MRI FOLLOW-UP OF ABDOMINAL AORTIC ANEURYSMS AFTER ENDOVASCULAR REPAIR

Sandra Cornelissen

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MRI follow-up van abdominale aorta aneurysmata na endovasculaire behandeling

(met een samenvatting in het Nederlands)

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Sandra Adriana Petronella Cornelissen

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Promotoren:	Prof. dr. ir. M.A. Viergever
	Prof. dr. W.P.Th.M. Mali
	Prof. dr. F.L. Moll
Co-promotor:	Dr. ir. L.W. Bartels

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General Introduction

The abdominal aortic aneurysm

The aorta is the largest artery in our body. It carries blood from the left ventricle of the heart to all our organs and extremities. The aortic wall contains elastic fibers which enable it to expand when it receives the pulsatile blood flow from the heart and return to normal size between cardiac contractions. Congenital or acquired weaknesses of the aortic wall can lead to a dilatation of the aorta. A dilatation of the abdominal aorta with more than 50 % of its normal diameter or an aortic diameter larger than 3 cm is called an abdominal aortic aneurysm (AAA).[3] The prevalence of AAA in men aged 65 to 80 years is between 4% and 8%.[4] The etiology of AAA is not yet understood. Smoking is associated with aneurysm expansion while diabetes and a low ankle-brachial index are associated with lower growth rates.[5] The natural history of an aneurysm is aneurysm growth which increases rupture risk.[6] Aneurysm rupture is a highly lethal condition. Half of the patients do not reach the hospital alive, and the reported in-hospital mortality in the Netherlands is 41 %.[7] A diameter of 5.5 cm is generally seen as an indication for treatment because rupture risk then outweighs treatment risk.[6,8,9]

Endovascular aneurysm repair

Until the 90's the only treatment option available to prevent rupture was open aortic surgery. During such a procedure, a laparotomy is performed and a vascular prosthesis is anastomosed with the aorta during which the aorta needs to be clamped. The aneurysm sac is opened, its contents are removed and it is closed around the vascular prosthesis. After open aortic repair, the patient is usually admitted to an intensive care unit. The reported peri-operative mortality lies between 3.8 and 8 %.[10] After open aortic surgery, imaging surveillance is generally not necessary. Since the 90's infrarenal aortic aneurysms can also be treated with a minimally invasive endovascular technique (EVAR) in which an endoprosthesis is introduced in the abdominal aortic aneurysm via the common femoral and iliac arteries. Aneurysms and access vessels should meet certain anatomic criteria to be suitable for this technique. [11] The endoprosthesis is carefully placed caudal to the renal arteries and lands distally in the common iliacs or external iliac arteries depending on the anatomy of the aneurysm. The Dutch Randomized Aneurysm Management trial (DREAM) and the British Endovascular Aneurysm Repair trial (EVAR-1) compared open surgery with endovascular treatment and showed a reduction in peri-operative mortality in favor of endovascular treatment. [12,13] However, in the long-term this difference was not sustained.[14,15]

Late complications of endovascular aneurysm repair

After EVAR more secondary interventions are needed than after open repair owing to late complications. Aneurysm size changes form the basis of the follow-up after EVAR, because aneurysm growth increases rupture risk. If endoleak or migration of the endograft is found in a growing aneurysm, treatment is indicated.[16] Occlusive complications also form an indication for secondary intervention. Endoleak is defined as persistent blood flow in the aneurysm sac, which denotes the area between the endoprosthesis and the aortic wall. Different types of endoleak are recognized according to their source (Figure 1).[1,2] Type I endoleak occurs at the proximal or distal attachment sites, type II endoleak denotes retrograde flow via branching arteries, type III endoleak arises from disconnection of graft modules or a defect in the graft and type IV endoleak refers to graft porosity. Type I and III endoleak have been reported to promote aneurysm growth, type II endoleak often has a more benign course.[17]

Imaging modalities for endovascular treatment follow-up

Long-term imaging surveillance after EVAR is necessary to monitor aneurysm sac size and to diagnose complications in time. At the end of the EVAR-procedure a completion angiogram is acquired to confirm the position and patency of the endoprosthesis, the patency of the renal arteries and to diagnose endoleaks. Digital subtraction angiography has been the gold standard for endoleak detection in the literature, however due to its invasiveness, it is now mainly used for complex cases and has been mostly replaced by noninvasive modalities in the standard follow-up.[18-21] An all-in-one approach is generally used by performing yearly CTA exams. However, the accumulation of radiation dose and the repeated use of nephrotoxic contrast agent are disadvantages of CT follow-up.[22] Also ultrasound and MRI are suitable modalities with strengths and weaknesses for different aspects of the follow-up.[18] Alternatively, some institutions primarily monitor aneurysm size by ultrasound and only perform additional imaging in case of aneurysm growth, which is less invasive and probably more cost-effective.[23] In case of aneurysm growth, additional imaging for endoleak detection can be performed with CTA,[24-26] contrast-enhanced ultrasound,[27] or contrast-enhanced MRI in case of an MR compatible endoprosthesis. MRI has been shown to be more sensitive to endoleak than CT.[28-33] When an endoleak is found, treatment of the endoleak can be considered to try to stop aneurysm growth. Endoleaks can usually be treated in an endovascular procedure by placement of extension cuffs, embolization of the endoleak or relining of the endoprosthesis, depending on the source of the endoleak.[34]

What happens inside the aneurysm after endovascular treatment?

Although endoleaks cause aneurysm growth in a subgroup of patients, the etiology of aneurysm size changes is not fully understood. Type I and III endoleaks have been reported to promote aneurysm growth.[17] However, shrinking aneurysms in the presence of endoleak as well as growing aneurysms without evidence of endoleaks also occur. The latter phenomenon has been termed endotension. Its reported prevalence varies from 5 to 7 %.[17,35] Endotension is associated with an increased rupture risk,[36] but the underlying cause is still debated.[37] Consequently, no treatment target is available. The ultimate treatment option is conversion to open surgery. Multiple possible causes for endotension have been suggested in the literature such as endoleaks with different hemodynamics which remain undetected on CT or processes which take place in the aneurysm sac. Magnetic resonance imaging is an interesting modality for investigating both. Besides its superior sensitivity for endoleak, MRI has been reported to be suitable to visualize the contents of the aneurysm sac thanks to its superior soft tissue contrast. Hyperintense regions in the aneurysm sac on T2-weighted images have been shown to correspond to unorganized thrombus, while hypointense areas correspond to organized thrombus. [38,39] Detailed imaging of the consistency of the aneurysm sac and more accurate endoleak detection may shed new light on the problem of endotension. Alternatively, such knowledge will potentially increase the insight in aneurysm size changes after EVAR, and may lead to a more patient specific follow-up in the future.

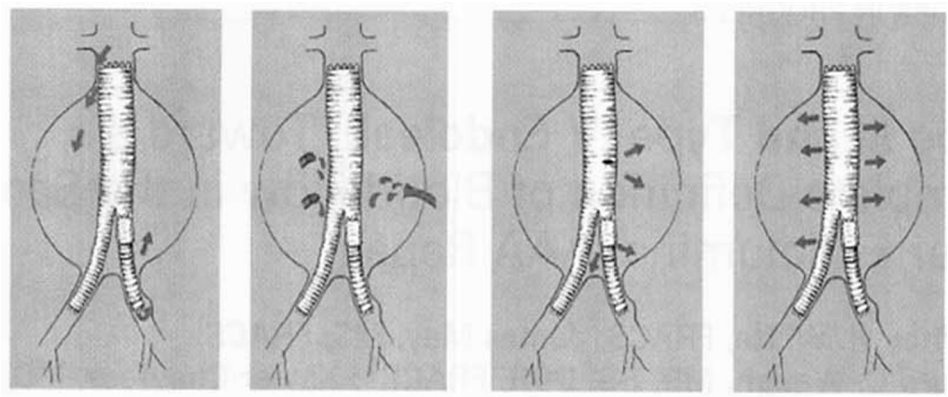

Figure 1: Schematic drawing of endoleak types. A) type I endoleak from proximal or distal attachment sites, B) type II endoleak originating from patent branching arteries, C) type III endoleak refers to disconnection of graft modules or a defect in the graft and D) type IV endoleak denoting graft porosity. [1,2]

Thesis outline

This thesis aims to increase insight in aneurysm size changes with MRI. The first two chapters focus on improving endoleak detection with MRI by using a blood pool contrast agent. A blood pool contrast agent is a special contrast agent with a long intravascular retention time which allows for a long time between contrast injection and imaging and potentially allows for detection of endoleaks with different hemodynamics like slow-flow or intermittent endoleaks. **Chapter 2** describes the visualization of endoleaks with blood pool contrast agent enhanced MRI in patients with nonshrinking aneurysms without evidence of endoleak on CT. This technique is used to visualize graft porosity in **chapter 3**.

In the following chapters the superior soft tissue contrast of MRI is used to visualize aneurysm sac contents. The capabilities of MRI in terms of endoleak detection and its ability to discriminate organized and unorganized thrombus are the basis for a complete approach of the aneurysm sac. In **chapter 4**, a semiautomatic method is developed to quantify aneurysm sac contents based on the signal intensities of the aneurysm sac on pre-contrast T1-weighted, pre-contrast T2-weighted and postcontrast T1-weighted images allowing for measurement of unorganized thrombus volume, organized thrombus volume and endoleak volume in the aneurysm sac. This method is applied to patients with a nonshrinking aneurysm years after EVAR in **chapter 5**. The relation between aneurysm sac contents and endoleak volume is investigated. In **chapter 6** longitudinal changes in aneurysm sac contents are assessed and its relation with future aneurysm size changes is investigated.

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2

Detection of occult endoleaks after endovascular treatment of abdominal aortic aneurysm using magnetic resonance imaging with a blood pool contrast agent: preliminary observations

Sandra A.P. Cornelissen, Mathias Prokop, Hence J.M. Verhagen, Miraude E.A.P.M. Adriaensen, Frans L. Moll, Lambertus W. Bartels

Objective To determine whether blood pool contrast agent-enhanced magnetic resonance imaging (MRI) can visualize endoleaks that are occult on computed tomography (CT) in patients with nonshrinking aneurysms after endovascular aneurysm repair.

Materials and methods Written informed consent was obtained for this prospective institutional review board approved study. Twelve patients with nonshrinking aneurysms but no evidence of endoleak on CT angiography and delayed CT underwent MRI with a blood pool contrast agent (Gadofosveset trisodium, Bayer Schering Pharma, Berlin, Germany). Patients could participate once in the study. T1-weighted images were acquired before injection, 3 minutes and 30 minutes after injection. Two blinded readers independently scored the images into 'endoleak', 'possible endoleak' or 'no endoleak' by comparing postcontrast MR images with precontrast images. Weighted kappas with linear weighting scheme were calculated for interobserver agreement.

Results One MRI exam was nondiagnostic because of patient motion. In the successful 11 MRI exams, MRI 3 minutes after injection demonstrated endoleak in 2/11 MRI exams (18%) and possible endoleak in 2/11 MRI exams (18%). After 30 minutes, MRI demonstrated endoleak in 6/11 scans (55%) and possible endoleak in 1/11 scans (9%). Weighted kappa was 0.78 and 0.89 for early and late postcontrast images.

Conclusion Endoleaks that are occult on CT can be detected by MRI with blood pool contrast agents. Late phase MRI 30 minutes after injection revealed additional endoleaks not seen 3 minutes after injection.

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Introduction

The goal of endovascular abdominal aortic aneurysm repair (EVAR) is to prevent aneurysm rupture by exclusion of the aneurysm sac from blood flow. Successful EVAR should stop aneurysm growth and lead to shrinkage of the aneurysm sac. A complication of EVAR is the presence of endoleak, the leakage of blood into the excluded aneurysm sac, which is associated with aneurysm growth and rupture.

Endoleaks are divided in subtypes according to their source.[1] Type I endoleaks represent leakage along attachment sites, type II endoleaks denote leakage from branching arteries, type III endoleaks result from defects in graft material or graft component disconnection and type IV endoleaks represent graft porosity. The role of endoleaks in aneurysm size changes is not entirely clear. While type I and III endoleaks have been shown to be associated with continuing aneurysm growth, this is still debated for type II endoleaks. Additionally, not all aneurysms shrink when no endoleak is found. The reported prevalence of nonshrinking aneurysms without visible endoleak vary from 27 % during the first year of follow-up [2] to 70 % in the first 20 months after EVAR.[3] Furthermore, aneurysm growth without evidence of endoleak has been found in 5 – 7 % of cases.[3, 4] This finding has been named endotension. The cause of endotension is still unknown; various etiologies have been suggested such as undetected slow-flow endoleak or graft porosity.[5] The characterization of endoleaks is important because current treatment strategies differ per endoleak type. Type I endoleaks are mostly treated endovascularly by placement of extension cuffs, while type II endoleaks are usually treated conservatively or by coil embolization of the arterial branches which communicate with the aneurysm sac. Type III endoleaks mostly result in conversion to surgery, although endovascular solutions are sometimes possible. In case of type IV endoleak placement of a new graft inside the present graft has been reported.[6] In patients with endotension the mechanism is still unclear, so no endovascular treatment is available and the only available treatment option is conversion to surgery.

The imaging evaluation of a suspected endoleak is usually performed using computed tomography angiography (CTA) combined with precontrast CT and/or delayed CT.[7-9] Contrast enhanced magnetic resonance imaging of endoleak with either extracellular contrast agents [10-12] or the weak protein binding Gadobenate dimeglumine (MultiHance, Bracco, Italy)[13] has been shown to have a higher sensitivity for detection of endoleaks than CTA and delayed CT. Endoleak imaging always involves a trade–off between the longest possible postinjection delay to allow for maximum accumulation of the contrast agent in the endoleak and the decrease of intravascular enhancement that results from the longer postinjection delay. Blood pool contrast agents allow for a longer possible postinjection delay due to their longer serum half-life. Ferumoxytol (an iron-oxide based blood pool contrast agent) has been used earlier for the detec-

tion of endoleak.[14]

Recently, the gadolinium-based protein-binding blood pool contrast agent gadofosveset trisodium (Vasovist, Bayer Schering Pharma, Berlin, Germany) has been approved for clinical use. This blood pool contrast agent has been shown to be useful for high-resolution steady state MR angiography.[15, 16] Using this contrast agent, T_1-weighted MR images with intravascular enhancement can be acquired until approximately 1 hour after injection.[17]

The purpose of our pilot study was to evaluate if MRI with a blood pool contrast agent could detect endoleaks that were occult on arterial CTA and delayed CT in patients with nonshrinking aneurysms at least one year after EVAR.

Materials and methods

Patients

Written informed consent was obtained from all participants in this institutional review board approved prospective cohort study. Bayer Schering Pharma (Berlin, Germany) provided the blood pool contrast agent used (gadofosveset trisodium) and financial support for the study. The authors had full control of the data and information submitted for publication.

Inclusion criteria were a nonshrinking aneurysm at least one year after EVAR with no endoleak detected on arterial CTA and delayed phase CT. For the inclusion of potentially eligible patients, we first screened the radiology reports for absence of endoleak on routine CTA and delayed CT. We then re-evaluated the scans of these potentially eligible patients for the presence of endoleak to ensure that no endoleaks were missed at routine interpretation. This was done in consensus by two observers (SAC, resident radiology with 4 years experience in EVAR follow-up and HJV, vascular surgeon with 10 years experience in EVAR follow-up).

The same observers evaluated aneurysm size change by measurement of aneurysm diameter in consensus on the two most recent yearly CT evaluations. Aneurysm diameter was measured on the transverse section with maximal aneurysm cross-section using digital calipers. A diameter change of 5 mm or more was considered significant.[18] In case the aneurysm cross section was elliptical, the minor axis of the ellipse was measured to estimate true maximum aneurysm diameter according to the reporting standards.[18]

Exclusion criteria were claustrophobia or the presence of MR incompatible devices. Patients were allowed to participate once. From June 2006 to April 2008, 24 eligible patients who visited the outpatient clinic for EVAR follow-up were asked to participate. Two patients refused participation. After informed consent, the MRI exam had to be stopped in one patient due to claustrophobia, 4 patients were not scanned due to

logistical problems (one patient had DSA on day of the planned MRI, in two patients no MRI time slot was available soon enough after the preceding CT, one patient went abroad), in one patient surgical removal of the endoprosthesis was performed before the MRI appointment. After MRI one patient was excluded because a previously unnoticed endoleak was found when re-examining the CT.

