VALIDATION OF ENDOVASCULAR ANEURYSM SEALING

JT BOERSEN

VALIDATION OF ENDOVASCULAR ANEURYSM SEALING FOR TREATMENT OF ABDOMINAL AORTIC ANEURYSM

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**VALIDATION OF ENDOVASCULAR ANEURYSM SEALING FOR
TREATMENT OF ABDOMINAL AORTIC ANEURYSM**

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The journey is the reward

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GENERAL INTRODUCTION AND THESIS OUTLINE

INTRODUCTION

Infrarenal abdominal aortic aneurysm (AAA)

Infrarenal abdominal aortic aneurysm (AAA) is commonly defined as a diameter of the abdominal aorta ≥ 3 cm. AAA treatment may be considered when the risk of rupture becomes higher than the operative risk, including a maximum diameter of 5 cm or 5.5 cm for female and male patients, respectively. Rapid annual aneurysm growth of > 1 cm / year, and aneurysms that are symptomatic are also considered indications for treatment ¹.

EndoVascular Aneurysm Repair (EVAR)

Endovascular aortic aneurysm repair (EVAR) is the preferred treatment for infrarenal abdominal aortic aneurysm. Most types of EVAR endografts consist of a main body (bifurcating stent component) and contralateral limb to replace the diseased part of the aorta. Fixation in most of endograft designs is based on radial force in the proximal and distal landing zones, gained by appropriate oversizing of the stent diameter with regard to the vessel wall diameter in the landing zones in the infrarenal aortic neck (15 % - 30 %) and common iliac arteries (10 % – 15 %). In addition, hooks or a suprarenal bare metal stent extension are incorporated in some endograft designs to enhance fixation.

The EVAR procedure is favoured because of a low 30-day mortality rate compared to open repair, however, significant more reinterventions are required during follow-up (odds 2.08 in favour of open repair) ². Sac enlargement after EVAR, due to loss of sealing, has been reported in a range of 0.2 % to 41 % ³. Type I and III endoleaks, respectively caused by blood leakage into the aneurysm at the proximal (Ia) or distal (Ib) seal zone, or due to a stent component separation, are considered high flow endoleaks. These endoleaks usually require reinterventions due to a risk of secondary rupture¹. The role of type II endoleak due to a retrograde flow from the inferior mesenteric or lumbar artery is less clear, and current guidelines report no treatment if total aneurysm sac growth during follow-up is < 10 mm compared to baseline ¹.

Employing EVAR outside the instructions for use (IFU) has been associated with a higher (late) mortality and incidence of type Ia endoleak, graft thrombosis and reinterventions compared to on-label use ^{4,5}. Around 30 % of AAA patients cannot be treated within the instructions for use (IFU) of commercially available EVAR devices due to anatomical restrictions ⁶. These restrictions may include a hostile infrarenal neck anatomy (length < 10 mm, tapered, angulation > 90 degrees, mural thrombus and calcification and a large diameter) in up to 44 % of patients ⁷, or presence of a concomitant common iliac artery (CIA) aneurysm in around 20 % of AAA patients ^{8,9}.

Figure 1. A) Endovascular aortic repair; B) Endovascular aortic sealing; C) top view of bifurcation EVAR; D) top view of dual lumen configuration EVAS.

EndoVascular Aneurysm Sealing (EVAS)

Endovascular aneurysm sealing (EVAS) with the Nellix endosystem (Endologix Inc., Irvine, CA, USA) has offered an alternative to treatment of infrarenal AAA^{10,11}. The concept of EVAS is based on sealing of the entire aneurysm and stent fixation inside the aneurysm sac, and this is obtained by polymer filling of endobags that surround two stent frames (Figure 1B). The objective of EVAS has been to reduce the incidence of endoleaks (mainly type II and III) and associated reinterventions by obliterating the aneurysm space, and a simpler procedure with no bifurcating stent component and no need for contralateral limb cannulation. The early clinical results for on-label use have been promising, but are limited to results at 30-days and 1-year follow-up for a limited number of patients^{12,13}.

The EVAS endosystem consists of balloon-expanding cobalt-chromium stent frames that are 10 mm in diameter, each covered by an endobag. The stent flow lumen is lined with a layer of polytetrafluorethylene (PTFE) to provide a smooth surface that should reduce the risk of stent thrombosis. The endobag consists of a polyethylene terephthalate (PET) bag which is proximally and distally sutured to the stentframe. The proximal and distal stent ring are uncovered. The polymer is based on polyethylene glycol (PEG), and is injected through a fill line inserted distal to the endobag. Polymerization takes about 3-5 minutes at body temperature (37 degrees).

Patient eligibility for EVAS is based on preoperative computed tomography angiography (CTA) measurements of aortoiliac anatomy at baseline. Planning consists of aortoiliac length and volume measurements to determine the stent frame lengths (right and left) and polymer volume prior to surgery. The planning is important, as endosystems dedicated to the patient anatomy should be available during surgery. In addition, polymer cartridges (40mL) need 20 minutes of thawing prior to the procedure, and accurate volume estimation will reduce costs by prevention of unused polymer cartridges.

Different from EVAR is that actual sizing, including measurements of stentframe lengths and endobag fill volumes in EVAS is part of the surgical procedure. A calibration catheter with radiopaque markers at 1 cm distances is used to determine the stentframe lengths on the angiogram during surgery. The catheter is advanced over a stiff guide wire to anticipate for the stiffness of the stent delivery system during implantation of the endosystems. Polymer volume is determined by a prefill of the endobags with saline with an intended fill pressure of 180 mmHg. Simultaneous injection of saline into both endobags is performed under continuous monitoring of pressure by a pressure transducer attached to the fill line. If completion angiography confirms good sealing, the saline volume is aspirated and a similar volume of polymer is injected until a pressure of 180 mmHg is reached.

The proximal uncovered EVAS stent ring (4 mm) is preferably positioned across the orifice of the most distal renal artery to seal the total available infrarenal neck length. Accordingly, flow lumens to both legs originate in the juxtarenal aorta. This situation is different from a native aorta bifurcation or EVAR endograft with a bifurcating stent component (Figure 1C and 1D). The transition of the aortic flow lumen into two 10-mm stent lumens creates a

mismatch area that might increase flow recirculation in the suprarenal aorta after EVAS. The relatively high resistance of the peripheral vessels compared to the renal arteries at rest causes flow recirculation in the infrarenal aorta during early diastole, and this has been associated with atherosclerosis and blood coagulation in some regions¹⁴. It is unknown if flow recirculation in the suprarenal aorta is enhanced after EVAS. In this thesis, several features of the EVAS therapy are studied. The research questions for this thesis are provided in the thesis outline.

THESIS OUTLINE

In-vitro tests can be used to study design properties in a controlled setting, but not all conditions can simply be studied in-vitro due to variations in anatomy and physiology between patients. In essence, clinical outcomes are required to validate theoretical capabilities. On the other hand, basic knowledge is required to clarify (unexpected) clinical events. This thesis aims at technical and clinical validation of several new features of the EVAS technology. Chapters 1-3 focus mainly on clinical validation, while chapters 4-6 have a focus on technical validation of the stent design.

Chapter 2. What is the reproducibility of preoperative CTA volume measurements of aortoiliac flow lumen and precision in estimation of perioperative (pre)fill volume of the endobags?

The estimation of the aortoiliac flow lumen volume has become relevant in EVAS, as adequate fixation and aneurysm exclusion will rely on proper volume estimation and injection of the required polymer volume into the endobags. In this chapter the reproducibility and precision of preoperative CTA volume measurements was assessed by comparison with endobag prefill volumes. 3Mensio Vascular (Pie Medical, Bilthoven, the Netherlands) is dedicated software for vascular procedure planning and was used to perform measurements of aortoiliac flow lumen at the preoperative CTA.

Chapter 3. What are the changes in aortoiliac anatomy at the 30-day follow-up CTA concerning infrarenal neck and aneurysm diameter, aortoiliac length, aortic neck angulation, and aneurysm and thrombus volume?

