by type					
					I	II	III	IV	V	Indeter-minate		I	II	III	IV	V	Indeter-minate
Haulon et al.	2001	31	31	18	1	17	0	0	0	0	10[c]	1	9	0	0	0	0
Cejna et al.	2002	32	18	9[b]	1	6	1	0	0	1	8[b]	1	5	1	0	0	1
Insko et al.	2003	9	9	6	2	4	0	0	0	0	4	2	2	0	0	0	0
Ayuso et al.	2004	17	17	10	0	6	1	0	0	3	5	0	3	1	0	0	1
Ersoy et al.	2004	6	6	6	NR	NR	NR	NR	NR	NR	2	NR	NR	NR	NR	NR	NR
Pitton et al.	2005	52	252	131	7	93	21	0	0	10	62[c]	8	42	10	0	0	2
Van der Laan et al.	2006	28	35	23	2	6	1	0	0	14	11	2	3	1	0	0	5
Alerci et al. [a]	2009	43	43	24	0	13	0	0	0	11	12[c]	1	7	0	0	0	4
Wieners et al.	2010	32	32	21	0	21	0	0	0	0	12	0	12	0	0	0	0
Cantisani et al.	2011	108	108	24	0	21	3	0	0	0	20[c]	0	18	2	0	0	0
Total		358	551	272	13	187	27	0	0	39	146	15	101	15	0	0	13

*NR: Not Reported

[a] Only results of observer 2

[b] Endoleaks detected on biphasic CTA's and compared to MRI. Endoleaks detected on uniphasic CTA's are not shown in this table

[c] Number of endoleaks detected on CTA (Reference standard in this studies was defined as consensus reading between MRI and/or CTA and/or DSA).

DISCUSSION

The principal finding of this systematic review is that MRI detects significantly more endoleaks compared to CTA in patients after EVAR, especially type II endoleaks. The detection of these additional type II endoleaks is clinically relevant because these endoleaks require treatment in patients with aneurysm growth according to both the Society for Vascular Surgery (SVS) as well as European Journal of Vascular and Endovascular Surgery (EJVES) guidelines.[4,8]

Methodological quality assessment revealed several potentially relevant differences between included studies. First, mean time interval between CTA and MRI exceeded 1 month in two studies[5,11] and was unclear in two studies.[10,12] Longer time interval between CTA and MRI may increase the detection of additional endoleaks by MRI because during this time interval new endoleaks could have developed or increased in volume or severity. We decided to include these studies because of the limited available data on this topic. Second, in the majority of included studies (8/11; 73%), the presence of endoleak was assessed on delayed-phase CTA. For the detection of type II endoleaks, delayed-phase imaging is crucial and the absence of delayed-phase imaging could have resulted in overestimation of the additional value of MRI for the detection of endoleaks. Three other QUADAS items deserve to be mentioned (Appendix II). The first item (item 12, Appendix II) concerns the availability of clinical data during MRI assessment. This item was scored 'unclear' in nine studies and 'no' in two studies. However, for accurate MRI and CTA assessment, the availability of clinical data is not a strict necessity. The second item (reporting of uninterpretable and intermediate test results; item 13, Appendix II) was scored 'yes' in three studies and 'no' in eight studies. Appropriate reporting of these results is relevant because in clinical practice it is important to know if image quality is adequate to assess endoleak presence because it may guide treatment decisions. The last item (explanation on withdrawals from the study; item 14, Appendix II) was scored 'yes' in three studies and 'no' in eight studies. Reporting of withdrawals is important because, for clinical implementation of MRI in EVAR follow-up, it is important to know if patients tolerate the MR examination and administration of MR contrast agents.

Overall, MRI examinations demonstrated 126 additional endoleaks compared to CTA. However, MRI missed two type I endoleaks that were detected by CTA.[10,12] One distal type I endoleak (IB) was masked because of vessel-wall calcifications and platinum markers of the distal limb stent graft. This type I endoleak was detected with a triphasic CT protocol. On the unenhanced scan, calcifications were identified and could be differentiated from the endoleak present on the CTA images. Alerci et al. reported on the second missed type I endoleak (only one of two observers mentioned this endoleak).[15] However, their consensus reading (MRI + CTA) concluded that there was no type I endoleak on both CTA and MRI. We chose to use the numbers of endoleaks of the second observer because they were most close to the consensus reading. In clinical practice, it is crucial to detect type I endoleaks because they often result in AAA growth and may even lead to aneurysm rupture. Besides these two type I endoleaks, MRI and CTA detected both all type I endoleaks. Furthermore, we would like to emphasise that we view MRI as a complementary technique to CTA in the case of aneurysm growth. Therefore, the missed type I endoleaks are less relevant because in our proposed diagnostic strategy CTA would probably have detected these endoleaks (Figure 3).

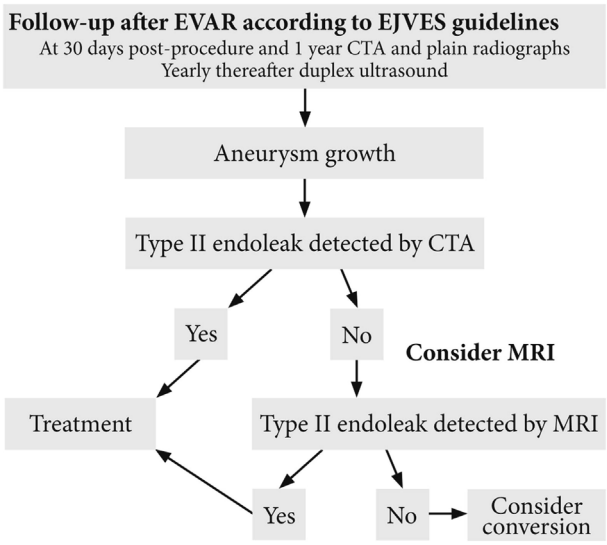


Figure 3. Proposed diagnostic algorithm for post-EVAR imaging in patients with aneurysm growth.

Nowadays, type III endoleaks due to graft failure are infrequently encountered because of the new-generation nitinol stent grafts, longer overlap zones between the modular components and stronger polyester fabrics. MRI detected all type III endoleaks detected by CTA. However, Pitton et al. detected 11 additional type III endoleaks with MRI compared to CTA.[10] Type III endoleaks are fast-flow endoleaks that require appropriate treatment. In this study, only two patients who underwent re-intervention had a negative biphasic CTA examination and an additional endoleak on MRI.[10] These two patients had a type II endoleak that was embolised and a type III endoleak (dislodgement due to kinking of the stent graft) that required late conversion. Although 11 additional type III endoleaks were found by MRI, treatment of a type III endoleak was only reported in one patient. This is in contrast to current guidelines that recommend treating all type III endoleaks.[4,8] However, it is unclear how many times this patient was imaged because MRI was a part of the standard follow-up protocol.

We compared MRI with CTA because CTA is the most commonly used imaging technique to evaluate the presence of endoleak during post-EVAR follow-up. This systematic review demonstrates that MRI has a higher sensitivity compared to CTA for the detection of endoleaks, especially type II endoleaks. The main reason for this finding is probably the superior MRI soft-tissue contrast and, subsequently, the improved contrast sensitivity for small and slow-flow endoleaks. Furthermore, in four studies (4/11; 36%), albumin-binding contrast agents were administered, which are characterised by a higher relaxivity (2–5 times higher) compared to conventional extracellular agents.[11,15-17] These contrast agents have a prolonged intravascular

retention in the circulation that allows a longer time interval between contrast administration and post-contrast imaging.[18,19] Both higher relaxivity and prolonged intravascular retention could have improved the sensitivity of MRI.

The bulk of additional endoleaks detected with MRI concerned type II endoleaks. Unfortunately, individual data on aneurysm growth was lacking, which is crucial for treatment decisions because type II endoleaks which cause AAA diameter growth require treatment according to current guidelines.[4,8] Although Wieners et al. reported that six of nine (67%) additional endoleaks on MRI occurred in patients with AAA growth, further prospective studies are required to determine the exact value of MRI in patients with AAA growth.[17] Furthermore, Cornelissen et al. detected two additional type II endoleaks in patients with AAA growth with MRI among 11 patients with non-shrinking AAA after EVAR and no endoleak at CTA.[16]

Limitations

Meta-analysis was not meaningful because of the large heterogeneity in the included studies. Besides the previously mentioned AAA growth, several other interesting covariates (stent-graft type, the use of albumin-binding contrast agents and the use of T1 spin-echo sequences) could not be analysed because of the large heterogeneity and the lack of individual data in the study reports. Most studies concerned patients with nitinol stent grafts that generally did not hamper assessment (Table 3). It is well known that other stent-graft types (Elgiloy and stainless steel) can hamper diagnostic MR assessment because of metal-induced susceptibility artefacts, even when T1 spin-echo sequences are used. These stent-graft types are not good candidates for MR evaluation. Prior *in vitro* work demonstrated that Zenith (Stainless Steel; Cook, Bloomington, IN, USA) and Lifepath (Elgiloy; Baxter, Morton Grove, IL, USA) stent grafts are not assessable by MRI.[20] For these stent-graft types, CTA and contrast-enhanced ultrasound remain the preferred imaging modalities.

The use of albumin-binding high-relaxivity contrast agents as well as T1-weighted spin-echo post-contrast MR imaging seem to increase sensitivity for the detection of endoleak.[15,16,17] Albumin-binding contrast agents could be promising for the detection of slow-flow endoleaks in patients with aneurysm growth and no endoleaks on CTA because of the prolonged intravascular retention as well as the higher relaxivity. In the included studies, mainly nitinol stent grafts were imaged and especially for other stent-graft types (e.g., Elgiloy and stainless steel) T1-weighted spin-echo sequences may be preferable because images are less affected by susceptibility artefacts.[20] Nevertheless, prospective studies are required to determine the exact value of albumin-binding contrast agents and T1-weighted spin-echo sequences.

Besides CTA, contrast-enhanced ultrasound is used to detect endoleaks in patients after EVAR. A meta-analysis by Mirza et al. reported a good pooled sensitivity (98%) and specificity (88%) of contrast-enhanced ultrasound with CTA used as a reference standard.[21] This meta-analysis shows that contrast-enhanced ultrasound is a clinically interesting alternative to CTA. However, for the evaluation of stent-graft position and fractures, contrast-enhanced ultrasound is inferior to CTA.[22]

Time-resolved MR angiography (MRA) sequences can also be used to detect endoleaks. The advantage of this type of sequence is the superior temporal resolution, which enables better assessment of contrast dynamics over time. The disadvantage of this sequence is the generally

inferior spatial resolution compared to conventional post-contrast T1-weighted imaging, which can potentially result in missing small endoleaks. Furthermore, time-resolved acquisitions are based on gradient echo sequences, which are more sensitive to susceptibility artefacts that can degrade image quality. However, time-resolved MRA may have an additional diagnostic value to T1-weighted post-contrast imaging in the classification of endoleaks and can be combined with conventional T1-weighted imaging without significant time penalty.[23-25]

For MRI imaging of endoleaks with blood pool agents, no standard MRA sequences are reported in the literature. For comparability of studies and to reduce heterogeneity, it is important that in prospective studies MRA sequences are standardised to extrapolate results to clinical practice. In this review, studies were included that compared CTA to MRI T1-weighted post-contrast imaging. Verification with an independent reference standard (e.g., digital subtraction angiography, DSA) was not systematically performed in the included studies. However, DSA may also miss endoleaks especially when non-selective DSA is performed. Prospective studies are required to compare CTA and MRI to selective DSA.

Finally, it is important to mention that metal-induced susceptibility artefacts due to surgical clips and stainless-steel coils can also hamper MRI assessment of post-EVAR patients. MR-compatible clips and coil material (i.e., platinum) are advisable if MRI follow-up is considered. It is also important to mention that not all patients are good candidates for MRI due to contraindications such as claustrophobia, certain other types of metal implants and the presence of implanted pacemakers or internal cardioverter/defibrillators.

CONCLUSION

MRI is more sensitive than CTA for the detection of post-EVAR endoleaks, especially for the detection of type II endoleaks which has treatment consequences in patients with AAA growth. MRI is therefore an interesting complementary imaging modality to CTA that must be considered, especially in patients with post-EVAR AAA growth of unknown origin.

REFERENCES

1 Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg 1991 Nov;5(6):491-9.
2 Volodos NL, Karpovich IP, Troyan VI, Kalashnikova Y, Shekhanin VE, Ternyuk NE, et al. Clinical experience of the use of self-fixing synthetic prostheses for remote endoprosthetics of the thoracic and the abdominal aorta and iliac arteries through the femoral artery and as intraoperative endoprosthesis for aorta reconstruction. Vasa Suppl 1991;33:93-5.
3 White GH, Yu W, May J, Chaufour X, Stephen MS. Endoleak as a complication of endoluminal grafting of abdominal aortic aneurysms: classification, incidence, diagnosis, and management. J Endovasc Surg 1997 May;4(2):152-68.
4 Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg 2011 Jan;41 Suppl 1:S1-S58.
5 Haulon S, Lions C, McFadden EP, Koussa M, Gaxotte V, Halna P, et al. Prospective evaluation of magnetic resonance imaging after endovascular treatment of infrarenal aortic aneurysms. Eur J Vasc Endovasc Surg 2001 Jul;22(1):62-9.
6 Rozenblit AM, Patlas M, Rosenbaum AT, Okhi T, Veith FJ, Laks MP, et al. Detection of endoleaks after endovascular repair of abdominal aortic aneurysm: value of unenhanced and delayed helical CT acquisitions. Radiology 2003 May;227(2):426-33.
7 Koole D, Moll FL, Buth J, Hobo R, Zandvoort HJ, Bots ML, et al. Annual rupture risk of abdominal aortic aneurysm enlargement without detectable endoleak after endovascular abdominal aortic repair. J Vasc Surg 2011 Dec;54(6):1614-22.
8 Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg 2009 Oct;50(4 Suppl):S2-49.
9 Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003 Nov 10;3:25.
10 Pitton MB, Schweitzer H, Herber S, Schmiedt W, Neufang A, Kalden P, et al. MRI versus helical CT for endoleak detection after endovascular aneurysm repair. AJR Am J Roentgenol 2005 Nov;185(5):1275-81.
11 Ersoy H, Jacobs P, Kent CK, Prince MR. Blood pool MR angiography of aortic stent-graft endoleak. AJR Am J Roentgenol 2004 May;182(5):1181-6.
12 Insko EK, Kulzer LM, Fairman RM, Carpenter JP, Stavropoulos SW. MR imaging for the detection of endoleaks in recipients of abdominal aortic stent-grafts with low magnetic susceptibility. Acad Radiol 2003 May;10(5):509-13.
13 Cejna M, Loewe C, Schoder M, Dirisamer A, Holzenbein T, Kretschmer G, et al. MR angiography vs CT angiography in the follow-up of nitinol stent grafts in endoluminally treated aortic aneurysms. Eur Radiol 2002 Oct;12(10):2443-50.
14 van der Laan MJ, Bartels LW, Viergever MA, Blankensteijn JD. Computed tomography versus magnetic resonance imaging of endoleaks after EVAR. Eur J Vasc Endovasc Surg 2006 Oct;32(4):361-5.
15 Alerci M, Oberson M, Fogliata A, Gallino A, Vock P, Wyttenbach R. Prospective, intraindividual comparison of MRI versus MDCT for endoleak detection after endovascular repair of abdominal aortic aneurysms. Eur Radiol 2009 May;19(5):1223-31.
16 Cornelissen SA, Prokop M, Verhagen HJ, Adriaensen ME, Moll FL, Bartels LW. Detection of occult endoleaks after endovascular treatment of abdominal aortic aneurysm using magnetic resonance imaging with a blood pool contrast agent: preliminary observations. Invest Radiol 2010 Sep;45(9):548-53.
17 Wieners G, Meyer F, Halloul Z, Peters N, Ruhl R, Dudeck O, et al. Detection of type II endoleak after endovascular aortic repair: comparison between magnetic resonance angiography and blood-pool contrast agent and dual-phase computed tomography angiography. Cardiovasc Intervent Radiol 2010 Dec;33(6):1135-42.

18 Pintaske J, Martirosian P, Graf H, Erb G, Lodemann KP, Claussen CD, et al. Relaxivity of Gadopentetate Dimeglumine (Magnevist), Gadobutrol (Gadovist), and Gadobenate Dimeglumine (MultiHance) in human blood plasma at 0.2, 1.5, and 3 Tesla. Invest Radiol 2006 Mar;41(3):213-21.
19 Eldredge HB, Spiller M, Chasse JM, Greenwood MT, Caravan P. Species dependence on plasma protein binding and relaxivity of the gadolinium-based MRI contrast agent MS-325. Invest Radiol 2006 Mar;41(3):229-43.
20 van der Laan MJ, Bartels LW, Bakker CJ, Viergever MA, Blankensteijn JD. Suitability of 7 aortic stent-graft models for MRI-based surveillance. J Endovasc Ther 2004 Aug;11(4):366-71.
21 Mirza TA, Karthikesalingam A, Jackson D, Walsh SR, Holt PJ, Hayes PD, et al. Duplex ultrasound and contrast-enhanced ultrasound versus computed tomography for the detection of endoleak after EVAR: systematic review and bivariate meta-analysis. Eur J Vasc Endovasc Surg 2010 Apr;39(4):418-28.
22 Perini P, Sediri I, Midulla M, Delsart P, Mouton S, Gautier C, et al. Single-centre prospective comparison between contrast-enhanced ultrasound and computed tomography angiography after EVAR. Eur J Vasc Endovasc Surg 2011 Dec;42(6):797-802.
23 Cohen EI, Weinreb DB, Siegelbaum RH, Honig S, Marin M, Weintraub JL, et al. Time-resolved MR angiography for the classification of endoleaks after endovascular aneurysm repair. J Magn Reson Imaging 2008 Mar;27(3):500-3.
24 Lookstein RA, Goldman J, Pukin L, Marin ML. Time-resolved magnetic resonance angiography as a noninvasive method to characterize endoleaks: initial results compared with conventional angiography. J Vasc Surg 2004 Jan;39(1):27-33.
25 van der Laan MJ, Bakker CJ, Blankensteijn JD, Bartels LW. Dynamic CE-MRA for endoleak classification after endovascular aneurysm repair. Eur J Vasc Endovasc Surg 2006 Feb;31(2):130-5.
26 Ayuso JR, de Caralt TM, Pages M, Riambau V, Ayuso C, Sanchez M, et al. MRA is useful as a follow-up technique after endovascular repair of aortic aneurysms with nitinol endoprostheses. J Magn Reson Imaging 2004 Nov;20(5):803-10.
27 Cantisani V, Ricci P, Grazhdani H, Napoli A, Fanelli F, Catalano C, et al. Prospective comparative analysis of colour-Doppler ultrasound, contrast-enhanced ultrasound, computed tomography and magnetic resonance in detecting endoleak after endovascular abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2011 Feb;41(2):186-92.

APPENDIX I

Exact search terms used in literature search

Pubmed: 121 articles

(("MRA"[Title/Abstract] OR "MRI"[Title/Abstract] OR "Magnetic Resonance Imaging"[Title/Abstract] OR "Magnetic Resonance Angiography"[Title/Abstract] OR "Magnetic Resonance Angiographies"[Title/Abstract] OR "Magnetic Resonance Imaging"[Mesh] OR "Magnetic Resonance Angiography"[Mesh])

AND

("endoleak"[Title/Abstract] OR "endoleaks"[Title/Abstract] OR "Perigraft Leak"[Title/Abstract] OR "perigraft leaks"[Title/Abstract] OR "endotension"[Title/Abstract] OR "endoleak"[Mesh]))

AND

(("EVAR"[Title/Abstract] OR "endovascular"[Title/Abstract] OR "aneurysm repair"[Title/Abstract] OR "aneurysm surgery"[Title/Abstract] OR "aortic stent"[Title/Abstract]) OR "aortic stent graft"[Title/Abstract] OR "AAA"[Title/Abstract] OR "aortic aneurysm"[Title/Abstract] OR "aortic aneurysms"[Title/Abstract] OR "aorta aneurysm"[Title/Abstract] OR "aorta aneurysms"[Title/Abstract] OR "Aortic Aneurysm, Abdominal"[Mesh] OR "Aortic Aneurysm"[Mesh])

Embase: 178 articles

('nuclear magnetic resonance imaging'/exp OR 'magnetic resonance angiography'/exp OR mra:ab,ti OR mri:ab,ti OR (magnetic AND resonance AND imaging:ab,ti) OR (magnetic AND resonance AND angiography;ab,ti) OR (magnetic AND resonance AND angiographies;ab,ti))

AND

(endoleak;ab,ti OR endoleaks:ab,ti OR (perigraft AND leak:ab,ti) OR (perigraft AND leaks:ab,ti) OR endotension:ab,ti OR 'endoleak'/exp)

AND

('abdominal aorta aneurysm'/exp OR 'abdominal aorta aneurysm' OR 'endovascular surgery'/exp OR 'endovascular surgery' OR 'aorta aneurysm'/exp OR 'aorta aneurysm' OR evar:ab,ti OR endovascular:ab,ti OR ('aneurysm'/exp OR aneurysm AND repair:ab,ti) OR ('aneurysm'/exp OR aneurysm AND surgery:ab,ti) OR (aotic AND stent:ab,ti) OR (aortic AND ('stent'/exp OR stent) AND graft:ab,ti) OR aaa:ab,ti OR (aortic AND aneurysm:ab,ti) OR (aortic AND aneurysms:ab,ti) OR ('aorta'/exp OR aorta AND aneurysm:ab,ti) OR ('aorta'/exp OR aorta AND aneurysms:ab,ti))

APPENDIX II

Quality of the studies based on the criteria as proposed by the QUADAS checklists

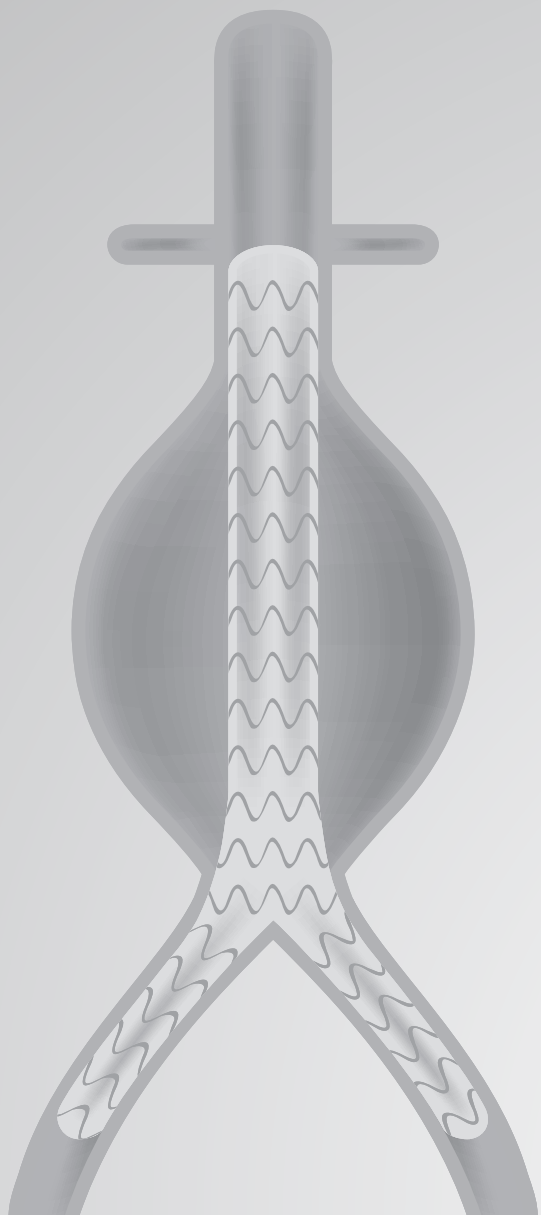
Author, journal, year	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14
Haulon, Eur. J. Vasc. Endovasc. Surg., 2001	Yes	Yes	Yes (DSA)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Cejna, Eur. Radiol., 2002	Yes	Unclear	Yes (CTA)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	Yes
Insko, Acad. Radiol., 2003	Yes	No	Yes(CTA/DSA)	Yes	Yes	No	Yes	Yes	Yes	Unclear	Unclear	Unclear	No	No
Ayuso, J. Magn. Reson. Imaging, 2004	Yes/No	Yes	Yes (CTA)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Ersoy, Eur. J. Radiol., 2004	Yes	Yes	Yes (CTA)	No	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Unclear	No	Yes
Pitton, Am. J. Roentgenol., 2004	Yes	Yes	Yes (CTA)	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	Unclear	Yes	No
Vd Laan, Eur. J. Vasc. Endovasc. Surg., 2006	Yes	Yes	Yes (CTA)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Alerci, Eur. Radiol., 2008	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Cornelissen, Invest. Radiol., 2010	No	Yes	Yes (CTA)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Wieners, Cardiovasc. Interv. Radiol., 2010	Yes	No	Yes (CTA)	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	No	No
Cantisani, Eur. J. Vasc. Endovasc. Surg., 2011	Yes	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	No	No

Questions according to the different items:

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Were selection criteria clearly described?
3. Is the reference standard likely to correctly classify the target condition?
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
6. Did patients receive the same reference standard regardless of the index test result?
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13. Were uninterpretable/ intermediate test results reported?
14. Were withdrawals from the study explained?