In a case-report we reported that expected graft porosity for a specific type of endograft [19] was shown by MR imaging with Vasovist in three patients (Chapter 3, this thesis). [20] These patients will not be mentioned further. The analysis presented in this paper is based on data from the remaining 12 patients acquired in this prospective study.

CT protocol

For the routine follow-up of patients after EVAR, arterial CTA and delayed CT were performed to allow for detection of early and late endoleaks.

CTA was performed on a 64-detector-row scanner (Brilliance-64, Philips Medical Systems, Cleveland, OH) with 64x0.625mm collimation, following injection of 120 ml of Iopromide (Ultravist 300, Bayer Schering Pharma, Berlin, Germany) at 6 ml/s (36g iodine at 1.8g/s). The spiral scan was initiated by bolus triggering 7s after a threshold of 100 Hounsfield units in the abdominal aorta at the level of the celiac trunk was reached. Scan speed was chosen such that the total scan time was approximately 15s to ensure sufficient enhancement of the aneurysm. Exposure parameters were 120 kVp and 250 mAs ($CTDI_{vol}$ = 14.7 mGy).

The delayed scan was performed with 64x0.625mm collimation and a post-threshold delay of 90s. Exposure parameters were 120 kVp and 100 mAs ($CTDI_{vol}$ = 5.9 mGy).

MR protocol

The MRI-examination was conducted on a clinical 1.5-T machine (Achieva, Philips Healthcare, Best, the Netherlands) with intravenous administration of the blood pool contrast agent gadofosveset trisodium (Vasovist; Bayer Schering Pharma, Berlin, Germany, currently Ablavar, Lantheus Medical Imaging).

Blood-pool contrast agent

Gadofosveset trisodium is a gadolinium-based blood pool contrast agent which binds reversibly to human serum albumin. It remains in the circulation for an extended period of time.[17] The relaxivity of this agent bound to albumin is 19 mM^{-1} sec^{-1} at 1.5 T.[21] We used the approved dosage of 0.03 mmol/kg (corresponding to 9 – 12 ml per patient) with a flow rate of 1 mL/sec followed by a 30 ml saline flush at a flow rate of 1 mL/sec.

Acquisition

A wrap-around body coil was used as receive coil. Transverse T_1-weighted spin echo images were acquired which included the aneurysm. The scan volume extended from the renal arteries to the distal attachment sites of the endoprosthesis in the common iliac arteries. Scans were acquired at three time points: before injection of gadofosveset trisodium, 3 minutes after injection (early postcontrast images) and 30 – 70 minutes after injection (late postcontrast images). Between the early and late postcontrast images patients were allowed to get off the table and walk around. The variations in postinjection delay for the late phase post contrast images were due to varying scanner availability, for efficiency reasons we tried to scan another patient in between. Acquisition parameters were repetition time / echo time 580 msec/15 msec, slice thickness 3.0 mm, 60 slices, FOV 270x385 mm^2, acquisition matrix 179 x 256, NSA 1, acquisition time 5 min 27 sec. A regional saturation slab was placed on the abdominal fat to prevent ghosting artifacts resulting from breathing. Phase encoded arrhythmia rejection (PEAR, Philips Medical Systems, Best, the Netherlands) was used to minimize breathing artifacts.

Image Analysis

Two researchers blinded to the identity of the patients independently reviewed all MRI scans (MEA, radiologist, 4 years experience in EVAR follow-up imaging and HJV). Firstly, early postcontrast images were compared with precontrast images. Secondly, early and late postcontrast images were compared with precontrast images. The scans were rated as 'endoleak', 'possible endoleak', 'no endoleak' or nondiagnostic due to artifacts. Endoleak was defined as high signal intensity on the postcontrast image outside the lumen inside the aneurysm sac which was not present on the precontrast image. If feeding vessels were visible, this was recorded. Cases with discrepant ratings by the two observers were re-evaluated in a consensus session with a third observer (MP, cardiovascular radiologist, more than 10 years experience in EVAR follow-up imaging) and a final decision was made.

Analysis of interobserver agreement

The weighted kappa-coefficient with linear weighting scheme was calculated to measure interobserver agreement (Medcalc 10.1.3.0, available at: www.medcalc.be).

TABLE 1. Patient Details

			AAA			Endoleak on MRI	
Patient number	**Age (yr)**	**Sex**	**Size (cm)**	**Size change**	**Time since EVAR (yr)**	**3 min p.i.**	**30 min p.i.**
1	73.4	M	5.3	Stable	1.3	-	(+)
2	70.4	F	4.1	Stable	8.0	(+)	+
3	82.4	M	6.7	Growth	2.0	-	+
4	76.8	M	4.2	Stable	2.0	-	+
5	81.7	F	5.8	Stable	1.0	-	-
6	80.4	M	6.2	Stable	2.1	-	-
7	71.5	M	6.3	Stable	1.9	+	+
8	76.4	M	5.7	Stable	8.2	(+)	+
9	90.3	M	8.7	Growth	1.0	ND	ND
10	75.7	M	4.7	Stable	1.0	-	-
11	61.9	M	6.6	Growth	2.0	+	+
12	79.1	M	6.5	Stable	0.9	-	-

Patient 3: 2 months later surgical conversion due to growth and neck dilatation

Patient 5: High signal intensity in aneurysm sac on precontrast T1-w image

Patient 7: 1.3 year later migration, placement aortic cuff

Patient 11: Type II endoleak with feeding lumbar artery

AAA indicates abdominal aortic aneurysm; p.i., postinjection delay; -, no endoleak; (+), possible endoleak; +, endoleak; SI, signal intensity; EVAR, endovascular abdominal aortic aneurysm repair; MRI, magnetic resonance imaging.

TABLE 2. Details of the Endoprostheses

Prosthesis (Manufacturer)	**Metal Support**	**Fabric**	**Expansion**	**#**
Low-permeability Excluder (Gore, Flagstaff, AZ)	Nitinol	ePTFE	Self	1
Talent (Medtronic Vascular)	Nitinol	Polyester	Self	9
EVT/Ancure (Guidant, Menlo Park, CA)	None	Polyester	Balloon	1
Aorto-uniiliac Guidant (Guidant, Menlo Park, CA)	None	Polyester	Self	1

TABLE 3. Number of Patients With Detected Endoleaks on Early and Late Postcontrast Images

	Early Postcontrast	Late Postcontrast
Endoleak	2	6
Possible endoleak	2	1
No endoleak	7	4

Results

Patient characteristics

Patient details are given in Table 1. Twelve patients were included, 10 men with age range of 62 to 90 years (mean age, 76.8 years) and 2 women who were 70 and 81 years old. Median time after EVAR was 2 years (range, 1 – 8 years). At the time of the study, median AAA diameter on CTA was 60 mm (range, 41 – 87 mm). Three patients had a growing aneurysm, 9 patients had a nonshrinking but stable aneurysm for at least one year on their inclusion date.

Patients underwent the MRI exam within a median of 23 days after CTA (range 13-49 days). One MRI exam was nondiagnostic due to motion artifacts, resulting in 11 successful MRI exams. Details of the endoprostheses are given in Table 2.

No adverse reactions were observed after injection of contrast agent.

Endoleaks

Only the 11 successful MRI studies were included in the analysis. An endoleak was detected on early postcontrast MR imaging in 2/11 exams (18 %) and on late postcontrast imaging in 6/11 exams (55 %) (Table 3). More endoleaks were detected on late postcontrast images than on early postcontrast images.

Discrepant readings needed to be resolved by consensus reading in 2 patients for early postcontrast images and in 1 patient for late postcontrast images. The weighted kappa with linear weighting for the rating of the 11 successful MRI examinations into the categories 'endoleak', 'possible endoleak' and 'no endoleak' on early postcontrast images was 0.78 (95% CI: 0.52, 1.0). This value increased to 0.89 (95%CI: 0.70, 1.1) for late postcontrast images.

MRI images showing endoleaks are shown in Figures 1-5. All endoleaks were more clearly visible and appeared larger on late postcontrast images than on early postcontrast images (Fig. 1-4). An example rated as 'possible endoleak' on early postcontrast images and as 'endoleak' on the late postcontrast images, is shown in Figure 1. Endoleaks which were detected on early postcontrast images are shown in Figures 2 and 4.

Figure 5 shows a patient in whom the precontrast signal intensity of the aneurysm sac was already high, making it hard to detect an endoleak by comparing the precontrast and postcontrast images. Also image subtraction after image registration did not show areas with higher signal intensity on the postcontrast images compared to the precontrast images, which is why the images were classified as 'no endoleak'.

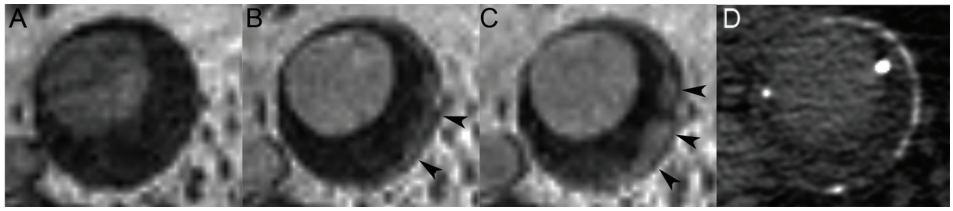

Figure 1: Patient no. 2 in Table 1. Stable aneurysm, 8 years after placement of an Ancure endoprosthesis. Transverse precontrast(A), early postcontrast(B), late postcontrast(C) T1-weighted spin echo image (TR/TE 580ms /15ms) and delayed CT(D) at the same location. B) arrowheads point to region of 'possible endoleak', C) arrowheads point to endoleak, D) no endoleak is visible.

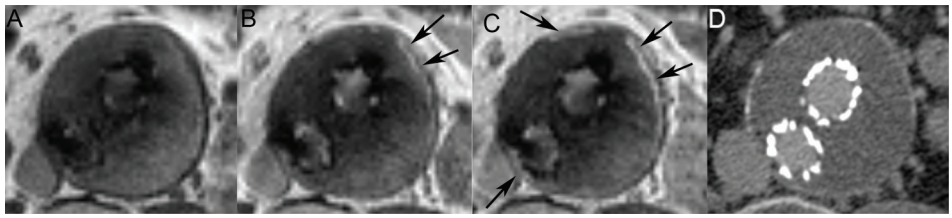

Figure 2: Patient no. 7 in Table 1. Stable aneurysm, 2 years after EVAR. Transverse precontrast(A), early postcontrast(B), late postcontrast(C) T1-weighted spin echo image (TR/TE 580 ms/15ms) and delayed CT(D) at the same location. In B) and C) arrows point to endoleak. Signal loss around stent in A), B), and C), are due to metal-induced susceptibility artifacts caused by stent components. In D) no endoleak is visible.

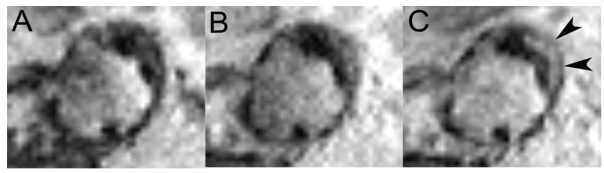

Figure 3: Patient no. 3 in Table 1. Growing aneurysm, 2 years after EVAR. transverse precontrast(A), early postcontrast(B) and late postcontrast(C) T1-weighted spin echo image (TR/TE 580ms /15ms) through growing aneurysm at level of the proximal attachment sites in the aneurysm neck. The early postcontrast image (B) was scored as 'no endoleak'. Arrowheads in C) point to endoleak.

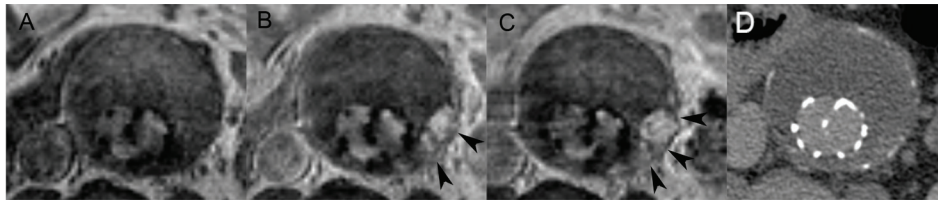

Figure 4: Patient no. 11 in Table 1. Growing aneurysm, 2 years after EVAR Transverse precontrast(A), early postcontrast(B), late postcontrast(C) T1-weighted spin echo image (TR/TE580ms /15ms) and delayed CT(D) at the same location. Arrowheads in B) and C) point to endoleak. In D) no endoleak is visible. Signal loss around stent in A), B) and C), are because of metal-induced susceptibility artifacts caused by stent components.

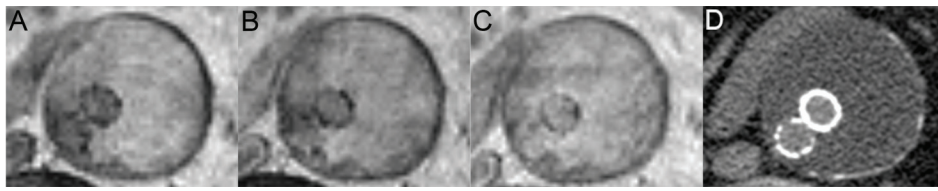

Figure 5: Patient no. 5 in Table 1. Stable aneurysm, 2 years after EVAR.Transverse precontrast(A), early postcontrast(B), late postcontrast(C) T1-weighted spin echo image (TR/TE580 ms/15ms) and delayed CT(D) at the same location. The aneurysm sac has high signal intensity on the MR images before contrast injection. No areas were identified with higher signal intensity on the postcontrast images, which is why the images were classified as 'no endoleak', also image subtraction did not reveal endoleak. Also in (D) no endoleak is visible.

One patient demonstrated an endoleak in the periphery of the aneurysm near the proximal attachment site which could only be seen on the late phase (Fig. 3). Only in one patient a patent lumbar artery could be identified as feeding vessel which classified the slow-flow endoleak as a type II endoleak.

Minimal areas of signal loss due to susceptibility artifacts were observed around the stent-graft, which deteriorated endoleak detection in the direct vicinity of the endograft (figures 2 and 4). Both these patients had a Talent (Medtronic Vascular) endograft. The artifacts of this prosthesis have been earlier described.[22]

Discussion

In this pilot study, we demonstrated that contrast-enhanced MRI using a blood pool contrast agent could detect endoleaks in patients with prior EVAR that were occult on arterial CTA and delayed CT. Endoleak was detected in 55 % (6/11) of the successful MR-exams on late postcontrast MR imaging in patients without endoleak on CTA and delayed CT. More endoleaks were detected on late postcontrast images than on early postcontrast images. These additional endoleaks were most likely detected because of the longer time available for accumulation of contrast agent in the aneurysm sac because of slow-flow or intermittent leakage. In additon, the high relaxivity of gadofosveset trisodium bound to albumin may play a role in the improved visualization, because of the larger T_1 shortening per dose of contrast agent than can be obtained with commonly used extracellular contrast agents. We presented a method with a higher sensitivity for the detection of endoleaks than currently used methods and demonstrated its efficacy in patients with nonshrinking aneurysms. We chose for this patient group because especially in these patients it is interesting to further investigate the role of endoleaks in aneurysm size changes. We demonstrated that for such research MRI with a blood pool contrast agent is suitable because it is currently the most sensitive method for endoleak detection.

In our pilot study, we demonstrated that the majority of our patients had slow-flow endoleaks that were undetected at CTA. This doesn't necessarily mean that these endoleaks are responsible for the lack of shrinkage of the aneurysms. From a scientific point of view it would be interesting to investigate whether more endoleaks would be observed with use of MR imaging with gadofosveset trisodium in patients with a shrinking aneurysm compared to CTA. However, from a clinical perspective such information on slow-flow endoleak in shrinking aneurysms would probably not lead to changes in treatment strategy.

If no endoleak is detected in a patient with a growing aneurysm, surgery is the most common treatment, but it is limited to those patients with a good cardiovascular status. Re-lining with a new endograft has also been suggested if graft porosity is the presumed cause.[6] Ultrasound or CT-guided thrombin injection into the region of an endoleak has been reported as a treatment strategy for patients with growing aneurysms and type II endoleaks detected with CTA or ultrasound.[23-25] By detecting and localizing endoleaks that are occult on CT, MRI with a blood pool contrast agent could be used to guide thrombin injection in patients that have not previously been considered candidates for this treatment.