Essential for EVAS is conformation of the endosystem to the patient's anatomy or vice versa, as potential unfilled space around the stents may cause endoleak and affect device positional stability during follow-up. In this chapter changes in aortoiliac anatomy were assessed post-EVAS at the 30-days follow-up CTA to study conformability of the Nellix endosystem. 3Mensio was used to assess changes in aortoiliac anatomy post-EVAS. This was done by comparing the aortoiliac anatomy on the preoperative and 30-day postoperative CTA.

Chapter 4. What is the rate of stent migration, stent occlusion, endoleak and reinterventions of endovascular aortic sealing (EVAS) with the Nellix endosystem in treatment of concomitant and isolated common iliac artery (CIA) aneurysms after one year?

EVAS of large CIA aneurysms with a maximal flow lumen diameter < 35 mm can be performed within the IFU. In addition, EVAS can be used to treat large isolated CIA aneurysms, but this application is outside the IFU¹⁵. In this chapter the clinical outcome of EVAS in treatment of large concomitant and isolated common iliac artery aneurysms in 72 patients was studied. The primary endpoints were occurrence of stent migration, stent thrombosis, endoleak, and need for aneurysm-related reinterventions during 1-year follow-up.

Chapter 5. What is the influence of a dual lumen configuration after EVAS on complex secondary flows (recirculation) in the suprarenal aorta and common iliac artery, and the flow in the renal artery, compared to two EVAR stents and an aneurysm control under physiologic resting conditions?

In this chapter, the influence of a dual lumen configuration on flow recirculation in the suprarenal aorta and common iliac artery was studied and compared to EVAR and an aneurysm control. The models were tested under physiologic resting conditions in an in-vitro cardiovascular setup. The flow was visualized with laser particle imaging velocimetry. Image analysis included calculations of flow patterns and quantitative flow parameters associated with thrombosis and blood coagulation. The methods to quantify the flow had to be developed and validated, and this was also part of this research.

Chapter 6. What is the influence of positioning of EVAS on flow recirculation proximal to the endobags, and flow profile in the renal artery under physiologic resting conditions?

A larger infrarenal neck diameter results in a larger mismatch volume and in potential a larger region of flow recirculation. In addition, positioning variability of the endosystem, i.e. due to an asymmetric location of the renal orifice, may be associated with different hemodynamics proximal to the endobags and in the renal arteries. In this chapter the influence of neck diameter and positioning of EVAS on flow proximal to the endobags and in the renal artery was studied. The method was similar to the previous chapter, but with creation of aneurysm models with different neck diameters and positioning of the endosystem.

Chapter 7. How large are gutter volume and chimney stent compression in chimney EVAR and chimney EVAS configurations, and what influence does chimney stent compression has on renal volumetric flow compared to a juxtarenal aneurysm control, studied in an in-vitro setup under physiologic resting conditions?

Feasibility of chimney EVAS (ch-EVAS) with parallel grafts in the renal arteries to treat a juxtarenal aneurysm has been demonstrated ^{16,17}. Common technical issues with chimney EVAR (ch-EVAR) are gutter formation and chimney stent graft compression, respectively inducing a risk of type Ia endoleak or stent thrombosis by obstructing renal flow. In this chapter gutter formation and chimney stent graft compression were compared between ch-EVAR and ch-EVAS configurations in relation to renal flow. Seven identical flow phantoms of a juxtarenal aneurysm were created, including four ch-EVAR and two ch-EVAS configurations. Gutter formation and chimney stent graft compression were determined at a CT of each model with use of 3Mensio software. Renal flow was studied under physiologic resting conditions in a vitro cardiovascular setup and compared to an aneurysm control.

A general discussion concludes the thesis.

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2

VALIDATION OF PRE-PROCEDURAL AORTIC ANEURYSM VOLUME CALCULATIONS TO ESTIMATE PROCEDURAL FILL VOLUME OF ENDOBAGS IN ENDOVASCULAR AORTIC SEALING

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ABSTRACT

Background. Endovascular aortic sealing (EVAS) with a sac anchoring endoprosthesis excludes abdominal aortic aneurysms based on polymer filling of endobags. Primary objective was to assess the reliability of pre-procedural computed tomography (CT) scans based calculations of required endobag volume in relation to intraoperative volume of the endobags.

Methods. Forty elective EVAS patients were included. Pre-procedural estimations of endobag volume were based on CT segmentations of aortic flow lumen volume, including both automated and manually-adjusted segmentations, performed by two experienced users. Additionally, changes in maximum AAA diameter, thrombus volume and total AAA volume were calculated from pre- and post-procedural CT scans.

Results. Automatically determined volumes were comparable to manually-adjusted calculations (75.3 mL vs. 75.7 mL) and inter-observer agreement regarding pre-EVAS calculations of prefill volume appeared almost perfect with an intra-class correlation coefficient of 0.98 (95% CI: 0.96-0.99). The mean pressure of the endobags was 185 mm Hg. Manually-adjusted pre-procedural volume calculations underestimated procedural volume of the endobags (-11.3 ± 9.9 mL). Differences between pre-EVAS and procedural volume measurements were independent from endobag pressure ($R=-0.06$, $P=0.72$), preprocedural thrombus volume ($R=-0.303$, $P=0.057$) and changes in total AAA volume ($R=0.02$, $P=0.91$). A significant association was determined between differences in pre-EVAS and endobag volume *versus* changes in thrombus volume pre- and post-procedural ($R=0.39$, $P=0.01$).

Conclusions. In this validation study, pre-procedural volume measurements underestimate the actual fill volume of the endobags. It should be advised to perform a prefill of the endobags during the EVAS procedure.

INTRODUCTION

The Nellix™ endosystem (Endologix, Irvine, CA, USA) introduces a new concept of endovascular treatment of infrarenal abdominal aortic aneurysms (AAA), called endovascular aortic sealing (EVAS). Each endosystem (one for each iliac artery) consists of a balloon expandable cobalt chromium covered stent that is surrounded by an endobag. The concept of EVAS is based on filling endobags inside the aortic aneurysm flow lumen with polymer that cures in 3-5 minutes to minimize type 1 and 2 endoleaks ^{1,2}. The balloon-expandable stents provide a flow lumen to each iliac artery.

During the procedure a prefill of the endobags with non-heparinized saline solution is recommended to estimate the final volume of polymer needed in the endobags, thereby aiming at an intended fill pressure in the endobags of 180 mm Hg. Higher pressure (and thus volume) increases the risk of procedural aortic perforation, whereas lower pressure (and thus volume) will enhance the risk of inadequate sealing, with a subsequent type 1a endoleak. When the intended pressure of 180 mm Hg has been reached and control angiography shows no endoleak, the prefill solution is aspirated from the endobags and polymer is injected until the intended pressure has been reached.

In addition to the standard pre-operative aorto-iliac length and diameter measurements, volume measurements are performed during sizing and planning to estimate the required volume of polymer during the procedure. It is worthwhile to reliably estimate the volume of polymer pre-procedurally, since polymer is stored in 40-mL cartridges and each one has to be thawed at the start of the procedure, requiring 15 to 20 minutes. Additionally, reliable pre-procedural estimation of prefill volume could make prefill of the endobags redundant, thereby reducing fluoroscopy time and nephrotoxic contrast in some patients.

In this validation study, we examine the reliability of the pre-procedural estimations of the required endobag volume. Second, the accuracy of automated volume calculations is compared to manually-adjusted volume measurements. Furthermore, inter-observer variability of manually-adjusted volume measurements is assessed.

MATERIALS AND METHODS

Forty consecutive patients (7 at St. Elisabeth Hospital, Tilburg, 10 at Rijnstate Hospital, Arnhem, and 23 at St. Antonius Hospital, Nieuwegein) underwent elective surgical repair of an infrarenal abdominal aortic aneurysm with the Nellix Endosystem and were included in this study. This study was approved on August 13th 2014 by the respective Institutional Review Boards and was registered as Nellix Volume Validation Trial (study no. W14.052). Patient informed consent was obtained upon agreement for treatment.