PART TWO

Dedicated imaging studies in EVAR patients



CHAPTER 7

MRI with a weak albumin-binding contrast agent has additional value for the detection of endoleaks in patients with enlarging aneurysm of unknown origin after EVAR

Manuscript in preparation

H.J.A. Zandvoort[1], J. Habets[2], F.L. Moll[1], L.W. Bartels[3], E.P.A. Vonken[2], T. Leiner[2], J.A. van Herwaarden[1]

[1] Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands
[3] Image Sciences Institute, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT

Objectives

Computed Tomography Angiography (CTA) is the current gold standard for the detection of endoleaks after endovascular aneurysm repair (EVAR) but can miss endoleaks, even in growing abdominal aortic aneurysms (AAA). The purpose of this study was to examine the additional value of (delayed phase) Magnetic Resonance Imaging (MRI) with a weak albumin-binding contrast agent in post-EVAR patients with aneurysm growth, but without certain endoleak on CTA.

Methods

A MRI scan was performed in all patients with AAA growth ≥5 mm after EVAR and no or uncertain endoleak on CTA in the period between April 2011 and August 2013. All MRI scans were performed on a 1.5-T clinical scanner after administration of a weak albumin-binding contrast agent (Multihance, gadobenate dimeglumine, Bracco, Italy). The presence of endoleaks was assessed by visually comparing pre-contrast and post-contrast T1-weighted images. Post-contrast images were acquired 5 and 15 minutes after contrast administration.

Results

Twenty-one patients (20 men) with a median age of 75 years (interquartile range (IQR) 68 - 79) were evaluated. Median interval between EVAR and MRI was 38 months (IQR 16 - 44). Median aneurysm growth during follow-up after EVAR was 11 mm (IQR 7 - 15). At CTA, 16 patients (76%) had no detectable endoleak. Five patients (24%) had suspected but uncertain endoleak. On the post-contrast MRI images, endoleak was observed in 15 patients (71%) and for all patients with uncertain endoleak on CTA, an endoleak was detected on MRI. Feeding vessels were detected in 10/15 patients (67%) and were all, except one, lumbar arteries.

Conclusions

In patients with enlarging aneurysms of unknown origin after EVAR, MRI with a weak albumin-binding contrast agent has strong additional value for both the detection and determination of the origin of the endoleak.

INTRODUCTION

Endovascular aneurysm repair (EVAR) is an suitable alternative for conventional open abdominal aortic aneurysm (AAA) repair. However, a relevant common complication after EVAR is the occurrence of endoleak. Although incidence of different endoleaks varies in literature and depends on patient selection and type of stent-graft used, it is assumed that type I endoleaks occur in 0% to 10% of the patients and the incidence of type II endoleaks ranges from 10% to 25%.[1] Type III and type IV endoleaks are less common with the use of recent generation stent-grafts.

Besides these four endoleak types, some authors consider endotension as the fifth endoleak type. Endotension is defined as continued pressurization of the aneurysm sac after EVAR treatment without endoleak detected on computed tomography angiography (CTA) images.[2] Recent results from a study investigating a multicenter patient population showed that the 5-year post-EVAR rate of AAA sac enlargement in a certain cohort of patients was 41%.[3] Since depressurization of the aneurysm sac to arrest aneurysm growth is the main goal of endovascular aneurysm repair, increasing aneurysm diameter after EVAR can be considered as failure of treatment.

Optimal non-invasive imaging is crucial to detect the exact cause of aneurysm sac enlargement and to determine the best treatment strategy. However, CTA is not always able to detect the endoleak, not even in the presence of growing aneurysms.[4] Prior work has shown that MRI is more sensitive than CTA for endoleak detection, especially for slow flow and type II endoleaks.[4] Besides standard gadolinium contrast agents, albumin-binding contrast agents can be used for MRI examinations.[5-7] The purpose of this study was to examine the additional value of Magnetic Resonance Imaging (MRI) with a weak albumin-binding contrast agent (gadobenate dimeglumine) for the detection of endoleaks in post-EVAR patients with aneurysm growth, but without or uncertain endoleak on CTA.

METHODS

Patient inclusion

This study included patients with continued aneurysm growth ≥ 5 mm after EVAR of an infrarenal aneurysm and treated with a nitinol endograft. Inclusion took place between April 2011 and August 2013. During regular CTA follow-up, all patients had no or uncertain endoleak and were therefore eligible for further evaluation with MRI.

Patients were excluded if they had MRI-specific contraindications as claustrophobia or MRI incompatible implants or stainless steel endografts. The study protocol was approved by the local medical ethics committee and all patient data were prospectively collected.

CTA

In our routine CTA follow-up after EVAR, an arterial and delayed phase CTA were performed. CTA scans were performed on a 256-slice CT scanner (Philips Medical Systems, Best, The Netherlands) with a standardized acquisition protocol. Scan parameters for arterial phase and

delayed phase (stated between parentheses) were: slice thickness, 0.9 mm (0.9 mm); collimation, 128 × 0.625 mm (128 × 0.625 mm); pitch, 0.2 (0.9) and rotation time 0.27 seconds (0.4 seconds). Radiation exposure parameters were 100 kVp in patients ≤70 kg and 120kVp ≤ 70 kg for arterial phase and 120 kVp for delayed phase with 200 mAs and 100 mAs respectively. An intravenous injection of 120 mL nonionic contrast (Ultravist-300, Bayer Schering Pharma, Berlin, Germany) was followed by a 60-mL saline chaser bolus at a rate of 6 mL/s.
The scan was started using bolus-triggering software with a threshold of 100 HU over baseline. The delayed phase scan was performed after a post-threshold delay of 50 s.

MRI

All MRI scans were performed on a 1.5-T clinical scanner (Ingenia (R4.2), Philips Healthcare, Best, The Netherlands) after administration of a weak albumin-binding contrast agent. A single dose of 0.15 mmol/kg gadobenate dimeglumine (Multihance, Bracco, Italy) was administrated at a rate of 1 mL/s followed by a 30 mL saline flush at a rate of 1 mL/s.
A 28-element phased-array body coil was used for signal reception. Pre-contrast and post-contrast T1-weighted fat suppressed dual-echo Dixon sequences were used to assess the presence of endoleaks.
Scan parameters were: TR/TE1/TE2/α 5.9 ms/1.8 ms/4.0 ms/15°; slice thickness 2mm, field of view 450x345mm^2, and acquisition time of 18 seconds. A regional saturation slab was located on the abdominal wall to prevent breathing artefacts. Post-contrast images were acquired 5 and 15 minutes after contrast administration.

Image analysis

The presence of endoleaks was assessed by visually comparing pre-contrast and post-contrast T1-weighted images. Endoleak was defined as high intensity signal inside the aneurysm sac on the post-contrast images not present on the pre-contrast images.
All MRI scans were first evaluated by a highly experienced cardiovascular MRI radiologist and all cases were then discussed in a multidisciplinary meeting with vascular surgeons and radiologist and final classification was reached by consensus. The scans were qualified as "endoleak", "uncertain endoleak", "no endoleak" or "not assessable ". The origin of the endoleak was also assessed and communicating arteries were scored as "origin visible", "probably origin visible" and "origin not visible".

Data presentation

Discrete variables are shown as number and percentages. Continuous variables are expressed as median values with interquartile range (IQR). Differences in diameter were assessed by non-parametric testing. Values of $P<.05$ were considered significant and all analyses were performed with SPSS statistics (version 20; IBM, Armonk, NY)

RESULTS

Baseline characteristics

Twenty-one patients (20 men; 95.2%) were included in this study and median age at time of EVAR was 75 years (IQR 68-79). Median preoperative diameter was 58 mm (IQR 55-66) and during a median follow-up of 38 months (IQR 16-44) the aneurysm diameter increased to 75 mm (IQR 62-79) (*P<0.001*). Sixteen patients (76%) had no detectable endoleak on their CTA examination prior to the MRI examination. All baseline characteristics are listed in Table 1.

MRI analysis

Twenty MRI examinations (95%) were appropriate for the analysis of endoleaks. One examination was not assessable due to motion artefacts. The remaining 20 examinations were of good quality for endoleak evaluation. All results are presented in Table 2.

An endoleak was observed in 15 patients (75%) on the post-contrast MRI images. An example is shown in Figure 1. Ninety-three per cent (14/15 patients) had a type II endoleak on the delayed post-contrast MRI images. One patient had a type II endoleak but had also some contrast enhancement at the proximal site of the aneurysm which could be possibly qualified as a type Ia endoleak.

For 10/15 patients with a type II endoleak, at least 1 feeding artery was visible. In all cases, except 1, the feeding artery was a lumbar artery. All patients that were included in this analysis because of uncertain endoleak on CTA (n=5) had a visible origin of their endoleak on MRI images and for 3/5 patients even multiple feeding arteries visible on MRI images were detected.

The patient with an uncertain endoleak on MRI was evaluated by digital subtraction angiography since he had 9 mm enlargement in 15 months after EVAR. During this angiography procedure a type II endoleak was detected and treated by coil embolization of the feeding lumbar artery.

Table 1. Baseline characteristics.

Parameter	N=21
Preoperative aneurysm diameter	58 mm (55-66)
Aneurysm diameter at last CTA	75 mm (62-79)
Aneurysm growth	11 mm (7-15)
Time between EVAR and MRI	38 months (16-44)
Time between last CTA and MRI	32 days (22-50)
Reason for inclusion	
Growth with no endoleak on CTA	16 (76%)
Growth with uncertain endoleak on CTA	5 (24%)

Values presented as median with interquartile range (IQR) or as absolute number with percentage (%)

Table 2. Results of endoleak detection by MRI.

Patient	FU time between EVAR and MRI(months)	Growth since EVAR (mm)	Endoleak detected by CTA	Endoleak detected by MRI	Type endoleak on MRI	Feeding artery visible
1	12	7	no	yes	II	yes
2	11	13	no	yes	II	probably
3	43	15	no	yes	II	no
4	17	11	uncertain	yes	II	yes
5	43	6	uncertain	yes	II	yes
6	39	15	uncertain	yes	II	yes
7	25	12	uncertain	yes	II	yes
8	22	7	no	no	-	-
9	21	12	uncertain	yes	II	yes
10	38	6	no	yes	II	probably
11	75	6	no	yes	II	probably
12	10	17	no	no	-	-
13	45	9	no	no	-	-
14	38	12	no	yes	II	probably
15	45	20	no	no	-	-
16	79	27	no	yes	II	yes
17	57	16	no	yes	II	yes
18	43	7	no	yes	I and II	yes
19	13	7	no	N/A	-	-
20	28	11	no	yes	II	yes
21	15	9	no	uncertain	-	-

N/A, not assessable

DISCUSSION

We demonstrated in this study that MRI with the use of a weak albumin-binding contrast (gadobenate dimeglumine) is able to detect additional endoleaks in patients with no or uncertain endoleak on CTA. In 15/21 (71%) patients an endoleak was detected. A previous study by Cornelissen and al. showed comparable results.[6] They studied 12 patients with non-shrinking aneurysms after EVAR and no evidence of endoleak on CTA. In 6 of 11 technical successful MRIs with the weak albumin-binding contrast agent gadofosveset trisodium (Vasovist; Bayer Schering Pharma, Berlin, Germany) endoleaks were detected by MRI.[6] Since this contrast agent was no longer commercially available we had to prove the value of another albumin-binding contrast agent in this study. The current used contrast agent, gadobenate dimeglumine, was previously used for endoleak detection by Alerci et al. and MRI with this contrast agent showed to be superior to CTA for endoleak detection.[5]

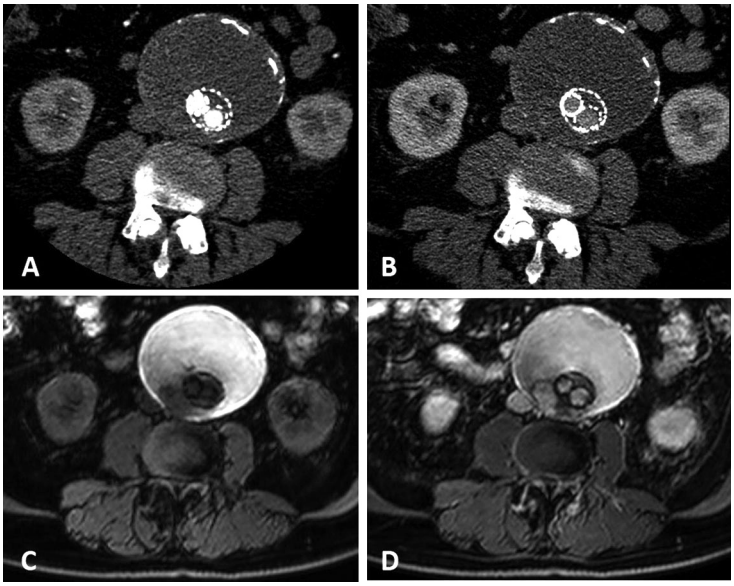


Figure 1. A patient post-EVAR with continued aneurysm growth with no endoleak on arterial phase (A) and late phase (B) CTA, and pre-contrast T1 fat suppressed images (C). The post-contrast T1 fat suppressed images (D) clearly demonstrated a type II endoleak originating from a lumbar artery.

In contrast to Alerci and coworkers who analyzed a series of patients in follow-up after EVAR, we included merely patients with aneurysm growth after EVAR and no or uncertain endoleak on CTA. This inclusion criteria was chosen since only for this group of patients a detected endoleak would have consequences for treatment.

One of the explanations for continued aneurysm expansion after EVAR without detectable endoleak is that this so-called endotension might actually be low-flow type II endoleaks below the detection limit of CTA.[8] Given the results of this study it seems a credible theory since we found in the majority of patients a type II endoleak.

However, 4/15 (19%) patients had no detectable endoleak on MRI. This ensures that other theories about the origin of endotension can not be ignored. A potential role is played by the intraluminal thrombus. Pressure may remain high in the excluded aneurysm sac due to transmission of the pressure through the intraluminal thrombus around graft attachment zones or through the permeable graft material.[8-10] In addition, it is known that intraluminal thrombus is associated with degeneration of the underlying vessel wall.[11, 12] Although this is highly speculative, intraluminal thrombus may possibly also contribute to further expansion of the aneurysm without the presence of endoleak.

The used protocol and contrast agent were reasonable for the determination of the origin of endoleaks. Detection of feeding vessels might improve the chance of successful treatment by superselective embolization as type II endoleaks are often fed by multiple vessels.[13]

For 10/15 patient with a type II endoleak, at least 1 feeding artery was visible. Gadobenate dimeglumine provides improved vascular enhancement in more distal vessels of the peripheral

circulation compared to standard extracellular gadolinium chelates.[14] Furthermore, in pedal arteries it was proven that MRI with Gadobenate dimeglumine was able to visualize significantly more patent vessels than selective digital subtraction angiography in the pedal arteries.[15]

The clinical significance of additional detected type II endoleaks in patients with aneurysm growth will be seen in the future. It is clear that for this group of patients, in accordance with the international guidelines, a secondary intervention is indicated because of continued expansion of the aneurysm.[16, 17] However, for the most common used techniques, transarterial and translumbar embolization, technical success rates appear to be good but clinical success varies widely in current literature.[18-21]

Sarac et al. described long-term follow-up results after embolization. After five years, freedom from explant was 88.8%, freedom from second embolization procedure 75.8% and freedom from continued sac growth was just 43.7%.[22]

This study has some limitations. First, we analyzed a small group of patients since growth after EVAR without endoleak on CTA is uncommon in our endovascular treated population. In addition, the time between CTA and MRI could possibly have some influence. Although we had the ambition to plan the MRI within 30 days after CTA this was not possible for all patients due to logistical reasons. With a delay between CTA and MRI it is theoretically possible that the endoleak arose in the intervening time although this is very unlikely.

For the surveillance after EVAR, CTA remains the current technique of choice. However, aneurysm sac enlargement is an occasionally occurring but clinically relevant phenomenon in patients after EVAR. When delayed phase CTA is not able or inconclusive to detect an endoleak in these group of patients, further analysis with MRI is useful. MRI with a weak albumin-binding contrast agent has strong additional value for both the detection and determination of the origin of the endoleak.

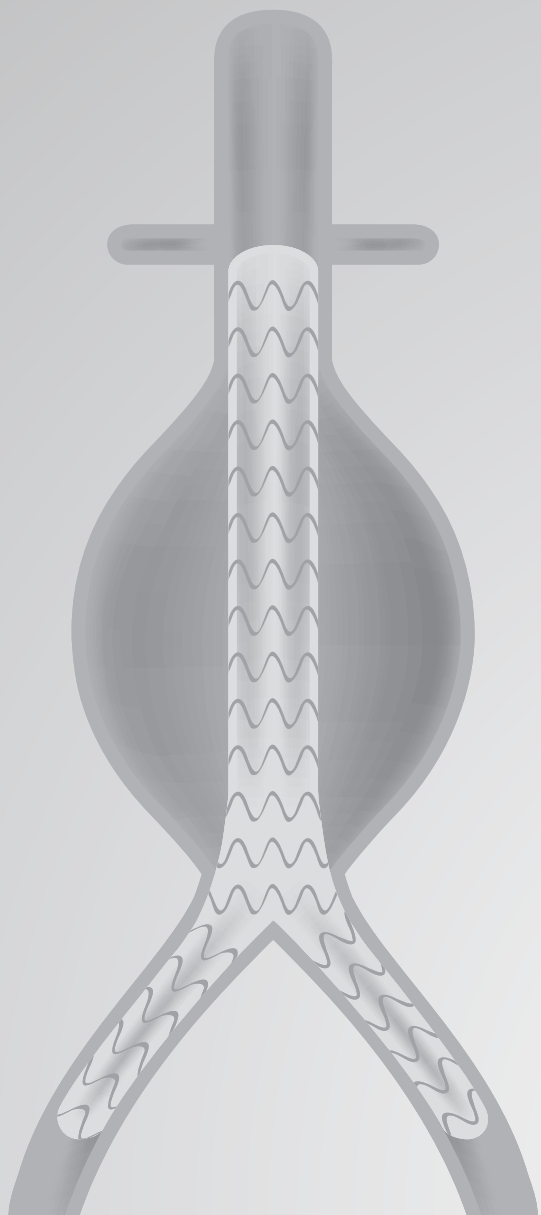
REFERENCES

1. Veith FJ, Baum RA, Ohki T, Amor M, Adiseshiah M, Blankensteijn JD, et al. Nature and significance of endoleaks and endotension: summary of opinions expressed at an international conference. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 2002;35(5):1029-35.
2. Gilling-Smith G, Brennan J, Harris P, Bakran A, Gould D, McWilliams R. Endotension after endovascular aneurysm repair: definition, classification, and strategies for surveillance and intervention. Journal of endovascular surgery : the official journal of the International Society for Endovascular Surgery. 1999;6(4):305-7.
3. Schanzer A, Greenberg RK, Hevelone N, Robinson WP, Eslami MH, Goldberg RJ, et al. Predictors of abdominal aortic aneurysm sac enlargement after endovascular repair. Circulation. 2011;123(24):2848-55.
4. Habets J, Zandvoort HJ, Reitsma JB, Bartels LW, Moll FL, Leiner T, et al. Magnetic resonance imaging is more sensitive than computed tomography angiography for the detection of endoleaks after endovascular abdominal aortic aneurysm repair: a systematic review. Eur J Vasc Endovasc Surg. 2013;45(4):340-50.
5. Alerci M, Oberson M, Fogliata A, Gallino A, Vock P, Wyttenbach R. Prospective, intraindividual comparison of MRI versus MDCT for endoleak detection after endovascular repair of abdominal aortic aneurysms. Eur Radiol. 2009;19(5):1223-31.
6. Cornelissen SA, Prokop M, Verhagen HJ, Adriaensen ME, Moll FL, Bartels LW. Detection of occult endoleaks after endovascular treatment of abdominal aortic aneurysm using magnetic resonance imaging with a blood pool contrast agent: preliminary observations. Invest Radiol. 2010;45(9):548-53.
7. Wieners G, Meyer F, Halloul Z, Peters N, Ruhl R, Dudeck O, et al. Detection of type II endoleak after endovascular aortic repair: comparison between magnetic resonance angiography and blood-pool contrast agent and dual-phase computed tomography angiography. Cardiovasc Intervent Radiol. 2010;33(6):1135-42.
8. White GH, May J, Petrasek P, Waugh R, Stephen M, Harris J. Endotension: an explanation for continued AAA growth after successful endoluminal repair. Journal of endovascular surgery : the official journal of the International Society for Endovascular Surgery. 1999;6(4):308-15.
9. Heikkinen MA, Arko FR, Zarins CK. What is the significance of endoleaks and endotension. Surg Clin North Am. 2004;84(5):1337-52, vii.
10. de Uhlenbrock AG, Wintzer C, Imig H, Morlock MM. Fluid transfer as a mechanism leading to endotension. Med Eng Phys. 2010;32(8):914-20.
11. Koole D, Zandvoort HJ, Schoneveld A, Vink A, Vos JA, van den Hoogen LL, et al. Intraluminal abdominal aortic aneurysm thrombus is associated with disruption of wall integrity. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 2013;57(1):77-83.
12. Kazi M, Thyberg J, Religa P, Roy J, Eriksson P, Hedin U, et al. Influence of intraluminal thrombus on structural and cellular composition of abdominal aortic aneurysm wall. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 2003;38(6):1283-92.
13. Baum RA, Stavropoulos SW, Fairman RM, Carpenter JP. Endoleaks after endovascular repair of abdominal aortic aneurysms. J Vasc Interv Radiol. 2003;14(9 Pt 1):1111-7.
14. Wyttenbach R, Gianella S, Alerci M, Braghetti A, Cozzi L, Gallino A. Prospective blinded evaluation of Gd-DOTA- versus Gd-BOPTA-enhanced peripheral MR angiography, as compared with digital subtraction angiography. Radiology. 2003;227(1):261-9.
15. Kreitner KF, Kunz RP, Herber S, Martenstein S, Dorweiler B, Dueber C. MR angiography of the pedal arteries with gadobenate dimeglumine, a contrast agent with increased relaxivity, and comparison with selective intraarterial DSA. J Magn Reson Imaging. 2008;27(1):78-85.
16. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1-S58.

17. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 2009;50(4 Suppl):S2-49.
18. Baum RA, Carpenter JP, Golden MA, Velazquez OC, Clark TWI, Stavropoulous SW, et al. Treatment of type 2 endoleaks after endovascular repair of abdominal aortic aneurysms: Comparison of transarterial and translumbar techniques. Journal of Vascular Surgery. 2002;35(1):23-9.
19. Nevala T, Biancari F, Manninen H, Aho PS, Matsi P, Makinen K, et al. Type II endoleak after endovascular repair of abdominal aortic aneurysm: effectiveness of embolization. Cardiovasc Intervent Radiol. 2010;33(2):278-84.
20. Gorich J, Rilinger N, Sokiranski R, Kramer S, Schutz A, Sunder-Plassmann L, et al. Embolization of type II endoleaks fed by the inferior mesenteric artery: using the superior mesenteric artery approach. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2000;7(4):297-301.
21. Sheehan MK, Barbato J, Compton CN, Zajko A, Rhee R, Makaroun MS. Effectiveness of coiling in the treatment of endoleaks after endovascular repair. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 2004;40(3):430-4.
22. Sarac TP, Gibbons C, Vargas L, Liu J, Srivastava S, Bena J, et al. Long-term follow-up of type II endoleak embolization reveals the need for close surveillance. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 2012;55(1):33-40.

PART THREE

Clinical outcome after EVAR



CHAPTER 8

Results of endovascular repair of infrarenal aortic aneurysms using the Endurant stent graft

Accepted with revisions in J Vasc Surg.

H.J.A. Zandvoort[1], F. Bastos Gonçalves[2], H.J.M. Verhagen[2], D.A.B. Werson[3], F.L. Moll[1], J.P.P.M. de Vries[3], J.A. van Herwaarden[1]

[1] Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Department of Vascular Surgery, Erasmus Medical Center, Rotterdam, The Netherlands
[3] Department of Vascular Surgery, St.Antonius Hospital, Nieuwegein, The Netherlands

ABSTRACT

Objective

Recent reports showed that the Endurant stent graft is safe and effective for endovascular repair (EVAR) of abdominal aortic aneurysms (AAA). However, due to its relatively recent introduction, only short-term follow-up (FU) data is available so far. This study presents the 4-year results using this device.

Methods

All clinical data including detailed anatomical information of the first 100 consecutive patients treated with the Endurant stent graft for an infrarenal AAA in three Dutch high volume hospitals were prospectively collected. Computed tomographic angiography (CTA) was routinely performed before the procedure, within 1 month, and at 1-year post-EVAR. Thereafter the imaging modality during yearly follow-up was individualized (duplex ultrasonography or CTA). Study endpoints were primary clinical success, overall and AAA related mortality and sac morphology changes and endoleak during follow-up. Estimates were obtained using Kaplan-Meier plots.

Results

100 consecutive patients (88 men) with a median age of 74 years (67-79) and median AAA diameter of 58 mm (55-65) were included between December 2007 and March 2009. 19 patients (19%) were treated outside the instructions for use. Median follow-up was 48 months (interquartile range: 36-53) and no patients were lost. One contained rupture was observed after 1.5 months due to graft-infection. None of the patients had graft migration and 2 type Ia endoleaks and 5 type Ib endoleaks were found. Primary clinical success was 97% at 1 year, 90% at 2 years, 84% at 3 years and 77% at 4 years. Twenty-seven secondary interventions were performed in 19 patients: 1 conversion, 6 type II embolizations, 8 limb extensions, 6 endovascular treated limb occlusions, 3 proximal cuffs and 3 other secondary interventions. Over time, maximum aneurysm diameter decreased ≥5 mm since initial EVAR in 58% of the patients and remained stable in 32%, while 10% of the patients had growth ≥5mm. All-cause mortality was 12% at 1 year, 16% at 2 years, 18% at 3 years and 20% at 4 years, with a 3% AAA-related mortality at 4 years.

Conclusions

This study reveals the 4-year follow up data of the Endurant stent graft for AAA treatment. Although this stent graft has a more liberal instructions for use compared to most competitors, its use results in a very low AAA-related mortality with adequate prevention of rupture or aneurysm growth. Although patients with very challenging anatomy were treated in our series, secondary intervention rates were comparable for patients treated within IFU and outside IFU.

INTRODUCTION

Endovascular aneurysm repair (EVAR) is increasingly seen as the primary choice of treatment for abdominal aortic aneurysms (AAA) for patients who are anatomically suitable for endovascular repair.[1] Since the introduction of the latest generation stent grafts, also patients with shorter or more angulated proximal aortic necks or tortuous, small or calcified iliac arteries can be safely treated endovascularly.[2] The Endurant stent graft (Medtronic Cardiovascular, Santa Rosa, CA, USA) has received FDA approval in December 2010 and is widely used for EVAR.
Recent results showed that this device is safe and effective in the short-term for treatment of patients with AAAs.[3-7] However, due to its relatively recent introduction, only short-term follow-up (FU) data is available. Introduction in Europe, however, dates from early 2008 and longer-term results from this geographic region are now starting to arise. These are necessary to assess the durability of treatment with this particular stent graft. Therefore, the purpose of this study was to analyze the 4-year results of our first 100 consecutive patients[7] treated with an Endurant graft for an abdominal aortic aneurysm.

METHODS

Patients
This study is a FU study of the cohort described by van Keulen et al. in September 2011.[7] The first 100 consecutive patients who were electively treated with the Endurant stent graft for an infrarenal aneurysm in three Dutch high volume and tertiary vascular referral hospitals (University Medical Center, Utrecht, Erasmus University Medical Center, Rotterdam and St. Antonius Hospital, Nieuwegein) were included.

Follow-up
All clinical data, as well as imaging FU data of these first 100 consecutive patients were prospectively collected in a database. Regular FU was performed at 1 month and 12 months post-EVAR, and yearly thereafter. Computed tomographic angiography (CTA) was routinely performed within 1 month after the EVAR procedure and at 1-year post-EVAR. For subsequent annual FU visits the choice of imaging modality was individualized (duplex ultrasonography or CTA), according to local protocols.
All available CTA datasets of included patients were transferred to a workstation (3Mensio Medical Imaging BV, Bilthoven, The Netherlands) for analysis with the support of a 3D reconstruction with central lumen line. Measurements were performed by experienced physicians and also pre-EVAR CT-scans have been evaluated for baseline aortic anatomy. The following characteristics were investigated on the CTA scans: AAA diameter, existence of endoleaks, patency of renal arteries, diameter of the AAA neck and distance from the most distal renal artery to the most proximal stent graft ring. The CTA scans were also checked for any other EVAR-related complications.
Duplex ultrasonography (DU) was performed by experienced operators and data about maximum aneurysm diameter, patency of the endograft and patency of the native iliac / femoral arteries

as well as any detectable endoleaks were obtained from the ultrasound report. In case of doubt or complication at Duplex imaging an additional CT scan was performed.
Furthermore, all complications, secondary interventions, outpatient department visits, readmissions, deaths and causes of death were documented and analyzed. Causes of death at another place than the initial treating hospital were investigated by contacting the treating general practitioner or responsible medical specialist in case of death.
The primary study endpoint was primary clinical success, as defined in the reporting standards for endovascular aortic aneurysm repair.[8] Secondary endpoints were overall and AAA related mortality and sac morphology changes and the occurrence of endoleak. The morphology of the proximal aneurysm neck of the study patients was classified as within or outside the IFU of the Endurant stent graft, IFU criteria were proximal neck length ≥10 mm with non-significant calcification, and/or non-significant thrombus with ≤60° infrarenal and ≤45° suprarenal angulation, or proximal neck length ≥15 mm with non-significant calcification, and/or non-significant thrombus with ≤75° infrarenal and ≤60° suprarenal angulation and neck diameter 19-32 mm. We defined <50% calcification and <50% thrombus as non-significant. Neck calcification and thrombus were measured 10 mm below the most distal renal artery and defined as the percentage of the circumference calcified or covered with thrombus, respectively.
Sac growth was considered if the maximum aneurysm diameter increased by 5mm or more compared to the first post-operative exam. Sac shrinkage was considered if the maximum diameter was reduced by 5mm or more. Definitions for complications and secondary interventions were coded and described according to the reporting standards for EVAR.[8]
The decision to treat an endoleak was taken according to the most recent guidelines.[9, 10] This resulted in treatment of all potential type I and III endoleaks. Type II endoleaks were only treated if they were associated with aneurysm growth and type II endoleaks without increased sac diameter were observed. The decision to treat limb occlusion or stenosis was based on the presence of clinical symptoms.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR) for not normally distributed variables. Differences were assessed by non-parametric testing. Categorical variables are presented as number and percentage.
The Kaplan-Meier (KM) method was used to assess primary clinical success and cumulative rates of survival. The log-rank test was used to compare KM estimates between patients that where treated within IFU and outside IFU.
Significance was assumed at $P \leq 0.05$. Statistical analysis was performed with SPSS software (SPSS statistics, version 20; IBM, Armonk, NY).

RESULTS

100 consecutive elective patients (88 men) were treated with the Endurant stent graft between December 2007 and March 2009. The median age was 74 years (IQR 67-79) and pre-operative screening for comorbidities showed that most of the patients had mild to severe systemic

disease (ASA I 6%, ASA II 45%, ASA III 48% and ASA IV 1%). The median AAA diameter was 58 mm (55-65). All other baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics.

Parameter	**Median (IQR)**	
Maximum diameter, mm	58 (55-65)	
Neck length (mm)	34 (22-43)	
Neck Diameter (mm)	27 (25-28)	
Neck Calcification (n)		
<25%	83	
25-50%	13	
50-75%	4	
>75%	0	
Neck Thrombus (n)		
<25%	64	
25-50%	20	
50-75%	8	
>75%	8	
Suprarenal Angulation (°)	23 (8-38)	
Infrarenal Angulation (°)	41 (25-61)	
	Right	**Left**
Diameter of the CIA (mm)		
1 cm	13 (16-20)	14 (16-19)
3 cm	14 (16-20)	14 (16-19)
5 cm	14 (16-19)	14 (16-19)
Diameter of the EIA (mm)	10 (9-12)	10 (9-11)
Male sex	88 (88%)	
Hypertension	54 (54%)	
Smoking	45 (45%)	
Diabetes	18 (18%)	
ASA classification		
I	6 (6%)	
II	45 (45%)	
III	48 (48%)	
IV	1 (1%)	

Abbreviations: CIA, common iliac artery; EIA, external iliac artery; ASA, American Society of Anesthesiologists.
Data are presented as median (IQR) or as number of patients positive for the variable (%).
Neck calcification and thrombus are measured 10 mm below the most distal renal artery and defined as the percentage of the circumference calcified or covered with thrombus, respectively.
Diameters of the common iliac arteries were measured 1, 3, and 5 cm distally of the aortic bifurcation, and the diameters in the external iliac arteries were measured 1 cm distally of the iliac bifurcation.

Table 2. Endoleaks during follow-up.

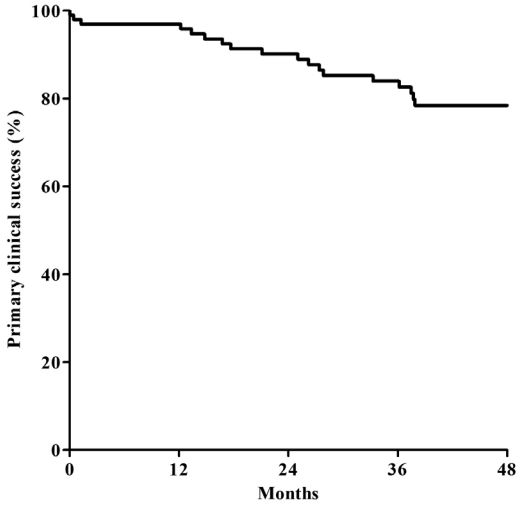
	Shrinkage ≥5 mm	Stable	Growth ≥5 mm
Type Ia endoleak (n, %)	-	-	2 (2%)
Type Ib endoleak (n, %)	-	-	5 (5%)[a]
Persisting type II endoleak after 30 days (n, %)	4 (4%)	5 (5%)	6 (6%)

[a]1 patient had both a type Ib and a type II endoleak but is shown as type Ib endoleak since that was the most likely cause of growth

Nineteen of the 100 included patients with AAAs had at least one anatomic characteristic that was considered a violation of the IFU of the Endurant stent graft : 3 patients had an aneurysm neck diameter > 32 mm, 1 patient had a suprarenal neck angulation > 60°, and 10 patients had an infrarenal neck angulation > 75°, 1 patient had an aneurysm neck length of 9 mm, and 1 patient had an aneurysm neck length of 12 mm along with an infrarenal angulation > 60°.
Furthermore, 3 patients had more than one anatomic characteristic outside the IFU of the Endurant. (all three patients had a suprarenal neck angulation > 60° combined with an infrarenal neck angulation > 75°).
The median FU was 48 months (IQR 36-53 months, maximum 62 months) and no patients were lost. Follow-up was >12 months in 88 patients, >24 months in 81 patients, >36 months in 73 patients and >48 months in 48 patients.
The median diameter of the aneurysm sac decreased from 58 mm (55-65 mm) preoperative to 51 mm (42-60 mm; P <.001) during FU. In total, 22 endoleaks (2 type Ia, 5 type Ib and 15 type II) were detected during follow-up (Table 2).

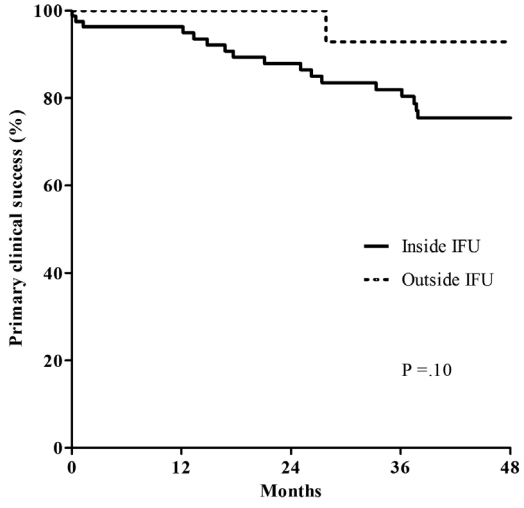
Primary clinical success

Primary clinical success (Figure 1) was 97% at 1 year, 90% at 2 years, 84% at 3 years and 77% at 4 years. When patients treated outside the IFU were compared to patients treated within the IFU, no difference was observed for primary clinical success rates. (Figure 2). One patient treated outside the IFU had a secondary intervention (for a type Ib endoleak with growth).
During follow-up, secondary procedures were performed in 19 patients (19%). In total, 27 reinterventions were performed (2 patients required 2 reinterventions and 3 patients required 3 reinterventions) (Table 3).
In 13 patients, the secondary intervention was performed for an endoleak combined with growth of the aneurysm. Further growth was arrested in 7 patients (62%) and there was shrinkage ≥5mm in 3 patients (23%). Enlargement continued in 2 patients (15%) (a patient with a type Ia endoleak and infected stent graft and a patient who underwent embolization of a type II endoleak). The patient without a detectable endoleak and growth was kept under strict surveillance.
Proximal cuff placement was performed in 3 patients after 38 days, 13 months and 41 months. All patients had aneurysm enlargement after EVAR (respectively 30 mm, 13 mm and 10 mm). The patient with 13 mm enlargement required a balloon expandable stent in the extension cuff 16 months after cuff placement and reballooning after 19 months due to a continuing type Ia endoleak.



No. At risk	100	88	75	62	38
SE.	.02	.03	.04	.05	.07

Figure 1. Primary clinical success
Kaplan-Meier survival curve shows primary clinical success during follow-up after endovascular aneurysm repair (EVAR). *SE*, Standard error.



No. At risk inside IFU	81	71	60	52	31
SE.	.02	.04	.05	.06	.08
No. At risk outside IFU	19	17	15	10	7
SE.	.00	.00	.07	.07	.07

Figure 2. Primary clinical success according to IFU groups
Kaplan-Meier survival curves show primary clinical success in patients treated inside IFU and outside IFU criteria during follow-up after endovascular aneurysm repair (EVAR). SE, Standard error.

Table 3. Secondary procedures.

Procedure	No. of procedures	Timepoint during FU (months)
Proximal cuff placement	3	1, 13, 41
Limb extension	**8**	21, 28, 33, 40, 54, 57
- Type Ib endoleak	*6*	15, 52
- Short sealing	*2*	
Embolization for type II endoleak	6	17, 18, 25, 26, 36, 38
Conversion for infected stent graft	1	21
Treatment for iliac limb occlusion	**6**	
- Embolectomy	*2*	Day 1 postoperative, 12
- Thrombolysis	*4*	19, 22, 37, 52
Other procedures	**3**	
- Balloon expandable stent for continuing type Ia endoleak	*1*	29
- Reballooning stent for continuing type Ia endoleak	*1*	32
- Graft limb stenting with a new graft limb because of <50% symptomatic stenosis	*1*	27

Secondary procedures performed during follow-up

The third patient had 10 mm growth in 1 year and except the presence of a type II endoleak which was present in all postoperative CTAs, progressive dilatation of the proximal neck resulted in insufficient seal length, and the presence of an occult type-Ia endoleak was suspected. In this context, a fenestrated cuff was placed and further aneurysm growth was arrested despite the presence of the type II endoleak.

A limb extension procedure was performed in 7 patients and was successfully placed in all cases. 5 patients (5%) were treated for a type Ib endoleak and 2 patients (2%) for short distal sealing. Five patients (71%) had the required 15 mm sealing according to the IFU, but the distal sealing zone turned out to be insufficient after a median follow-up of 33 months. Four patients with a type Ib endoleak had also continuing dilatation of the iliac arteries during follow-up indicating progression of the aneurysmatic disease. Data on sealing lengths and initial oversizing for all these patients are shown in Table 4.

Furthermore, in 4 patients (4%) an endograft limb occlusion occurred during follow-up. Three of them were successfully treated endovascularly while in the remaining patient endovascular therapy failed. One patient developed 2 re-occlusions, 7 and 10 months after the first embolectomy. All 4 patients were treated within IFU for the Endurant stent graft.

Mortality and aneurysm-related death

Nineteen patients (19%) died during follow-up. Causes of death were aneurysm related (n=3), malignancy (n=3), sepsis (n=3; 1 from respiratory, 1 gastrointestinal and 1 unknown focus), cardiac disease (n=2), gastrointestinal bleeding (n=1), pre-operatively existent renal insufficiency (n=1) and unknown (n=6). Two of the 3 aneurysm related deaths occurred within 30 days from the initial EVAR procedure. One patient (treated within IFU) developed an arterial occlusion in his lower leg 10 days postoperatively. After the start of heparin therapy, the patient suddenly became hemodynamically unstable. Autopsy showed that the cause of death was a gastrointestinal bleeding. The other patient (also treated within IFU) developed ventricular

tachycardia with a low-flow state one day postoperatively. This probably caused the occlusion of one of the limbs of the stent graft, which resulted in an ischemic leg. An embolectomy to solve this occlusion failed and the patient rejected further treatment, eventually dying 15 days after EVAR due to ischemic complications.

The third aneurysm related death occurred in the sequence of endograft infection. The patient (also within IFU) was re-administered to the hospital 38 days after EVAR because of abdominal complaints and high fever. On CTA examination, a large type Ia endoleak combined with a contained AAA rupture was observed. Due to stent graft infection the aneurysm had grown with complete disappearance of the infrarenal aneurysm neck. The patient's condition did not permit conversion to open stent graft removal and was therefore treated by proximal cuff placement with intentional coverage of the renal arteries. The patient received intravenous antibiotics but this couldn't prevent death from sepsis, 65 days after the initial EVAR. All 3 aneurysm related mortalities occurred within the first year of FU. Overall patient survival rates (Figure 3) were 88% at 1 year, 84% at 2 years, 82% at 3 years and 80% at 4 years.

In the patients that died from unknown causes, aneurysm related death was unlikely since all patients did not demonstrate AAA enlargement at their latest FU moment and only one patient had a demonstrable complication (a type-II endoleak without sac enlargement) on their last imaging surveillance exam.

Table 4. Patients with distal extension.

	Indication	Sufficient distal oversizing [c]	Aneurysm growth at moment of intervention	Sealing length postoperative R/L iliac	Sealing length before intervention R/L iliac	Sealing length after intervention R/L iliac
Patient 1	type Ib endoleak, progressive disease iliac artery	No	Growth	39 / 12	10 / 0	12 / 30
Patient 2	type Ib endoleak, progressive disease iliac artery	No	Growth	0 / 3	0 / 0	24 / 10
Patient 3 [b]	type Ib endoleak left, type Ib endoleak right, progressive disease iliac artery	Yes	Growth	30 / 28	15 / 0 0 / 38	16 / 43 N/A [a]
Patient 4	type Ib endoleak	Yes	Growth	16 / 22	13 / 0	34 / 76
Patient 5	type Ib endoleak, progressive disease iliac artery, retraction of the stent graft	No	Growth	13 / 25	0 / 0	44 / 58
Patient 6	short iliac seal	No	Growth	26 / 3	25 / 0	11 / 23
Patient 7	short iliac seal	No	Shrinkage	17 / 14	13 / 2	N/A [a]

[a] Only a duplex was performed after the secondary intervention
[b] The left limb was extended 40 months after EVAR and the right limb after 57 months
[c] Sufficient oversizing was defined as ≥10% oversizing of the iliac graft component in relation to the actual measured vessel diameter over a length of at least 15 mm in the common iliac artery

Aneurysm sac behavior and endoleak

The median diameter of the aneurysm sac decreased from 58 mm (55-65 mm) preoperative to 51 mm (42-60 mm; P < .001) during FU. Fourteen patients (14%) had at any moment during FU growth ≥5mm. Six of these patients (43%) had a type II endoleak and 1 patient had both a type Ib and type II endoleak. A type Ia endoleak was detected in 2 patients and 4 patients had a type Ib endoleak (Table 2). There was 1 patient with no detectable endoleak on CTA. On the last available imaging FU, maximum aneurysm diameter decreased ≥5 mm since initial EVAR in 58% of the patients and remained stable in 32%, while 10% of the patients had growth ≥5mm.

DISCUSSION

As far as we know, this study reveals the longest FU data so far of the Endurant stent graft for AAA treatment. The 1-year follow-up results were published in 2011 when the first 100 consecutive patients of 3 Dutch high volume hospitals had had their 1 year follow-up visit.[7] In the current manuscript we analyzed the mid-term follow-up results of these patients after a median follow-up of 48 months.

Primary clinical success was 97% at 1 year, 90% at 2 years, 84% at 3 years and 77% at 4 years. At a median FU of 48 months maximum aneurysm diameter decreased ≥5 mm since initial EVAR in 58% of the patients and remained stable in 32%, while 10% of the patients had growth ≥5mm. It is important to mention that this study also includes patients with a challenging anatomy for endovascular repair of an infrarenal AAA. As showed in our previous study[7], up to 48% of the patients would be outside the instructions for use depending on which of the, at that time commercially available, stent grafts would have been implanted. (48% outside the IFU of the Zenith stent graft, 40% outside the IFU for the Excluder stent graft and 27% outside the IFU for the Talent stent graft).

Even with the generally more liberal IFU of the Endurant stent graft, 19% of patients were outside this device´s recommendations. However, this does not affect the results. All aneurysm related deaths were treated within IFU and, as demonstrated in Figure 2, secondary intervention rates were comparable for patients treated within or outside IFU.