We do not know how long of a postinjection delay of 30 minutes is necessary. A less time-consuming protocol for detection of slow-flow endoleaks including continuous acquisition of scans for 30 minutes after contrast injection might be sufficient. Scanning might then be stopped as soon as a leak is visualized.

We chose to use T_1-weighted spin echo sequences for endoleak detection, because of its high signal to noise ratio in a moderate T_1ighted sequence. In our experience T_1-weighted spin echo sequences are more sensitive for endoleak than clinically used heavily T_1-weighted CE-MRA sequences. Recently described high resolution steady state MRA techniques may also be suitable for endoleak detection,[16] however these protocols need to be optimized for use in the abdomen to fit in one breath hold or to minimize artifacts from breathing motion with other techniques.

This study has a number of limitations. The main limitation is that we did not establish an independent reference standard. We studied a group of patients in which state-of-the art CT did not demonstrate endoleak. We considered presence of contrast enhancement on MRI within the aneurysm sac sufficient proof for the presence of an endoleak. We did not perform catheter angiography to confirm the endoleak and determine the endoleak type.

Secondly, there was a time interval between CT and MRI examinations of 13 – 49 days, potentially giving a time interval for formation of new endoleaks.

The presence of prostheses-related artifacts may have prevented us from detecting additional small endoleaks. Therefore, our results probably provide some underestimation of the true number of slow-flow endoleaks.

In summary, late postcontrast MR using a blood pool contrast agent was able to demonstrate endoleak in 55 % (6/11) patients in whom abdominal aortic aneurysms did not shrink after endovascular aneurysm repair but no endoleak could be found on CTA or delayed CT.

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The authors thank Joost van Herwaarden and Dennis de Bie for assistance in patient recruitment, Anneke Hamersma, and the MR technicians of the department of Radiology for their help in organizing and conducting this study.

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3

Visualizing type IV endoleak using magnetic resonance imaging with a blood pool contrast agent

Sandra A.P. Cornelissen, Hence J.M.Verhagen, Mathias Prokop, Frans L. Moll, Lambertus W. Bartels

Growing evidence suggests that graft porosity hampers aneurysm shrinkage in patients who have been treated with the original Excluder device. To our knowledge, this suspected porosity has never been visualized in such patients. We present three patients treated with the original Excluder device whose aneurysms did not shrink in the first 2 years after treatment. Computed tomography (CT) angiography and late phase CT did not show endoleak. We performed late phase magnetic resonance imaging with a blood pool agent to visualize graft porosity. Our cases illustrate the usability of a new contrast agent and a new imaging strategy for visualizing slow-flow endoleaks that can not be imaged using currently used imaging techniques with conventional contrast agents.

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Introduction

Aneurysms which shrink after endovascular repair (EVAR) have been successfully treated. The cause of endotension –aneurysm growth without endoleak– and stable aneurysm size in the absence of endoleak is still unclear.[1] It is likely that in such cases the aneurysm sac remains perfused or at least pressurized. One possible explanation is that endoleak is present, but not visualized by computed tomography angiography (CTA). Magnetic resonance (MR) based techniques may be used to further explore the role of endoleak in these cases.

Magnetic resonance imaging with use of conventional Gd-based contrast agent visualizes more endoleaks [2-4] and allows for more accurate endoleak classification than CTA.[5] One class of endoleak which has until now only been suspected but has not yet been visualized is leakage due to graft porosity of the original Excluder device (W.L. Gore, Inc, Flagstaff, Arizona, USA) presumably causing the low shrinkage rates associated with this device.[6, 7] We present three patients after EVAR with such an endoprosthesis in whom routine follow-up imaging with CT angiography demonstrated nonshrinking aneurysms without evidence of endoleak. In these patients graft porosity was visualized using a new MR contrast agent – a T1-shortening blood pool agent – in combination with late phase magnetic resonance imaging. These cases demonstrate a new way of imaging endoleaks that remained elusive with use of CTA.

Case report

From June to November 2006, three patients treated with an original Excluder endoprosthesis presented at the outpatient clinic with a nonshrinking aneurysm without endoleak on CTA and delayed phase CT. CT scans had been performed as part of the clinical follow-up protocol on a 64-slice scanner during injection of 36 g iodine (Iopromide 300 mg/mL; Schering, Berlin, Germany) at 1.8 g/s. Delayed phase CT was performed 90 seconds after injection. Clinical information about the patients is presented in the table. According to our clinical protocol, aneurysm size change was evaluated on the CTA exams by diameter measurements. The patients were asked to undergo one additional MR-exam. The study was approved by the institutional review board and written informed consent was obtained from the participants. During the MR-examination, a new contrast agent was used: Gadofosveset trisodium (Vasovist, Bayer Schering Pharma, Berlin, Germany). This agent is gadolinium-based and binds to albumin, through which it remains longer intravascular than currently used MR and CT-contrast agents.[8] Three sets of T_1-weighted spin echo images (TR/TE/flip angle 580 ms/15 ms/90°, slice thickness 3.0 mm, FOV 270x385 mm^2, acquisition matrix 179 x 256, 60 slices, NSA=1, acq. time 5 min 27 sec) were acquired, covering the area of the aor-

tic endoprosthesis. The first set was acquired before injection, the second early after contrast injection (3 to 10 minutes), and the third late after contrast injection (> 30 minutes). Both sets of postcontrast images were compared to the precontrast images to detect endoleaks. In all three patients contrast enhancement just outside the graft was visible in the late phase postcontrast images which was not present on the precontrast images or on the early phase postcontrast images. This is illustrated in the figure, in which slices through the endoleak are shown next to each other. The leaks we visualized were confined to the direct vicinity of the endoprosthesis and seemed connected to the prosthesis lumen, without a visible connection to a branching artery. For this reason the endoleaks were classified as graft porosity.

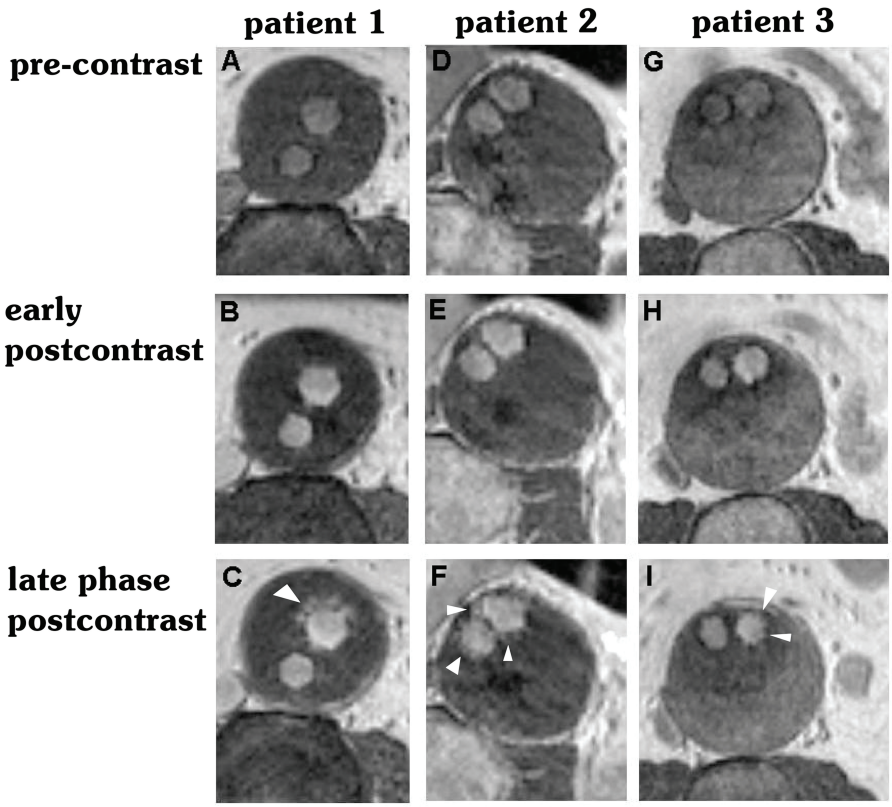

Figure. Transverse T1-weighted spin echo MR- images, the first row shows the precontrast, the second row the early phase postcontrast, and the third row the late phase postcontrast T1-weighted images. Each column consists of images from the same patient and the same anatomical location. In the last row, endoleak arising from graft porosity is visible in (C), (F), and (I). Arrowheads point to endoleak.

TABLE. CLINICAL INFORMATION OF PATIENTS

Patient no	Age (y)/ Sex	Initial EVAR date	Initial AAA diameter	Diameter of AAA in follow-up CT scan / date	Interval CT – MRI (days)
1	82/M	July 2004	58	58 / June 2006	15
2	80/M	Aug 2003	57	57 / Aug 2006	26
3	58/M	Jan 2004	62	64 / Nov 2006	45

Discussion

Our report presents a new imaging method to visualize endograft porosity which could until now not be visualized. Endoleaks due to porosity of the graft material (type IV endoleak) most probably remained occult in CTA exams because of the small delay between contrast agent injection and imaging.

To facilitate the detection of slow flow endoleaks, different timings of delayed CT images with respect to contrast agent injection have been advocated, varying from 60 seconds to 130 seconds after injection.[9-11] However, due to a rapid decrease in contrast agent concentration in the blood after injection of extracellular contrast agents, the contrast between blood and surrounding tissue decreases rapidly with time after injection. For MRI, recently a blood pool agent became available, which remains longer intravascular than currently used contrast agents. By using such an agent in combination with T1-weighted MRI, the delay between injection and imaging can be extended allowing for the accumulation of a higher amount of contrast agent in the endoleak while maintaining adequate contrast between blood and surrounding tissue.

The use of a blood pool agent for the detection of endoleak has been reported before. [12] In that study, the iron-oxide based blood pool agent Ferumoxytol was used. In that study none of the included patients had the original Excluder endograft. No endoleaks originating from graft porosity were visualized.

For visualizing type IV endoleaks we acquired two sets of postcontrast images, early postcontrast images 3 – 10 minutes after injection and late postcontrast images 30 – 70 minutes after injection. Although such a long delay between injection and imaging is clinically rather impractical, it was necessary for accurate detection of these type IV endoleaks. In these patients the early postcontrast images did not lead to endoleak detection. We do not know whether the long delay of 30 minutes was necessary. A less time-consuming protocol for detection of type IV endoleaks may result from the continuous acquisition of scans until 30 minutes after contrast injection. Scanning can then be stopped earlier when a leak is visualized. However, such an approach is less

comfortable for the patients than a 30-minute break.

A potential weakness of the comparison between CTA and MRI in these patients is the time between the CTA and the MRI exam. Due to logistical reasons, fifteen to forty-five days elapsed in between. In theory, the endoleak status of the patient could have changed during this time. However, we think graft porosity is more a chronic problem and will essentially not change in such a short time span.

Recent literature suggests graft porosity to be present only in the non-overlapping parts of the original Excluder endoprosthesis, where only one layer of ePTFE is present.[13] Comparison of the regions of endoleak on the MR-images with the CTA-images demonstrated that in two patients the region of endoleak corresponded to the region where no overlapping components of the endograft were present. In the third patient however, leakage was present in the region of non-overlapping graft components but in fewer slices than expected; for unknown reasons a large region of non-overlapping endograft was present which did not show porosity.

The presented cases illustrate that the extended delay between injection and imaging enabled us to visualize graft porosity. Furthermore, this imaging strategy probably enables us to visualize slow-flow endoleaks originating from other sources. The longer intravascular half-life of such agents may also allow for the visualization of intermittent endoleak. All these types of endoleaks can keep the aneurysm sac pressurized.

In conclusion, this technique is probably well suited to provide explanations for certain cases of endotension. In such cases treatment of slow-flow endoleaks or intermittent endoleaks, which can be identified with this imaging technique, might stop aneurysm growth.

Conclusion

To our knowledge in this study graft porosity was visualized in vivo through MR imaging using a blood pool contrast agent for the first time.

However, this technique has a much wider application. It can serve as a new strategy for investigating endotension. The role of endoleak in such cases can be more precisely investigated than in the past, possibly leading to endovascular treatment alternatives for patients diagnosed with endotension by conventional methods without the use of blood pool agents.

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4

Use of multispectral MRI to monitor aneurysm sac contents after endovascular abdominal aortic aneurysm repair

Sandra A.P. Cornelissen, Maarten J. van der Laan, Koen L. Vincken, Evert-Jan P.A. Vonken, Max A. Viergever, Chris J. Bakker, Frans L. Moll, Lambertus W. Bartels

Purpose: To validate a newly developed semi-automatic multispectral magnetic resonance imaging (MRI) tool for quantitatively monitoring aneurysm sac contents in patients after endovascular aneurysm repair (EVAR).

Methods: MRI studies from 24 EVAR patients were retrospectively analyzed. The precontrast T1-weighted and T2-weighted and the postcontrast T1-weighted images were displayed simultaneously. Two independent observers classified the aneurysm sac voxels into categories for endoleak, unorganized thrombus, or organized thrombus by interactively thresholding the multispectral images relative to the signal intensity of fat. Voxel classification was visualized as a color overlay on the MR images; when the observer changed the thresholds, the color overlay was updated immediately. The volumes of the voxels in each category were calculated and expressed in milliliters. The intra- and interobserver variability for measuring the volumes of endoleak and unorganized and organized thrombus were calculated; a Bland and Altman analysis was applied to determine the mean differences and the repeatability coefficient (RC).

Results: Mean aneurysm sac volume was 78±42 mL. The intraobserver mean difference for the endoleak volume was 0.5±1.9 mL with an RC of 3.7 mL; the interobserver mean difference was –0.8±3.6 mL (RC 7.1 mL). The intraobserver mean difference for unorganized thrombus volume was –1.2±4.4 mL (RC 8.6 mL); the interobserver mean difference was 0.3±6.3 mL with an RC of 12.3 mL. The intraobserver mean difference for organized thrombus volume was 0.8±5.0 mL (RC 9.7 mL); the interobserver mean difference was 0.4±6.3 mL (RC 12.4 mL).

Conclusion: Reproducible monitoring of aneurysm sac contents in EVAR patients is feasible with multispectral MRI in combination with our semi-automatic post-processing tool.

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Introduction

Not all aneurysm size changes after endovascular aneurysm repair (EVAR) can be explained by the presence or absence of endoleak visualized using ultrasound,[1,2] computed tomographic angiography (CTA), or magnetic resonance imaging (MRI)[3-11] in patients with an MR-compatible endoprosthesis. Shrinking aneurysms occur in the presence of endoleak, while not all aneurysms shrink when no endoleak is detected.[12,13] Moreover, 5% to 7% of aneurysms grow without visible endoleak on CTA (defined as endotension).[13-15] The etiology of endotension is probably low flow endoleak not visualized with older technology; nowadays, with the use of blood pool agents and MRI, these type of endoleaks can be visualized (Chapter 2 and 3, this thesis).[16-18]

A new concept for follow-up of a post-EVAR aneurysm beyond endoleak imaging is based on the observation that the accompanying thrombus exhibits changes in signal intensity on T_2-weighted images over time.[6] Prior to EVAR, mural thrombus may be present in the aortic aneurysm. During implantation of an endoprosthesis, a small amount of circulating blood in the aneurysm is excluded from the circulation. This blood forms additional thrombus material in which red blood cell remnants are phagocytosed and gradually replaced by soft fibrous connective tissue, which in time develops to dense fibrous connective tissue.[19] This development can be monitored with MRI. The signal intensity (SI) of the intra-aneurysmal thrombus on T_2-weighted MR images reflects the degree of thrombus organization.[19,20] In previous patient studies, the aneurysm sac was qualitatively classified as organized, partially organized, or unorganized based on its SI in T_2-weighted MR images.[6,20]

Moreover, MRI allows comprehensive evaluation of the aneurysm sac, including endoleak and thrombus remodeling using the combination of pre- and postcontrast T_1- and pre-contrast T_2-weighted images. However, use of this multispectral data to elucidate aneurysm size changes is cumbersome for human observers.[21] Therefore, we developed a post-processing tool for semi-automatic quantification of aneurysm sac contents to assist further research. With this tool, the observer can interactively subdivide aneurysm sac contents in endoleak and unorganized and organized thrombus volumes by setting thresholds on the differently weighted images. In this report, we demonstrate the utility and repeatability of our tool on MRI exams of EVAR patients.