Imaging

Pre- and 30-day post-procedural CT angiograms were acquired at the institution where each patient was treated. Scan acquisition was performed with a 256-slice CT scanner (Philips Brilliance iCT, Philips Healthcare, Eindhoven, The Netherlands). Scan acquisition parameters were: tube voltage 120 kV, increment 0.75, pitch 0.9, collimation 128x0.625 mm and slice thickness 1.5 mm. Iodine-containing contrast medium (300 mg I/mL) was administered intravenously at a rate of 4 mL/s, using 80 and 60 mL for pre- and post-procedural acquisition respectively. CT acquisition was performed during the arterial phase, using bolus triggering with a threshold of 100 Hounsfield units (HU).

Pre- and post-procedural measurements

Pre-EVAS volume calculations were based on measurements of aortic flow lumen volume, which were measured with a 3Mensio workstation (v6.1, 3Mensio Medical Imaging BV, Bilthoven, The Netherlands). The standard functionality for AAA analysis was used to obtain 3-dimensional (3D) visualizations of the aorta. Automatically segmentation of the contrast enhanced lumen and center lumen line (CLL) was performed. If necessary, the CLL was adjusted manually. Subsequently, specific measurements were performed at the 3D stretched view that was obtained. Measurements of aortic flow lumen volume were based on pre-estimated device lengths, which were determined by calculating the distance from the lowest renal artery until the landing zone of the devices. Subsequently, volume was measured using the functionality custom volume segmentation, requiring 4 user-defined segmentations of the flow lumen in 2-dimensions (2D) to calculate a 3-dimensional (3D) volume. Aortic flow lumen volume measurements were performed by two experienced EVAS physicians. Automatic contour detection was disabled during manual segmentation of the flow lumen volume. Moreover, automated measurements of aortic flow lumen volume were performed, using the functionality automated volume segmentation. The estimated endobag volume was calculated by subtracting the volume of the stents from aortic flow lumen volume, which was done for both manual and automated segmentations.

In addition, maximum AAA diameter, AAA thrombus volume and total AAA volume were measured at pre- and post-procedural CT scans. Both AAA thrombus volume and total volume were measured between the lowest renal artery and the aortic bifurcation

Procedural data

Prefill of the endobags (mL) and fill pressures (mm Hg) were prospectively recorded during surgery. Volume was read from the measurement scale on the syringes (60-mL) that were used for prefill, indicating volume with an accuracy of 1 mL. Endobag pressure was read from the pressure monitor connected to the fill lines, indicating pressure with an accuracy of 1 mm Hg. Additionally, device lengths that were used for treatment were prospectively registered.

Data-analysis

Statistical analysis was performed using IBM SPSS statistical analysis software v.22.0 (IBM Corp., Armonk, NY, USA). Inter-observer variability was evaluated with an inter-rater reliability test, considering an intra-class correlation coefficient (ICC) > 0.7 as good agreement between the two observers. Paired samples t-tests were performed to examine agreement between manually estimated and actual endobag volume measurements and agreement between manual and automated calculations of estimated volume. Bland-Altman plots were used to display outcomes. Additionally, paired samples t-tests were performed to assess differences between pre- and intraoperative measurements of AAA maximum diameter and volume (AAA flow lumen pre-EVAS and endobag plus stents post-EVAS). A P value < 0.05 was considered as a significant difference.

Differences between preoperative calculations of endobag volumes and prefill volume of the endobags were associated with fill pressure, preprocedural thrombus volume, and pre- and post-procedural changes in AAA thrombus and total AAA volume, which was performed with use of Pearson's correlation test. A P value < 0.05 was considered significant.

RESULTS

All 40 patients (mean age: 73, male: 34) underwent an uneventful EVAS procedure. Mean AAA diameter was 59.7 ± 7.9 mm and mean operative time was 83.2 ± 21.2 minutes. In 5 patients one of the Nellix endosystems was extended with an uncovered, self-expandable stent to overcome iliac artery tortuosity, combined with embolization of the internal iliac artery in 1 patient. The average prefill volume pressure was 185 mm Hg, ranging from 140 mm Hg to 240 mm Hg. There were no EVAS related complications at the 30-day CT scans.

Table 1 shows pre-EVAS volume calculations. The pre-estimated mean volume of the endobags based on manual calculations was 75.7 mL (17.7-180.5) vs. 75.3 mL (16.4-161.2) based on automated calculations (NS). The pre-EVAS calculated ratio between AAA volume and iliac arteries volume was 6.9 mL (89.3 mL vs. 13 mL).

Table 1. measurement outcomes

Pre-EVAS	Mean	SD	Range
Maximum AAA diameter (mm)	59.7	7.9	50.0-87.0
Volume (mL)			
Aorto-bi-iliac flow lumen	102.1	35.6	41.7-207.7
Aortic flow lumen	89.1	33.2	36.4-193.7
Iliac arteries flow lumen	13.0	6.1	5.2-38.7
Expected volume endobags (flow lumen minus volume stents) (mL)			
Manual	75.7	34.8	17.7-180.5
Automated	75.3	32.8	16.4-161.2
Procedural data			
Length (mm)			
Right Endosystem	164.8	12.6	140-180
Left Endosystem	162.8	13.0	130-180
Prefill volume endobags (mL)	86.9	37.0	25-195
Pressure endobags (mm Hg)	185	19	140-240

SD, standard deviation

The intra-class correlation coefficient regarding manual measurements of aortic flow lumen volume was 0.98 (95% confidence interval [CI]: 0.96-0.99), which indicates almost perfect inter-observer agreement between the two observers. Automated volume calculations were comparable to manual volume calculations (mean difference [manual – automated] was 0.4 mL; SD: 6; 95% CI: -1.5 to 2.3; $P=0.68$), which is illustrated in the Bland-Altman plot in Figure 1. The average pre-procedural estimated volume was lower than the actual prefill volume of the endobags (75.7 mL vs. 86.9 mL; -11.3 mL; SD: 9.9; 95% CI: -14.4 to -8.1, $P < 0.001$). The outcome is illustrated in a Bland-Altman plot in Figure 2, displaying the average of pre-EVAS and prefill volume on the x-axis and the difference on the y-axis. Differences were within a range from -33.7 to 6.5 mL.

Figure 1. Bland-Altman plot of manual vs. automated volume calculations of pre-EVAS aortic flow lumen in 3mensio. The mean and difference of manual and automated measurements are shown on the x- and y-axis respectively. The dashed lines indicate the mean difference (0.4 mL) of those two observations with the 95% confidence interval (mean $\pm$ 1.96SD).

Figure 2. Bland-Altman plot of pre-procedural estimated endobag volume vs. perprocedural endobag volume during prefill. The mean and difference of manual and automated measurements are shown on the x- and y-axis respectively. The dashed lines indicate the mean difference (11.3 mL) of those two observations with the 95% confidence interval (mean ± 1.96SD).

The outcomes of the paired samples t-test comparing pre- and post-procedural maximum AAA diameter and volumes (AAA flow lumen pre-EVAS and Nellix endosystem post-EVAS, thrombus and total AAA) are displayed in Table 2. Significant changes were found regarding pre- and post-EVAS AAA flow lumen (stents plus endobags volume post-EVAS) (89.1 mL vs. 98.1 mL), AAA thrombus volume (81.5 mL vs. 75.6 mL) and entire AAA volume (170.6 mL vs. 173.7 mL). There were no differences in maximum AAA diameter pre- and post-procedural (59.7 mm vs. 59.6 mm). Further analysis showed that variability in pre- and intraoperative measurements was associated with changes in thrombus volume ($R=0.39$, $P=0.01$). There was no association with changes in AAA total volume ($R=-0.02$, $P=0.91$), total aortic thrombus volume ($R=-0.303$, $P=0.057$), and endobag fill pressure ($R=-0.06$, $P=0.72$).