Considering the possible increase in complication rates resulting from the challenging anatomy presented in this cohort, this study revealed very low AAA-related mortality. All-cause mortality was 20% after 4 years with only a 3% AAA-related mortality at 1 and 4 years, all cases being either perioperative deaths or resulting of infection. The all-cause mortality rate, despite comparable or lower to more historical series[11, 12], can still be considered significant. This is possibly explained by the age and co-morbidities of this population, reflected in the ASA classification (48% of the patients were ASA III). Moreover, most patients died during the first year of follow-up (all-cause mortality 12% after 1 year) and no aneurysm related deaths were seen anymore thereafter.

Globally, a significant reduction in median AAA aneurysm diameter was observed over time (from 58 mm to 51 mm, P < .001). The diameter remained stable in one third of patients and nearly 60% had shrinkage >5 mm, suggesting successful aneurysm exclusion in a high percentage of patients. The rates of mid to long-term sac shrinkage in this cohort appears

comparable to previously reported rates of other stent grafts (60.9% after 3 years, 62.2% after 5 years and 63% after 5 years).[13-15]

Overall, in 15 patients a persisting isolated type II endoleak was detected. Most of these patients had a stable (5/15; 33%) or an enlarging aneurysm diameter (6/15; 40%). However, 4/15 (27%) patients had a type II endoleak while the aneurysm diameter decreased > 5 mm. This seems to be contradictory, but perhaps the decreased pressure in the aneurysm sac due to the low porosity of the fabric contributes more to the aneurysm sac size than the presence of a type II endoleak in these patients.

In 19 patients, one or multiple secondary procedures were performed. Primary clinical success after 4 years was 77%. This rate is comparable to other series with different devices after 4 years.[13, 16, 17] Secondary interventions were generally successful, particularly the interventions carried out for endoleaks combined with growth of the aneurysm. In 85% of the cases, the aneurysm growth was stopped or even shrinkage was shown. This underlines the importance of an adequate follow-up so that problems can be detected and treated.

In 4 patients (4%) an endograft limb occlusion occurred. Although this occlusion rate of 4% is comparable to other studies with this stent graft, [3, 5, 18] it is still substantial.

We recently specifically looked into the occlusions and suggest that the occlusion rate may be reduced by a more liberal intraoperative and early postoperative (re)intervention strategy.[18] The inclusion of patients with unfavorable anatomy and obstructive disease may probably also contribute to an increased chance of endograft occlusion, even if they are considered within IFU.[18]

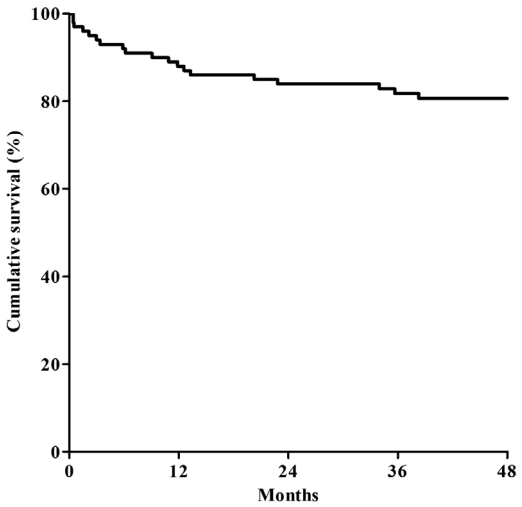


Figure 3. Overall survival
Kaplan-Meier survival curve shows overall survival after endovascular aneurysm repair (EVAR). SE, Standard error.

Despite the fact that most cases of stent graft occlusion have been suggested to occur due to technical errors,[18] review of the first post-operative CTA scans could not identify any anatomical or technical reasons that could have led to the occlusion of a limb during follow-up in one case. However, in the patient with the ventricular tachycardia it is likely that the occlusion is caused as a result of the low flow state. One other patient with a limb occlusion suffered from several other occlusions at different arteries as well despite the combined use of dipyridamole and acetylsalicylic acid. This possibly indicates a coagulation disorder although this was not demonstrated.

The number of distal extensions required after implantation was relatively high in this study population. Five patients underwent a secondary intervention for a type Ib endoleak and also 2 for short distal sealing of the graft. In 5 of 7 patients (71%) the IFU criteria for distal fixation (≥15 mm sealing and 10% to 25% oversizing) could not be met and the distal sealing zone shortened during FU causing in 5 patients an type Ib endoleak. This was in 4 of these 5 patients accompanied by a dilatation of their iliac arteries. Disease progression could possibly have led to further dilatation so that the sealing waned and an endoleak could arise. Another opportunity is that due to insufficient oversizing a type Ib endoleak could appear resulting in growth of the aneurysm by increased intrasac pressure.

The patient with no sealing in the right limb at the first post-operative CTA 1 month after EVAR could be considered as technical failure. The iliac sealing was probably too short by misinterpretation of the fluoroscopy images during the initial EVAR procedure.

Based on our experience with loss of distal seal during FU, we enhanced the focus on distal fixation and sealing and now try to achieve a distal landing zone of at least 30 mm.

Although all data were prospectively collected in a multicentre cohort, one of the limitations of this study is the relatively small number of patients and the retrospective analysis. In addition, this study describes the first experience with the Endurant stent graft in all 3 participating hospitals. We expect that results may further improve as experience with this stent graft increases. An example is our extra attention regarding the length of the distal landing zone.

Another limitation is the individualized choice of imaging modality according to local protocols in the different hospitals. Especially for follow-up visits after several years without any imaging complication duplex ultrasound was often used. Although this avoids radiation exposure to patients duplex ultrasound is less sensitive than CTA for the detection of endoleaks.[19]

CONCLUSIONS

This study reveals the 4-year follow up data of the Endurant stent graft for AAA treatment. Although this stent graft has a more liberal instructions for use compared to most other contemporary devices, its use results in a very low AAA-related mortality with adequate prevention from rupture or aneurysm growth. Although patients with challenging anatomy were treated in our series, secondary intervention rates were comparable for patients treated within and outside IFU. The number of distal extensions required after implantation was relatively high in this study population but the knowledge of the present results might aid in improving outcomes in future.

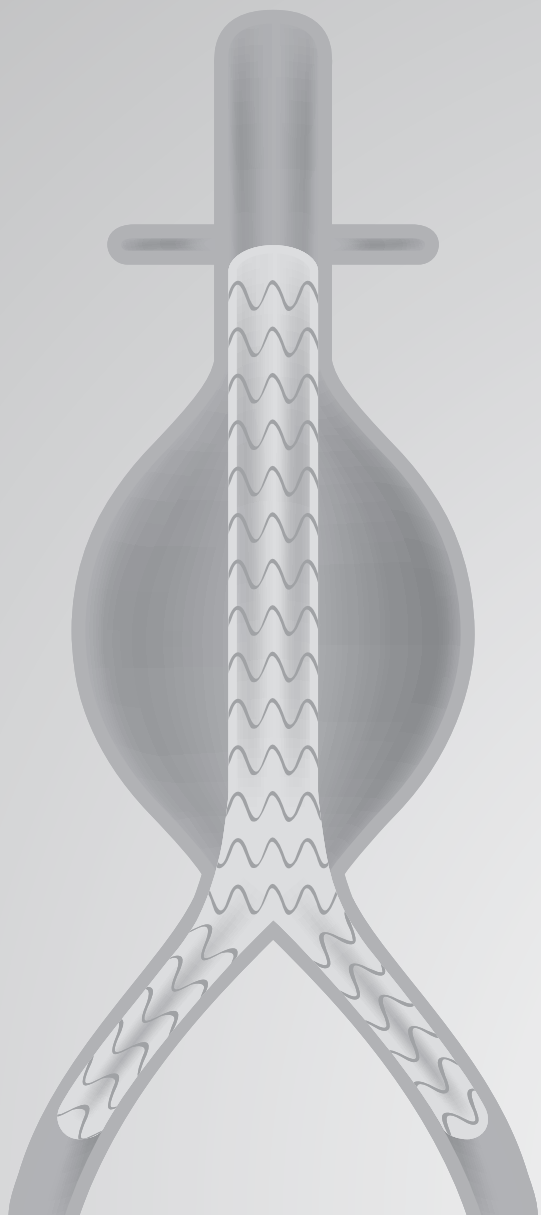
REFERENCES

1. Sachs T, Schermerhorn M, Pomposelli F, Cotterill P, O'Malley J, Landon B. Resident and fellow experiences after the introduction of endovascular aneurysm repair for abdominal aortic aneurysm. J Vasc Surg. 2011;54(3):881-8.
2. Verhagen HJ, Torsello G, De Vries JP, Cuypers PH, Van Herwaarden JA, Florek HJ, et al. Endurant stent-graft system: preliminary report on an innovative treatment for challenging abdominal aortic aneurysm. J Cardiovasc Surg (Torino). 2009;50(2):153-8.
3. Makaroun MS, Tuchek M, Massop D, Henretta J, Rhee R, Buckley C, et al. One year outcomes of the United States regulatory trial of the Endurant Stent Graft System. J Vasc Surg. 2011;54(3):601-8.
4. Rouwet EV, Torsello G, de Vries JP, Cuypers P, van Herwaarden JA, Eckstein HH, et al. Final results of the prospective European trial of the Endurant stent graft for endovascular abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 2011;42(4):489-97.
5. Stokmans RA, Teijink JA, Forbes TL, Bockler D, Peeters PJ, Riambau V, et al. Early results from the ENGAGE registry: real-world performance of the Endurant Stent Graft for endovascular AAA repair in 1262 patients. Eur J Vasc Endovasc Surg. 2012;44(4):369-75.
6. Troisi N, Torsello G, Donas KP, Austermann M. Endurant stent-graft: a 2-year, single-center experience with a new commercially available device for the treatment of abdominal aortic aneurysms. J Endovasc Ther. 2010;17(3):439-48.
7. van Keulen JW, de Vries JP, Dekker H, Goncalves FB, Moll FL, Verhagen HJ, et al. One-year multicenter results of 100 abdominal aortic aneurysm patients treated with the Endurant stent graft. J Vasc Surg. 2011;54(3):609-15.
8. Chaikof EL, Blankensteijn JD, Harris PL, White GH, Zarins CK, Bernhard VM, et al. Reporting standards for endovascular aortic aneurysm repair. J Vasc Surg. 2002;35(5):1048-60.
9. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg. 2009;50(4 Suppl):S2-49.
10. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1-S58.
11. De Bruin JL, Baas AF, Buth J, Prinssen M, Verhoeven EL, Cuypers PW, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med. 2010;362(20):1881-9.
12. Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med. 2010;362(20):1863-71.
13. Mertens J, Houthoofd S, Daenens K, Fourneau I, Maleux G, Lerut P, et al. Long-term results after endovascular abdominal aortic aneurysm repair using the Cook Zenith endograft. J Vasc Surg. 2011;54(1):48-57 e2.
14. Pitton MB, Scheschkowski T, Ring M, Herber S, Oberholzer K, Leicher-Duber A, et al. Ten-year follow-up of endovascular aneurysm treatment with Talent stent-grafts. Cardiovasc Intervent Radiol. 2009;32(5):906-17.
15. Hogg ME, Morasch MD, Park T, Flannery WD, Makaroun MS, Cho JS. Long-term sac behavior after endovascular abdominal aortic aneurysm repair with the Excluder low-permeability endoprosthesis. J Vasc Surg. 2011;53(5):1178-83.
16. Bastos Goncalves F, Jairam A, Voute MT, Moelker AD, Rouwet EV, ten Raa S, et al. Clinical outcome and morphologic analysis after endovascular aneurysm repair using the Excluder endograft. J Vasc Surg. 2012;56(4):920-8.
17. Verhoeven BA, Waasdorp EJ, Gorrepati ML, van Herwaarden JA, Vos JA, Wille J, et al. Long-term results of Talent endografts for endovascular abdominal aortic aneurysm repair. J Vasc Surg. 2011;53(2):293-8.
18. van Zeggeren L, Bastos Goncalves F, van Herwaarden JA, Zandvoort HJ, Werson DA, Vos JA, et al. Incidence and treatment results of Endurant endograft occlusion. J Vasc Surg. 2013;57(5):1246-54; discussion 54.

19. Mirza TA, Karthikesalingam A, Jackson D, Walsh SR, Holt PJ, Hayes PD, et al. Duplex ultrasound and contrast-enhanced ultrasound versus computed tomography for the detection of endoleak after EVAR: systematic review and bivariate meta-analysis. Eur J Vasc Endovasc Surg. 2010;39(4):418-28.

PART THREE

Clinical outcome after EVAR



CHAPTER 9

Technical considerations and results of chimney grafts for the treatment of juxtarenal aneursyms

J Vasc Surg. 2013 Sep;58(3):607-15

J.L. Tolenaar, H.J.A. Zandvoort, F.L. Moll, J.A. van Herwaarden

Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT

Objective

To present our initial experience and technical considerations for the use of chimney grafts in the treatment of patients that require endovascular aneurysm repair with aortic branch preservation.

Methods

All patients treated with a chimney procedure between October 2009 and June 2011 were included in our analyses. Chimney procedures were only performed in patients that were unsuitable for open repair and without opportunity to use fenestrated grafts (because of unsuitable anatomy or emergency operation). Open brachial or axillary access was used to deploy covered chimney grafts in the target vessels, and subsequently, a stent graft was deployed via femoral cut-down access.

Results

Thirteen patients (12 males; mean age, 77.2 ± 6.2 years; mean maximal diameter, 71.4 ± 10.2 mm) underwent a chimney procedure with the preservation of 22 aortic side branches. Primary technical success was 92.3% due to occlusion of one renal artery within 24 hours. Thirty-day mortality was 0%. Infrarenal mean neck length was 2.6 mm ± 3.2 mm (range, 0-8 mm) and could be extended to 27.3 mm ± 9.9 mm (range, 18-53 mm) by the use of chimney grafts. During follow-up (median, 10.8 months; interquartile range, 7.4-19.4), one patient died from complications from mesenteric ischemia based on a stenosis of the celiac trunk attributable to the bare stent of the stent graft, and one patient died from aneurysm rupture. Other complications included late occlusion of one renal artery and a type II endoleak, which was unsuccessfully treated with coil embolization and required laparotomy. If we disregard the ruptured patient who had an enormous increase of aneurysm diameter, mean aortic aneurysm diameter reduced from 70.7 ± 10.3 mm (range, 54-89 mm) to 66.7 ± 13.9 mm (range, 48-96 mm) during follow-up (P = .13). In three patients, the aneurysm diameter decreased by more than 5 mm and in two patients, the diameter increased by more than 5 mm. The aneurysm diameter remained stable in the other eight patients.

Conclusions

Until off-the-shelf fenestrated or branched stent grafts become available, the chimney procedure offers a minimally invasive treatment option in patients requiring aneurysm exclusion with side branch revascularization. Although long-term follow-up has to be awaited, the initial results show that chimney grafts can help to decrease or stabilize the aneurysm diameter in most patients, but aneurysm rupture was not prevented in all patients.

INTRODUCTION

Open surgical repair for complex abdominal aortic aneurysms is associated with a high mortality rate in high-risk patients.[1-3] The development of fenestrated and branched endoprosthesis has offered a minimally invasive treatment option in patients requiring aneurysm repair with aortic side branch preservation. Although good results have been obtained, the role of these devices is currently limited because they have to be customized to the patient's anatomy, making these procedures time-consuming, complex, and expensive.[4-8] Furthermore, a certain percentage of patients is rejected for a custom-made fenestrated graft because of anatomic considerations. Standardized fenestrated and branched stent grafts are currently being developed so patients can be treated in an acute setting, but these grafts are yet not widely available.[9] The "chimney procedure" offers a readily available alternative for the treatment of acute aneurysms in patients with challenging anatomy.[10]

The chimney technique can be used as a bailout procedure for unintentional coverage of vital side branches or can be planned as an alternative procedure to extend the aortic neck in patients considered ineligible for fenestrated or branched stent grafts.[11-13] Recently, several authors have presented their series and two reviews showed excellent results, with a technical success rate of 94.8% and 30-day mortality of 7.1%.[14, 15] Although these results are already promising, the technique is evolving.[11-15] We analyzed our clinical experience with chimney grafts in the treatment of complex abdominal aneurysms and present our results and technical considerations for these procedures.

METHODS

Patient selection

All high-risk patients with a juxtarenal or suprarenal abdominal aortic aneurysm with severe to high rupture risk (>6 cm for fusiform aneurysms or >5 cm for saccular aneurysms), considered ineligible for both open surgical as branched or fenestrated endovascular repair, were included. Patients treated with a chimney procedure between October 2009 and June 2011 at University Medical Center Utrecht were included. Operation indications included juxta- or suprarenal aortic aneurysms, persisting proximal type I endoleak or stent graft migration after conventional endovascular aneurysm repair (EVAR) and para-anastomotic aneurysm after open surgical aneurysm repair.

Conventional endovascular repair was prohibited in all cases due to a proximal landing zone smaller than 5 mm or <10 mm in combination with severe angulation of the aortic neck (>60°). Significant comorbidities (eg, chronic obstructive lung disease, congestive heart failure, and coronary artery occlusive disease), an American Society of Anesthesiologists score of 3 or more, or a hostile abdomen precluded these patients for open surgical repair. Two of the patients presented with an aortic rupture, requiring acute intervention. For all other patients, Cook Medical was consulted for a customized endoluminal prosthesis based on the Zenith fenestrated system (William A. Cook Australia Pty Ltd, Brisbane, Australia), but all requests were declined because of an unfavorable anatomy, including severe angulation (>45°), too narrow diameter of the aorta or target branches, or too challenging iliac artery access.

Preoperative planning was based on computed tomographic angiography (CTA) with <1.5-mm slices. The goal of the intervention was to obtain a proximal landing zone of at least 15 mm, determining the extent of the procedure and the number of chimney grafts. If <15-mm landing zone could be obtained with a maximum of two chimneys, the patient was rejected for this procedure.

Procedure

All procedures were performed under fluoroscopic control (Veradius; Philips Medical Systems, Best, The Netherlands). Surgical access to both femoral arteries and the left brachial artery was obtained. After administration of 100 IU/kg heparin, a 0.035-inch hydrophilic guidewire (Radifocus; Terumo Medical, Tokyo, Japan) was used to position a pigtail angiographic catheter above the ostium of the renal arteries. Via the brachial access, a long 10 or 12F Hydrofilic flexor sheath (Cook Medical, Bloomington, Ind) was positioned approximately 10 cm cranial to the first target vessel. Then, all planned target vessels were cannulated through the same brachial sheath with 0.035-inch hydrophilic guidewires, which were replaced by 0.035-inch Rosen guidewires (Merit Medical, Galway, Ireland).

Then, the main body of the stent graft was introduced from the groin, to the intended position, which was checked by angiography. Before deployment of the main device, self-expandable covered stents (Viabahn; Gore, Flagstaff, Ariz) were placed as chimneys in the designated target vessels. I and were planned to end above the (bare stent of) the main body of the stent graft. If not, they were extended with a second, similar-diameter, covered stent. After chimney deployment, the main body of the stent graft was deployed. Then, the chimneys were ballooned using a percutaneous transluminal angioplasty balloon with a similar diameter as the chimney. Contralateral leg and iliac extensions were inserted and deployed. Subsequently, the stent graft was ballooned only distally to the area of the chimneys.

Completion angiography was performed and finally, the wires and catheters were removed, and the access vessels were surgically closed. During the procedure, the activated clotting time was checked regularly to ensure an activated clotting time of ≥250 seconds. Postoperatively, patients were treated with dual-antiplatelet therapy (clopidogrel 75 mg daily and aspirin 100 mg daily) for 6 months. After 6 months, monoantiplatelet therapy was continued.

Surveillance and imaging protocol

Surveillance protocol included physical and laboratory examination and CTA prior to hospital discharge, after 6 months, 1 year, and yearly thereafter. Six weeks after the procedure, patients were checked with laboratory testing and physical examination. All CTA scans were acquired on a 64- or 256-slice CT scanner (Philips Medical Systems, Best, The Netherlands) with a standardized acquisition protocol (scan parameters: 0.9-mm slice thickness, 0.7-mm increment). Intravenous nonionic contrast (120 mL, Iopromide; Schering, Berlin, Germany), followed by a 60-mL saline chaser bolus, was injected at a rate of 6 mL/s. The scan was started using bolus-triggering software with a threshold of 100 HU over baseline. The acquired data sets were transferred to a workstation (3Mensio Vascular 4.3; 3Mensio Medical Imaging B.V., Bilthoven, The Netherlands) for assessment.

Analysis

The baseline, postoperative, and last available CTAs of all included patients were selected for analysis. A center vessel line was acquired and diameters of the affected aortas were measured perpendicular to the aorta at the level of the most distal target vessel, the most proximal target vessel, largest aortic diameter, and the intended landing zone. The area between the aortic wall and the covered stent graft created by the chimney grafts, the so-called "gutters," were measured at the most proximal level of the covered part of the stent graft (Figure 1).

Initial aortic neck length (eg, the distance between the aneurysm and the most proximal target vessel) and the length of the final landing zone after stent graft placement were measured along the center-vessel line. For every target vessel, an individual center-vessel reconstruction was generated to measure the chimney stent length in the vessel and the length of the stent covered by the stent graft. In addition, a crossing configuration of the chimney stent, defined as wherein one chimney crosses the other, thereby possibly compromising the aortic diameter and circumferential apposition of the stent graft, was objectified (Figure 2). Two-tailed Student t-test was used to determine statistical significance ($P < .05$).

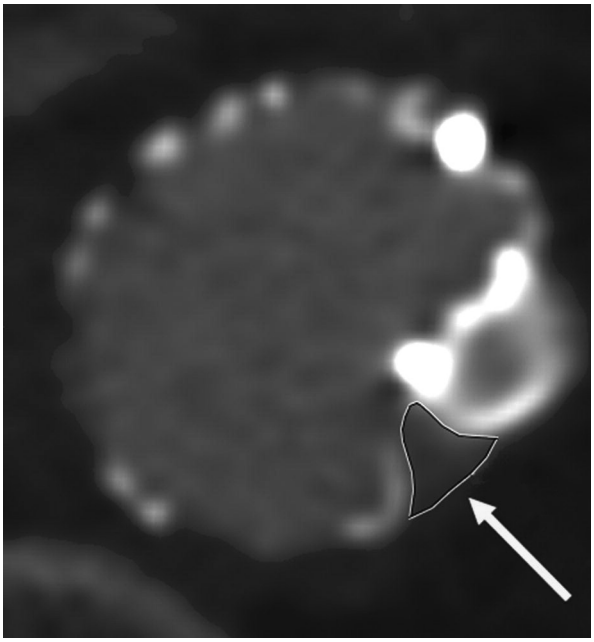


Figure 1. Area measurement of perigraft channel.

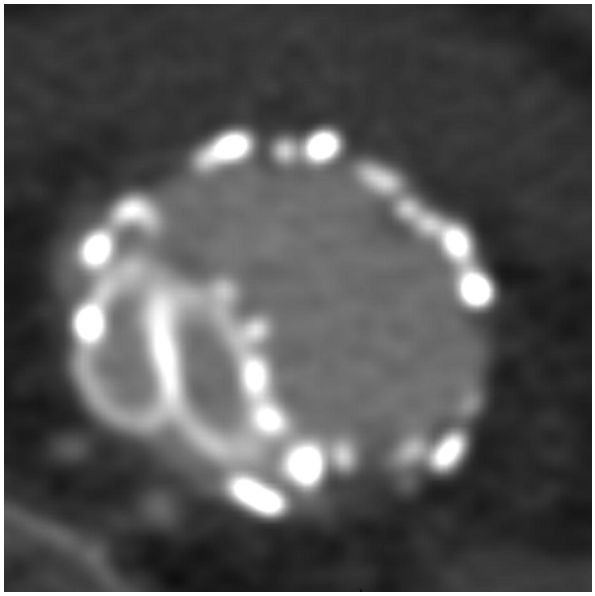


Figure 2. Crossing configuration of the chimney stents compromising stent graft apposition.