Methods

Data from a review board–approved study for the evaluation of MRI in the follow-up of aneurysms after EVAR were reviewed for this study.[10,11] The MRI scans had been captured on a clinical 1.5-T scanner (Gyroscan Intera; Philips Healthcare, Best, The Netherlands). A wrap-around synergy body coil was used for signal reception. Different signal

weightings were necessary for quantification of organized and unorganized thrombus volumes and endoleak volume. Transverse pre-contrast T_1-weighted spin echo [repetition time (TR) 580 ms / echo time (TE) 14 ms, acquisition time 2.30 minutes], transverse pre-contrast T_2-weighted turbo spin echo (TR 6146 ms / TE 100 ms / echo train length 17; acquisition time 2.21 minutes), and postcontrast T_1-weighted spin echo (as pre-contrast) acquisitions were acquired with 6-mm slice thickness, no slice gap, 30 slices, covering the entire aortic aneurysm with a field of view of 270 x 385 mm^2 and a 179×256 acquisition matrix, and voxel size 1.5×1.5 mm. A regional saturation slab was placed on the abdominal fat to prevent ghosting artifacts resulting from breathing; phase encoded arrhythmia rejection (PEAR; Philips Medical Systems) was also used to minimize breathing artifacts. No electrocardiogram gating was used. During administration of 40 mL of gadopentetate dimeglumine (Magnevist 0.5 mmol/mL; Schering, Berlin, Germany), a time-resolved contrast-enhanced MR angiogram (MRA) and a static MRA were acquired (results reported earlier[10,11]). Postcontrast scans were acquired ~2 minutes after contrast administration.

A significant intra-aneurysmal thrombus was visible in 24 of these MRI exams, forming the basis for the current study. Mean age of the 24 patients was 76±5.5 years, and the mean time after EVAR was 2.4±1.8 years. Four patients had an Excluder endograft (W. L. Gore & Associates, Flagstaff, AZ, USA) and 20 had an Ancure endograft (EVT, Menlo Park, CA, USA). All patients had normal renal function (estimated glomerular filtration rate >60 mL/min/1.73 m^2).

TABLE 1. Combination of Signal Intensities for the Different classification Categories

	T1-Weighted	T2-Weighted	T1- Weighted Postcontrast
Endoleak	Low	Mostly high	High
Unorganized thrombus	Low/high	High	Same as precontrast
Organized thrombus	Low	Low	Low

Each voxel has 3 intensities on the precontrast T1-weighted and T2-weighted images and the postcontrast T1-weighted image.

Quantifying Aneurysm Contents

The scans were analyzed with dedicated in-house software (Thrombix; Image Sciences Institute, Utrecht, The Netherlands). First, the nonluminal aneurysm sac thrombus was manually segmented from the level of the proximal attachment of the endograft to the native aortic bifurcation. Only aortic aneurysms were segmented; iliac aneurysms were not included. Most patients had an Ancure endograft, which is known to cause artifacts at the proximal and distal attachment sites.[22] However, these artifacts did not cause many problems in the segmentation because the nonluminal aneurysm sac thrombus for the most part started distal to the level of the proximal attachment of the endograft. Distally, the aneurysm sac thrombus was segmented up to the native bifurcation, while the distal attachment sites of the endograft were located distal to the native bifurcation.

Visual inspection revealed only negligible movement between the different acquisitions, thus no additional image registration was necessary. The precontrast T_1-weighted and T_2-weighted and the postcontrast T_1-weighted images were displayed simultaneously. The signal intensity of fat was estimated by drawing a region of interest in the periaortic fat in the center slice of the dataset. Fat was chosen as a reference tissue instead of muscle (which was used by Pitton et al.[19]), since fat had a consistent composition in all our patients and did not show contrast enhancement. Muscle proved less suitable in our elderly patient group because of different degrees of fatty atrophy dependent on the patient's level of activity, which led to inconsistent signal intensity of muscle.

To quantify aneurysm sac contents, observers classified the aneurysm sac voxels into the categories of endoleak, unorganized thrombus, or organized thrombus by interactively thresholding the multispectral images relative to the SI of fat. Based upon the user-determined thresholds, voxels were automatically classified according to the scheme shown in Table 1. Voxel classification was visualized as a color overlay on the MR images. When the observer changed the thresholds, the color overlay was updated immediately. Figure 1 demonstrates examples of multispectral MR images with the voxel classification shown in the color overlay. The volumes of the voxels in each category were calculated and expressed in milliliters. This process of voxel classification was performed twice by 2 observers independently (S.C. and M.L.).

Data Analysis

The intraobserver and interobserver variability of the volumes for endoleak and unorganized and organized thrombus were calculated; Bland and Altman difference of the means analysis, in which the differences of the paired measurements are plotted against their average, was applied.[23] The repeatability coefficient (RC; defined as 1.96 times the standard deviation of the mean differences) was also calculated. Analyses were performed using Excel (Microsoft, Redmond, CA, USA).

Results

Mean non-luminal aneurysm sac volume was 78±42 mL. The intraobserver mean difference of endoleak volume was 0.5 mL with an RC of 3.7 mL (Table 2); the interobserver mean difference was –0.8 mL with an RC of 7.1 mL. The intraobserver mean difference for unorganized thrombus volume was –1.2 mL with an RC of 8.6 mL; the interobserver mean difference was 0.3 mL with an RC of 12.3 mL. The intraobserver mean difference for organized thrombus volume was 0.8 mL (RC 9.7 mL); the interobserver mean difference was 0.4 mL (RC 12.4 mL). MR images with color overlay of both observers are shown in Figure 1 (C and D). In Figure 2, the differences are plotted against the means for the interobserver variability in measuring unorganized thrombus volume.

TABLE 2. Variability of measurements and repeatability coefficients

Endoleak volume, mL	Observer 1	0.5±1.9, 3.7
	Observer 2	0.1±1.6, 3.2
	Interobserver	–0.8±3.6, 7.1
Unorganized thrombus volume, mL	Observer 1	–1.2±4.4, 8.6
	Observer 2	–1.1±3.0, 5.8
	Interobserver	0.3±6.3, 12.3
Organized thrombus volume, mL	Observer 1	0.8±5.0, 9.7
	Observer 2	0.9±2.9, 5.7
	Interobserver	0.4±6.3, 12.4

Data are presented as the mean ± standard deviation, repeatability coefficient.

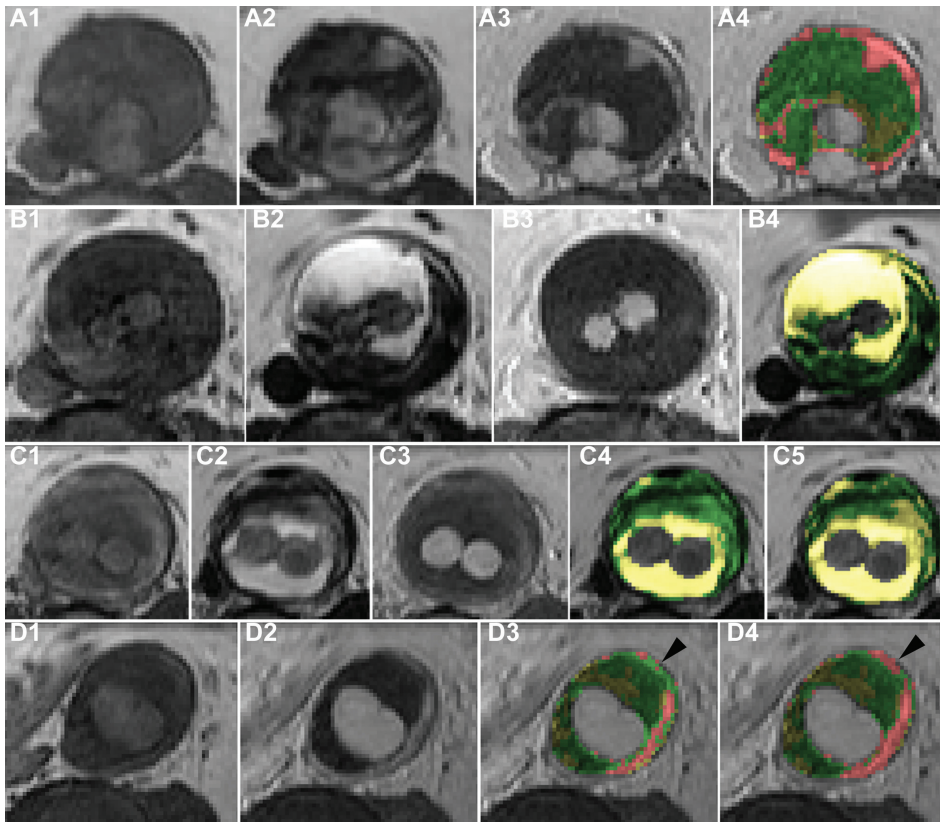

Figure 1. Precontrast (A1) T1-weighted and (A2) T2-weighted and (A3) postcontrast T1-weighted transverse spin echo images of the aneurysm sac 3.6 years after implantation of an Ancure endoprosthesis. (A4) Postcontrast T1-weighted image with a color overlay representing voxel classification. Precontrast (B1) T1-weighted and (B2) T2-weighted and (B3) postcontrast T1-weighted transverse spin echo images of the aneurysm sac 2 days after implantation of an Excluder endoprosthesis. (B4) Postcontrast T1-weighted image with a color overlay representing voxel classification. In this patient, the abrupt transition from organized to unorganized thrombus resulted in a small interobserver variation. Precontrast (C1) T1-weighted and (C2) T2-weighted and (C3) postcontrast T1-weighted transverse MR images 4 days after implantation of an Ancure endoprosthesis. (C4,C5) Color overlays on theT2-weighted images show the voxel classification of observers 1 and 2, respectively. In this patient, a gradual transition from unorganized to organized thrombus resulted in interobserver variation. Transverse (D1) precontrast and (D2) postcontrast T1-weighted images 3.1 years after implantation of an Ancure endoprosthesis. (D3,D4) Color overlays show the voxel classification of observers 1 and 2. Voxels that had lower signal intensity due to the partial volume effect (arrowheads) caused interobserver variation. Red, yellow, and green represent endoleak, unorganized thrombus, and organized thrombus, respectively.

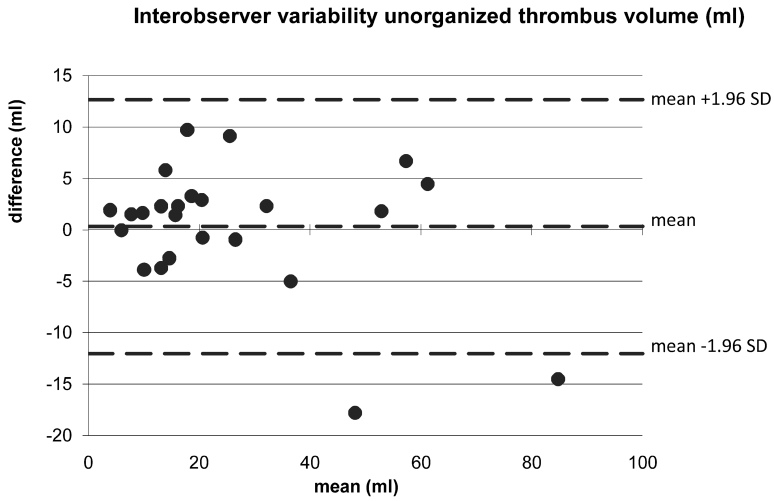

Figure 2. Bland and Altman plot of interobserver variability of unorganized thrombus volume (mL).

Discussion

With its excellent intra- and interobserver agreement, this semi-automatic tool offers us a new means of further evaluating aneurysm sac contents during surveillance after EVAR. The relation between aneurysm sac contents and aneurysm size changes, as well as endotension, can now be investigated. Prediction of aneurysm growth or shrinkage might be possible, which could lead to a more patient-specific follow-up schedule. Using this multispectral MRI tool, direct visual feedback was provided to the observers during interactive adjustment of the thresholds. While this subjective interactive thresholding led to interobserver variation, it also allowed voxel classification that could be directly viewed and adjusted by the observer.

Limitations

In our work, the interpretation of the MRI images was based on previous studies performed in an experimental canine model[18] and on aneurysm sac analysis with MRI before open surgery.[19,20] We did not perform direct histopathological correlation in our study because this is not feasible in patients after EVAR.

It could well be that unorganized thrombus is a consequence of slow flow endoleak, which can be further investigated with MRI after administration of a blood pool contrast agent.[16-18,24] Unfortunately, we did not have access to a blood pool contrast

agent when we performed this work.

Another limitation of our work is the interobserver variation. One source of interobserver variation was related to the "sharpness" in the transition in signal intensity (Fig. 1B,C). Another source of interobserver variation was the partial volume effect (Fig. 1D), which is partly a consequence of the rather large slice thickness in our study (6 mm). In future research, the influence of the partial volume effect can probably be lowered by reducing slice thickness, although a balance should be found because thinner slices will also lead to a decrease in the signal-to-noise ratio.

Conclusion

Reproducible monitoring of aneurysm sac contents in EVAR patients is feasible with multispectral MRI in combination with our semi-automatic post-processing tool. A longitudinal trial to assess the clinical value of quantifying aneurysm sac contents is currently being conducted at our institution.

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5

Chapter 5

Lack of thrombus organization in nonshrinking aneurysms years after endovascular abdominal aortic aneurysm repair

Sandra A.P. Cornelissen, Hence J. M. Verhagen, Joost A. van Herwaarden, Evert-Jan P. A. Vonken, Frans L. Moll, Lambertus W. Bartels

Objectives During endovascular abdominal aortic aneurysm repair (EVAR) blood is trapped in the aneurysm sac at the moment the endograft is deployed. It is generally assumed that this blood will coagulate and evolve into an organized thrombus. It is unknown whether this process always occurs, what its time span is and how it influences aneurysm shrinkage. With magnetic resonance imaging (MRI), quantitative analysis of the aneurysm sac is possible in terms of endoleak volume as well as unorganized thrombus volume and organized thrombus volume. We investigated the presence of unorganized thrombus in nonshrinking aneurysms years after EVAR.

Methods Fourteen patients with a nonshrinking aneurysm without endoleak on computed tomography/computed tomography angiography underwent MRI with a blood pool agent (gadofosveset trisodium). Precontrast T1- , precontrast T2- and postcontrast T1-weighted images (3 and 30 min after injection) were acquired and evaluated for the presence of endoleak. The aneurysm sac was segmented into endoleak, unorganized thrombus and organized thrombus by interactively thresholding the differently weighted images. The classification was visualized in real-time as a color overlay on the MR images. The volumes of endoleak, unorganized thrombus and organized thrombus were calculated.

Results Median time after EVAR was 2 years (range 1-8.2 years). The average aneurysm sac volume of the patients was 167 ± 107 ml (mean ± standard deviation). Nine patients had an endoleak on the postcontrast T1-w images 30 minutes after injection. On average, the aneurysm sac contained 78 ± 61ml unorganized thrombus, which corresponded to 51 ± 21 volume-percentage, irrespective of the presence of an endoleak on the blood pool agent enhanced MRI images (independent t-test, P = .8).

Conclusions In our study group half of the nonshrinking aneurysm sac contents consisted of unorganized thrombus years after EVAR.

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Introduction

The aneurysm size of patients after endovascular abdominal aortic aneurysm repair (EVAR) is closely monitored. Aneurysm shrinkage as well as the lack of aneurysm growth usually carries a good prognosis. In case of a growing aneurysm, rupture risk is increased. Many growing aneurysms are due to an endoleak. However, some aneurysms exhibit aneurysm growth without evidence of endoleak on computed tomography angiography (CTA) and delayed CT.[1-3] This phenomenon has been termed endotension. Different etiologies for endotension have been proposed such as slow flow endoleak below the detection threshold of CTA, intermittent (e.g. position-dependent) endoleak or stent graft porosity.[4] Magnetic resonance imaging (MRI) is more sensitive for endoleak than CT.[5-10] Slow flow endoleaks and graft porosity can be diagnosed with MRI after injection of a blood pool contrast agent (Chapter 2 and 3, this thesis).[11-14] Images with blood pool enhancement can then be acquired as long as 60 minutes after injection.[15]

Prior to EVAR, there is a large interpatient variation in the presence of thrombus in the aneurysm and its degree of organization.[16] During endograft deployment, a certain amount of blood is trapped between the intra-aneurismal thrombus and the endograft. It is generally assumed that this blood will coagulate and evolve into an organized thrombus. The time span in which this occurs as well as its influence on aneurysm shrinkage is unknown. The evolution of aneurysm sac contents is not monitored in the current, mostly CTA-based follow-up. In contrast, with MRI, visualization of thrombus organization is possible; unorganized thrombus has a high signal intensity on T2-weighted imaging, while thrombus organization leads to a decrease in signal intensity.[17] The changing appearance of the intra-aneurysmal thrombus in time has been described by Engellau et al.[18]

Recently, a new method for aneurysm sac monitoring with MRI has been described, which combines both the capabilities of MRI in terms of quantifying unorganized thrombus and in terms of endoleak imaging (Chapter 4 ,this thesis).[19] We used this method to investigate the presence of unorganized thrombus in nonshrinking aneurysms years after EVAR.