Table 2. outcome of paired samples t-test of pre- and post-EVAS aortic characteristics (post vs. pre)

Characteristics	Pre		Post		Paired Samples Test				
	Mean	Range	Mean	Range	Mean difference	SD	95 % CI of the difference		P-value
							lower	upper	
Maximum AAA diameter (mm)	59.7	50.0-87.0	59.6	48.4-84.0	-0.1	2.6	-1.0	0.7	0.74
Volume (mL)									
Flow lumen	89.1	36.4-193.7	98.1	41.9-184.1	8.9	9.0	6.1	11.8	<0.001
Thrombus	81.5	17.6-235.9	75.6	17.9-214.0	-5.9	10.0	-9.0	-2.7	0.001
Total AAA	170.6	106.0-339.7	173.7	107.3-345	3.1	8.0	0.5	5.6	0.02

The flow lumen post-EVAS was calculated by the volume of the endobags plus stents

DISCUSSION

In this prospective study of 40 patients that underwent EVAS with Nellix endosystems inter-observer agreement regarding pre-procedural estimated endobag volume was almost perfect (ICC=0.98), which is in line with former published studies showing good intra- and inter-observer agreement^{3,4}. Moreover, automated calculations with 3Mensio software were comparable to manually-adjusted calculations (75.3 mL vs. 75.7 mL). The average time to perform the 40 manually-adjusted volume calculations in this study was 9 minutes (range 7 - 10).

The Nellix endosystem is the first endoprosthesis based on complete filling of the aortic flow lumen surrounding the covered balloon expandable stents. To achieve a sufficient seal it is key to fill the endobags of the Nellix endosystem with a proper volume of polymer. Insufflating too much polymer will increase the risk of procedural aortic perforation, whereas too little volume may lead to endoleaks. Initial Nellix results are good; a clinical study evaluating 34 patients showed no migration after 2-years and only two (limited space) endoleaks¹. Moreover, first results of the Nellix endosystem combined with chimney grafts are promising^{5,6}. In the current study no type I or type II endoleaks were determined at either control angiography or at 30-day follow-up.

There are more reasons to be informed about the estimated volume of the endobags at the beginning of the EVAS procedure. Proper estimation of the number of cartridges will save time (physicians do not have to wait for thawing of the polymer), but also costs (approximately 750 euro for each cartridge) by avoiding thawing of unused polymer cartridges. Last but not least, a proper pre-EVAS volume estimation could make a prefill of the endobags with saline redundant in some patients., thereby reducing the number of angiographies during the procedure. However, prefill of the endobags with saline is also to judge the position of the endosystems. If not satisfied saline can be aspirated and the endobags can be repositioned to improve sealing, which is not possible with cured

polymer. From our experience, it appeared that prefill was especially useful in patients with challenging aortic neck anatomy.

In the current study, the definitive fill volume of the Nellix endobags was generally underestimated by pre-procedural aortic flow lumen volume measurements (86.9 mL vs. 75.7 mL) and substantial differences were found between patients. Only 4 patients had overestimation of the endobag volume and maximum difference was < 7 mL. Therefore, the risk of procedural aortic perforation is assumed to be very low, especially when careful monitoring of the endobag pressure will also be taken into account. Moreover, during filling of the endobags a pressure transducer will be used to determine the fill pressure inside the endobags thereby aiming at 180 mm Hg. When the aimed 180 mm Hg has been reached a digital subtraction angio will be performed to determine adequate sealing. When no endoleaks are present no additional polymer will be injected.

Differences between pre-calculated and intraoperative measurements were irrespective from prefill pressure and changes in total AAA volume, but associated with changes in pre- and post-EVAS thrombus volume. In other words, compression of thrombus might be one of the explanations of the underestimation of the pre-operative calculations. Truijers *et al.* studied changes in thrombus volume during the cardiac cycle, showing large interpatient variability in thrombus compressibility, which is probably due to intrinsic biomechanical properties of the thrombus⁷. Also in the current study large interpatient variability in thrombus compression was presented, which may explain large variability regarding differences between preoperative and intraoperative calculations of endobag volumes. Moreover, it has been described that the biochemomechanics of aortic thrombi are heterogeneous and variable between subjects⁸. Current research is focused on more precise prediction of eventual thrombus compression by analyzing Hounsfield units of AAA thrombus at pre-procedural CT-scans. Moreover, it would be interesting to examine whether dynamic imaging of the AAA would result in more reliable pre-procedural estimation of endobag volumes.

A limitation of this study is the fact that only 3Mensio software has been tested. Software of other often used workstations should also be validated. Another limitation is the fact that volume segmentation was based on similar centerline reconstructions performed by J.T.B., excluding variations in length that may result from inter-observer variability in reconstruction of the centerline. Recent studies showed good inter-observer agreement for measurements of aorto-iliac length, which is measured along the center lumen line in 3Mensio^{3,9}. Ghatwary *et al.* reported maximum repeatability coefficients (1.96SD) of 6.0 mm (3.5%) and 7.2 mm (4.4%) for the distance from the lowest renal artery until the right and left iliac bifurcation, respectively³. It is therefore supposed that inter-user variability regarding calculation of the centerline is low and has minimal influence on pre-procedural calculations of prefill volume. Moreover, shifting the distal landing zone ± 1 cm will result at maximum in a few millilitres volume difference, since the AAA account for most of the aortic flow lumen volume, which was found in this study. Similarly, differences

between pre- and intraoperative length measurements may result in slight inaccuracies in pre-procedural volume calculations, which we suppose only small inaccuracies, again because of a small flow lumen volume that is covered by the stents inside the iliac arteries. Moreover, the accuracy to distinguish flow lumen from thrombus will be influenced by the timing of the contrast injection during CT-angiography. In the current study we used a standardized protocol. However, when patients are referred from other centers with different imaging protocols the error rate to calculate volumes may be higher.

CONCLUSIONS

In the current study pre-procedural volume calculations underestimated the actual endobag volumes of the Nellix endosystems and cannot replace prefill of the endobags during endovascular aortic sealing. This is partially due to compression of the aneurysm thrombus during filling of the endobags. Prefill of the endobags is still mandatory with careful monitoring of the aimed fill pressure of 180 mm Hg according instructions for use.

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3

CHANGES IN AORTOILIAC ANATOMY AFTER ELECTIVE TREATMENT OF INFRARENAL ABDOMINAL AORTIC ANEURYSMS WITH A SAC-ANCHORING ENDOPROSTHESIS

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ABSTRACT

Objective. Endovascular aortic sealing (EVAS) with the Nellix endosystem (Endologix, Irvine, CA, USA) is a new concept to treat infrarenal abdominal aortic aneurysms (AAAs). By sealing the aneurysm, potential endoleaks may be avoided. Early results of EVAS are good, but no data have been published regarding periprocedural changes in aortoiliac anatomy. In this study, we reviewed 27 consecutive patients who underwent elective EVAS repair of an AAA.

Method. Specific AAA- (diameter, length from renal arteries to aortic bifurcation, suprarenal and infrarenal neck angulation, AAA volume, thrombus volume, and flow lumen volume), and iliac artery characteristics (length, angulation, location of most severe angulation with reference to the origin of the common iliac artery) were determined at pre- and post-procedural reconstructed computed tomography angiograms.

Results. No type I and II endoleaks were seen at 30-day follow-up. Total AAA volume, suprarenal and infrarenal angulation, as well as aortic neck diameter did not change significantly post-EVAS. AAA flow lumen increased significantly (mean difference: -4.4 mL, 95% CI: 2.0 to -8.6 mL) and AAA thrombus volume decreased (mean difference: 3.2 mL, 95% CI: 2.0 to -1.1 mL). AAA length (125.7 mm vs 123.1 mm), left common iliac artery length (57.6 mm vs 55.3 mm), and right and left maximum iliac artery angulation (right: 37.4° vs 32.2°; left: 43.9° vs 38.4°) were reduced significantly and the location of maximum angulation was further from the iliac artery origin post-EVAS, suggesting slight straightening of the aortoiliac anatomy.

Conclusion. Most aortoiliac anatomic characteristics remained unchanged post-EVAS. Filling of the endobags to a pressure of 180 mm Hg may lead to lost thrombus volume in some patients, probably due to squeezed liquid into lumbar or inferior mesenteric artery. The absolute differences in pre- and post-EVAS aortoiliac lengths were small, so preoperative sizing is accurate to select the stent lengths.