RESULTS

A total of 13 patients (12 male; mean age, 77.2 ± 6.2 years) underwent a chimney procedure. All patients were considered ineligible for open repair due to extensive comorbidities (Table 1). Indications for aneurysm repair with a chimney graft were as follows. Six patients had a primary juxtarenal or suprarenal aneurysm, three patients had developed a para-anastomotic aneurysm after prior open surgical repair, and four patients had stent graft migration after conventional EVAR requiring proximal stent graft extension. Two patients presented with aortic rupture and underwent a chimney procedure in an emergency setting. On preprocedural CTA, the mean maximum aneurysm diameter was 71.4 mm ± 10.2 mm (range, 54.0-89.0 mm), with a mean infrarenal neck of 2.6 mm ± 3.2 mm (range, 0-7 mm).

A total of 22 side branches were revascularized with the use of chimney grafts, 19 renal arteries, 2 superior mesenteric arteries, and 1 celiac trunk. Five patients underwent a single renal artery chimney, six patients had bilateral renal revascularization, one patient had a chimney for the superior mesenteric artery, and one patient underwent a total renovisceral revascularization. More detailed technical descriptions are listed in Table 2. In our series, no functional renal arteries were sacrificed to reduce the number of chimneys. All branch stents used were self-expandable covered stents. To acquire extra radial force, additional placement of balloon-expandable stents into the chimney grafts was considered desirable in only one case. This was the patient who underwent a total renovisceral revascularization with the use of four chimney grafts (patient 12).

Primary technical success was 92.3%, with adequate cannulation and chimney placement of all target vessels and exclusion of the aneurysm. One renal artery was occluded within 24 hours after the procedure. Complete occlusion of the right renal artery was objectified with Duplex ultrasonography and CTA 3 days postoperative confirming the total occlusion of the right renal artery. The covered stent was, however, fully deployed, without signs of kinking or significant stenosis. A cause for the occlusion was not found on CTA, but given the early presentation, the occlusion was considered due to technical failure. As this patient developed acute renal failure (maximal creatinine, 711 µmol/L), he was submitted to the intensive care unit for hemodialysis after which creatinine levels stabilized to 212 µmol/L (glomerular filtration rate, 27 mL/min/1.73 m^2) at discharge. Further surveillance of the kidney function was performed by the nephrologist, and the most recent creatinine level decreased to 131 µmol/L (glomerular filtration rate, 49 mL/min/1.73 m^2)

Median hospital stay was 4.0 days (interquartile range, 3-9.5 days), and only one patient was admitted to the intensive care unit during 6 days. Overall 30-day mortality was 0%. Postoperative course was complicated in two patients (15.4%); one patient developed a pulmonary embolism, successfully treated with anticoagulation therapy, and one patient received antibiotics for a postoperative wound infection.

Median follow-up was 10.8 months (interquartile range, 7.4-19.4) during which one patient died of a procedure-related event. This patient (patient 11) had a solitary functional kidney and was treated for an 8.8-cm suprarenal aneurysm with a chimney graft to the right renal artery. Since the patient had a dominant and patent celiac trunk, we decided to cover the mesenteric artery, which was extremely calcified and nearly occluded at the origin, to obtain an adequate proximal landing zone. Postoperative scan, however, showed a partial stenosis of the celiac trunk attributable to the proximal bare stent ring of the stent graft. During hospitalization, the patient did not develop complaints and was discharged in good health. However, 2 months later, the patient was submitted to another hospital with abdominal complaints and despite additional stenting of the celiac trunk and a patent chimney graft, he developed multiple organ failure and eventually died, most likely due to mesenteric ischemia.

One other patient died because of an aneurysm-related event. Patient 7 was treated with a chimney procedure for the revascularization of the right renal artery after stent graft migration. Follow-up CTA at 1 year showed an increase in aneurysm diameter of more than 10 mm, which was thought to be caused by a type Ib endoleak attributable to insufficient distal sealing of the stent graft. However, despite the distal extension of both limbs 18 months after the initial chimney procedure, the aneurysm diameter did not stabilize. In view of the poor physical condition of the patient, we decided to follow a conservative policy with strict radiologic surveillance. After 26 months of follow-up, the patient presented at the emergency department of a local hospital with a hemodynamic collapse. The CTA scan showed an increase in aneurysm diameter to 110 mm, with a rupture and large retroperitoneal hematoma. The chimney graft in the renal artery and stent graft were still in a good position. Given the extensive medical history, unfavorable prognosis, and poor condition of the patient, a decision was made to discontinue any further treatment.

Table 1. Baseline Characteristics of chimney patients.

Patient	Gender	Age	Operation indication	Comorbidities	Acute vs planned	Maximum aneurysm diameter	Pre-op GFR	Duration of hospitali-zation	Total no. of chimneys	No. of renal chimneys	No. of chimneys Truncus/ SMA
Patient 1	M	74,9	Para-anastomotic aneurysm	Bifurcationprothesis AAA, COPD gold IV Reuma	Acute	74	>60	3	1	1	0
Patient 2	M	88,7	Migration EVAR	Urolithiasis Myocardial infarction EVAR	Planned	89	59	4	2	2	0
Patient 3	M	81,6	Juxtarenal AAA	Myocardial infarction ICD COPD Renal insufficiency	Planned	72	42	8	2	2	0
Patient 4	M	68,5	Juxtarenal AAA	PAOD	Planned	54	>60	2	1	1	0
Patient 5	M	74,9	Juxtarenal AAA	Myocard infarct low anterior resection rectumcarcinoma Paroxismal atrial flutter	Planned	63	>60	2	2	2	0
Patient 6	M	75.0	Juxtarenal AAA	COPD Lobectomie right lung Atriumfibrileren	Planned	66	>60	3	2	2	0
Patient 7	M	85,5	Migration EVAR	CABG EVAR Renal insufficiency	Planned	80	37	3	1	1	0
Patient 8	F	79,9	Juxtarenal AAA	COPD Mitralis valve insufficiency	Planned	68	>60	9	1	1	0
Patient 9	M	65,6	Migration EVAR	Bileteral nephrectomy Hemodialysis	Acute	75	<20	3	1	0	1
Patient 10	M	79,9	Para-anastomotic aneurysm	PAOD Open surgical aneurysm repair	Planned	61	47	10	2	2	0

Table 1 continued

Patient 11	M	77,9	Para-anastomotic aneurysm	COPD gold III CABG Aorta valve replacement PAOD Renal insufficiency	Planned	88	33	7	1	1	0
Patient 12	M	75,3	Suprarenal AAA	COPD gold III Hernia diafragmatica	Planned	73	>60	4	4	2	2
Patient 13	M	76,4	Migration EVAR	COPD DM II Pneumectomy right Sigmoidresection Atrial fibrillation PAOD EVAR	Planned	65	>60	41	2	2	0

AAA, Abdominal aortic aneurysm; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EVAR, endovascular aneurysm repair; F, female; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; M, male; PAOD, peripheral arterial occlusive disease; SMA, superior mesenteric artery.

Table 2. Radiologic/technical characteristics and patient outcome.

Patient	Length aortic neck below target vessel (mm)	Diameter aortic neck (mm)	Length of landing zone (mm)	Area gutters (mm^2)	Crossing confi-guration	Stent graft (% oversizing)	Target artery	Diameter target vessel (mm)
Patient 1	0	28.8	20.1	5	No	Endurant (24 %)	Left renal	6
Patient 2	0	25.2	39.2	36.1	Yes	Endurant (10 %)	Left Renal Right renal	8 7
Patient 3	0	29.8	28.2	10.1	Yes	Endurant (33 %)	Left Renal Right Renal	7 8
Patient 4	7	30.1	25	22.4	No	Endurant (30 %)	Left Renal	6
Patient 5	2	24.9	23	15.8	No	Endurant (25 %)	Left Renal Right Renal	7 7
Patient 6	4	22.7	18	28.1	No	Excluder (28%)	Left Renal Right Renal	5 8
Patient 7	0	22.1	28	5.3	No	Endurant (23 %)	Right Renal	6
Patient 8	7	21.8	18	10.1	No	Excluder (24 %)	Right Renal	6
Patient 9	0	29.7	33	11.2	No	Endurant (21 %)	SMA	12
Patient 10	0	31.1	23	13.2	No	Endurant (18 %)	Left Renal Right Renal	6 6
Patient 11	0	29.3	26	10.3	No	Endurant (15%)	Right Renal	5
Patient 12	0	25.7	53	8.8	No	Endurant (29 %)	Left Renal Right renal SMA Celiac Trunk	6 6 8 7
Patient 13	0	25.4	21	7.6	No	Endurant AUI (35%)	Left Renal Right Renal	7 7

AUI, Aorto-uni-iliac; *SMA*, superior mesenteric artery.
Bare stent of first stent graft located at the level of the renal arteries.
† Stent reinforced with Scuba stent.

Table 2. Continued

Stent used (size)	Length covered by stent (mm)	Length chimney in artery (mm)	Length chimney above stent (mm)	Shrinkage or growth (> 5 mm)	Complications / secondary interventions
Fluency (6x60)	19	14	11	Shrinkage	
Fluency (9x80) Fluency (8x80)	71.1 33.4	8.9 41.6	0 5	Growth	Type II endolaek requiring coil embolization and finally conversion
Viabahn (7x50) Viabahn (9x100)	37.1 50.3	12.9 49.7	0 0	Stable	
Viabahn (7x50)	26.0	21.6	2	Stable	
2x Viabahn (7x50) Viabahn (7x50)	38.2 22.2	15.8 27.8	15.2 0	Stable	Occlusion after one month right renal
2x Viabahn (6x50) 2x Viabahn (8x50)	24.2 26.0	20.6 14.2	3 6	Shrinkage	
Fluency (6x60)	22.7	19.3	18	Growth	Type Ib endoleak requiring extension of the left and right limb. Finally died from rupture
2x Viabahn (6x50)	19.9	24.1	7	Stable	Spontaneous resolved type Ia Endoleak
Viabahn (13x100)	79.9	17.1	3	Stable	
2x Viabahn (7x50) Viabahn (7x50)	37.9 35	12.1 15	0 0	Stable	
3x Viabahn (6x100, 6x50 and 6x25)	86.2	17.3	4.5	Stable	Stenosis celiac trunc due to bare stent, died from intestinal ischemia
Viabahn (7x50) † Viabahn (7x50) † Viabahn (9x50) † Viabahn (8x50) †	31.8 30.3 21.7 35.3	18.2 19.7 16.3 11.7	0 0 12 3	Shrinkage	
Viabahn (8x50 and 8x25) Viabahn (8x50)	21.1 25.1	19.9 12.4	21 12	Stable	Occlusion right renal artery within 24 h

There were two nonaneurysm-related deaths during follow-up (patients 3 and 5). Autopsy confirmed that the death of patient 5 was a cancer-related death, wherein during autopsy was shown that the stent grafts were still in a good position with sufficient aneurysm exclusion. No autopsy was obtained for patient 3, but clinical symptoms revealed that this patient died 26 months after surgery from (pre-existing) heart failure. The last scan showed a stable aneurysm with patent chimneys.

One patient had a proximal type I endoleak on the first postoperative CTA, which was not seen perioperatively on the final control angiogram. Since the nitinol aortic stent did not show complete deployment, shortly after the EVAR without primary ballooning of the stent graft, the patient was treated conservatively and was kept under strict surveillance after which the proximal type I endoleak resolved spontaneously after 1 month. One other patient with aortic enlargement during follow-up had a type II endoleak requiring coil embolization and finally, after unsuccessful embolization, a laparotomy was performed. When the aneurysm was opened without aortic clamping, it was confirmed that the stent graft was still in a good position without proximal type I endoleak, and only a large type II endoleak from a lumbar artery was present and ligated.

The patency rate of the chimney was 90.9% with the loss of a renal artery in two patients. One renal artery was lost within 24 hours because of technical failure, and 1 renal artery (patient 5) was thrombosed after 1 month of follow-up. On the postoperative CTA, this chimney showed some kinking, which was at that time accepted. However, because of the occlusion of this chimney, all chimneys are ballooned after deployment of the main stent graft. Both patients did not develop renal failure requiring hemodialysis.

Aortic aneurysm diameter reduced from 71.4 ± 10.2 mm (range, 54-89 mm) to 70 ± 18.0 mm (range, 48-110 mm) during follow-up (P = .69). In three patients, the aneurysm diameter decreased by more than 5 mm and in two patients, the diameter increased by more than 5 mm. The aneurysm diameter remained stable in the other eight patients.

The mean neck length in patients was initially 2.6 mm ± 3.2 mm (range, 0-8 mm) and could be extended to 27.3 mm ± 9.9 (range, 18-53 mm) by the use of chimney grafts (Table 2). The mean length of the stent in the artery was 20.0 ± 9.5 mm (range, 8.9-49.7 mm). The mean area of the gutters decreased from 14.1 mm^2 ± 9.3 mm^2 (range, 5-36.1) to 9.2 mm^2 ± 6.2 mm^2 (range, 0-22.9) (P < .05). There was no correlation between the extent of the area of the gutters and the presence of type I endoleaks (P = .2) and also no correlation between the extent of the area of the gutters and aneurysm growth (P = .6).

DISCUSSION

In the current endovascular era, innovation of stent grafts and the introduction of branched and fenestrated stent grafts have broadened the surgeons' armamentarium, and patients with juxta- or suprarenal abdominal aneurysms can nowadays be treated in a minimally invasive way. These techniques are, however, not widely available, expensive, and technically demanding. Fenestrated and branched stent grafts have to be customized to the specific anatomy of the patient, resulting in a prolonged delivery time. Therefore, custom-made fenestrated stent grafts cannot be used in an acute setting. Furthermore, the instructions for use are strict, and many patients are

considered ineligible due to their unfavorable anatomy. The chimney procedure provides a "bail-out" solution for these patients.11-15 Using off-the-shelf stent grafts and stents offers an opportunity for preserving the vascularization of aortic side branches in both acute and planned settings.

This study shows the feasibility of the chimney technique with a primary technical success rate of 92.3% and a 30-day mortality rate of 0%, which is in line with previous reported results.[11-15] Although these results are promising, the success of the chimney graft remains highly dependent on patient selection, preoperative assessment, and experience of the operator. In our institution, the use of the chimney technique is, therefore, restricted to high-risk patients with large aneurysms who are ineligible for open surgical as branched or fenestrated endovascular repair. Our results demonstrate that in most of these patients (85%) with large aneurysms, the aneurysm stabilizes or even shrinks during follow-up.

Mutiplanar views and three-dimensional reconstruction are needed for a correct assessment and measurement of the intended landing zone. The interaction between chimney stents and the stent graft interferes with the apposition and sealing of the stent graft, making the presence of perigrafts channels inevitable. These perigraft channels are considered to be the weakness of the chimney procedure, as they provide an access for blood to course through, resulting in a type I endoleak with repressurization of the aneurysm and eventually failure of therapy. Many theories about the prevention and natural history of these channels have been proposed.[14] To ensure that the fabric of the stent graft completely enfolds the chimney graft to fill these channels, many authors advocate additional ballooning and oversizing. Kissing-balloon techniques are advocated by several authors; however, we believe this technique might pull graft material out of the gutters by stretching of the fabric and should, in our opinion, be avoided in patients without type Ia endoleaks on the completion angiogram. Lachat et al suggested that the calculation of the stent graft diameter should be based on an elliptic model, but most authors utilize a 30% oversizing.[16] As a rule of thumb, we use 20%-30% oversizing in all cases, with a tendency to oversize closer to 30% in cases when more than one chimney is needed. Our analysis did, however, not show that the area of the perigraft channels is directly related to the presence of type I endoleak, but no statements can be made, as the sample size is small. Furthermore, the area of the perigraft channels decreased significantly during follow-up. It seems that the chimney graft and the main body comply better during follow-up, which is probably a result of the radial forces of both prostheses. In patients with a small infrarenal aortic neck, these channels run to a "dead-end" that may result in thrombosis and prevention of a type I endoleak. In our study population, only one patient showed a primary type Ia endoleak, which spontaneously resolved, hypothetically due to the presence of a short aortic neck. Other important factors are believed to be the length of perigraft channels, since longer channels offer more resistance and are more likely to thrombose. Furthermore, antithrombotic therapy and high blood pressure control may also play a role in the patency of these channels.

The use of covered, uncovered, balloon, and self-expandable stents have all been described in the literature.[17-19] Uncovered stents generate a flow channel between the stent graft and aortic wall to maintain vascularization, where covered stents direct the blood directly to the target vessel. We believe covered stents are beneficial because pressurization of the perigraft channels is reduced, lowering the chance of type I endoleaks, especially in the absence of any aortic neck.

Dislodging of a covered stent, however, directly compromises the side branch and, therefore, covered stents have to be placed well into the target vessel to secure a good fixation.
Deployment of stents in the vicinity of side branches always harbors the risk of unintentional coverage of a side branch. During a chimney graft procedure, not only the stent graft itself but also the covered chimney graft might obliterate the orifice of a next side branch, of which the physician should be aware. Ischemic complications related to the bare stenting proximal to the covered area of the stent graft can be catastrophic, such as in one of our patients, but are highly uncommon.[20]
Most self-expandable peripheral stents are made of nitinol, which is a "shape-memory" alloy. Because of its mechanical properties, the material tends to remain in its original shape, making the material capable of undergoing large deformations without experiencing permanent deformation. These properties not only generate the required radial force, by constantly trying to regain its initial diameter, but also might straighten the stent during and after deployment. During the procedure, the physician should be aware of these properties. Although a less steep angulation of the chimney stent might result in a prolonged covered part of the stent, making the perigraft channels longer and more likely to thrombose, the interference with the graft apposition and fixation will be greater. In case of a crossing chimney grafts configuration, the stent graft apposition is compromised to an even larger extent. Two of our first three patients had a crossing configuration of both chimneys, and although these patients did not show any complications, we believe this should be avoided. However, the mobility of the guidewires and stents make it challenging and hard to control for the operator to guide the cranial part of the chimneys to the desirable direction.
This study has some important limitations that should be addressed. The small population and heterogeneity for disease and used treatment methods make it impossible to determine which variables are associated with the success or failure of therapy. Duration of follow-up was short, and no long-term outcomes were available. However, the current evidence consists of only case series, and it is not likely that there will be randomized controlled trials. With growing experience and constantly refining the techniques, we get a better insight into the applicability of chimney grafts for endovascular repair of juxtarenal aneurysms. Until standardized fenestrated and branched stent grafts have become widely available, the chimney graft offers a good alternative in the treatment for patients with a juxtarenal aneurysm, however, long-term outcome should be awaited to fully comprehend the position of the chimney procedure in the surgeons' treatment strategy.

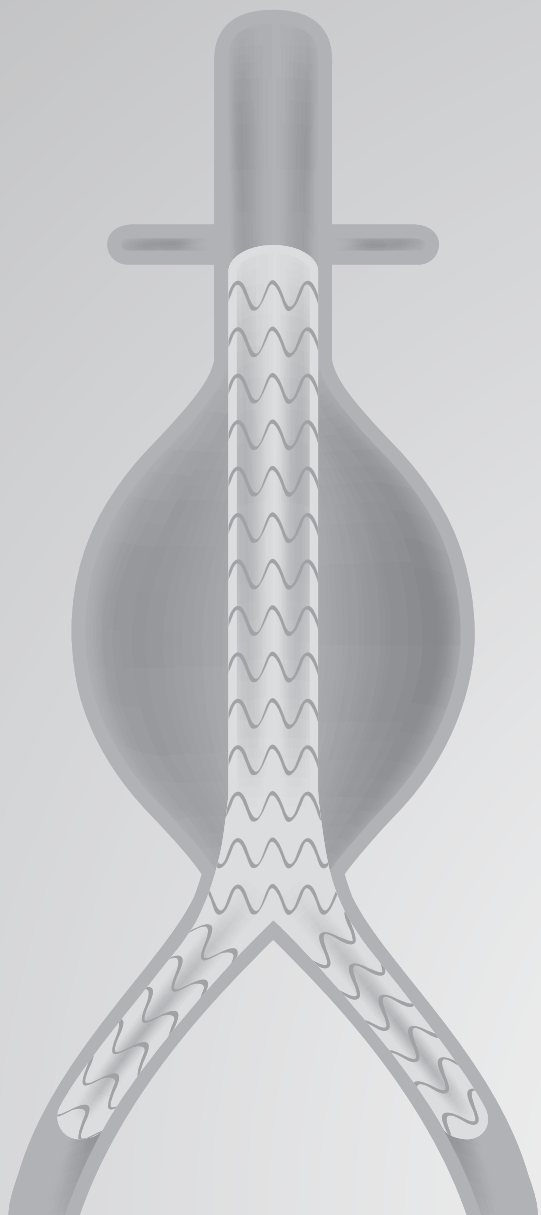
CONCLUSIONS

Until standardized fenestrated or branched endoprothesis become widely available, the chimney procedure offers a good alternative in patients requiring aneurysm exclusion with side branch revascularization. Although initial results show absence of aneurysm growth in most patients, long-term follow-up has to be awaited.

REFERENCES

1. Faggioli G, Stella A, Freyrie A, Gargiulo M, Tarantini S, Rodio M, et al. Early and long-term results in the surgical treatment of juxtarenal and pararenal aortic aneurysms. Eur J Vasc Endovasc Surg 1998;15: 205-11.
2. Knott AW, Kalra M, Duncan AA, Reed NR, Bower TC, Hoskin TL, et al. Open repair of juxtarenal aortic aneurysms (JAA) remains a safe option in the era of fenestrated endografts. J Vasc Surg 2008;47: 695-701.
3. West CA, Noel AA, Bower TC, Cherry KJ Jr, Gloviczki P, Sullivan TM, et al. Factors affecting Outcomes of open surgical repair of pararenal aortic aneurysms: a 10-year experience. J Vasc Surg 2006;43:921-7.
4. Amiot S, Haulon S, Becquemin JP, Magnan PE, Lermusiaux P, Goueffic Y, et al. Fenestrated endovascular grafting: the French multicentre experience. Eur J Vasc Endovasc Surg 2010;39:537-44.
5. Anderson JL, Adam DJ, Berce M, Hartley DE. Repair of thoracoabdominal aortic aneurysms with fenestrated and branched endovascular stent grafts. J Vasc Surg 2005;42:600-7.
6. Greenberg RK, Sternbergh WC III, Makaroun M, Ohki T, Chuter T, Bharadwaj P, et al. Intermediate results of a United States multicenter trial of fenestrated endograft repair for juxtarenal abdominal aortic aneurysms. J Vasc Surg 2009;50:730-7.
7. Semmens JB, Lawrence-Brown MM, Hartley DE, Allen YB, Green R, Nadkarni S. Outcomes of fenestrated endografts in the treatment of abdominal aortic aneurysm in Western Australia (1997-2004). J Endovasc Ther 2006;13:320-9.
8. Verhoeven EL, Vourliotakis G, Bos WT, Tielliu IF, Zeebregts CJ, Prins TR, et al. Fenestrated stent grafting for short-necked and juxtarenal abdominal aortic aneurysm: an 8-year single-centre experience. Eur J Vasc Endovasc Surg 2010;39:529-36.
9. Chuter T, Greenberg RK. Standardized off-the-shelf components for multibranched endovascular repair of thoracoabdominal aortic aneurysms. Perspect Vasc Surg Endovasc Ther 2011;23:195-201.
10. Greenberg RK, Clair D, Srivastava S, Bhandari G, Turc A, Hampton J, et al. Should patients with challenging anatomy be offered endovascular aneurysm repair? J Vasc Surg 2003;38:990-6.
11. Coscas R, Kobeiter H, Desgranges P, Becquemin JP. Technical aspects, current indications, and results of chimney grafts for juxtarenal aortic aneurysms. J Vasc Surg 2011;53:1520-7.
12. Donas KP, Pecoraro F, Torsello G, Lachat M, Austermann M, Mayer D, et al. Use of covered chimney stents for pararenal aortic pathologies is safe and feasible with excellent patency and low incidence of endoleaks. J Vasc Surg 2012;55:659-65.
13. Lee JT, Greenberg JI, Dalman RL. Early experience with the snorkel technique for juxtarenal aneurysms. J Vasc Surg 2012;55:935-46.
14. Moulakakis KG, Mylonas SN, Avgerinos E, Zapapetrou A, Kakisis JD, Brountzos EN, et al. The chimney graft technique for preserving visceral vessels during endovascular treatment of aortic pathologies. J Vasc Surg 2012;55:1497-503.
15. Tolenaar JL, van Keulen JW, Trimarchi S, Muhs BE, Moll FL, van Herwaarden JA. The chimney graft, a systematic review. Ann Vasc Surg 2012;26:1030-8.
16. Lachat M. Multiple chimneys: technique, results and limitations. London: 33rd CX Symposium; 2011.
17. Bruen KJ, Feezor RJ, Daniels MJ, Beck AW, Lee WA. Endovascular chimney technique versus open repair of juxtarenal and suprarenal aneurysms. J Vasc Surg 2011;53:895-904.
18. Hiramoto JS, Chang CK, Reilly LM, Schneider DB, Rapp JH, Chuter TA. Outcome of renal stenting for renal artery coverage during endovascular aortic aneurysm repair. J Vasc Surg 2009;49: 1100-6.
19. Sugiura K, Sonesson B, Akesson M, Bjorses K, Holst J, Malina M. The applicability of chimney grafts in the aortic arch. J Cardiovasc Surg (Torino) 2009;50:475-81.
20. Subedi SK, Lee AM, Landis GS. Suprarenal fixation barbs can induce renal artery occlusion in endovascular aortic aneurysm repair. Ann Vasc Surg 2010;24:113.