TABLE I. Combination of Signal Intensities for the Different classification Categories

	T1-Weighted	T2-Weighted	T1- Weighted Postcontrast
Endoleak	Low	Mostly high	High
Unorganized thrombus	Low/high	High	Same as precontrast
Organized thrombus	Low	Low	Low

Materials and Methods

Patients

Data from an institutional review board approved study into the use of a blood pool contrast agent for the detection of slow flow endoleak were reviewed for this study.[11,12] Written informed consent was obtained from all participants. Fourteen patients with a nonshrinking aneurysm without endoleak on CT/CTA more than one year after EVAR with an MR compatible endoprosthesis underwent MRI with intravenous administration of a blood pool contrast agent (gadofosveset trisodium, Vasovist; Bayer Healthcare, Berlin, Germany). The MRI-examinations were conducted on a clinical 1.5-T MR scanner (Achieva; Philips Healthcare, Best, the Netherlands).

MRI acquisition

Transverse pre-contrast T_1-weighted spin echo (repetition time [TR] 580 ms; echo time [TE] 14 ms; acquisition time 5.27 minutes), pre-contrast T_2-weighted turbo spin echo (TR 6130 ms; TE 100 ms; echo train length 17; acquisition time 4.30 minutes), and post-contrast T_1-weighted spin echo (as pre-contrast) acquisitions were acquired both 3 minutes (early postcontrast) and 30 minutes after injection (late postcontrast) with 3-mm slice thickness, no slice gap, 60 slices, field of view of 270 x 385 mm^2, a 179×256 acquisition matrix, voxel size 1.5×1.5 mm, covering the entire aortic aneurysm. A regional saturation slab was placed on the ventral abdominal wall to prevent ghosting artifacts from breathing. Phase-encoded arrhythmia rejection (PEAR, Philips Healthcare, Best, The Netherlands) was used to further minimize breathing artifacts.

Image analysis

Aneurysm volumes and the volumes of the intra-aneurysmal thrombus were measured with OsiriX (open source software, version 3.8.1, www.osirix-viewer.com) on the CTA data which were acquired before EVAR. To correct for patient motion between the MR imaging sequences all images were rigidly registered to the early postcontrast T_1-w images using the Elastix software.[20] As a first step in the quantification of aneurysm sac contents, the aneurysmal thrombus was manually segmented from the level of the proximal attachment of the endograft to the native aortic bifurcation; iliac aneurysms were not included. A few voxels in the direct vicinity of the stent-graft suffered from signal loss due to susceptibility artifacts.[21] These voxels were not included in the segmentation of the aneurysm sac. Then, the aneurysm sac voxels were classified based on the precontrast T_1- and T_2-weighted and late postcontrast T_1-weighted images in the categories endoleak, unorganized thrombus volume, or organized thrombus volume.

This was done interactively by thresholding the multispectral images relative to the SI of fat according to the scheme shown in Table I. This method and its interobserver agreement were described earlier (chapter 4, this thesis).[19] To eliminate interobserver variability, two observers classified the aneurysm sac voxels in consensus in this study. The volumes of all voxels in each category were calculated and expressed in milliliters.

The postcontrast images acquired 3 and 30 minutes after contrast injection were evaluated for the presence of endoleak by two experienced observers. In case of discrepant ratings a third observer decided whether endoleak was present.[12]

The amount of unorganized thrombus in patients with and without evidence of endoleak on postcontrast T_1-w images was compared with the independent *t*-test after normality was assessed with the Kolmogorov-Smirnov test. A *P* value <.05 was considered significant. Statistical analysis was performed using SPSS 16.0 (SPSS, Chicago, IL).

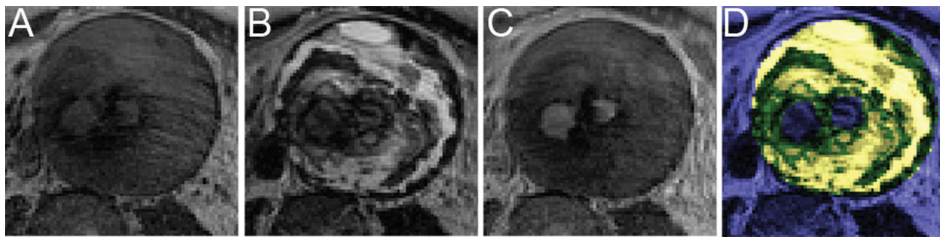

Figure 1. Transverse pre-contrast T1-w(A), T2-w(B), and T1-w images 30 minutes (C) after injection of gadofosveset trisodium in patient with Talent endoprosthesis 1 year after EVAR (patient 10, Table II). The aneurysm of this 90-year-old patient increased 23 mm in diameter during one year without detectable endoleak. Voxel classification overlays are shown in (D), yellow represents unorganized thrombus, green represents organized thrombus, blue voxels are voxels outside the aneurysm sac. A large unorganized thrombus volume is visible in B which is yellow in D. Unorganized thrombus volume was 244 mL/56 %; organized thrombus volume was 195mL/44%; the volume of the aneurysm sac was 439 ml. The presence of unorganized thrombus was confirmed by aspiration of approximately 300 ml of blood from the aneurysm sac.

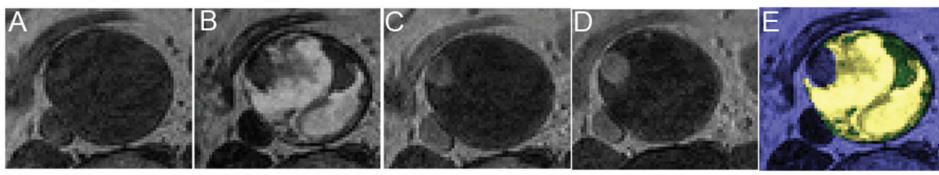

Figure 2. Transverse (A) pre-contrast T1-w,(B) T2-w,(C)T1-w images 3 minutes and (D) 30 min after injection of contrast agent in patient 8 years after implantation of a Guidant aorto-uniiliac device with a stable aneurysm diameter (patient 9, Table II). Voxel classification overlays are shown in (E), yellow represents unorganized thrombus, green represents organized thrombus, blue voxels are voxels outside the aneurysm sac. This patient had a subtle endoleak peripheral in the aneurysm sac more caudally. The aneurysm sac volume was 130 mL, of which 61% had the aspect of unorganized thrombus.

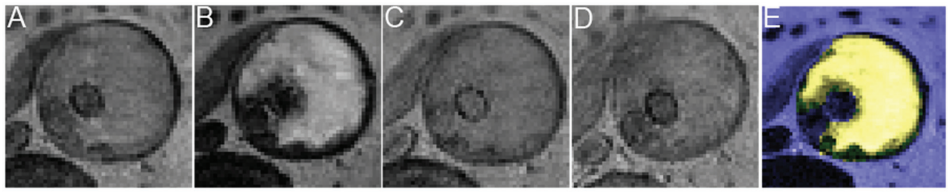

Figure 3. Transverse (A) pre-contrast T1-w,(B) T2-w,(C)T1-w images 3 minutes and (D) 30 min after injection of contrast agent in patient 1 year after implantation of an Excluder Low Permeability device (patient 6, Table II). Voxel classification overlays are shown in (E), yellow represents unorganized thrombus, green represents organized thrombus, blue voxels are voxels outside the aneurysm sac. There was no evidence of endoleak. The aneurysm sac had a high signal intensity before injection of contrast agent. The aneurysm sac volume was 86 mL, of which 79% had a high SI on the T2-weighted images representing unorganized thrombus.

Results

The results of the individual patients are given in Table II. Examples images are shown in Figs 1-3. The presence of unorganized thrombus was confirmed in patient 10 who had a large growing aneurysm containing a large volume of unorganized thrombus (Fig 1). In this patient a CT-guided thrombin injection was performed, which was preceded by aspiration of aneurysm sac contents. Approximately 300 ml of blood was aspirated from the aneurysm sac, confirming the presence of unorganized thrombus.[22] In two patients more than 70% of the aneurysm sac consisted of unorganized thrombus. The average aneurysm sac volume of all patients was 167 ± 107 ml. The average unorganized thrombus volume was 78±61ml, which corresponded to 51% ± 21 % of aneurysm sac volume (Table III). In two patients the aneurysm sac already had high signal intensity on the T1-weighted images before contrast injection (Fig 3). In nine patients endoleak was visualized on the postcontrast images 30 minutes after injection.[11,12] In patients with endoleak the mean unorganized thrombus volume was 71 ± 44 ml (52% ± 19 % of aneurysm sac volume) which was not significantly different from 91 ± 89 ml (49% ± 26 % of aneurysm sac volume) in patients without endoleak. The three growing aneurysms were larger than the stable aneurysms (303 ± 110 ml compared with 130 ± 72, $P = .007$, independent *t*-test). Mean unorganized thrombus volume in patients with a growing aneurysm was 137 ± 112 ml (42% ± 29 % of aneurysm sac volume) compared with 62 ± 32ml (53% ± 19 % of aneurysm sac volume) in patients with a stable aneurysm ($P = .4$, independent *t*-test).

TABLE II. Individual patient results.

Patient	Sex	Age (yr)	Preop AAA vol(mL)	Preop thrombus vol(mL)	Time (yr)	Endoprosthesis	Endoleak Volume (mL)	Unorganized thrombus (%)	Size change
1	M	82	151	19	1.9	OGE	16	74	Stable
2	M	73	177	80	1.3	Talent	≤1	51	Stable
3	F	70	NA	NA	8.0	EVT/Ancure	4	62	Stable
4	M	81	NA	NA	2.9	OGE	≤1	63	Stable
5	M	82	206	17	2.0	Talent	≤1	8	Growth
6	F	82	125	25	1.0	LPGE	0	79	Stable
7	M	71	289	199	1.9	Talent	11	44	Stable
8	M	58	313	211	2.9	OGE	23	44	Stable
9	M	76	NA	NA	8.2	Guidant AUI	6	61	Stable
10	M	90	413	207	1.0	Talent	0	56	Growth
11	M	76	152	66	1.0	Talent	0	39	Stable
12	M	81	175	48	3.1	Talent	0	9	Stable
13	M	62	197	0	2.0	Talent	27	62	Growth
14	M	79	180	103	.9	Talent	0	61	Stable

EVT/Ancure (Guidant, Menlo Park, Calif); Guidant AUI, aorto-uniiliac Guidant (Guidant); OGE, Original Excluder, LPGE, Low Permeability Excluder (Gore, Flagstaff, Ariz); Talent, Talent endoprosthesis (Medtronic Vascular, Minneapolis, Minn).

Preop AAA vol represents the total aneurysm volume (including the lumen) before EVAR.

Time (yr) represents the time after EVAR in years.

Preop thrombus volume represents the thrombus volume measured on the preoperative CTA examination. In three patients, no digital preoperative CTA scan was available, denoted as NA.

The column endoleak volume represents endoleak volume measured on blood pool agent enhanced MRI images 30 minutes after injection. Unorganized thrombus is given as volume percentage of nonluminal aneurysm sac volume.

TABLE III. Summary statistics

	Endoleak volume	Unorganized thrombus volume	Organized thrombus volume	Aneurysm sac volume
Mililiters (mean ± sd)	6 ± 9 ml	78 ± 61 ml	83 ± 71 ml	167 ± 107 ml
Volume percentage (mean ± sd)	4% ± 6 %	51% ± 21 %	45% ± 24 %	

Discussion

Aneurysm sac contents after EVAR naturally change in time. Blood is trapped in the aneurysm sac during the deployment of the endograft which is assumed to coagulate and to evolve into an organized thrombus.

An improved understanding of the evolution of aneurysm sac contents may increase our insight in aneurysm size changes and endotension. A few studies have demonstrated the capabilities of MRI for assessment of aneurysm sac contents. Recently, a method for quantification of aneurysm sac contents with MRI has been developed. Based on the signal intensity on T1- and T2-weighted images and postcontrast T1-weighted images the volumes of unorganized thrombus, organized thrombus and endoleak in the aneurysm sac can be determined. [19]

We used this method in patients with nonshrinking aneurysms without evidence of endoleak on CTA. To reach the highest possible sensitivity for endoleak we used a blood pool contrast agent and acquired postcontrast images after a long delay of 30 minutes. We found no significant relation between non-organization of thrombus and endoleak; however, this could represent a type II error, due to a small number of patients.

Our results demonstrate that we do not yet fully understand the evolution of aneurysm sac contents in time. A far lower amount of unorganized thrombus would be expected after several years if the aneurysm sac merely represented an organizing thrombus. Perhaps these areas with high signal intensity on T2-weighted images represent a part of the aneurysm sac which will remain fluid and may never lead to thrombus. The use of anticoagulant medication could play a role. All our patients used acetyl salicylic acid (100 mg per day). Two patients used Acenocoumarol. The unorganized thrombus volume in these two patients was not different from the other patients.

Probably, multiple processes take place simultaneously with buildup and break down of thrombus leading to an equilibrium situation of organized thrombus and unorganized thrombus volume. To gain more insight in the evolution of the aneurysm sac, we are currently conducting a longitudinal study to investigate early postoperative changes in the thrombus mass with MRI. We think the possibility of endoleak is still not completely excluded in the five patients in whom no endoleak was visualized. Possibly these patients suffer from endoleaks with different hemodynamics which cannot be demonstrated even with blood pool agent enhanced MRI (e.g. intermittent or position-dependent endoleak). The possibility of occult endoleak is supported by the observation of high signal intensity in the aneurysm sac on T1-weighted images before contrast injection of almost the entire aneurysm sac in two patients. This suggests the presence of methemoglobin in the aneurysm sac, which is a breakdown product of hemoglobin present in recently thrombosed material. Alternatively, other still unknown mechanisms leading to an increase in unorganized thrombus may be

present (eg, inflammatory reactions, exudation of fluid through graft fabric, or thrombus fibrinolysis). These differences in composition of the aneurysm sac remain occult on CT because of insufficient contrast resolution.

A limitation of our study is that we did not include patients with shrinking aneurysms. To determine the clinical significance of our findings, future studies in patients with shrinking aneurysms are advocated.

In summary, our data show that the amount of unorganized thrombus in the aneurysm sac several years after EVAR is higher than expected. Thus, the aneurysm sac does not merely represent an organizing thrombus. More knowledge on the evolution of aneurysm sac contents potentially increases the insight in aneurysm size changes. Therefore, MRI data from larger patient numbers are needed as well as longitudinal data on changing aneurysm sac contents in time. This data can then serve as reference data for patients with complicated sac behavior such as aneurysm growth with or without detectable endoleak.

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6

Longitudinal change in thrombus organization in the first year after EVAR

Sandra A.P. Cornelissen, Joost A. van Herwaarden, Hence J.M. Verhagen, Evert-Jan P.A. Vonken, Joffrey van Prehn, Frans L. Moll, Willem P.Th.M. Mali, Max A. Viergever, Lambertus W. Bartels

Purpose The purpose of this study was to investigate whether the longitudinal assessment of aneurysm sac contents after endovascular abdominal aortic aneurysm treatment (EVAR) is feasible with magnetic resonance imaging (MRI). We studied whether aneurysm sac contents could predict future aneurysm size changes.