INTRODUCTION

Endovascular aortic sealing (EVAS) with the Nellix™ endosystem (Endologix, Irvine, CA, USA) is an innovative method to exclude infrarenal abdominal aortic aneurysms (AAAs) ^{1,2}. The concept of EVAS is based on sealing of the aneurysm and both common iliac arteries by polymer filling of endobags that surround cobalt chromium balloon-expandable covered stents. The stents provide flow lumens to both legs, and sealing of the aneurysm prevents movement of the EVAS system and type I and II endoleaks ^{3,4}. According to the instructions for use, common iliac artery aneurysms, up to 35 mm, can be treated with EVAS ⁵.

Filling of the endobags has to be performed with care and is based on preoperative volume calculations. The volume of the flow lumen from the lowest renal artery to both expected landing zones in the common iliac arteries has to be calculated. During treatment, the endobags will be prefilled with nonheparinized saline until an intended fill pressure of 180 mm Hg has been reached in both endobags. When digital subtraction angiography confirms a good position of the endosystems and adequate sealing of the endobags (no type I and II endoleaks), the prefilled saline is withdrawn from the endobags and the same amount of polymer is injected, again until a fill pressure of 180 mm Hg has been reached. In case of any sealing issues, a secondary fill with additional polymer can be done. It is of utmost importance not to expand the volume of the AAA during filling of the endobags to avoid the risk of rupture. It is worthwhile to determine whether the Nellix endobags and stents may increase unfavorable aortoiliac characteristics like supra- and infrarenal angulation, aortic volume expansion, and common or external iliac artery tortuosity, that may lead to post-EVAS complications like type IA endoleaks, aortic rupture, and thrombotic events, respectively. So far, limited data are available regarding eventual changes in pre-EVAS and post-EVAS aortoiliac characteristics, which is the subject of this study.

MATERIALS AND METHODS

The local St. Antonius Hospital Ethical Committee approved this study.

Patient population

From July 2013 to July 2014, 27 patients underwent elective EVAS of infrarenal AAAs with the Nellix endosystem and were included in this study. Preprocedural computed tomography (CT) scans were acquired within 3 months before surgery and follow-up scans were acquired 4 to 6 weeks post-EVAS. By purpose, anatomical characteristics of all patients were within the Nellix instructions for use, including nonaneurysmal neck length of ≥ 10 mm, aortic neck diameter of 18 to 32 mm, maximum aortic blood flow lumen diameter of ≤ 60 mm, and common iliac artery diameter of 8 to 35 mm. The aim in all procedures was for a primary fill pressure of 180 mm Hg, which was considered sufficient to gain an adequate seal and within a safe range of pressure that could be exerted on the aortic wall, thereby not risking peroperative aneurysmal perforation during filling of the endobags

Imaging/data

CT angiograms were performed with a 256-slice CT scanner (Philips Healthcare, Eindhoven, The Netherlands) and were acquired with a tube voltage of 120kV, tube current time product of 180 mAs, increment of 0.75 mm, pitch of 0.9 and collimation of 128 mm $\times$ 0.625 mm. CT-scans were reconstructed at 1.5-mm slice thickness. Xenetix300 contrast was administered intravenously at a rate of 4 mL/s, administering, respectively, 80 and 60 mL for pre- and postprocedural acquisitions. Scan acquisition was performed during the arterial phase, using bolus triggering with a threshold of 100 HU.

Data analysis

Specific AAA and iliac artery measurements were performed on the preprocedural and 1-month post-EVAS CT angiograms using a 3Mensio workstation (3Mensio Medical Imaging BV, Bilthoven, The Netherlands). Measurements were performed at 3-dimensional (3D) vessel segmentations in 3Mensio, including vessel view (Figures 1a and 1b) and stretched view (Figures 1c and 1d) visualizations. 3D visualizations were obtained by following the standard actions of AAA analysis in 3Mensio, including segmentation of the contrast-enhanced lumen and reconstruction of a center lumen line (CLL). At the post-EVAS CT scan, the CLL was reconstructed through the center of the endobags. For reproducible measurements of AAA length, the CLL reconstruction started at the distal edge of the lowest renal artery and ended at the aortic bifurcation.

Figure 1. Example of pre-EVAS AAA and iliac visualizations in 3Mensio. Fig 1A and 1C depict the 3D overview that was used for angulation measurements. Fig 1B and 1D show the stretched views that were used for AAA diameter, length, and volume measurements and iliac length, angulation, and sealing zone measurements.

AAA-specific measurements:

- Diameters (mm). Diameters were measured in 2 orthogonal directions that were used to compute the average diameter for different levels:
 - Baseline (lowermost renal artery)
 - 5 mm, 10 mm, and 15 mm below the lowest renal artery
 - Maximum AAA diameter
- Length (mm). AAA length was measured over the CLL, from the lowest renal artery to the aortic bifurcation.
- Angulation (°). Maximum supra- and infrarenal angulations were measured pre- and post-EVAS. Angulations were calculated with the tortuosity tool, measuring the curvature of the centerline. Maximum supra- and infrarenal angulations were defined as the maximum angle of the centerline proximal and distal from the lowest renal artery, respectively.

- Volume (mL). The entire volume of the aneurysm (between the lowest renal artery and the aortic bifurcation) was calculated pre- and post-EVAS. Flow lumen volume of the aorta pre-EVAS and the volume of the endobags plus stents were calculated post-EVAS. The function in 3Mensio that automatically segments volume was used to measure flow lumen volume, and custom volume segmentation was used to measure the entire AAA volume and the endobags volume. Pre-EVAS thrombus volume was calculated by the difference in AAA volume and flow lumen, whereas the post-EVAS thrombus volume was calculated by the difference between AAA volume and the volume of the Nellix endobags, including the balloon-expandable stents.

3D visualizations of the common and external iliac arteries were similarly performed. CLLs were reconstructed for both iliac arteries, starting at the origin of the common iliac arteries and extending to the distal external iliac arteries. Post-EVAS the CLL was reconstructed through the center of the EVAS stent and continued in the lumen of the native external iliac artery.

Common iliac artery measurements:

- Length (mm). Iliac artery length was measured between the origin of the common iliac arteries and the iliac bifurcation (proximal edge of the internal iliac artery).
- Angulation (°). The maximum angle of the common iliac arteries was measured pre- and post-EVAS with the tortuosity tool. The location of the maximum angulation pre- and post-EVAS was identified.

Statistics

Measurement outcomes were analyzed with IBM SPSS 22.0 software (IBM Corp, Armonk, NY, USA). A Shapiro-Wilk test was performed to assess normal distribution of the data. In case of normal distributed data, mean and standard deviations were calculated and a parametric paired samples t-test was performed to compare pre- and post-EVAS measurements of aorto-iliac anatomy. In case of skewed data, median and interquartile ranges were calculated and pre- and postprocedural measurements were compared with a related samples Wilcoxin ranked-signed test. Outcomes were considered significant at a p value < 0.05 . Moreover, a scatter plot was calculated to compare the location of the distal end of the stents with the location of maximum iliac artery angulation post-EVAS.

RESULTS

All 27 patients (25 male; mean age 73 years, SD 5 years) underwent an uneventful EVAS procedure. The average surgery time was 72 minutes (range 55-112 minutes), and blood loss was 99 mL (SD 54 mL). Completion angiography showed none of the patients had a type I or II endoleak. In 4 patients, one of the EVAS systems had to be extended with a self-expandable bare-metal stent for better alignment with the native common iliac artery. In 1 patient there appeared to be a dissection of the external iliac artery, which was also treated with an uncovered self-expandable stent. All other procedures were uneventful. The mean hospital stay was 2 days. The 30-day mortality rate was 0%. CT scans at 30 days showed no type I or II endoleaks.

Pre and post-EVAS AAA characteristics are reported in Table 1. There were no significant changes in the mean infrarenal neck diameter (baseline: 22.8 mm vs 22.9 mm, baseline+5: 23.4 mm vs 23.3 mm, baseline+10: 24.1 mm vs 24.2 mm, and baseline+15: 25 mm vs 25.5 mm), in suprarenal angulation (17.4° vs 15.7°), or in infrarenal neck angulation (36.3° vs 32.6°). No significant differences were found regarding the diameter of the aneurysm (54.8 mm vs 55.8 mm), and volume of the aneurysm (152.8 mL vs 154.1 mL). Small, but significant changes in length of the aneurysm (125.7 mm vs 123.1 mm), flow lumen volume (87.2 mL vs 91.8 mL), and aortic thrombus volume (65.5 mL vs 62.3 mL) appeared.