PART FOUR
Summary, general discussion, and future perspectives



CHAPTER 10

Summary, general discussion, and future perspectives

Imaging is the common denominator for the different studies on abdominal aortic aneurysms (AAAs) described in this thesis. Imaging is important in all stages of AAA disease and is essential for screening and detection of AAAs. Furthermore, imaging is indispensable for preoperative planning of endovascular aneurysm repair (EVAR) and contributes to optimal placement of the stent graft during an endovascular procedure. Imaging is also used after AAA treatment to evaluate outcome and detect complications such as endoleak or stent graft migration.

AAA imaging and aneurysmal wall degeneration

AAA pathophysiology is a complex multifactorial process characterized by degeneration and loss of collagen, elastin, and smooth muscle cells, and by inflammatory infiltration in the aortic wall.[1, 2] These changes result in thinning of the aortic wall and aortic dilation and may eventually lead to aneurysm rupture.[1, 2]

Knowledge of pathophysiologic processes in the aortic wall is of great importance for identifying risk factors, searching for predictive markers of AAA progression, and discovering potential targets for (medical) treatment. Histologic and biochemical analysis of AAA wall characteristics contribute to a better insight in AAA pathophysiology but are currently restricted to patients who undergo open surgical AAA repair. Combining AAA wall characteristics that reflect the severity of aneurysmal disease and markers that are measurable in all AAA patients may lead to new predictors of AAA progression and rupture risk. In Part 1 of this thesis, we examined associations between aneurysmal wall degeneration and AAA imaging.

Maximum aneurysm diameter is one of the most important determinants of AAA disease, and risk of rupture increases with increasing diameter.[3, 4] However, small aneurysms also rupture.[4] This suggests that more factors than diameter are of interest for the analysis of rupture risk. It is possible that a proportional diameter or diameter ratio of the aneurysm is more suitable to use for the estimation of rupture risk; for example, a large AAA of 6 cm will have increased more when the native aortic diameter was 1.8 cm compared with a native diameter of 2.7 cm.

The value of diameter ratio is discussed in **Chapter 2**. Orthogonal maximum aneurysm diameter and suprarenal aortic diameter, as a surrogate measure for the native aorta, were measured on preoperative computed tomography angiography (CTA) scans, and diameter ratio was calculated. Associations with histologic and biochemical characteristics of the aneurysm wall were tested for diameter ratio and absolute maximum diameter.

We observed that diameter ratio and AAA diameter showed some relationships with AAA wall characteristics. This relationship was mainly present for histologic variables and was less pronounced for the measured biochemical parameters. AAA ratio and diameter were associated with less elastin in the media and more vascular smooth muscle cells and collagen in the adventitia, processes that may occur in AAAs with larger diameters. No associations with inflammatory parameters or proteases and AAA size measurements were found, not confirming claims that a larger AAA has a more advanced stage of disease. We were not able to prove the relevance of AAA diameter ratio over absolute diameter.

However, maximum aneurysm diameter is currently the only variable that has proven itself for determining whether surgical intervention is indicated. Perhaps convincing evidence for other parameters being reliable predictors of AAA progression and rupture risk will be found in the near future.

The association between intraluminal thrombus (ILT) on CTA and aneurysm wall characteristics was investigated, and results are reported in **Chapter 3**. ILT is present in nearly all aneurysms, but ILT thickness differs from patient-to-patient. Little is known about the development of ILT, but a possible formation mechanism might consist of platelet activation just after the aneurysm neck, induced by high shear stresses, that results in thrombus formation downstream at sites of low wall shear stress.[5]

Previous studies have shown that ILT is associated with growth of the aneurysm.[6, 7] In addition, histologic analysis of an AAA vessel wall covered with ILT showed a decreased amount of smooth muscle cells and elastic fibers in the media layer compared with an AAA vessel wall without ILT.[8] An analysis of preoperative CTA scans of 83 patients in the aneurysm Express Biobank confirmed that the aneurysm walls in patients with thicker ILT had a reduced amount of smooth muscle cells and elastin. In addition, ILT was associated with AAA diameter and the proteolytic enzyme matrix metalloproteinase-2. These findings suggest that ILT affects vascular integrity and may contribute to accelerated growth and increased rupture risk of the aneurysm. Why ILT is associated with loss of elastin fibers and smooth muscle cells and growth of the aneurysm is still unclear. ILT may have an indirect effect on AAA wall weakening because thrombus, due to coverage of the vessel wall, is associated with local hypoxia in the underlying vessel wall.[9] In vitro studies have shown that hypoxia provides an upregulation of matrix metalloproteinase-2 in the smooth muscle cells. Future research on the effects of hypoxia on the AAA vessel wall and the differences between normoxic and hypoxic AAA tissue would be interesting.

Dedicated imaging studies

EVAR has developed in the years since its introduction in the 1990s by Parodi and Volodos. Randomized controlled trials have showed that the minimally invasive techniques of EVAR lead to a reduction in perioperative mortality and morbidity.[10, 11] However, compared with open AAA repair, EVAR is associated with an increased rate of reinterventions and stent graft complications.[12, 13] The stent grafts that were used in the randomized trials, though, are different from the ones currently used. Stent grafts have technically improved, and with more experience among vascular interventionists, results have improved as well. Long-term durability of EVAR remains an important issue, however, particularly for young patients because of their increased life expectancy.

One of the essential factors of a sustainable long-term outcome after EVAR is the proximal aneurysm neck. Several factors, including length, diameter, pulsatility, and angulation of the neck, influence the ability to obtain adequate sealing of the stent graft.[14-16] Accurate preoperative analysis of the aneurysm neck is required to prevent proximal complications such as stent graft migration and type Ia endoleak.

Previous studies with dynamic CTA scans have shown that pulsatile distension occurs during the cardiac cycle.[17-19] A significant difference was observed between the maximum diameter measured during diastole and the maximum diameter measured during systole.[19] Mean diameter changes of 9% to 11% were reported, raising the thought that proximal fixation may be less secure in patients with large pulsatility.[19] Van Keulen et al.[16] confirmed this hypothesis and showed that preoperative pulsatile distension was significantly higher in patients with stent graft migration than in patients without stent graft migration.

Young healthy people have an even higher pulsatile distension, with reported mean diameter changes of 30% at the suprarenal level and 25% at the infrarenal level.[20] In **Chapter 4**, we therefore examined whether a difference could be observed in pulsatile distension between young and old aneurysm patients. The pulsatile distension of 25 consecutive EVAR patients aged ≤65 years was compared with the pulsatile distension of 25 consecutive patients aged >65 years. No difference in pulsatile distension between young and old patients was observed at the suprarenal or infrarenal level.

Risk factors for AAA disease and atherosclerosis are similar, and although whether atherosclerosis is causally linked to AAA is still unclear, atherosclerosis develops parallel with aneurysmal dilatation.[21] Thus, if a younger patient has an AAA that is large enough to be considered for treatment, the aortic wall proximal to the aneurysm is probably more affected by atherosclerosis than the aortic wall of an individual of the same age without an AAA. Atherosclerosis is associated with increased stiffness of the vessel wall, which might explain why no difference in pulsatile distension was found in the current study.[22]

This study only analyzed the pulsatile distension of the aneurysm neck, and no conclusions can be drawn about any difference between young and old AAA patients regarding the occurrence of proximal aneurysm neck complications. However, we do not expect that young patients will have more pulsatile distension-related complications after EVAR.

In previous studies examining pulsatile distension, we described the distension in the orthogonal plane perpendicular to a central lumen line (CLL). The previous studies, however, did not account for any through-plane movement in the craniocaudal direction.

In **Chapter 5**, we examined the presence of through-plane movement. At different levels of the aorta, all located on a fixed distance from a branching artery, we followed the movement of a center point in the aorta during 8 phases of a dynamic CT scan by using 3-dimensional coordinates.

The movement in the craniocaudal plane was small, and at levels relevant for EVAR, even smaller around the renal arteries. The effect of this movement seems to be minimal and would probably have no effect on the fixation of the stent graft. It also means that the results of previous studies analyzing pulsatile distension in a fixed plane will not be much disturbed by through-plane movement.

The study described in this chapter, however, was only able to focus on the movement of the entire aorta during the cardiac cycle. Future research should include an analysis of distension of the aortic wall parallel to the CLL, which should illustrate whether the aorta also stretches in the longitudinal direction during the cardiac cycle. This potential elongation of the aorta should be studied on preoperative and postoperative scans to see if there is any effect for the stent graft. Elongation and subsequent shorting of the aorta during the cardiac cycle might influence the proximal and distal sealing of the endograft.

A frequent and clinically relevant complication after EVAR is the occurrence of endoleak. Today, endoleak is the most common reason for a secondary intervention after EVAR.[23] Endoleaks appear to be the main cause of post-EVAR rupture and are a strong independent predictor of growth after EVAR.[24, 25] This illustrates the importance of adequate detection of endoleaks.

Chapters 6 and **7** of this thesis discuss postoperative imaging follow-up of EVAR patients. For postoperative imaging, the current international guidelines recommend a CTA scan 1 and 12

months after EVAR.[26, 27] When an endoleak or other abnormality that can be followed up conservatively is observed on the first postoperative CTA, an additional CTA is recommended 6 months after EVAR and annually after the 1-year follow-up.[26, 27] If no endoleak, growth, or other abnormality is found during the first year, an annual duplex examination may be sufficient.[26, 27] Although CTA is the gold standard for the detection of endoleaks, CTA may miss endoleaks. Other imaging modalities, such as magnetic resonance imaging (MRI), have therefore been interesting alternatives for the detection of endoleaks. The results of a literature review on the detection of endoleaks on CTA compared with the detection of endoleaks on MRI are presented in **Chapter 6**. In 11 studies totalling 369 patients, 146 endoleaks were found on CTA scans, and all, except 2, were also detected on MRI. Furthermore, 132 additional endoleaks were detected on MRI, and 69% were classified as type II endoleak. Unfortunately, details about post-EVAR growth in these patients were limited. Information on growth is essential because, according to the current international guidelines, only a type II endoleak accompanied by growth requires treatment.[26, 27]

The detection of endoleaks in patients with an enlarging aneurysm after EVAR is discussed in **Chapter 7**. Patients with ≥5-mm growth of the aneurysm documented by arterial and delayed-phase CTA, without or with unclear endoleak, were evaluated by MRI with administration of a weak albumin-binding contrast agent. Previous studies showed that MRI with a weak albumin-binding contrast agent has additional value for the detection of endoleaks. In our study population of 21 patients, a type II endoleak was found in 15 patients, and the origin of endoleak was detected in most patients.

We therefore believe that in selected patients with enlarging aneurysms of unknown origin after EVAR, MRI with weak albumin-binding contrast agents is a promising imaging technique for endoleak evaluation. However, MRI will not replace CTA and duplex in regular follow-up because of the cost, the reduced applicability due to contraindications (metal implants, claustrophobia), and longer acquisition time. MRI with a weak albumin-binding contrast agent should be seen as a valuable addition to the existing follow-up schedule. The results of **Chapter 7** are only related to the detection of endoleaks. A follow-up study should focus on the treatment of detected endoleaks.

Clinical outcome after evar

In this part of the thesis we focus on the clinical outcome after EVAR. EVAR is currently the treatment of first choice for patients with suitable anatomy, and for several years, most AAA surgery has been performed endovascularly.[28] Since the introduction of the latest-generation stent grafts, patients with shorter or more angulated proximal aortic necks or tortuous, small, or calcified iliac arteries can also be safely treated by EVAR.[29] In **Chapter 8** we analyze the medium-term results of our first 100 consecutive patients treated with an Endurant stent graft for an infrarenal AAA.

Treatment in 19 of the 100 evaluated patients was outside the instructions for use (IFU) because these patients had a shorter, wider, or more angulated suprarenal or infrarenal aneurysm neck than the IFU prescribed. Primary clinical success after 1, 2, 3, and 4 years of follow-up was 98%, 90%, 84%, and 77%, respectively. There was no difference in the clinical success between the patients treated within the IFU and those treated outside the IFU. The overall mortality was 20%

after 4 years, and aneurysm-related mortality was 3%. Considering the possible increase in complications resulting from the challenging anatomy present in this cohort, this study revealed very low AAA-related mortality.
A notable finding was the relatively high number of distal extensions placed in this study population. Of 8 patients who received a distal extension, 5 were for a type Ib endoleak. Although IFU criteria for distal fixation (≥15 mm sealing and 10% to 25% oversizing) could not be met, progressive dilatation of the common iliac arteries was observed in 4 of these patients. This dilation could possibly be the result of progression of the disease, but for the proximal side, pulsatile distension is known to influence fixation of the stent graft.[16] Preoperative pulsatile distension at the iliac level is significant during the cardiac cycle,[30] but whether iliac pulsatile distention continues after implantation of the stent graft is unknown. Because pulsatile distension remains present at the proximal side, iliac pulsatile distension is also expected to remain significant after EVAR.

Chapter 9 discusses the results of the chimney technique. This endovascular technique offers an opportunity for preserving the vascularization of aortic side branches in patients with juxtarenal and suprarenal aneurysms. Through brachial access, self-expandable covered grafts (chimney grafts) were deployed in aortic side branches and were planned to end above the main body of the stent bare graft. After deployment of the chimney grafts, the main device was deployed through femoral cutdown access. A juxtarenal or suprarenal aneurysm was treated in 13 patients, of which 2 were in an acute setting. These patients were unfit for open repair and had no other option because a customized fenestrated graft was not possible due to the acute setting or was rejected by the manufacturer. The perioperative mortality was 0%, and during a median follow-up of 11 months, aneurysm-related mortality was 15%. This mortality rate is considerable, but it must not be forgotten that these patients had large aneurysms (mean diameter >70 mm), severe comorbidities, and were absolutely unfit for open repair.
One of the key issues in the treatment with the chimney technique is the occurrence of "gutters" along the main device that can provide a passage for blood into the aneurysm sac, resulting in a type Ia endoleak.31 A type Ia endoleak occurred in 1 patient in our series because of incomplete deployment of the main device in the aorta; however, this endoleak resolved spontaneously.
The gutters along the grafts in our series decreased during follow-up, and there was no relationship with growth or development of type Ia endoleak. Although no firm conclusions can be drawn because of the small number of patients, this is an interesting result, and whether this phenomenon is described in other studies as well remains to be seen. Self-expandable chimney grafts were used for all patients and all target vessels. The ability of adapting a little to the environment in which the chimney graft is deployed makes a self-expandable graft probably the most suitable for use as chimney graft.
The use of the chimney technique is an acceptable method for exclusion of an aneurysm while preserving side branch revascularization and is a good alternative until fenestrated endoprostheses become widely available. However, current evidence is mainly based on small case series. Long-term results from greater series have to be awaited to consider the position of the chimney technique in the treatment of juxtarenal and suprarenal aneurysms.

FUTURE PERSPECTIVES

This thesis shows that several issues of AAA disease merit attention in future research. Treatment of AAAs is aimed to prevent the dilatating aneurysm wall from rupture. Up to now, diameter has been the major determinant of AAAs and the only proven tool to assess rupture risk and decide whether surgical treatment is indicated. Research should focus on new, advanced imaging techniques that provide information on the progression of AAAs and rupture risk. Peak wall stress and peak wall rupture risk, predicted using finite element analysis, appeared to be better predictors of rupture than maximum diameter.[32] Validation of these biomechanical models is necessary, and it would be informative to see if spots with high wall stress that are prone to rupture have other histologic and biochemical wall characteristics compared with spots with low wall stress.

Hybrid imaging techniques, such as positron-emission tomography (PET)/CT, and recently PET/MRI can combine morphologic and functional imaging of the abdominal aorta. Analysis of metabolic, biochemical, and inflammatory activity combined with anatomic imaging should lead to a better insight in the pathophysiology of AAA disease and to a better individualized assessment of rupture risk.

Future research should also focus on patient selection and outcome after EVAR. The indication for EVAR is widening continuously. The use of modified endovascular techniques, such as the chimney technique, and the use of latest-generation stent grafts makes EVAR possible for many patients. Older age and severe comorbidities also seem not to hamper successful EVAR, given the reported acceptable results in octogenarians and nonagenarians.

But what is the best treatment for young people? The lack of long-term results that focus specifically on young patients makes EVAR in young patients still controversial. Open aneurysm repair is often chosen for younger patients to avoid reinterventions and complications. This is somewhat remarkable, because the relative risk reduction of perioperative mortality after aneurysm repair is the greatest in younger patients who undergo EVAR.[33] Large (randomized) studies will have to answer the question of which treatment is the most durable for young patients. Appropriate attention should also be paid to the cost and radiation exposure, because these are other objections for the use of EVAR in young patients.

EVAR can only prove itself as a better alternative than open repair if long-term results are good. Despite having been introduced more than 20 years ago, EVAR is still rapidly evolving. Long-term results of new and currently used stent grafts should focus on reducing the number of secondary interventions. As described in **Chapter 8**, the secondary intervention rate in medium-term follow-up was substantial. Adequate preoperative planning may contribute to diminish the number of secondary interventions.

The importance of sufficient proximal fixation is often emphasized, but given the results in **Chapter 8**, attention should also be focused on distal fixation of the endograft. As mentioned, iliac pulsatile distension may play a role after stent graft implantation. Decreased distal sealing may occur as a result of iliac pulsatile distension potentially causing type Ib endoleak or stent graft retraction. Extension of the iliac limbs up to the internal iliac artery during the initial EVAR procedure could probably ensure adequate distal fixation.

Endoleaks are common and clinically relevant complications after EVAR. Type II endoleak, the most frequently detected endoleak, is also the most discussed one along with endotension. However, consensus has been reached that type II endoleaks in growing aneurysms should be treated. Transarterial and translumbar embolization are the two most commonly used techniques for type II treatment. Both techniques seem to have good technical success rates, but clinical success varies widely in the published reports. Important aspects that influence the clinical success are patient selection, the number of embolized afferent vessels, the embolization agent, and the definition of clinical success. Owing to heterogeneity of these issues in the available literature, no preferred treatment can yet be designated.

High-level evidence is necessary to know which method for elimination of type II endoleaks with growth yields the most sustainable result. Embolization of 1 or more vessels combined with direct sac puncture might be a better option than one of them as the sole treatment.[34] Clinical success should by all means be defined as stabilization or decrease of the aneurysm diameter and/or aneurysm volume and not as disappearance of the endoleak.

As with type II endoleak, endotension is still being debated. The term "endotension" was introduced in late 1990s to describe the phenomenon in which a patient had a sustained aneurysm after EVAR but without detectable endoleak on CTA. It is suggested that endotension is caused by an endoleak that remains below the limit of detection on CTA. This hypothesis is supported by the findings in **Chapter 7**, because a low-flow type II endoleak was detected in most patients.

Another theory suggests that pressure through the porous wall of the graft and passed by thrombus in the aneurysm sac may cause increased pressure on the vessel wall. The influence of the ILT in preoperative patients, as discussed in **Chapter 3**, might also play a role in post-EVAR patients. Because continued growth after EVAR has to be considered as failure of treatment, endotension deserves attention in future research.

ILT may be one of the potential targets of new studies. The composition of ILT in patients with endotension sometimes seems unorganized and inhomogeneous, and previously mentioned hybrid imaging techniques may provide more knowledge about the role of ILT. An analysis of patients with a shrinking aneurysm to see whether the same variations in thrombus consistency are present as in patients with endotension would be an interesting study. If this is the case, the findings on thrombus differences in enlarging aneurysms may become less relevant.

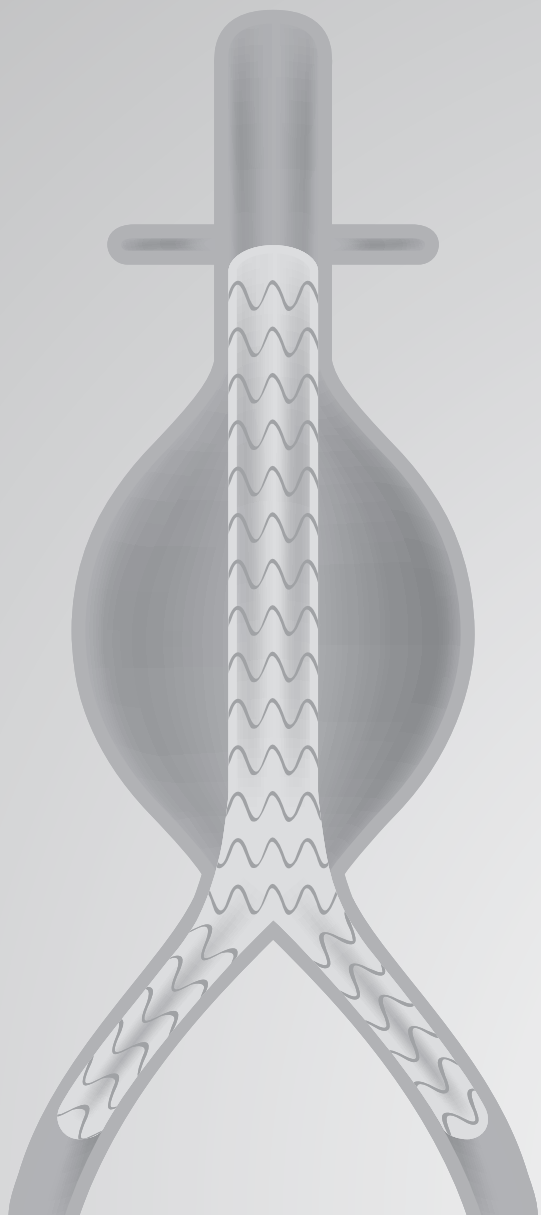
This thesis has aimed to provide insights into abdominal aortic aneurysms and endovascular repair. Future research will hopefully further improve the knowledge about aneurysmal disease and lead to advances in the (endovascular) treatment of AAA.