Materials and Methods In this prospective study, 30 patients underwent MRI-exams the day before EVAR, within 6 weeks after the procedure, 6 months and 1 year after EVAR. Pre-contrast T1-weighted, pre-contrast T2-weighted and postcontrast T1-weighted images were acquired. The nonluminal aneurysm sac was manually segmented on the MR images. Then, the endoleak volume, the unorganized thrombus volume and the organized thrombus volume were determined by interactively classifying the voxels in the aneurysm sac in the corresponding categories, based on the signal intensities on the differently weighted MR images. The volumes were expressed in mL and as volume-percentage of the aneurysm sac. Total aneurysm volume was measured on the postoperative CT-scan and the last available follow-up CT-scan, a 10 % change in aneurysm sac volume was used as criterion for aneurysm size change.

Results The unorganized thrombus volume relative to the aneurysm sac significantly decreased in time (from 50%±18% postoperatively to 34%±15% after a year, $P<0.05$) whereas the organized thrombus volume significantly increased (from 45%±20% postop to 55%±12% after a year, $P < 0.05$). Mean available CT-follow-up of aneurysm volume was 3.5 ± 1.6 years. Aneurysm sac contents were not significantly different in shrinking (n=7), stable (n=16) and growing (n=7) aneurysms. Twelve patients had a type 2 endoleak on the postoperative CT, 6 additional endoleaks were detected with MRI. A larger endoleak volume was measured in endoleaks visible on both modalities than those only visible on MRI (11 mL vs 2 mL, $P = 0.008$). Our data suggest that the unorganized thrombus after a year is higher in patients with vitamin K antagonists, however patient numbers are small (50% vs 31%, $P = 0.029$, $n = 3$).

Conclusions Longitudinal changes in aneurysm sac contents can be evaluated with MRI. One third of the aneurysm sac still consists of unorganized thrombus one year after EVAR with unknown etiology. We found no relation between aneurysm sac contents and aneurysm size changes in our patient group.

Introduction

After EVAR, patients undergo prolonged follow-up to diagnose late complications which may need treatment to prevent rupture. Aneurysm size change is an important parameter in the follow-up after endovascular abdominal aortic aneurysm repair (EVAR). In case of aneurysm growth, rupture risk is increased, but the etiology of aneurysm growth is not always clear. Endoleak has been identified as a cause,[1] but aneurysm growth without evidence of endoleak also occurs.[2,3] This phenomenon has been termed endotension.[4] The etiology of endotension is the subject of much debate.

One of the possible causes of endotension may be a missed endoleak. Some endoleaks are occult on computed tomography (CT) for hemodynamical reasons such as slow-flow endoleak, intermittent endoleak or stent graft porosity.[4] It has been shown that magnetic resonance imaging (MRI) is more sensitive for endoleak detection.[5-11] It is also known that slow-flow endoleaks can be diagnosed with MRI with a blood pool contrast agent (Chapter 2 and 3, this thesis).[12-15]

Endotension may also be caused by still unknown processes originating in the aneurysm sac and vessel wall itself, for example inflammatory reactions, or fibrinolytic processes.[4] The contents of the aneurysm sac and its evolution in time cannot be visualized using CT-imaging due to a lack of soft tissue contrast. However, thanks to its superior soft tissue contrast, visualization of aneurysm contents and its evolution in time can be performed with MRI.[16] In a dog model the signal intensity ratio of the intra-aneurysmal thrombus on T_2-weighted images relative to muscle has been shown to correlate with the degree of thrombus organization; an increase in thrombus organization corresponds to a decrease in signal intensity ratio on T_2-weighted imaging.[17] A qualitative analysis of signal intensities of the aneurysmal thrombus by two radiologists in human patients who underwent surgical repair have been shown to correlate to unorganized thrombus.[18]

Recently, a post-processing method has been described which integrates the use of MRI both for endoleak detection and for visualization of aneurysm sac contents (Chapter 4, this thesis).[19] With this method, the aneurysm sac can be interactively divided in regions of unorganized thrombus, organized thrombus and endoleak based on pre-contrast T_1-weigthed, T_2-weighted and postcontrast T_1-weighted images. It has been shown that in patients with a stable or growing aneurysm sac, years after EVAR, the aneurysm sac still contains a large amount of unorganized thrombus (Chapter 5, this thesis).[20] The authors suggested that longitudinal data on changing aneurysm sac contents in time is needed to serve as reference data for complicated sac behavior.

The purpose of this study was to investigate whether the longitudinal assessment of aneurysm sac contents is feasible with MRI and if so, whether aneurysm sac contents can predict aneurysm size changes.

Methods

Written informed consent was obtained from all participants in this institutional review board approved prospective longitudinal study. In the outpatient clinic of vascular surgery, patients with an abdominal aortic aneurysm suitable for EVAR were asked to participate. Participating patients underwent 4 MRI exams, the first exam on the day before EVAR, the second exam postoperatively (1 day – 6 weeks after EVAR), the third exam after 6 months and the fourth exam 1 year after EVAR. Exclusion criteria were claustrophobia or the presence of MR incompatible devices. In our center only MR-compatible endoprostheses were used for EVAR.[21]

The MRI examinations were done in addition to our standard institutional follow-up protocol which consisted of a CTA within thirty days after the procedure, after one year, and yearly thereafter.

MRI protocol

The MRI scans were acquired on a clinical 1.5-T scanner (Achieva; Philips Healthcare, Best, The Netherlands). A wrap-around synergy body coil was used for signal reception. Transverse pre-contrast T_1-weighted spin echo (repetition time [TR] 580 ms; echo time [TE] 14 ms; acquisition time 5 minutes 27 seconds), transverse pre-contrast T_2-weighted turbo spin echo (TR 6146 ms; TE 100 ms; echo train length 17; acquisition time 4 minutes 30 seconds), and postcontrast T_1-weighted spin echo (as pre-contrast) acquisitions were acquired with 3-mm slice thickness, no slice gap, 60 slices, covering the entire aortic aneurysm with a field of view of 270 x 385 mm^2 and a 179×256 acquisition matrix, resulting in an acquired voxel size of 1.5×1.5×3.0 mm^3. A regional saturation slab was placed over the subcutaneous fat layer on the ventral abdominal wall to prevent ghosting artifacts resulting from breathing. Phase encoded arrhythmia rejection (PEAR; Philips Healthcare, Best, The Netherlands) was also used to minimize breathing artifacts. During administration of 40 mL of gadopentetate dimeglumine (Magnevist 0.5 mmol/mL; Bayer Healthcare, Berlin, Germany) in two boluses a time-resolved contrast-enhanced MR angiogram (MRA) and a static MRA were acquired. The transverse T_1-weighted spin echo imaging was repeated approximately 2 minutes after contrast administration.

Quantifying aneurysm contents

To eliminate patient motion the scans were rigidly registered using open source image registration software (Elastix, available at: elastix.isi.uu.nl).[22] Next, the nonluminal aneurysm sac was manually delineated on the postcontrast T_1-weighted images. These voxels were interactively classified in the categories endoleak, unorganized thrombus

and organized thrombus with custom written software.[19] In this way the endoleak volume, unorganized thrombus volume and volume of organized thrombus could be calculated. The rules for classification were as follows: voxels showing enhancement in the postcontrast T_1-weighted spin echo acquisition were classified as endoleak. Non-enhancing voxels with high signal intensity on the T_2-weighted images were classified as unorganized thrombus.[17-19] Classification was performed by two experienced observers (S.A.C. and E.P.V.) in a consensus meeting.

Data analysis

Patients were divided into three categories: shrinking, stable and growing aneurysms, based on the change in aneurysm volume between the last available CT scan and the postoperative CT exam. Aneurysm volumes were measured on the available yearly follow-up CT scans from the renal arteries to the native aortic bifurcation using dedicated software (3surgery; 3Mensio Medical Imaging BV, Bilthoven, the Netherlands).[23] Ten percent change in aneurysm sac volume was used as the criterion for aneurysm growth or shrinkage; aneurysms that changed less than ten percent in aneurysm volume were analyzed in the category of stable aneurysms.

After assessing normality with the Kolmogorov-Smirnov test, continuous variables across groups were compared with independent t-tests, if not normally distributed, the Mann-Whitney U test was used. Normally distributed continuous variables from the same patients at different points in time were compared with the dependent t-test, in case of non-normality the Wilcoxon signed-rank test was used. Linear regression was used to compare continuous variables. Dichotomous variables were compared using the Chi-square test. A P-value < 0.05 was considered to indicate statistical significance. Statistical computations were performed with SPSS version 19.0 (SPSS Inc., IBM).

Results

Patient characteristics

In a period of two years 46 consecutive patients were recruited. The MRI exam had to be stopped in 6 patients because of claustrophobia, 7 patients could not undergo the MRI exams because of their medical condition, 1 patient had a pacemaker implanted after EVAR which rendered him unsuitable for further MRI exams, 1 patient was not scanned due to logistical problems, 1 patient died after a myocardial infarction. This resulted in 30 patients. In 5 patients the pre-operative MRI exam was not performed due to logistical reasons. This resulted in 25 patients with the full set of 4 MRI exams and 5 patients with the 3 MRI exams after EVAR.

Mean patient age was 72 ± 8 years (mean ± SD), one patient was female. Six patients were treated with an Excluder endoprosthesis (W. L. Gore & Associates,Flagstaff, AZ, USA), 24 patients were treated with a Talent endoprosthesis (Medtronic Vascular, Santa Rosa, CA, USA). The mean total aneurysm volume 2 days after EVAR was 169 ± 57 ml.

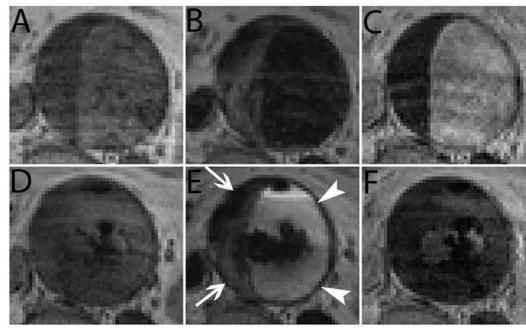

Figure 1 Precontrast T1-weighted (A,D), T2-weighted (B,E) and postcontrast T1-weighted (C,F) images through the aneurysm sac of one patient on the same anatomical location. The upper row is acquired before EVAR, the lower row one day after EVAR. On the postoperative T2-weighted image (E) the pre-existent thrombus (arrows) has a lower signal intensity than the blood excluded from the circulation (arrowheads). Ventral in the aneurysm sac a small amount of air is present which is a normal postoperative finding shortly after EVAR.

Pre-operative versus postoperative

Typical images acquired before and after EVAR are shown in Figure 1. The mean preoperative thrombus volume was 58 ± 44 ml, after EVAR the nonluminal aneurysm sac volume was 102 ± 43 ml, which comprised everything between the aortic wall and the endoprosthesis. The preexistent thrombus could be clearly distinguished from the blood trapped in the aneurysm sac on the postoperative T2-weighted images (Figure 1).

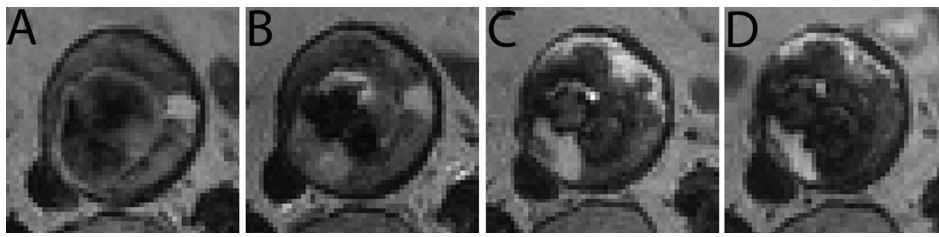

Figure 2: T2-weighted images before EVAR (A), postoperative (B), 6 months (C) and 1 year (D) after EVAR. The unorganized thrombus volume (high signal intensity) decreases in time. This patient had a shrinking aneurysm without evidence of endoleak.

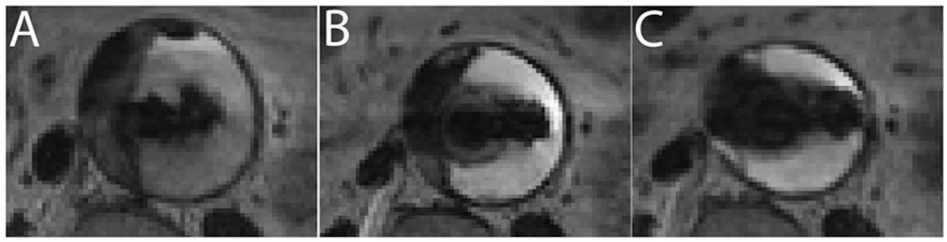

Figure 3: postoperative T2-weighted image (A), after 6 months (B) and after 1 year (C) in the same patient as Figure 1. The unorganized thrombus volume increases in time. This patient had a shrinking aneurysm despite a type 2 endoleak caudal in the aneurysm sac. Susceptibility artifacts cause signal loss of the voxels around the endoprosthesis. Such voxels were not included in the segmentation and not analyzed.

TABLE I. ENDOLEAK, UNORGANIZED AND ORGANIZED THROMBUS VOLUME IN TIME (N=30)

	Pre-EVAR	Post-EVAR	6months	1 year
Endoleak volume	-	2mL (0-29 mL) 3% (0-28%)	5mL (0-39 mL) 6% (0-32%)	5mL (0-27mL) 9% (0-27%)
Unorganized thrombus volume	23mL±18mL 40%±15%	51mL±27mL 50%±18% †	39mL±27mL 39%±18%	32mL±24mL 34%±15% †
Organized thrombus volume	34mL±28mL 59%±14%	45mL±28mL 45%±20%†	47mL±23mL 53%±15%	47mL±27mL 55%±12% †
Nonluminal aneurysm sac volume	58±44 mL	102±43 mL	93±41 mL	87±48 mL

† P<.05, paired samples *t*-test, Endoleak volume is described using median and range. Unorganized and organized thrombus volumes are described using mean ± standard deviation. Pre-operatively the nonluminal aneurysm sac volume equals the pre-existent mural thrombus. Volumes are expressed in milliliters (mL) and as percentage of nonluminal aneurysm sac volume (%).

Change in aneurysm sac contents over time

Figures 2 and 3 illustrate the change in aneurysm sac contents in time. There was a large interpatient variation; some patients showed a decrease in unorganized thrombus volume over time (Figure 2), while others exhibited an increase in unorganized thrombus volume (Figure 3). The endoleak volumes, unorganized and organized thrombus volumes in the aneurysm sac on the different points in time are summa-

rized in Table I. For the whole group, the unorganized thrombus volume significantly decreased during the first year after EVAR (Figure 5, Table I). The percentage of the nonluminal aneurysm sac consisting of organized thrombus increased in time (Figure 6). After one year, on average 34 % of the nonluminal aneurysm sac still consisted of unorganized thrombus. Three patients used vitamin K antagonists, the other patients used acetylsalicylic acid for prevention of thrombo-embolic events. Our data suggest that the percentage of the aneurysm sac consisting of unorganized thrombus after a year is higher in patients with vitamin K antagonists (50 % vs 31 %, $P = 0.029$), although patient numbers are small.

TABLE IIA. Endoleak volume (ml) at different points in time for shrinking, stable and growing aneurysms

	Postoperative		6 months		1 year	
	Median	**Range**	**Median**	**Range**	**Median**	**Range**
Shrinkage (n = 7)	3	0-11	4	0-9	4	1-6
Stable (n = 16)	1	0-28	5	0-39	5	0-23
Growth (n = 7)	4	0-29	9	0-18	16	3-27
All patients (n = 30)	2	0-29	5	0-39	5	0-27

TABLE IIB. Unorganized thrombus volume (ml) at different points in time for shrinking, stable and growing aneurysms

	Preoperative		Postoperative		6 months		1 year	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Shrinkage (n = 7)	18	14	53	26	35	27	28	28
Stable (n = 16)	25	18	50	29	40	25	31	21
Growth (n = 7)	26	26	51	28	39	34	38	31
All patients (n = 30)	23	18	51	27	39	27	32	24

TABLE IIC. Organized thrombus volume (ml) at different points in time for shrinking, stable and growing aneurysms

	Preoperative		Postoperative		6 months		1 year	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Shrinkage (n = 7)	35	45	49	36	39	25	33	23
Stable (n = 16)	36	25	48	27	50	24	51	27
Growth (n = 7)	25	12	33	22	48	22	53	30
All patients (n = 30)	34	28	45	28	47	23	47	27

TABLE IID. Nonluminal aneurysm sac volume (ml) at different points in time for shrinking, stable and growing aneurysms

	Preoperative		Postoperative		6 months		1 year	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Shrinkage (n = 7)	54	57	106	46	78	48	65	42
Stable (n = 16)	62	42	104	44	97	38	89	43
Growth (n = 7)	50	34	93	42	97	46	105	61
All patients (n = 30)	58	44	102	43	93	41	87	48

Endoleak volume, unorganized thrombus volume and organized thrombus volume in milliliters at different points in time for patients with shrinking, stable and growing aneurysms. 10 % change in aneurysm volume on last available CT-follow-up compared with postoperative CT exam was used as criterion for shrinkage or growth. Aneurysm sac contents were not significantly different in shrinking, stable and growing aneurysms.