Table 1. AAA characteristics before and after EVAS (N = 27)

Characteristics	Pre-EVAS		Post-EVAS		Paired Samples Test (pre-post)				
	Mean	Range	Mean	Range	Mean difference	SD	95 % CI of the difference		P-value
Aortic neck diameter (mm)							lower	upper	
Baseline	22.8	18.5-27	22.9	19-28	0	1.1	-0.5	0.4	0.97
Baseline +5 mm	23.4	18.8-28	23.3	19.5-28.5	0.1	1.2	-0.4	0.6	0.64
Baseline +10 mm	24.1	19.3-28	24.2	20.5-30.5	-0.1	1.4	-0.7	0.5	0.74
Baseline +15 mm	25	19.5-33.5	25.5	21-33.3	-0.5	1.9	0.4	-1.3	0.15
Aortic neck angulation ($^\circ$)									
AASuprarenal	17.4	5-57	15.7	4-53	1.7	7.4	1.4	-1.3	0.25
Infrarenal	36.3	15-57	32.6	11-59	3.7	11.8	2.3	-1.0	0.12
AAA diameter (mm)	54.8	35-80	55.8	35-71	-1	6.4	1.2	-3.5	0.43
AAA length (mm)	125.7	85-163.5	123.1	83-156.5	2.6	4.5	0.9	0.8	0.01
Volume (mL)									
AAA flow lumen	87.2	33.7-146.2	91.8	35.1-167.7	-4.4	10.4	2.0	-8.6	0.04
AAA thrombus	65.5	9.1-155	62.3	11.2-143.1	3.2	10.6	2.0	-1.1	0.04
Total AAA	152.8	42.8-301.2	154.1	46.3-307.9	-1.3	6.5	1.2	-3.9	0.31

The baseline for aortic neck diameters was defined by the lowermost renal artery. The flow lumen volume post-EVAS was calculated by the volume of the endobags plus stents

Iliac arteries characteristics pre- and post-EVAS are summarized in Table 2. The mean sealing length for the right and left common iliac arteries was 31.6 and 33.1 mm, respectively. Significant differences were found in changes in the length of the common iliac arteries and maximum angulation pre- and postprocedural (37.4° vs 32.3° and 43.9° vs 38.4°, respectively, for the right and left iliac artery). The location of the maximum angulation, with the origin of the common iliac artery as a reference point, changed significantly for both the right and left common iliac arteries (25.2 to 33.4 mm and 25.3 to 31.6 mm, respectively). The location of maximum angulation post-EVAS appeared to be at the location of the distal end of the Nellix stents (right common iliac artery: 33.4 mm vs 31.6 mm; left commons iliac artery: 31.6 vs 33.1 mm). The mean difference between the location of maximum angulation and distal end of the stent was +1.9 mm (standard deviation [SD], 20.2; 95% confidence interval [CI], -9.8 to 6.1; $p = 0.64$) and -1.5 mm (SD, 21.8; 95% CI, -7.1 to 10.1; $p = 0.73$) for the right and left iliac artery, respectively, suggesting an association with the location of the maximum angulation with the distal landing zone. The outcomes are illustrated by the scatter plot in Figure 2, comparing the location of the distal end of the stent with the location of maximum angulation post-EVAS for both right and left common iliac arteries. This figure shows that the location of maximum angulation post-EVAS varies with reference to the distal end of the stents. After a median follow-up of 7 months none of the studied patients suffered from Nellix obstruction, nor iliac artery obstructions.

Table 2. Summary iliac arteries characteristics and outcome of paired samples test (N=27)

Characteristics	Pre-EVAS		Post-EVAS		Paired Samples Test				
	Mean	Range	Mean	Range	Mean difference	SD	95 % CI of the difference		P-value
							lower	upper	
Iliac arteries length (mm)									
Right	58.9	32-94	57.2	31-94	1.7	5.4	-0.5	3.9	0.12
Left	57.6	33-100	55.3	29-90	2.4	4.9	0.4	4.3	0.02
Maximum angulation (°)									
Right	37.4	8-76	32.3	8-59	5.1	10.9	0.8	9.4	0.02
Left	43.9	13-86	38.4	5-79	5.5	11.7	0.9	10.1	0.02
Location maximum angle (mm)									
Right	25.2	4-60	33.4	5-60	-8.2	16.7	-14.8	-1.6	0.02
Left	25.3	3-90	31.6	3-67	-6.3	15.9	-12.6	-0.1	0.05

Figure 2. Location of the distal end of the stent vs. the location of maximum angulation post-EVAS for both right and left common iliac arteries. The locations (mm) are measured with reference to the right and left common iliac artery origin, respectively.

DISCUSSION

The use of a sac-anchoring endoprosthesis for endovascular aortic aneurysm repair does not significantly change the diameters of the infrarenal neck or supra- and infrarenal angulation. However, a significant decrease in ILT volume was determined without an increase of AAA diameter and AAA volume. No type I or II endoleaks were determined at the 30-day post-EVAS CT scan. The maximum angulation as well as the lengths of the iliac arteries were reduced, suggesting straightening of the iliac arteries due to the Nellix stents post-EVAS. Significant changes were noted in AAA length, probably due to a combination of slight straightening of the infrarenal neck (mean difference: -3.7° , not significant) as well as slight increase of the aortic volume. However, the average aortic length changed by < 3 mm, which is not clinically important, and these changes will not lead to overestimation of the needed length of the stents to gain adequate seal.

The results of this study are in line with former analyses of the first-generation EVAS devices ^{2,6}. The current study conducted a more detailed overview of periprocedural changes in aortoiliac anatomy with EVAS using a newer generation device. Modifications of the aortoiliac anatomy are due to different independent factors: aneurysm volume and length modifications are caused by filling of the endobags, whereas changes in iliac angulations and lengths are due to the distal part of the endobags, but mainly due to the distal stents. Measurements were performed according to standards that have been reported for measurements of aortic ⁷ and iliac characteristics ⁸, using anatomical landmarks to improve reproducibility of the measurements. Furthermore, we evaluated the changes in iliac angulation post-EVAS.

Literature has shown that some intraluminal thrombi (ILT) –or at least parts of the thrombus- may vary in volume, due to external compression. In a recent review by Labruto F and coworkers (9) it has been shown that not all thrombi are organized, but some are minimally organized, or do contain unorganized (ie, mostly fluid) parts. ⁹ These unorganized parts can be compressed due to squeezing of the fluid components. Magnetic resonance imaging (MRI) is most accurate for ILT depiction and determination of differences in the internal structure of ILT. It is a limitation of this current study that no MR imaging was performed of patients with a significant decrease in aortic thrombus volume. This is the subject of an actual study, as well as in-vitro compression tests of explanted aortic thrombi after open aortic aneurysm repair.

Moreover, Wilson JS and coworkers ¹⁰ showed in their extensive review that the biochemomechanics of ILT are dynamic and thrombus should not be treated as an inert and homogeneous substance. Most ILT consists of three layers (luminal, medial, and abluminal) and in some patients a liquid interface has been found between the abluminal layer and the aortic wall. This liquid interface can be squeezed. Besides, the matrix of the abluminal layer is almost completely degraded and soft. According to the law of physics thrombus cannot be compressed. Truijers and coworkers studied changes in volume of thrombus in AAA during the cardiac cycle ¹¹. Large interpatient variability was found for volume changes (0.2 mL to 13.5 mL), which was independent from pulse pressure, initial thrombus volume, and aneurysm size. In our study, a larger variability was determined for changes of thrombus volume (–21.7 mL to 20 mL), which was also independent of aneurysm size. Large interpatient variability in changes of AAA thrombus volume may depend on the size of the liquid interface, suggesting that liquids maybe squeezed out of the ILT into patent branches (e.g. lumbar arteries and inferior mesenteric artery) which can explain the determined lost thrombus volume. The aneurysm sac in 1 patient was not completely filled by the endobags, which induced additional thrombus formation.