REFERENCES

1. MacSweeney ST, Powell JT, Greenhalgh RM. Pathogenesis of abdominal aortic aneurysm. Br J Surg. 1994;81(7):935-41.
2. Nordon IM, Hinchliffe RJ, Loftus IM, Thompson MM. Pathophysiology and epidemiology of abdominal aortic aneurysms. Nat Rev Cardiol. 2011;8(2):92-102.
3. Lederle FA, Johnson GR, Wilson SE, Ballard DJ, Jordan WD, Jr., Blebea J, et al. Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. JAMA. 2002;287(22):2968-72.
4. Scott RA, Tisi PV, Ashton HA, Allen DR. Abdominal aortic aneurysm rupture rates: a 7-year follow-up of the entire abdominal aortic aneurysm population detected by screening. J Vasc Surg. 1998;28(1):124-8.
5. Biasetti J, Gasser TC, Auer M, Hedin U, Labruto F. Hemodynamics of the normal aorta compared to fusiform and saccular abdominal aortic aneurysms with emphasis on a potential thrombus formation mechanism. Ann Biomed Eng. 2010;38(2):380-90.
6. Parr A, McCann M, Bradshaw B, Shahzad A, Buttner P, Golledge J. Thrombus volume is associated with cardiovascular events and aneurysm growth in patients who have abdominal aortic aneurysms. J Vasc Surg. 2011;53(1):28-35.
7. Wolf YG, Thomas WS, Brennan FJ, Goff WG, Sise MJ, Bernstein EF. Computed tomography scanning findings associated with rapid expansion of abdominal aortic aneurysms. J Vasc Surg. 1994;20(4):529-35; discussion 35-8.
8. Kazi M, Thyberg J, Religa P, Roy J, Eriksson P, Hedin U, et al. Influence of intraluminal thrombus on structural and cellular composition of abdominal aortic aneurysm wall. J Vasc Surg. 2003;38(6):1283-92.
9. Vorp DA, Lee PC, Wang DH, Makaroun MS, Nemoto EM, Ogawa S, et al. Association of intraluminal thrombus in abdominal aortic aneurysm with local hypoxia and wall weakening. J Vasc Surg. 2001;34(2):291-9.
10. Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. Lancet. 2004;364(9437):843-8.
11. Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med. 2004;351(16):1607-18.
12. De Bruin JL, Baas AF, Buth J, Prinssen M, Verhoeven EL, Cuypers PW, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med. 2010;362(20):1881-9.
13. Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med. 2010;362(20):1863-71.
14. de Vries JP. The proximal neck: the remaining barrier to a complete EVAR world. Semin Vasc Surg. 2012;25(4):182-6.
15. van Herwaarden JA, van de Pavoordt ED, Waasdorp EJ, Albert Vos J, Overtoom TT, Kelder JC, et al. Long-term single-center results with AneuRx endografts for endovascular abdominal aortic aneurysm repair. J Endovasc Ther. 2007;14(3):307-17.
16. van Keulen JW, Moll FL, Barwegen GK, Vonken EP, van Herwaarden JA. Pulsatile distension of the proximal aneurysm neck is larger in patients with stent graft migration. Eur J Vasc Endovasc Surg. 2010;40(3):326-31.
17. Muhs BE, Vincken KL, van Prehn J, Stone MK, Bartels LW, Prokop M, et al. Dynamic cine-CT angiography for the evaluation of the thoracic aorta; insight in dynamic changes with implications for thoracic endograft treatment. Eur J Vasc Endovasc Surg. 2006;32(5):532-6.
18. Teutelink A, Rutten A, Muhs BE, Olree M, van Herwaarden JA, de Vos AM, et al. Pilot study of dynamic cine CT angiography for the evaluation of abdominal aortic aneurysms: implications for endograft treatment. J Endovasc Ther. 2006;13(2):139-44.

19. van Herwaarden JA, Bartels LW, Muhs BE, Vincken KL, Lindeboom MY, Teutelink A, et al. Dynamic magnetic resonance angiography of the aneurysm neck: conformational changes during the cardiac cycle with possible consequences for endograft sizing and future design. J Vasc Surg. 2006;44(1):22-8.
20. van Prehn J, Vincken KL, Sprinkhuizen SM, Viergever MA, van Keulen JW, van Herwaarden JA, et al. Aortic pulsatile distention in young healthy volunteers is asymmetric: analysis with ECG-gated MRI. Eur J Vasc Endovasc Surg. 2009;37(2):168-74.
21. Johnsen SH, Forsdahl SH, Singh K, Jacobsen BK. Atherosclerosis in abdominal aortic aneurysms: a causal event or a process running in parallel? The Tromso study. Arterioscler Thromb Vasc Biol. 2010;30(6):1263-8.
22. van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. Stroke. 2001;32(2):454-60.
23. Schlosser FJ, Muhs BE. Endoleaks after endovascular abdominal aortic aneurysm repair: what one needs to know. Curr Opin Cardiol. 2012;27(6):598-603.
24. Schanzer A, Greenberg RK, Hevelone N, Robinson WP, Eslami MH, Goldberg RJ, et al. Predictors of abdominal aortic aneurysm sac enlargement after endovascular repair. Circulation. 2011;123(24):2848-55.
25. Schlosser FJ, Gusberg RJ, Dardik A, Lin PH, Verhagen HJ, Moll FL, et al. Aneurysm rupture after EVAR: can the ultimate failure be predicted? Eur J Vasc Endovasc Surg. 2009;37(1):15-22.
26. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg. 2009;50(4 Suppl):S2-49.
27. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1-S58.
28. Sachs T, Schermerhorn M, Pomposelli F, Cotterill P, O'Malley J, Landon B. Resident and fellow experiences after the introduction of endovascular aneurysm repair for abdominal aortic aneurysm. J Vasc Surg. 2011;54(3):881-8.
29. Verhagen HJ, Torsello G, De Vries JP, Cuypers PH, Van Herwaarden JA, Florek HJ, et al. Endurant stent-graft system: preliminary report on an innovative treatment for challenging abdominal aortic aneurysm. J Cardiovasc Surg (Torino). 2009;50(2):153-8.
30. van Keulen JW, Moll FL, Vonken EJ, Tolenaar JL, Muhs BE, van Herwaarden JA. Pulsatility in the iliac artery is significant at several levels: implications for EVAR. J Endovasc Ther. 2011;18(2):199-204.
31. Moulakakis KG, Mylonas SN, Avgerinos E, Papapetrou A, Kakisis JD, Brountzos EN, et al. The chimney graft technique for preserving visceral vessels during endovascular treatment of aortic pathologies. J Vasc Surg. 2012;55(5):1497-503.
32. Fillinger MF, Marra SP, Raghavan ML, Kennedy FE. Prediction of rupture risk in abdominal aortic aneurysm during observation: wall stress versus diameter. J Vasc Surg. 2003;37(4):724-32.
33. Schermerhorn ML, O'Malley AJ, Jhaveri A, Cotterill P, Pomposelli F, Landon BE. Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. N Engl J Med. 2008;358(5):464-74.
34. Funaki B, Birouti N, Zangan SM, Van Ha TG, Lorenz JM, Navuluri R, et al. Evaluation and treatment of suspected type II endoleaks in patients with enlarging abdominal aortic aneurysms. J Vasc Interv Radiol. 2012;23(7):866-72; quiz 72.

PART FOUR
Summary, general discussion, and future perspectives



CHAPTER 11

Nederlandse samenvatting

(voor niet ingewijden)

Aneurysma is afkomstig van het Griekse woord ἀνεύρυσμα (verwijding). Een aneurysma van de abdominale aorta (AAA) is dan ook een lokale verwijding van de buikslagader (abdominale aorta). De meest gehanteerde definitie van een AAA is gebaseerd op de diameter van de abdominale aorta en men spreekt van een AAA als de diameter van de aorta meer dan 3 centimeter is. Een andere veel gebruikte definitie is een dilatatie van ten minste 50% ten opzichte van de normale diameter van de aorta.
AAAs komen bij 4-7% van de bevolking voor en belangrijke risicofactoren voor het ontstaan van een AAA zijn hoge leeftijd, mannelijk geslacht en roken. De meeste aneurysmata ontstaan asymptomatisch en kunnen, na een periode waarin het aneurysma steeds groter wordt, uiteindelijk scheuren (ruptureren). Zo'n ruptuur is potentieel levensbedreigend en ongeveer 50% van de patiënten met een ruptuur bereikt levend het ziekenhuis waarna 30-70% van de patiënten alsnog overlijdt tijdens of na een spoedoperatie.
Om een ruptuur te voorkomen kan een AAA preventief chirurgisch worden behandeld. Behandeling van een AAA is geïndiceerd als het risico op een ruptuur het risico overstijgt dat gepaard gaat met een operatie.

DEEL 1

AAA beeldvorming en afbraak van de aneurysmawand
Hoe een aneurysma precies ontstaat, is nog onduidelijk. Wel is bekend dat het een multifactorieel complex proces is dat wordt gekenmerkt door het verlies van gladde spiercellen en bindweefsel (collageen en elastine) en infiltratie van ontstekingscellen in de wand van de aorta. Deze veranderingen resulteren in het dunner worden van de vaatwand en zorgen voor dilatatie van de aorta wat uiteindelijk kan leiden tot een ruptuur van het aneurysma.
Kennis van het ziekteproces in de wand van de aorta is van groot belang voor het identificeren van AAA risicofactoren, het zoeken naar voorspellende markers van AAA progressie en het ontdekken van mogelijke aangrijpingspunten voor nieuwe (medicamenteuze) therapieën.
De analyse van weefsel uit de wand van het AAA draagt bij aan een beter inzicht in het ziekteproces van AAAs. In de Aneurysma Express Biobank worden AAA vaatwandweefsel, bloed, klinische gegevens en follow-up gegevens verzameld van patiënten die een open operatie van hun AAA hebben ondergaan in het Universitair Medisch Centrum Utrecht of het Sint Antonius Ziekenhuis in Nieuwegein. Maar omdat weefsel van de aorta alleen kan worden verkregen bij patiënten die open worden geopereerd, is het van belang om een brug te slaan tussen de AAA vaatwandkarakteristieken en parameters die meetbaar zijn bij alle AAA patiënten. In deel 1 van dit proefschrift is gekeken of er associaties bestaan tussen parameters van vaatwanddegeneratie van de aorta en beeldvorming van het AAA.
De maximale aneurysmadiameter is een van de belangrijkste determinanten van AAA ziekte en het risico op rupturering neemt toe bij een grotere diameter. Toch zijn er ook patiënten die een klein aneurysma hebben dat ruptureert. Mogelijk is de diameter ratio van het aneurysma, de verhouding tussen de aneurysmadiameter en de oorspronkelijke diameter van de aorta, daarom meer geschikt om te gebruiken als maat voor het aneurysma. Een aneurysma met een diameter van 6 cm bij een patiënt met een oorspronkelijke aortadiameter van 1,8 cm is tenslotte meer

gegroeid dan bij een patiënt met een oorspronkelijke aortadiameter van 2,7 cm.
De waarde van de diameter ratio wordt behandeld in **hoofdstuk 2**. Op preoperatieve Computed Tomography Angiography (CTA)-scans van patiënten in de Aneurysma Express Biobank werd de maximale aneurysmadiameter en de oorspronkelijke aortadiameter, gemeten op een hoger gelegen en niet gedilateerd gedeelte van de aorta, bepaald. Zowel voor de diameter ratio als de maximale aneurysmadiameter werd gekeken of er onderscheidende associaties waren met weefseleigenschappen van de AAA vaatwand. Er werden wel enkele associaties gevonden maar deze waren niet sterk en er bleek geen duidelijk verschil tussen het gebruik van de maximale aneurysmadiameter of diameter ratio. Er kon niet overtuigend worden aangetoond dat een grotere aneurysmadiameter of diameter ratio een verder gevorderd ziektestadium in de AAA vaatwand weergeeft.
Het feit blijft echter dat op dit moment de maximale aneurysmadiameter het enige criterium is dat zich in voldoende mate heeft bewezen om te bepalen of chirurgisch ingrijpen is geïndiceerd. Andere parameters zullen zich in de nabije toekomst moeten bewijzen als betrouwbare voorspellers van AAA progressie en ruptuurrisico.
In **hoofdstuk 3** is op preoperatieve CTA-scans de intraluminale thrombus (ILT) onderzocht. Deze thrombus (een bloedstolsel in het bloedvat) zit tegen de wand van de aorta en is vrijwel in alle aneurysmata aanwezig, maar verschilt in dikte per patiënt. Eerdere studies hebben aangetoond dat thrombus is geassocieerd met groei van het aneurysma. Daarnaast toonde analyse van AAA vaatwand die is bedekt met ILT aan, dat er minder gladde spiercellen en elastine vezels aanwezig zijn in deze vaatwand ten opzichte van AAA vaatwand zonder ILT.
Uit analyse van de preoperatieve CTA-scans van patiënten in de Aneurysma Express Biobank bleek dat patiënten met een dikke ILT inderdaad een verlaagde hoeveelheid gladde spiercellen en elastine in hun vaatwand hadden. Daarnaast hadden patiënten met een dikke ILT een grotere AAA diameter en werd er tevens een associatie gevonden tussen de ILT dikte en een enzym dat zorgt voor afbraak van de vaatwand (MMP2). Deze bevindingen suggereren dat ILT de vaatwand integriteit aantast en dat een dikkere ILT mogelijk bijdraagt aan een snellere groei en grotere ruptuurkans van het aneurysma.

DEEL 2

Geavanceerde beeldvormende onderzoeken bij EVAR patiënten

Deel 2 van dit proefschrift gaat over beeldvormende onderzoeken bij patiënten die een endovasculaire behandeling van een aneurysma (EVAR) ondergaan. EVAR werd begin jaren 90 gelijktijdig ontwikkeld door de Oekraïense en Argentijnse chirurgen Nicholas Volodos en Juan Parodi als alternatief voor de ingrijpende klassieke open operatie. Bij deze open operatie wordt via een grote snee in de buik (laparotomie) het aneurysma uitgeschakeld door een flexibele kunststof buis in te hechten in het aangedane gedeelte van de aorta.
EVAR is echter minimaal invasief en via een toegang in de lies wordt vanaf de binnenkant van het bloedvat (endovasculair) een buisje van synthetisch materiaal, ondersteund door een metalen structuur, (stent graft) in de aorta geplaatst op de plek van het aneurysma. Deze stent graft verstevigt de aorta en zorgt ervoor dat het bloed dat vanuit het hart de aorta wordt ingepompt

geen druk meer kan uitoefenen op de verzwakte vaatwand. Gerandomiseerde studies hebben aangetoond dat EVAR, in vergelijking met een open operatie, een minimaal invasieve procedure is die leidt tot een reductie in mortaliteit en morbiditeit rondom de operatie. In vergelijking met open aneurysma uitschakeling gaat EVAR echter wel gepaard met een hoger aantal stent graft complicaties en secundaire interventies (heroperatie om een complicatie op te lossen) op de langere termijn. De stent grafts die zijn gebruikt in deze trials zijn echter niet vergelijkbaar met de types die tegenwoordig worden gebruikt. Door technische ontwikkelingen zijn de stent grafts verbeterd en ook de ervaring onder vaatchirurgen is sterk toegenomen. Desondanks blijft de duurzaamheid van EVAR op de lange termijn een belangrijk punt van aandacht en dat geldt met name voor jonge patiënten in verband met hun hogere levensverwachting.
Een van de essentiële factoren van een duurzaam resultaat van EVAR op de lange termijn is de proximale aneurysmanek. De proximale aneurysmanek is het stuk van de niet gedilateerde aorta, dat loopt van de onderste nierslagader tot het begin van het aneurysma. Voor een optimaal resultaat na een EVAR procedure moet het bovenste gedeelte van de stent graft zich in de proximale nek bevinden en goed aaneengesloten zijn tegen de wand van de aorta. Of de stent graft goed tegen de vaatwand aan kan liggen is afhankelijk van verschillende factoren zoals de lengte, diameter, pulsatiliteit en angulatie (kromming) van de proximale aneurysmanek. Nauwkeurige preoperatieve analyse van de nek is van groot belang om complicaties als migratie (beweging) van de stent graft en lekkage langs de bovenrand van de stent graft te voorkomen. Dynamische CTA-scans zijn voor die analyse geschikt. Op een standaard statische CTA-scan wordt een opname gemaakt van de aorta op een bepaald moment tijdens de hartcyclus. De diameter van de aorta verandert echter tijdens de hartcyclus als gevolg van de elasticiteit van de vaatwand en de pulserende bloedstroom. De gemeten diameter op een statische CTA-scan kan dus de maximale diameter, minimale diameter of ergens daar tussenin zijn.
Met dynamische CTA-scans, waarbij 1 hartslag wordt opgedeeld in 8 fases en de aorta wordt afgebeeld in elke fase, kan de distensie (uitrekking) van de aorta tijdens 1 volledige hartslag worden gevolgd. Eerder onderzoek met deze scans heeft aangetoond dat er sprake is van pulsatiele distensie in de proximale aneurysmanek tijdens de hartcyclus en dat de pulsatiele distensie in patiënten met stent graft migratie significant hoger is dan in patiënten zonder stent graft migratie. Tevens bleek dat gezonde jonge mensen een nog hogere pulsatiele distensie hebben.
In **hoofdstuk 4** is daarom onderzocht of er een verschil is in pulsatiele distensie tussen jonge en oude patiënten die een EVAR behandeling ondergaan. De preoperatieve pulsatiele distensie van een groep met 25 patiënten <65 jaar werd vergeleken met de pulsatiele distensie van een groep patiënten >65 jaar. Zowel op het niveau boven de nierslagader als onder de nierslagader was er geen verschil in pulsatiele distensie tussen de jonge en oude patiënten.
De risicofactoren voor AAA ziekte en slagaderverkalking (atherosclerose) zijn vergelijkbaar en hoewel het onduidelijk is of atherosclerose causaal verband houdt met AAA, ontwikkelen atherosclerose en AAA zich veelal parallel. Aangezien atherosclerose is geassocieerd met een toegenomen stijfheid van de vaatwand kan dit verklaren waarom er geen verschil in pulsatiele distensie werd gevonden in de huidige studie.
In deze studie is alleen de pulsatiele distensie van de proximale aneurysmanek geanalyseerd en er kunnen derhalve geen uitspraken worden gedaan over het optreden van complicaties in de proximale aneurysmanek. Het lijkt echter niet waarschijnlijk dat jonge patiënten meer kans

zouden hebben op dit soort complicaties die ontstaan door pulsatiele distensie van de proximale aneurysmanek.
De pulsatiele distensie wordt gemeten in het orthogonale vlak, het vlak loodrecht op een centrale lumen lijn (CLL) door het midden van de aorta. In voorgaande studies werd voor alle 8 fases op hetzelfde niveau van het lichaam naar de aorta gekeken. Als de aorta in het lichaam echter omhoog of omlaag zou bewegen, de zogeheten through-plane beweging, zou de pulsatiele distensie dus niet in elke fase op hetzelfde niveau van de aorta worden gemeten.
In **hoofdstuk 5** is met een nieuwe methode onderzocht of deze through-plane beweging aanwezig is. Op verschillende niveaus van de aorta, allen gelegen op een vaste afstand van een aftakkende arterie, werd met behulp van 3D-coördinaten de beweging van de aorta gevolgd gedurende de 8 fases van een dynamische CTA-scan. De beweging in de cranio-caudale richting (van het hoofd naar de voeten) was klein en rondom de nierslagaders, relevant voor de fixatie van de stent graft bij EVAR, was de beweging zelfs nog kleiner. Het effect van de through-plane beweging van de aorta lijkt dus minimaal en dit suggereert dat deze niet van invloed is op de fixatie van de stent graft. Daarnaast betekent het dat de resultaten van voorgaande studies slechts in zeer beperkte mate zijn verstoord door through-plane beweging.
De studie zoals beschreven in dit hoofdstuk heeft zich echter alleen kunnen richten op de beweging van de aorta als geheel. Vervolgonderzoek zou moeten bestaan uit het analyseren van distensie van de aortawand parallel aan de CLL. Dit moet aantonen of de aorta ook uitrekt en inkrimpt in de longitudinale richting tijdens de hartcyclus. Dit zou gevolgen kunnen hebben voor zowel de proximale (bovenrand) als ook de distale (onderrand) fixatie van de stent graft.

Een regelmatig voorkomende en klinisch relevante complicatie na EVAR is het ontstaan van een endoleak. Een endoleak is lekkage van bloed langs de stent graft in de aneurysmazak (de ruimte tussen de buitenkant van de stent graft en de wand van de aorta). Endoleaks worden ingedeeld in verschillende types. De belangrijkste types zijn type I en II endoleaks. Type I endoleaks zijn lekkages langs de stent graft ter hoogte van de bovenrand (type Ia) of onderrand (type Ib) van de stent graft. Bij een type II endoleak blijft er een bloedstroom bestaan in de oorspronkelijke aneurysmazak via kleine zijtakjes van de aorta. Op dit moment is een endoleak de meest voorkomende reden voor een secundaire interventie na EVAR. Uit de literatuur blijkt tevens dat endoleaks een sterke onafhankelijke voorspeller zijn van groei van het aneurysma na EVAR en de belangrijkste oorzaak zijn van een ruptuur na EVAR. Adequate detectie van endoleaks is derhalve van groot belang. In **hoofdstuk 6** en **hoofdstuk 7** van dit proefschrift wordt gekeken naar de postoperatieve beeldvorming gedurende de follow-up van EVAR patiënten. De huidige internationale richtlijnen adviseren voor de postoperatieve beeldvorming een CTA-scan één en twaalf maanden na EVAR. Indien een endoleak of andere afwijking die conservatief vervolgd kan worden wordt waargenomen op de eerste CTA, wordt een extra CTA geadviseerd 6 maanden na EVAR en jaarlijks na de 1 jaars follow-up. Als er geen endoleak, groei of andere abnormaliteit wordt gevonden tijdens het eerste jaar kan daarna worden volstaan met een jaarlijkse duplex (combinatie van echografie en kleurendoppler). Hoewel CTA dus de gouden standaard is voor de detectie van endoleaks kan CTA endoleaks missen. Andere beeldvormende technieken zoals Magnetic Resonance Imaging (MRI) zijn daarom interessante alternatieven voor de detectie van endoleaks.

In **hoofdstuk 6** worden de resultaten gepresenteerd van een literatuurstudie die de detectie van endoleaks op CTA-scans vergelijkt met de detectie van endoleaks op MRI-scans. Op basis van 11 studies met in totaal 369 patiënten werden 146 endoleaks gevonden op CTA-scans die allemaal, op 2 na, ook werden gevonden op de MRI-scans. Daarnaast werden op de MRI-scans 132 additionele endoleaks gevonden waarvan het merendeel (69%) een type II endoleak betrof. De onderliggende studies rapporteerden slechts in beperkte mate of het gevonden endoleak gepaard ging met groei van het aneurysma. Dit is zeker voor de additioneel gevonden type II endoleaks van belang, omdat volgens de huidige inzichten een type II endoleak slechts behandeling vereist als het gepaard gaat met groei van het aneurysma.
Als vervolgonderzoek werd een prospectieve studie gestart die is beschreven in **hoofdstuk 7**. Alle patiënten die na EVAR ≥ 5 mm groei van het aneurysma hadden en waarbij op een CTA-scan geen of een onduidelijk endoleak werd gevonden, kwamen in aanmerking voor verdere evaluatie middels een MRI-scan met een blood pooling contrastmiddel. Dit contrastmiddel blijft langer in het vaatstelsel aanwezig waardoor ook endoleaks met een lage stroomsnelheid kunnen worden gevonden.
Uit de resultaten bleek dat een MRI-scan met een dergelijk contrastmiddel een sterke additionele waarde heeft voor de detectie van endoleaks. Bij 15 van de 21 patiënten werd een type II endoleak gevonden, waarbij 1 patiënt mogelijk ook een type Ia endoleak had. Daarnaast bleek dat voor de gevonden type II endoleaks ook de oorsprong van het endoleak veelal (bij 67% van de patiënten) te detecteren was door het aankleuren met contrast van de aanvoerende arteriën. Onverklaarbare aneurysmagroei na EVAR is een goede indicatie is om additioneel een MRI-scan te maken met een blood pooling contrastmiddel. MRI zal de rol van CTA en duplex in de reguliere follow-up echter niet vervangen vanwege de kosten, de minder brede toepasbaarheid als gevolg van contra-indicaties (metalen implantaten, claustrofobie) en de langere scantijd, maar het is een waardevolle aanvulling op het bestaande follow-up schema.