Relation between aneurysm sac contents and aneurysm size changes

On average 3.5 ± 1.6 years follow-up of aneurysm volume assessed with CT was available. Seven patients had a shrinking aneurysm, 16 patients had a stable aneurysm and 7 patients showed aneurysm growth when the last available CT-scan was compared with the postoperative CT exam. Endoleak volume, unorganized thrombus volume

and organized thrombus volume were not significantly different in shrinking, stable and growing aneurysms (Table II). The unorganized thrombus volume and its course in time was not significantly different for the different endografts. Re-interventions took place in seven patients: two because of migration, two for treatment of endoleak, one balloon dilatation, one femoro-femoral crossover bypass because of graft kinking and one graft extension was performed to treat a growing iliac aneurysm. We found no differences in aneurysm sac contents between patients with and without re-interventions.

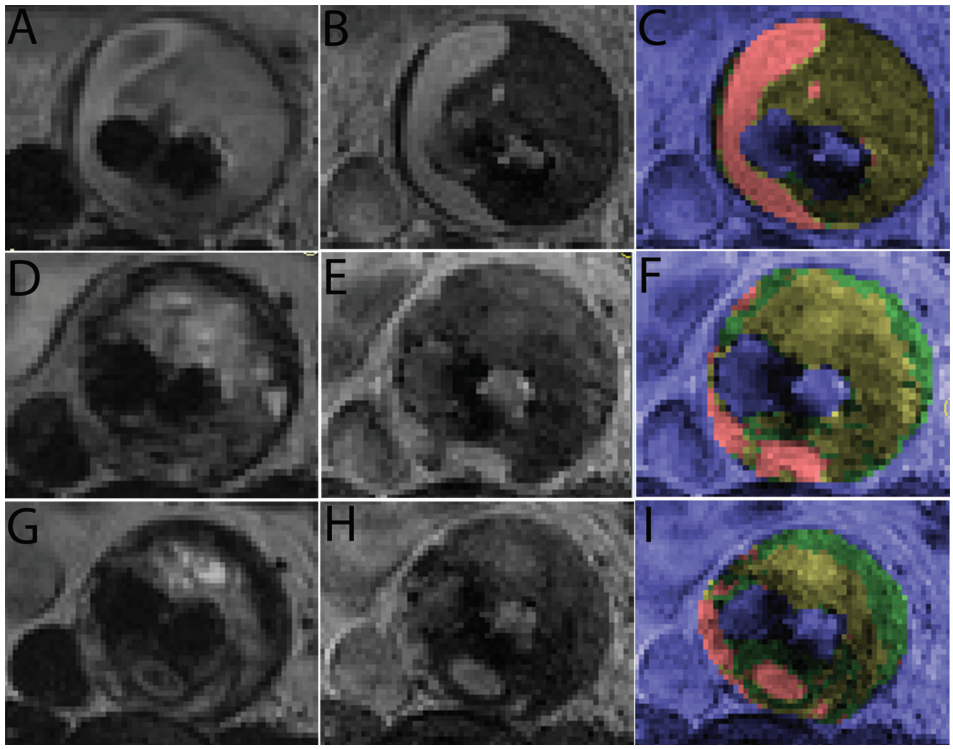

Figure 4 Images of one patient: different rows represent different points in time, the columns show different signal weightings. Postoperative images in the first row (A,B,C), images after 6 months in the second row (D,E,F), images after one year in the third row(G,H,I). T2-weighted images in the first column (A,D,G), postcontrast T1-weighted images in the second column (B,E,H), images with a color overlay representing the voxel classification performed by the observers are in the third column (C,F,I). *Red* represents endoleak, *yellow* represents unorganized thrombus, *green* represents organized thrombus. Voxels outside the aneurysm sac are colored *blue*. In this patient no mural thrombus was present before EVAR, which is why on the postoperative images no organized thrombus was present. This patient had a growing aneurysm with a type 2 endoleak.

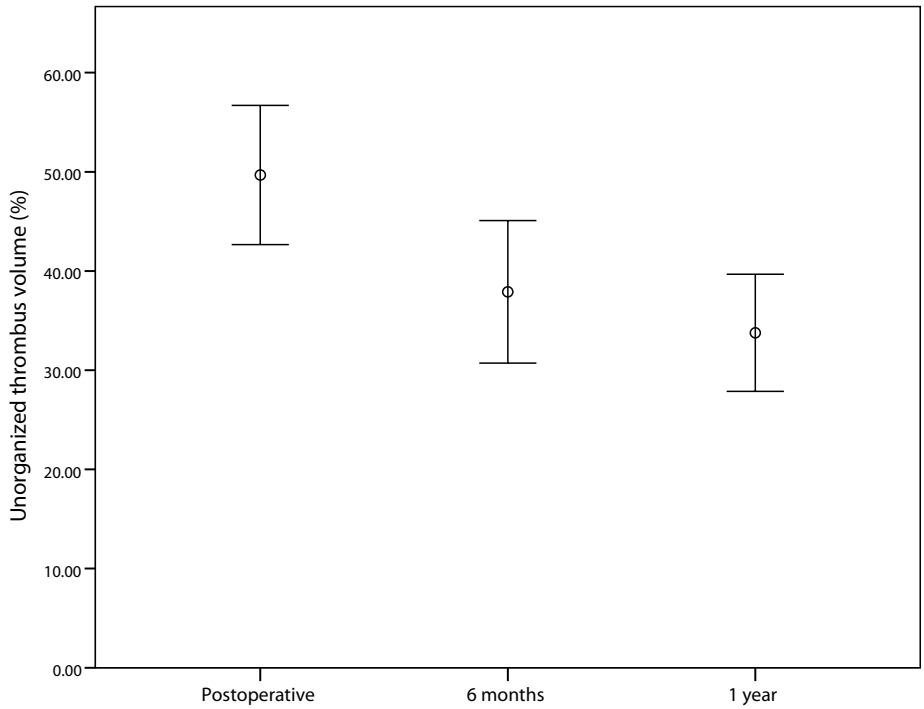

Figure 5: Unorganized thrombus volume in time expressed in percentage of nonluminal aneurysm sac volume. The unorganized thrombus volume significantly decreased during the year after EVAR (paired *t*-test, $P < .05$).

Unorganized thrombus and endoleak

Figure 4 demonstrates the appearance of unorganized thrombus in combination with an endoleak. Twelve patients had a type 2 endoleak on the postoperative CT-exam, MRI showed 6 additional endoleaks. Nine type 2 endoleaks were depicted on the CT-exams after one year, of which six occurred in growing aneurysms. Three endoleaks were persisting endoleaks, six were endoleaks not visible postoperatively. Postoperatively detected endoleaks were not significantly related with aneurysm growth, however the presence of endoleak on CT after one year was significantly related to aneurysm growth ($P = 0.001$). There was a trend towards larger endoleak volumes on MRI after 1 year in growing aneurysms (Mann-Whitney U test, P=0.088).). The endoleaks which were also detected on CT were larger than the endoleaks which remained occult on CT (11 ml vs 2 ml, P = 0.008). We found no relation between the unorganized thrombus volume and endoleak volume at the different points in time.

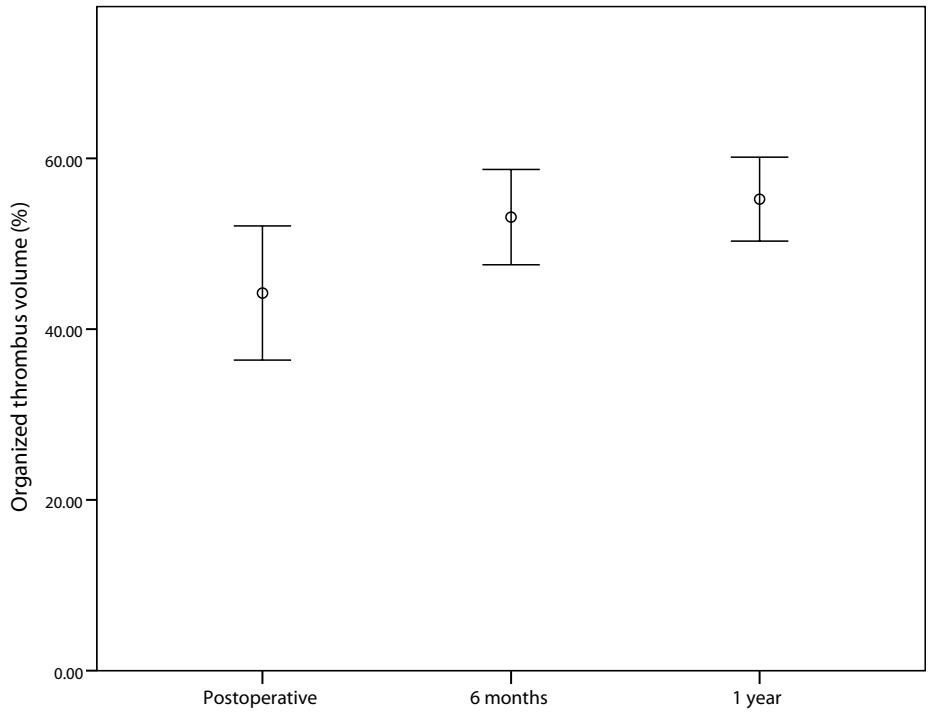

Figure 6: Organized thrombus volume in time expressed in percentage of nonluminal aneurysm sac volume. The percentage of the aneurysm sac consisting of organized thrombus significantly increased in time (paired *t*-test, $P < .05$).

Discussion

During endovascular aortic aneurysm repair blood is trapped between the endograft and the aneurysm wall or pre-existent mural thrombus. It is generally assumed that this blood will coagulate over time and will evolve into an organized thrombus.[17] However, it was observed that nonshrinking aneurysms still contain a substantial amount of unorganized thrombus several years after EVAR.[20] The etiology of this finding and its clinical relevance are unknown. Longitudinal data on the evolution of aneurysm sac contents in time potentially increases our understanding of the processes underlying the observed lack of thrombus organization. To our knowledge, only one study has been reported which describes changes in aneurysm sac contents after EVAR on MRI.[16] In this study, these changes were qualitatively assessed, no quantitative analysis of the temporal evolution of aneurysm sac contents has been performed. We used a recently published semi-automatic classification method to quantify longitudinal changes in aneurysm sac contents in the first year after EVAR.[19]

We showed that longitudinal changes in aneurysm sac contents can be visualized and quantified with MRI. Postoperatively, the blood excluded from the circulation could be clearly distinguished from preexistent mural thrombus on the T_2-weighted images (Figure 1). On average the unorganized thrombus volume decreased in time, however there was a large variation between patients. We found a high amount of unorganized thrombus in the aneurysm sac after a year of 34 ± 15 percent. This number is lower than the previously reported 51 percent in patients with nonshrinking aneurysms years after EVAR without evidence of endoleak on CT.[20] Obviously, the aneurysm sac thrombus does not behave like a normal thrombus. For unknown reasons, a large part of the thrombus remains hyperintense on the T_2-weighted images so probably remains fluid. This might be related to a lack of coagulation. We saw a possible relation with the use of vitamin K antagonists, although patient numbers are small. Alternatively, occult endoleak might play a role, or some kind of fluid accumulation due to osmotic processes. The most likely explanation is that the thrombus is not completely encapsulated but has some connection with the body cavity. The clinical significance is still unclear, we found no difference in unorganized thrombus volume between shrinking, stable and growing aneurysms. However, the number of patients in each group is small, which could have resulted in a type II error.

In agreement with the literature, more endoleaks were detected with MRI than on the CT images. [7,8,10,11] With the method we used for quantification of aneurysm sac contents also the volume of the endoleak could be measured. We found that the endoleaks which were also detected with CT were significantly larger than the endoleaks only detected on MR images.

This study has some limitations: obviously, the number of patients in the study group is small. To gain more certainty about the significance of thrombus organization, larger studies are warranted, but logistically challenging. Patient discomfort related to repeated MRI examination will be an important factor causing a relatively large percentage of drop-outs. However, for future studies the scan protocol can probably be shortened by using fast fat suppressed T_1-weighted images before and after contrast administration instead of the spin echo imaging we used. We chose to obtain longitudinal data in the first year after EVAR. It might well be that longitudinal analysis of thrombus organization during a longer period after EVAR or with other intervals between the examination time points would provide more clarity on aneurysm size changes.

To our knowledge, this is the first study to visualize and quantify the evolution of aneurysm sac contents with MRI in the first year after EVAR. There seems to be large variations in sac behavior but in general, the aneurysm sac shows progressive thrombus organization in time. Interestingly, after one year the aneurysm sac is not a completely organized thrombus: still one third of the aneurysm sac consists of unorganized thrombus. Future research with MRI in larger patient groups is warranted to investigate its underlying mechanism and clinical relevance.

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7

Discussion

In the research described in this thesis the use of MR imaging for investigating the aneurysm sac and its contents was explored. **Chapters 2** and **3** are about studies in which MRI with a blood pool contrast agent was used to detect slow-flow endoleaks in patients with a nonshrinking aneurysm without evidence of endoleak on CT. In 9 of 14 patients endoleaks were found which were not visible on CT. It was found that images acquired 30 minutes after contrast agent injection depicted more endoleaks than images acquired three minutes after injection. Between the two sets of images all patients were mobilized and walked around.

The clinical significance of the slow-flow endoleaks we found is not yet clear. A drawback of our study is that we only studied nonshrinking aneurysms, so we cannot conclude that the endoleaks we found are responsible for the lack of aneurysm shrinkage. The next step is to investigate the occurrence of slow-flow endoleaks in shrinking aneurysms. If such endoleaks are also present in shrinking aneurysms, they are not clinically significant and might even represent a normal finding.

The higher detection rate of endoleaks on images acquired 30 minutes after injection could be explained either by slow-flow endoleaks or by intermittent endoleaks. These two types of endoleaks could not be distinguished by our study design. Intermittent endoleaks could be dependent on body position, or could depend on respiratory motion or the cardiac cycle. From a scientific point of view it is interesting to investigate the precise nature of intermittent endoleaks, even though its clinical significance is not yet clear. It might be possible to investigate dependency on body position by MRI. However, this would involve repeating the MRI exam with and without mobilizing the patient between the two sets of images acquired 3 and 30 minutes after injection. This is rather cumbersome and involves a large patient effort. Moreover, it would still not allow distinguishing the different types of non-position dependent endoleaks. Ultrasound imaging seems more suitable for this purpose. Then a direct interaction between patient and observer is possible, which theoretically allows real dynamic imaging of the endoleak with high spatial and temporal resolution. This could be performed in different body positions with and without breathhold. Sparse literature is present about this topic. We only found one abstract in the literature in which the positional dependence of intermittent endoleaks was studied with duplex ultrasound. The authors reported that they found intermittent endoleaks in 13 of 27 patients with endotension with evidence of positional dependency in 11 patients.[1] These patients came from a patient population of more than 1200 patients, which led to a prevalence of less than 1 %. This low prevalence is a problem for the scientific analysis of endotension and intermittent endoleaks. A large patient population would be needed to collect just a small number of cases.

Apart from its higher sensitivity for endoleak detection, another advantage of using MRI for follow-up imaging after EVAR compared to other modalities like CT and ultrasound imaging is the excellent soft tissue contrast which can be exploited to

evaluate thrombus consistency. The evolution of aneurysm sac contents in patients after EVAR is not known because histologic analysis of the aneurysm sac after EVAR in patients is virtually impossible. In a dog model with artificially created aneurysms as well as in tissue obtained in humans during open aneurysm surgery hyperintense areas in the aneurysm sac on T_2-weighted MR-images have been shown to correspond to unorganized thrombus. [2,3]

Based on this knowledge we developed a semiautomatic classification method to interactively quantify aneurysm sac contents in terms of unorganized thrombus, organized thrombus and endoleak based on the signal intensities on T_1-weighted, T_2-weighted and post-contrast T_1-weighted images (**Chapter 4**). We showed that reproducible monitoring of aneurysm sac contents in EVAR patients is feasible with multispectral MRI.