On the other hand, it is obvious that the interface between thrombus and flow lumen might be hard to define properly on the CT scans in some patients (due to poor cardiac output, asymmetrical or irregular thrombus load, no proper arterial phase CT-scans, etc). This limitation may be of influence on the accuracy of our thrombus volume measurements.

However, the interobserver tests for AAA and thrombus volume measurements showed good agreement between two observers.

Fill pressures of 180 mm Hg appear to be safe and do not lead to an increase of the total AAA volume. The fill pressures in the current study were sufficient for adequate seal, because no endoleaks were determined during the 1-month follow-up.

Suprarenal and infrarenal angulation remained unchanged because the lack of suprarenal fixation of the Nellix endosystem. Moreover, the most proximal and uncovered stents of the balloon-expandable Nellix stents are in the center of the inflated endobags and do not attach to the infrarenal neck, which might also explain the unchanged infrarenal neck angulation. Recently, Coulston and coworkers evaluated the effect of 3 different EVAR stents on straightening of the aortoiliac anatomy after elective treatment of AAA¹². Straightening of the infrarenal aorta and iliac arteries was found. As it appears for all EVAR procedures, the stent delivery devices partially straighten the infrarenal aorta and iliac arteries. This straightened configuration will be partially sustained by the stent grafts after the delivery devices and stiff guidewires are withdrawn. Other than the commercially available modular endografts, the polymer of the Nellix systems might induce slight straightening.

Figure 2 shows substantial variability regarding the location of the maximum iliac artery angulation post-EVAS with reference to the distal end of the stents. The location of the maximum angulation changed from inside to outside the final distal end of the Nellix endosystems, and vice versa, in a significant number of patients. So far, predicting where the maximum angulation will be post-EVAS is difficult. Physicians should focus on the distal ends of the relative stiff Nellix stents and perform a completion angiography without stiff guide wires. In case of non-alignment of the stents to the iliac arteries, or kinking of the arteries, the use of self-expandable stents to extend the Nellix endosystems is advised for improved alignment and to minimize the risk of thrombosis. Another reason for post-EVAS thrombosis is the occurrence of pillowing of the endobags into the Nellix stents during curing of the polymer. According to instructions for use the Nellix balloons should be inflated during polymer curing (2-3 minutes) to avoid pillowing.

Because there appear only minimal differences in aortoiliac lengths pre- and post-EVAS, we suggest that preprocedural length measurements may be accurate for measuring stent lengths. Device lengths are currently determined periprocedurally by calculating the length between the lowest renal artery and the distal landing zones, which is performed with a calibration catheter under fluoroscopic guidance. Accurate preprocedural length measurements could diminish the need for periprocedural length measurements, thus reducing fluoroscopy time and potentially further simplifying the procedure.

Study limitations

One of the major limitations is the lack of data regarding eventual changes in aortoiliac morphology beyond one month. So far, the median clinical follow-up of the patients is 7

months, and no Nellix obstructions or iliac artery obstructions have been determined. Moreover, the patients who were included in this study consisted of the first 27 cases in one single center, including mostly patients who had straightforward anatomy, with an average infrarenal neck angulation of 36.3° (range 15°-57°). Changes in supra- and infrarenal neck angulations may be less pronounced in this group of patients. Another limitation is the fact that intra- and interobserver variability for angulation measurements has not been assessed in the current study. However, recently we determined interobserver variability in a group of 35 patients pre and post endovascular abdominal aortic aneurysm repair. Angulation measurements were performed with use of digital callipers over the center lumen line. Variability appeared to be low with an average intraclass correlation coefficient around 0.7 for angulation measurements of the supra- and infrarenal aorta pre- and postprocedural (unpublished data). It has been shown that variability of length measurements using 3Mensio software is low ^{13,14}. Moreover, methods that have been used to measure infrarenal neck and AAA diameter and volume have shown good intra- and interobserver agreement ¹⁴, and were not reexamined in this study.

Because measurements were performed at static CT acquisitions, dynamic changes that occur during the cardiac cycle were excluded. Studies have shown that these dynamic changes may contribute to significant changes in AAA diameter ^{15,16} and thrombus and flow lumen volume ¹¹. In our study, variability in measurements was largest for thrombus and flow lumen volume, which would therefore have been interesting to examine with dynamic imaging modalities. In addition, Van 't Veer et al demonstrated a significant association between intra-aneurysmal pressure and the entire AAA volume ¹⁷. In this study, we would expect that larger endobag fill pressures might lead to a larger increase in AAA volume. Similarly, larger fill pressures might also explain large interpatient variability regarding changes in thrombus volume.

CONCLUSIONS

The use of the EVAS endosystem does not change aortic neck angulation or total aortic aneurysm volume. Filling of the endobags to a pressure of 180 mm Hg may lead to lost thrombus volume in some patients, probably due to squeezing of liquid components in branch arteries. No type I or II endoleaks were determined at 1-month follow-up. The average maximum iliac artery angulation will be decreased after implantation of the stents, but whether the location of this angulation will be displaced is hard to predict. Completion angiography should be performed without stiff guide wires, and also focus on the alignment of the distal end of the stents in the iliac arteries. The absolute differences in pre- and post-EVAS aortoiliac lengths were small, so preoperative sizing is accurate to select the stent lengths.

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4

MULTI-CENTRE EXPERIENCE ON TREATMENT OF CONCOMITANT AND ISOLATED COMMON ILIAC ARTERY ANEURYSMS WITH A SAC-ANCHORING ENDOSYSTEM

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ABSTRACT

Purpose. Endovascular aneurysm sealing (EVAS) is an innovative method to exclude abdominal aortic aneurysms (AAA). One of the advantages of EVAS is the possibility to exclude common iliac artery aneurysms (CIAA) without hypogastric artery intervention as well. The study reports the multi-centre experience of elective treatment of concomitant and isolated CIAAs with one-year follow-up.

Methods. Data of 72 patients with a concomitant (≥ 24 mm) or isolated CIAA (> 35 mm) were retrieved from nine experienced endovascular centres consisting patient demographics, anatomic characteristics, procedure technical details and follow-up imaging. Electronic patient medical files were assessed for device-related complications (wire-form fractures, stent obstruction, migration, and endoleaks) detected at follow-up imaging. In addition, reinterventions, ischemic complications and mortality rates were assessed.

Results. The median age of 72 patients (71 males) with 96 CIAAs was 74.9 years. More than half of patients (52.1%) were ASA score ≥ 3 , and 59.7% (43) had a CIAA > 35 mm. Twenty-one patients (29.2%) were treated for an isolated CIA aneurysm. The median procedure time was 98 min (IQR: 90-123 min) and no endograft migration occurred during a median follow-up of 11.9 months (IQR: 9.2-15.6 months). Stent occlusion occurred in four patients (5.6%), with a reintervention performed in all cases. Endoleaks (one type IA, two type IB and two type II) occurred in five patients (6.9%) without aneurysm growth, and had no reintervention to date. The all-cause mortality was 4.2% (N=3) with one procedure-related death at 7 days post-procedure due to haemorrhagic stroke. The freedom from endoleak and reintervention after 1-year was 92.5% and 92.9%, respectively.

Conclusion. Early results of EVAS for elective treatment of isolated and concomitant CIA aneurysms are promising with minimal need for additional treatment of hypogastric arteries. The incidence of stent graft obstruction is comparable to CIAA repair with other endovascular devices. Long-term follow-up is required to prove sustained durability.

INTRODUCTION

In 17-20% of patients with infrarenal abdominal aortic aneurysms (AAA) a concomitant common iliac artery aneurysm (CIAA) with a maximum diameter > 24 mm exists ^{1,2}. The presence of a concomitant CIAA during conventional endovascular aneurysm repair (EVAR) has been associated with a higher incidence of type IB endoleaks (9.1% vs. 4.3%), endograft occlusion (5.9% vs. 4.4%) and subsequent reinterventions (23.0% vs. 15.6%) during longer term follow-up ². Embolization with coils or vascular plugs of the internal iliac artery and endograft extension to the external iliac artery can be used to overcome a missing distal sealing zone, but this has been associated with a significant risk of ischemic complications including buttock claudication (23% - 28%) ^{3,4} and erectile dysfunction (17%) ⁴. Iliac branched device (IBD) can be used in combination with EVAR to overcome this issue, but adds substantial costs to the procedure ⁵.