DEEL 3

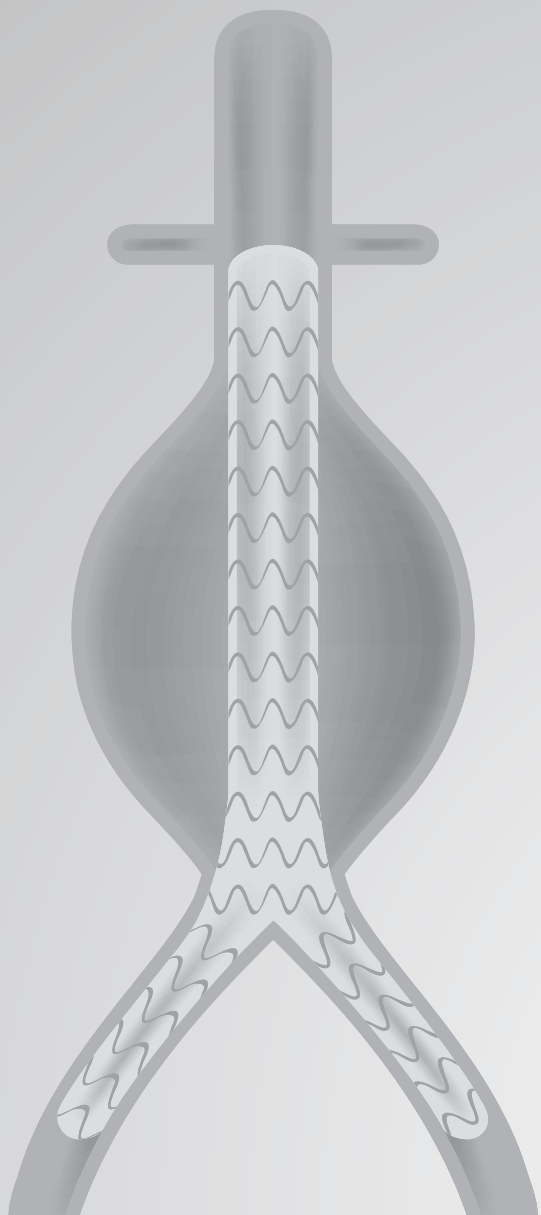
Klinische uitkomst na EVAR

De klinische uitkomsten na EVAR worden behandeld in deel 3 van dit proefschrift. Voor patiënten met een geschikte anatomie is EVAR inmiddels in veel ziekenhuizen de behandeling van eerste keus. Sinds de introductie van de Endurant, één van de laatste generatie stent grafts, kunnen ook patiënten met een korte en meer gebogen proximale aneurysmanek of een gekronkelde, smalle en verkalkte arteria iliaca (slagader naar de benen toe) veilig endovasculair worden behandeld. In **hoofdstuk 8** worden de middellange termijn resultaten beschreven van de eerste 100 opeenvolgende patiënten die zijn behandeld met deze Endurant stent graft. Van de 100 patiënten die werden geëvalueerd vielen 19 buiten de instructions for use (IFU) van de fabrikant omdat deze patiënten een kortere, wijdere nek of een grotere angulatie van de nek hadden dan de IFU voorschreven.
Na 1,2,3 en 4 jaar follow-up was het primaire klinische succes respectievelijk 98%, 90%, 84% en 77%. Er was geen verschil in klinisch succes tussen de patiënten die binnen de IFU en buiten de IFU werden behandeld. Deze resultaten zijn vergelijkbaar met die van eerder op de markt

gekomen stent grafts die gelijktijdig commercieel verkrijgbaar zijn. Ook het percentage patiënten waarbij het aneurysma kleiner wordt na EVAR (ongeveer 60%) was vergelijkbaar. De overall mortaliteit na 4 jaar was 20% en de aneurysma gerelateerde mortaliteit bedroeg 3%. Gezien de mogelijk verhoogde kans op complicaties als gevolg van de uitdagende anatomie van sommige patiënten, is deze AAA mortaliteit laag.
Een opvallende bevinding was het relatief hoge aantal distale extensies (een verlenging van de onderkant van de stent graft) dat werd geplaatst in deze studiepopulatie. In totaal kregen 8 patiënten een distale extensie waarvan 5 voor een type Ib endoleak.
Momenteel zijn er nog geen andere groepen die hun middellange termijn ervaringen met deze stent graft hebben gepubliceerd. De resultaten van de Endurant kunnen derhalve alleen nog maar worden vergeleken met eerder op de markt gekomen stent grafts van andere fabrikanten. Meerdere (middel)lange termijn resultaten zijn zeer gewenst om de duurzaamheid van de Endurant goed te kunnen beoordelen.
Hoofdstuk 9 beschrijft de resultaten van de chimney (schoorsteen) techniek. Deze endovasculaire techniek biedt de mogelijkheid om de doorbloeding van belangrijke grote zijtakken van de aorta, die onder andere de nieren, darmen, lever, maag, milt en alvleesklier van bloed voorzien, te behouden indien het aneurysma boven deze aftakkingen begint. Via een toegang in de arm wordt een zelf-ontplooibare kleine stent (de chimney graft) ontvouwen in een van de aftakkende slagaders van de aorta die behouden moet worden omdat deze anders zou worden afgesloten door de hoofd stent graft. Deze chimney graft eindigt vervolgens boven de hoofd stent graft die vanuit de lies omhoog wordt gevoerd. Op die manier kan de stent graft hoger worden geplaatst dan een aftakkende arterie omdat deze blijvend van bloed wordt voorzien door de chimney graft die als een schoorsteen langs de stent graft omhoog loopt en boven de rand van stent graft uitsteekt.
Dertien patiënten met een juxta- of suprarenaal aneurysma (aneurysma tot naast of boven de nierslagader) die niet geschikt waren voor open of gefenestreerde behandeling (EVAR met een op maat gemaakte stent graft met gaatjes ter hoogte van de aftakkende arteriën), werden endovasculair behandeld. Deze patiënten waren in een te slechte conditie om een open operatie aan te kunnen en hadden geen andere optie aangezien een gefenestreerde stent graft niet mogelijk was door de acute situatie of omdat deze was geweigerd door de fabrikant. De mortaliteit rondom de operatie was 0% en tijdens de mediane follow-up van 11 maanden overleden 2 patiënten, 1 ten gevolge van een aneurysma ruptuur en 1 na de complicaties van een vernauwde truncus coeliacus (vertakkende slagader naar onder andere lever, maag, milt en alvleesklier). Deze mortaliteit is aanzienlijk maar men moet niet vergeten dat deze patiënten grote aneurysmata hadden (gemiddelde diameter >70 mm) met ernstige comorbiditeit en absoluut ongeschikt waren voor open chirurgische behandeling. De aneurysmadiameter nam af of bleek gelijk in 11 patiënten.
Een van de kernpunten in de behandeling met de chimney techniek is de kans op het ontstaan van zogeheten gutters (gootjes) door de aanwezigheid van de chimney grafts. Deze gutters kunnen zorgen voor een doorgang van het bloed langs de stent graft naar de aneurysma zak, resulterend in een type Ia endoleak. In deze serie had 1 patiënt een type Ia endoleak doordat de stent graft in de aorta niet volledig ontplooid was. Dit endoleak verdween echter spontaan. De gutters langs de stent grafts werden kleiner gedurende de follow-up en er werd geen relatie

gevonden met groei van het aneurysma of het ontstaan van een type Ia endoleak. Hoewel door de kleine serie hier geen harde conclusies aan kunnen worden verbonden is dit toch een interessant gegeven.
Het gebruik van de chimney techniek is een acceptabele methode voor het uitschakelen van een aneurysma met behoud van doorbloeding van de zijtakken van de aorta en is een goed alternatief totdat gefenestreerde stent grafts op grote schaal verkrijgbaar zijn. Het huidige bewijs is echter vooral gebaseerd op kleine case series. Lange termijn resultaten zullen moeten worden afgewacht om te kunnen zeggen wat de plaats van de chimney techniek is in de behandeling van juxta- en suprarenale aneurysmata.

In **hoofdstuk 10** worden tot slot de voorgaande hoofdstukken samengevat en de resultaten bediscussieerd. Tevens wordt er een visie voor de toekomst gegeven. Toekomstig onderzoek moet zich richten op geavanceerde non-invasieve beeldvormende technieken die informatie kunnen verschaffen over AAA-progressie en de kans op het ontstaan van een ruptuur. Daarnaast zal er aandacht moeten zijn voor patiëntselectie en de klinische uitkomsten van EVAR. Het gebruik van vernieuwende endovasculaire technieken, zoals de chimney techniek, en de snelle technische vooruitgang die leidt tot de ontwikkeling van nieuwe stent grafts, zorgen ervoor dat een EVAR behandeling inmiddels voor veel AAA patiënten mogelijk is. Lange termijn resultaten moeten meer inzicht geven in de duurzaamheid van EVAR. Daarnaast moeten nieuwe studies zich richten op het terugdringen van het aantal secundaire interventies. Toekomstig onderzoek kan hopelijk bijdragen aan meer kennis over aneurysmata van de abdominale aorta en leiden tot verbetering van de (endovasculaire) behandeling.



APPENDICES

Review committee
List of publications
Dankwoord
Curriculum vitae

REVIEW COMMITTEE

Prof. Dr. G. Pasterkamp
Experimental Cardiology Laboratory
University Medical Center Utrecht
Utrecht, The Netherlands

Prof. Dr. I.H.M. Borel Rinkes
Department of Surgery
University Medical Center Utrecht
Utrecht, The Netherlands

Prof. Dr. W.P.T.M. Mali
Department of Radiology
University Medical Center Utrecht
Utrecht, The Netherlands

Prof. Dr. H.J.M. Verhagen
Department of Vascular Surgery
Erasmus Medical Center
Rotterdam, The Netherlands

LIST OF PUBLICATIONS

Zandvoort HJ, Moll FL, Domanian A, van Keulen JW, Vonken EP, van Herwaarden JA. Preoperative infra- and suprarenal aortic pulsatile distension is comparable between relatively young and older patients with an abdominal aortic aneurysm. *Ann Vasc Surg. 2013 Oct 27. Epub ahead of print*

Tolenaar JL, **Zandvoort HJ**, Moll FL, van Herwaarden JA. Technical considerations and results of chimney grafts for the treatment of juxtarenal aneursyms. *J Vasc Surg. 2013 Sep;58(3):607-15.*

Zandvoort HJ*, Habets J*, Reitsma JB, Bartels LW, Moll FL, Leiner T, van Herwaarden JA. Magnetic resonance imaging is more sensitive than computed tomography angiography for the detection of endoleaks after endovascular abdominal aortic aneurysm repair: a systematic review. *Eur J Vasc Endovasc Surg. 2013 Apr;45(4):340-50.*

Tolenaar JL, **Zandvoort HJ**, Hazenberg CE, Moll FL, van Herwaarden JA. The double two-chimney technique for complete renovisceral revascularization in a suprarenal aneurysm. *J Vasc Surg. 2013 Aug;58(2):478-81.*

van Zeggeren L, Bastos Gonçalves F, van Herwaarden JA, **Zandvoort HJ**, Werson DA, Vos JA, Moll FL, Verhagen HJ, de Vries JP. Incidence and treatment results of Endurant endograft occlusion. *J Vasc Surg. 2013 May;57(5):1246-54*

Zandvoort HJ*, Koole D*, Schoneveld A, Vink A, Vos JA, van den Hoogen LL, de Vries JP, Pasterkamp G, Moll FL, van Herwaarden JA. Intraluminal abdominal aortic aneurysm thrombus is associated with disruption of wall integrity. *J Vasc Surg. 2013 Jan;57(1):77-83*

Zandvoort HJ, van Herwaarden JA, Habets J, Leiner T, Moll FL. (2013). Type II endoleaks: what are the best means to detect them? In JP Becquemin (Ed.), *Controversies and updates in vascular surgery 2013* (pp 128-33). Marseille: divine [id]

Bastos Gonçalves F, Verhagen HJ, Chinsakchai K, van Keulen JW, Voûte MT, **Zandvoort HJ**, Moll FL, van Herwaarden JA. The influence of neck thrombus on clinical outcome and aneurysm morphology after endovascular aneurysm repair. *J Vasc Surg. 2012 Jul;56(1):36-44*

Zandvoort HJ, Waasdorp EP, van Herwaarden JA, Moll FL. (2012). AAA imaging and preoperative EVAR planning; essential for EVAR success? In JPPM de Vries (Ed.), *Latest insights into abdominal aortic aneurysms and endovascular repair* (pp 39-46). Turijn: Edizioni Minerva Medica

Koole D, Moll FL, Buth J, Hobo R, **Zandvoort HJ**, Pasterkamp G, van Herwaarden JA; EUROSTAR collaborators. The influence of smoking on endovascular abdominal aortic aneurysm repair. *J Vasc Surg. 2012 Jun;55(6):1581-6*

** These authors contributed equally to the manuscript*

Zandvoort HJ, Habets J, Leiner T, Moll FL, van Herwaarden JA. (2012). Review of Type 2 endoleaks. In RM Greenhalgh (Ed.), *Vascular and Endovascular Controversies Update* (pp 302-8). London: BIBA Medical

Zandvoort HJ, Moll FL, van Herwaarden JA. Re: "pragmatic minimum reporting standards for endovascular abdominal aortic aneurysm repair". *J Endovasc Ther. 2011 Dec;18(6):819*

Koole D, Moll FL, Buth J, Hobo R, **Zandvoort HJ**, Bots ML, Pasterkamp G, van Herwaarden JA; EUROSTAR collaborators. Annual rupture risk of abdominal aortic aneurysm enlargement without detectable endoleak after endovascular abdominal aortic repair. *J Vasc Surg. 2011 Dec;54(6):1614-22*

Verhage RJ, **Zandvoort HJ**, ten Kate FJ, van Hillegersberg R.How to define a positive circumferential resection margin in T3 adenocarcinoma of the esophagus. *Am J Surg Pathol. 2011 Jun;35(6):919-26*

DANKWOORD

Dit proefschrift zou niet tot stand zijn gekomen zonder de hulp van vele anderen. Daarom wil ik op deze plaats iedereen bedanken die direct en indirect een bijdrage heeft geleverd aan dit proefschrift. Een aantal van hen wil ik in het bijzonder bedanken.

Prof. Dr. F.L. Moll, beste professor, ik ben u zeer dankbaar dat u mij de mogelijkheid heeft gegeven om onder uw supervisie promotieonderzoek te kunnen doen. Door uw enthousiasme en toegankelijkheid heb ik de begeleiding altijd als zeer prettig ervaren. Ik bewonder uw charismatische manier van werken en het vermogen om op inventieve wijze het onderzoek steeds weer een stap vooruit te helpen. Dank voor de leerzame en plezierige tijd.

Dr. J.A. van Herwaarden, beste Joost, jouw enthousiasme en positiviteit zijn ongekend en werken aanstekelijk en inspirerend. Daardoor ging ik na ons wekelijkse overleg altijd vol goede moed weer aan de slag met de zaken die we hadden besproken, wetende dat het goed zou komen. Ik wil je ervoor bedanken dat je ondanks je drukke agenda altijd de tijd hebt gevonden om mij op een opbouwende en motiverende manier te begeleiden.

Prof. Dr. G. Pasterkamp, Prof. Dr. I.H.M. Borel Rinkes, Prof. Dr. W.P.T.M. Mali en Prof. Dr. H.J.M. Verhagen, hartelijk dank voor het plaatsnemen in de leescommissie en het kritisch beoordelen van dit proefschrift.

Drs. F. Bastos Gonçalves, Prof. Dr. H.J.M. Verhagen, Dr. J.P.P.M. de Vries en D.A.B. Werson. De samenwerking tussen Rotterdam, Nieuwegein en Utrecht op EVAR gebied is erg waardevol gebleken en vormt een goede bron voor interessant klinisch onderzoek. Veel dank voor jullie hulp bij het verzamelen van de data en de snelle en kritische revisies.

Dr. T. Leiner en Dr. J. Habets. Dank voor de samenwerking op het gebied van endoleaks. Ik hoop dat dit project een mooi vervolg kan krijgen.

Rob Hurks en Dave Koole, het is mooi dat de kruisbestuiving met de Aneurysma Express Biobank heeft geresulteerd in twee hoofdstukken. Rob, jouw optimisme maakt je een ideale partner om mee samen te werken. Dank voor je hulp en flexibiliteit. Dave, jouw bevlogenheid is onnavolgbaar en bewonderenswaardig. Dank voor de fijne samenwerking.

Jip Tolenaar, jouw enorme gedrevenheid heeft er mede voor gezorgd dat er twee mooie chimney stukken zijn gepubliceerd. Dank voor de goede samenwerking en succes met het afronden van jouw promotie.

Jasper van Keulen, jij hebt me wegwijs gemaakt in de 3mensio metingen en op afstand vanuit Yale geholpen met de eerste studie. Helaas kwam er veel te vroeg een eind aan de samenwerking. Aan jouw gretigheid en ambitie kan iedereen een voorbeeld nemen.

Co-auteurs: Dr. Ir. L.W. Bartels, Prof. Dr. G. Pasterkamp, Dr. J.B. Reitsma, A.H. Schoneveld, Dr. A. Vink, Dr. Ir. E.P.A. Vonken en Dr. J.A. Vos. Hartelijk dank voor jullie belangrijke bijdrage aan de diverse manuscripten.

Rob van den Heuvel, dankzij jou is het organisatorische gedeelte rond dit promotietraject op rolletjes verlopen. Dank voor je interesse en mooie bespiegelingen tijdens onze afspraken. Dit proefschrift kun je beschouwen als de laatste periodieke rapportage.

Susan Hora Siccama en Cobie van Veen. Dank voor zowel de ondersteuning en het regelen van allerhande zaken als de gezellige praatjes op het secretariaat.

Kamergenoten uit de Toren: Amir, Bas, Dave, Guus, Joyce, Rob en Vincent. Dank voor jullie interesse, hulp en adviezen op onderzoeksgebied. Maar ook de niet werkgerelateerde zaken waren zeer belangrijk. Mooie grappen, profcoach, goede en minder goede muziek, push-ups en basketbal, congressen, tour de france, borrels, ticket to ride, 'het terras op' in Tilburg en vele andere zaken maken dat ik met veel plezier terugkijk op de afgelopen periode. Jullie zijn topcollega's!

Buren van kamer 8.05 en 3.03: Crystel, Jonne, Marten, Sander en Vince. Het is altijd leuk als jullie langs komen op de vaatkamer. Dank voor de gezelligheid en natuurlijk de kleurenprintjes.

Alle stafleden en arts-assistenten van de afdeling chirurgie in het UMC Utrecht. Hartelijk dank voor jullie betrokkenheid en interesse.

Alle (oud-) collega onderzoekers van de afdeling chirurgie in het UMC Utrecht: Okan Bastian, Guido van Bogerijen, Dominique Buck, Benjamin Emmink, Samira Fegrachi, Margriet Fokkema, Arja Gerritsen, Klaas Govaert, Amy Gunning, Anne den Hartog, Leonie Haverkamp, Marjolein Heeres, Charlotte van Kessel, Jakob Kist, Pieter Leliefeld, Lutske Lodewijk, Femke Mauritz, Sjoerd Nell, Stefanie Peeters Weem, Claire Pennekamp, Emily Postma, Quirina de Ruiter, Pieter van der Sluis, Ernst Steller, Martin Teraa, Michel Teuben, Kari Trumpi, Dorine Tseng, Thomas Vellinga, Roy Verhage, Teus Weijs, Jantien Welleweerd en Peter Paul Wisman. Dank voor de vele mooie momenten binnen en buiten het UMCU.

Studenten Geneeskunde: Hector de Beaufort, Artin Domanian, Luuk van den Hoogen, Jeroen de Jonge en Arno de Wilde. Ik wil jullie bedanken voor de hulp bij de verschillende studies en hoop dat jullie enthousiast zijn geworden voor het onderzoek. Succes met het afronden van jullie studie.

Jeroen de Ruijter en Wendy Schoneveld. Dit proefschrift had er niet zo mooi uitgezien zonder jullie hulp. Dank voor jullie flexibele instelling en vakkundige werk.

Pubquizteam de Nijlpanda: Caroline, Laurens de H, Laurens W, Marijn en Roel. Het was erg relativerend om naast alle serieuze zaken ook iets met nutteloze kennis te kunnen doen. Bedankt voor de leuke en gezellige maandagavonden.

Vrienden van de Beaut en Impaala: Caroline, Charlotte, Greetje, Jan Willem, Laurens, Lisette, Marijn, Tim, Vincent en Wouter. In 2003 in Groningen begonnen en net ons 2e lustrum gevierd. Dank voor de geweldige feestjes, vakanties en talloze andere hoogtepunten in die tijd. Ik kijk uit naar nog vele jaren mooie vriendschap!

Beste Laurens, dank voor alle momenten die juist niets met het onderzoek te maken hadden. Jouw enthousiasme en plezier zijn aanstekelijk en maken je tot een echte gangmaker en goede vriend. De fietstochten, feestjes, en andere activiteiten hebben voor de broodnodige afleiding gezorgd. Ik ben blij dat je 10 december als paranimf naast me staat.

Familie IJtsma. Lieve Dick, Loes, Annemiek en Esther. Dank voor jullie belangstelling voor mijn onderzoek en de gezelligheid tijdens de bezoekjes aan Leiden, de wintersport en andere gelegenheden. Ik hoop dat er nog vele zullen volgen!

Lieve Hanneke, ik ben trots dat jij m'n zusje bent en bewonder jouw onbevangen en positieve mentaliteit. Je betekent erg veel voor me en ik vind het dan ook een eer dat jij als paranimf aan mijn zijde staat.

Lieve papa en mama, zonder jullie steun was dit niet gelukt. Dankzij jullie onvoorwaardelijke liefde en vertrouwen heb ik altijd kunnen doen wat ik graag wilde en ben ik geworden wie ik nu ben. Jullie zijn fantastische ouders! Dank dat jullie er altijd voor me zijn.

Lieve Margo, jij maakt me iedere dag gelukkig. We zijn beiden blij dat het boekje nu af is en ik verheug me op een mooie toekomst samen. Heel veel dank voor al je begrip en steun, maar bovenal je liefde. Je t'aime!

CURRICULUM VITAE

Herman Jan Albert Zandvoort was born on January 30, 1986, in Alphen aan den Rijn, the Netherlands. In 2003, he graduated from secondary school at the Praedinius Gymnasium in Groningen and started studying medicine at the University of Groningen. After completion of his senior internships at the Deventer Hospital and a research elective at the Department of Surgery of the University Medical Center Utrecht, under the supervision of Prof. Dr. R. van Hillegersberg, he graduated from medical school in 2010.
Following graduation, he had the opportunity to work as a PhD student at the Department of Vascular Surgery of the University Medical Center Utrecht under the supervision of Prof. Dr. F.L. Moll and Dr. J.A. van Herwaarden focussing on abdominal aortic aneurysms. The results of this research are presented in this thesis. In January 2014 he will start as a nontraining resident (ANIOS) at the Department of Surgery at the Reinier de Graaf Hospital in Delft under the supervision of Dr. M. van der Elst.