In **Chapter 5** we applied this method to patients with nonshrinking aneurysms more than a year after EVAR. Interestingly, we observed that years after EVAR 50 % of the aneurysm sac still consisted of high intensity thrombus on T_2-w images, indicating unorganized thrombus, in patients with and without endoleaks. This finding was somewhat unexpected, since it is generally assumed that blood coagulates and progresses into organized thrombus over a limited period of time, in the order of at most months. We found no relation with endoleak occurrence. The reason for the lack of organization is unclear. The possibility of endoleak presence is not totally excluded. Maybe these patients suffer from endoleaks with different hemodynamics which cannot be visualized with blood pool contrast agent-enhanced MRI. Or perhaps these areas with high signal intensity on T_2-weighted images represent a part of the aneurysm sac that will remain fluid and may never lead to thrombus. We can only speculate on its etiology. Osmotic or inflammatory reactions might lead to a translocation of fluid into the aneurysm sac. Alternatively, anticoagulant medication might play a role. All patients were using Ascal (acetylsalicylic acid, platelet aggregation inhibitor) for prevention of vascular thrombo-embolic events. It may well be that this drug influences the processes governing thrombus organization inside the aneurysm sac.

We could not draw conclusions on the clinical significance of this large amount of unorganized thrombus in the aneurysm sac, because only nonshrinking aneurysms were investigated. Studies in patients with shrinking aneurysms are warranted. If these also reveal large amounts of unorganized thrombus in the aneurysm sac, the finding is not clinically significant and might even be a normal phenomenon.

So as a next step we performed a longitudinal study in patients in the first year after EVAR which is described in **Chapter 6**. We found that longitudinal analysis of aneurysm sac contents with MRI is feasible. Variations in aneurysm sac contents over time were visualized and quantified. On average for the whole patient group the aneurysm sac showed progressive thrombus organization. However, there was a large variation between individual patients. In some patients with aneurysm shrinkage af-

ter one year the volume percentage of the aneurysm sac consisting of unorganized thrombus increased during the year, while in other patients with aneurysm shrinkage this percentage decreased. We found no relation between the postoperative amount of unorganized thrombus in the aneurysm sac and aneurysm size changes. In keeping with the findings of Chapter 5 still a substantial amount (30 %) of unorganized thrombus was present in the aneurysm sac after one year. Interestingly this was the case in patients with shrinking, stable and growing aneurysms. Unfortunately, our study only comprised a small number of patients (n=30), which is too small for definite conclusions regarding the clinical relevance of the presence of unorganized thrombus in the aneurysm sac or its changes over time.

However, we did show that the evolution of aneurysm sac contents is an interesting new topic which can be further investigated with MRI. Studies in larger patient groups over longer time intervals will potentially increase the insight in the normal evolution of aneurysm sac contents in uncomplicated aneurysms versus the evolution of aneurysm sac contents in patients with complications.

The long-term surveillance after EVAR to detect complications which need to be treated poses a substantial patient burden. In future research, specific attention should be paid to the possibility of predicting complications, which will hopefully lead to a patient-specific follow-up protocol. The methodology developed for our study provides the possibility to noninvasively monitor aneurysm sac contents with MRI in patients after EVAR. This paves the way for larger studies to assess its clinical value.

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8

Summary

In this thesis we report on the use of MRI in the follow-up of abdominal aortic aneurysms after endovascular repair.

First, the use of MRI with a blood pool contrast agent for the detection of slow-flow endoleak is described. Gadofosveset trisodium, a gadolinium-based agent that binds to albumin, is used as contrast agent. The albumin binding causes a long retention time of the contrast agent in the vascular system, which allows for a longer delay between injection and imaging than conventional extracellular contrast agents. In Chapter 2, the value of blood pool contrast agent-enhanced MRI for endoleak detection is investigated in patients who present with nonshrinking aneurysms more than a year after EVAR, without evidence of endoleak on CTA and delayed CT. In 55 % of the MRI exams endoleaks were visualized. Especially the late phase postcontrast imaging 30 minutes after injection proved valuable for endoleak detection. In Chapter 3, graft porosity is visualized with this technique in patients with an original Excluder endograft. In vitro, the presumed porosity of this graft was demonstrated before. With blood pool contrast agent-enhanced MRI, graft porosity is visualized in vivo for the first time. A clear increase in signal intensity around the endograft can be observed in the postcontrast T_1-weighted images acquired 30 minutes after injection.

In the following chapters the superior soft tissue contrast of MRI is used for the visualization of aneurysm sac contents. In Chapter 4 we present a method to quantify aneurysm sac contents based on the signal intensities in pre-contrast T_1- and T_2-weighted and postcontrast T_1-weighted images. With this method, a user can interactively determine the unorganized thrombus volume, the organized thrombus volume and the endoleak volume. In Chapter 5 the method is applied to patients with nonshrinking aneurysms more than a year after EVAR. This work demonstrates that – even years after EVAR – half of the nonshrinking aneurysm sac contents still consists of unorganized thrombus, irrespective of the presence of endoleaks. In Chapter 6 the longitudinal analysis of aneurysm sac contents in patients in the first year after EVAR is reported in relation with changes in aneurysm volume on long-term CT-follow up. Progressive organization of aneurysm sac contents is demonstrated which is reflected by an increase in the amount of organized thrombus volume and a decrease in unorganized thrombus volume in time. In this group, after one year still one third of the aneurysm sac consists of unorganized thrombus. No difference in the evolution of the aneurysm sac is found between stable, shrinking and growing aneurysms. Our data suggest a relation between a larger unorganized thrombus volume and the use of vitamin K antagonists.

In this thesis we explored the use of MRI in the follow-up after EVAR. Slow-flow endoleaks can be detected with MRI with a blood pool contrast agent, and aneurysm sac contents can be visualized and monitored with MRI. Further longitudinal studies with MRI could eventually provide more clarity on the processes in the aneurysm sac after EVAR.

A

De aorta is de grote lichaamsslagader die ontspringt uit het hart, en vervolgens via de borstholte naar de buik loopt om alle organen te voorzien van bloed. De wand van de aorta is elastisch en rekt uit als het bloed erin gepompt wordt bij iedere hartslag, waarna deze weer terugveert naar zijn normale diameter. Bepaalde aandoeningen kunnen leiden tot een verwijding van de aorta (aneurysma). Als de aorta te wijd wordt, kan deze scheuren (ruptuur). Dit is vaak dodelijk. Het ruptuurrisico van een aneurysma neemt toe naarmate de diameter toeneemt. Om een ruptuur te voorkomen worden aneurysmata met een diameter van 5.5 cm of meer behandeld.

In het verleden was operatieve behandeling de enige behandeloptie. Sinds de jaren 90 is een minimaal invasieve endovasculaire behandeling van aorta aneurysmata mogelijk, waarbij een vaatprothese in het aneurysma geplaatst wordt via de liesslagaders. Na deze minimaal invasieve behandeling (EVAR) zijn controles van de patiënt middels beeldvorming van het aneurysma noodzakelijk om late complicaties tijdig op te sporen. De basis van de follow-up wordt gevormd door veranderingen in grootte van het aneurysma, omdat aneurysmagroei het risico op ruptuur verhoogt. Idealiter blijft het aneurysma gelijk, of treedt krimp op met een ongewijzigde positie en configuratie van de endoprothese. Bij een groeiend aneurysma is oplettendheid geboden en wordt nader onderzoek gedaan naar de oorzaak, zoals lekkage van bloed in de aneurysmazak (endoleak) en migratie van de prothese. Als dit wordt gevonden, kan dit behandeld worden, teneinde de groei van het aneurysma te stoppen.

De follow-up van aneurysmagrootte kan geschieden met echografie, CT-onderzoek of MRI-onderzoek. Voor het aantonen van endoleak is de toediening van contrastvloeistof noodzakelijk. Zolang het contrastvloeistof zich in de bloedbaan bevindt, geeft dit een andere densiteit of signaalintensiteit van bloed op de beelden, waardoor lekkage kan worden afgebeeld. De gouden standaard voor het detecteren van endoleaks is van oudsher de digitale subtractie angiografie, echter deze techniek is steeds meer vervangen door niet-invasieve beeldvorming zoals CT angiografie en MR angiografie.

Endoleaks worden onderverdeeld in verschillende typen, afhankelijk van de bron van het endoleak. Type I endoleak is gedefinieerd als lekkage van bloed langs de uiteinden van de prothese ten teken van een prothese die niet perfect aansluit op de vaatwand. Type II endoleak staat voor teruglekkage vanuit zijtakken van de aorta door een omgekeerde stroomrichting, type III endoleak wordt veroorzaakt door delen van de prothese die zijn losgeraakt van elkaar of een defect in de prothese, bij een type IV endoleak is er sprake van porositeit van de endoprothese. Type I en III endoleak leiden over het algemeen tot aneurysmagroei, type II endoleak speelt waarschijnlijk een minder grote rol en wordt vaak afwachtend benaderd.

Er wordt niet altijd een verklaring gevonden voor aneurysmagroei. Vaak wordt in een groeiend aneurysma een endoleak gevonden, maar niet altijd. Dit laatste wordt endotensie genoemd. De oorzaak voor endotensie is nog onduidelijk, waardoor geen

gerichte behandeling mogelijk is. In geval van blijvende groei zonder aantoonbare oorzaak resteert als enige behandeloptie conversie naar chirurgie, dat wil zeggen dat de aanwezige endoprothese via een operatie wordt verwijderd en alsnog een vaatprothese wordt ingehecht in de aorta.

Verschillende oorzaken voor endotensie zijn gesuggereerd in de literatuur, zoals bijvoorbeeld endoleak die niet opgespoord kan worden met de standaard beeldvorming door bijvoorbeeld een langzame stroomsnelheid of intermitterende lekkage. Dit soort endoleaks zijn met de huidige technieken niet aan te tonen of uit te sluiten omdat de gebruikelijke contrastvloeistoffen al verdwenen zijn uit de bloedbaan voordat lekkage optreedt. Anderzijds is gesuggereerd dat processen die plaatsvinden in de aneurysmazak zelf aanleiding kunnen geven tot groei van het aneurysma.

In dit proefschrift is allereerst de toepassing van een nieuw contrastvloeistof voor het aantonen van endoleaks onderzocht. Hiervoor is gadofosveset trisodium gebruikt, dit is een gadolinium gebaseerd contrastvloeistof dat bindt aan albumine waardoor het langer in de bloedbaan blijft (blood pool contrastvloeistof). Tot ongeveer een uur na injectie kunnen met MRI beelden worden gemaakt met een verhoogde signaalintensiteit van het bloed. In **hoofdstuk 2** en **3** is dit contrastvloeistof gebruikt om endoleaks aan te tonen in patiënten met niet-krimpende aneurysmata zonder aangetoond endoleak op CT. In 9 van de 14 patiënten werden op deze wijze toch endoleaks gevonden. Deze waren duidelijker zichtbaar op de beelden 30 minuten na injectie dan 3 minuten na injectie. In **hoofdstuk 3** bleek het eveneens mogelijk om met deze techniek de porositeit van een specifieke endoprothese af te beelden.

Er is nog weinig bekend over de processen die plaatsvinden in het aneurysma na EVAR. In de aneurysmazak (tussen de endoprothese en de vaatwand) bevindt zich meestal zowel pre-existente wandstandige thrombus als bloed dat gevangen raakt tussen endoprothese en vaatwand tijdens het plaatsen van een endoprothese. In dierexperimenteel onderzoek is aangetoond dat dit bloed stolt en dat deze thrombus steeds verder organiseert in de tijd. Dit blijkt te correleren met veranderingen in signaal intensiteit op MRI-beelden. Een afname van signaalintensiteit op de T2-gewogen beelden komt overeen met een toename van de organisatiegraad van de thrombus. In **hoofdstuk 4** beschrijven we een methode die we hebben ontwikkeld om de aneurysmazak interactief onder te verdelen in ongeorganiseerd thrombusvolume, georganiseerd thrombusvolume en endoleak op basis van de signaalintensiteiten op de T_1-, T_2- en postcontrast T_1-gewogen MRI beelden van patiënten. In **hoofdstuk 5** wordt deze methode toegepast op patiënten met niet-krimpende aneurysmata meer dan een jaar na EVAR. Dit hoofdstuk laat zien dat in deze patiënten nog ongeveer de helft van de aneurysmazak uit ongeorganiseerde thrombus bestaat jaren na EVAR, zowel in patiënten met als zonder aangetoond endoleak. **Hoofdstuk 6** beschrijft de veranderingen in de samenstelling van de aneurysmazak in de tijd gedurende het eerste jaar na EVAR. We hebben onderzocht of er een verband was met veranderingen in aneu-

rysmavolume op lange termijn CT follow-up. Over het algemeen neemt de hoeveelheid ongeorganiseerde thrombus in de aneurys-mazak af, terwijl de hoeveelheid georganiseerde thrombus toeneemt in de tijd. Onze data laat geen verschil zien tussen krimpende, stabiele, en groeiende aneurysmata. Na één jaar bestaat nog ongeveer een derde deel van de aneurysmazak uit ongeorganiseerde thrombus. Onze data suggereert een mogelijke relatie tussen het gebruik van antistollingsmedicatie (vitamine K antagonisten) en een groter ongeorganiseerd thrombus volume. Echter de groep patiënten was klein waadoor we geen definitieve conclusies kunnen trekken.

Samenvattend hebben we in dit proefschrift het gebruik van MRI in de follow-up na EVAR nader onderzocht. MRI met een contrast vloeistof dat langer in de bloedbaan blijft heeft aanvullende waarde voor het aantonen van endoleaks. Dit is met name interessant voor patiënten met een groeiend aneurysma bij wie met CT geen endoleak wordt gevonden. Tevens hebben we een methode ontwikkeld om met MRI de inhoud van de aneurysmazak af te beelden en te monitoren in de tijd. Deze methode maakt longitudinale studies in grotere patiëntengroepen mogelijk om meer inzicht te krijgen in de processen die zich afspelen in de aneurysmazak en hun klinische betekenis. Hopelijk wordt het in de toekomst mogelijk om aneurysmagroei te voorspellen en kan zo de follow-up beter worden afgestemd op de individuele patiënt.

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S.A.P. Cornelissen, H.J.M. Verhagen, J.A. van Herwaarden, E.P.A. Vonken, F.L. Moll, L.W. Bartels, "Lack of thrombus organization in nonshrinking aneurysms years after endovascular abdominal aortic aneurysm repair", *Journal of Vascular Surgery, in press*

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S.A.P. Cornelissen, E.P.A. Vonken, J. Van Prehn, H.J.M. Verhagen, F.L. Moll, L.W. Bartels, "One year after endovascular abdominal aortic aneurysm repair (EVAR) one third of the aneurysm sac still consists of unorganized thrombus in patients with and without detectable endoleak", *European Congress of Radiology (ECR), March 2012, Vienna, Austria*

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Sandra

Sandra Cornelissen was born on May 11th, 1978 in Breda, the Netherlands. After high school at the Thomas More College in Oudenbosch, she decided to study in Amsterdam at the Vrije Universiteit. In 1996, she studied Medical Biology, in 1997, she combined this with a study in Computer Science at the same university with a special focus on image processing and computer graphics. In 1998 she finally got the chance to study medicine which she combined with her study in computer science. She did a master's project at the Radiotherapy department of the Antoni van Leeuwenhoek hospital in Amsterdam on semi-automatic delineation on multimodal images (prof. dr. M. van Herk). In 2002 she obtained her master's degree in Computer Science, and in 2004 she obtained her medical degree. In December 2004 she started working as a PhD student at the Image Sciences Institute in the University Medical Center Utrecht on a multidisciplinary project in Image Sciences, Radiology and Vascular Surgery, of which the results are described in this thesis. In July 2007 she started her residency Radiology at the University Medical Center Utrecht (prof. dr. J.P. van Schaik), which she continued in January 2010 at the Meander Medical Center in Amersfoort (dr. H.J. Baarslag) with a special focus on Interventional Radiology since January 2011 (drs. R.A.M. Gruijters).