Isolated common iliac artery aneurysms are uncommon, accounting for around 2% of intra-abdominal aneurysms ⁶. IBD can be successfully used to treat CIAA with preservation of internal iliac artery (IIA) flow ^{7,8}, but only 38 % of iliac artery anatomies fall within the instructions for use (IFU) of commercially available devices ⁵.

Endovascular aneurysm sealing (EVAS) with the Nellix endosystem (Endologix Inc., Irvine, CA, USA) involves a recently introduced concept for endovascular treatment of AAA, based on aneurysm exclusion by polymer filling of endobags that surround cobalt-chromium stents ⁹. The endosystem is designed to address endoleaks and migration seen in standard modular endografts, and can be used to treat concomitant CIAA with a maximum flow lumen diameter of 35 mm according to instructions for use ¹⁰. In addition, the stent design enables treatment of isolated CIAA, although, this would be outside the IFU. Few studies have been published on CIAA repair with the Nellix endosystem ^{11,12}. The present study employs a 1-year multi-centre experience on concomitant and isolated CIAAs treated with the Nellix endosystem.

METHODS

Patients and anatomical characteristics

Data was retrospectively collected by case report forms (CRFs) that were sent to nine centres, experienced in treatment of AAAs with the Nellix endosystem. The Institutional Review Board of each centre approved this study. Patient data was retrieved from the individual patient medical files, consisting of demographics (age, gender, comorbidities and prior AAA surgery) and anatomic characteristics. The operative risk of each patient was assessed by the American Society of Anaesthesiologists (ASA) classification¹³. Patient inclusion was based on the presence of a concomitant CIAA with a minimum outer to outer diameter of 24 mm¹. The inclusion of patients with an isolated CIAA was based on a minimum outer to outer diameter of 35 mm¹⁴. Ruptured aneurysms were excluded from this analysis. Anatomic characteristics were acquired from imaging reports of preoperative computed tomography angiograms (CTA) scans including infrarenal neck diameter, length, and angulation as well as diameter measurements of the abdominal aorta and common iliac arteries. The measurements were used to assess on- or off-label use of the device, based on the Nellix instructions for use (IFU) (common iliac artery (CIA) flow lumen diameter between 9-35 mm for concomitant CIAA). All isolated CIAA that have been treated were considered as outside of the IFU.

Procedure and follow-up

Procedure technical details were retrieved from the patient medical files, including device-related parameters (Nellix endosystem lengths, fill volume, and fill pressure of the endobags), and other technical details (embolization of one or both internal iliac arteries, use of stents in the external iliac arteries). Technical success was defined as successful deployment of the endosystems and retrieval of the delivery systems with no residual endoleak (i.e. successful aneurysm exclusion) and a patent stentgraft lumen on completion angiography¹⁵. Perioperative complications were assessed (presence of an endoleak, obstruction, thromboembolic complication) and any additional procedures performed during primary implantation were documented. Length of hospital stay, and in-hospital complications were registered. Follow-up data included post-operative imaging (≤ 60 days) as well as the longest follow-up imaging available up to 2 years. Most patients underwent a computed tomography angiography (CTA) within 60 days after the primary procedure, and at 1-yr follow-up. Duplex ultrasound or contrast-enhanced ultrasound (DUS/CEUS) was performed in patients with poor renal function (serum creatinine level > 1.2 mg/dL or estimated glomerular filtration ratio < 60 mL/min). Device-related complications were assessed from follow-up imaging reports, including stent migration > 10 mm relative to anatomical landmarks, any migration with need for reintervention¹⁵, thrombosis of one or both Nellix endosystems, and type IA, IB or II endoleaks.

Statistics

Data analysis was performed by an independent Core Lab (Syntactx, New York, NY, USA). Descriptive statistics were provided on baseline demographics, baseline vascular characteristics, procedure and occurrence of complications and reinterventions during follow-up. All outcomes were displayed by median and interquartile range (IQR). In addition, the primary stent patency and endoleaks during follow-up were determined with Kaplan-Meier analyses.

RESULTS

From April 2013 to May 2015 72 patients (71 male; median age: 74.9 years, range: 69.4-80.6 years) were treated for 96 CIAA in nine centres. The baseline characteristics of the 72 patients are displayed in Table 1. 52.1% of patients had severe comorbidities with an ASA score of ≥ 3 . The anatomical aorto-bi-iliac characteristics of all patients are shown in Table 2, and the distribution of the 96 CIAA diameters is shown in Figure 1. In total 51 patients (70.8%) had concomitant CIA aneurysmal disease, and 24 patients (33.3%) had bilateral CIAAs.

Table 1. Baseline patient characteristics (N=72)

Variable	N/Observations (%)	
Male	71 (72)	98.6%
Age (years)	74.9	69.4 - 80.6
Hypertension	60 (72)	83.3%
Cardiac history	43 (72)	59.7%
Stroke / CVA / TIA	12 (70)	17.1%
Previous AAA surgery	7 (71)	9.9%
Chronic pulmonary obstructive disease	16 (70)	22.9%
Malignancy	20 (67)	29.9%
Diabetic	12 (70)	17.1%
Renal Insufficiency	18 (71)	25.4%
Smoking history	32 (64)	50.0%
ASA class		
1, Normal	1 (69)	1.4%
2, Mild Symptomatic Disease	32 (69)	46.4%
3, Severe Symptomatic Disease	30 (69)	43.5%
4, Severe and Life Threatening	6 (69)	8.7%

Table 2. Baseline vascular characteristics (N=72)

Characteristics	Median	IQR
Infrarenal neck		
Length (mm)	27.5	18.5-45.8
Diameter (mm)	25	22-27.1
Angulation (°)	37.6	15-57
Maximum AA diameter (mm)	51	33.3-60
Maximum CIA diameter (mm)		
Right	31.7	25-42.8
Left	27	18-35

Figure 1. Distribution of CIA aneurysm diameters (mm).

Procedure technical details are listed in Table 3. Technical success was achieved in 98.6% (N=71) of cases. One patient undergoing EVAS with a periscope in the IIA had a low flow type IB endoleak on completion angiography in the common iliac artery, representing the single technical failure. Due to the low flow of this type IB endoleak it was left untreated. Perioperative embolization of the internal iliac artery was performed in 11 aneurysms in 10 patients (one bilateral), and was performed in case of a large concomitant IIA aneurysm (> 35 mm) (N=4) or aneurysms that involved the orifice of the IIA (N=7). Distal stents (i.e. bare metal stents or covered stentgrafts) were used in 21 patients (23 external iliac arteries), and were used to better align the distal end of the Nellix endosystem (15), treat external iliac artery stenosis (N=5), or to treat an external iliac artery dissection (N=3). In addition, one procedure employed Nellix-in-Nellix to exclude a concomitant

CIA aneurysm. The median in-hospital stay was 4 days (IQR: 3-7.5 days). Figures 2 and 3 show examples of EVAS of a concomitant CIAA and isolated CIAA, respectively, both with preservation of IIA flow and without the use of distal stent extensions.

Table 3. Procedure Technical Details (N=72)

Within IFU	31 (72)	43.1%
Procedure time (min)	98	90-123
Contrast volume (mL)	140	103-240
Fluoroscopy time (min)	11	9-12
Estimated blood loss (mL)	200	100-300
Vascular access		
Open CFA		70.2%
Percutaneous		29.8%
Nellix endosystems		
Device length (mm)		
Right	160	150-180
Left	170	160-180
Prefill performed	61 (71)	85.9%
Polymer fill volume (mL)	74	52-117
Polymer fill pressure (mm Hg)	190	182-205
Secondary fill performed	11 (69)	15.9%
Distal landing zone		
Embolization IIA (N=11)		
Amplatzer plugs		5
Coiling		2
Both		4
Distal extensions (N=21)		
Alignment		19
Dissection iliac artery		2

A

B

Figure 2. EVAS of concomitant iliac artery aneurysm disease; A) preoperative CTA, B) completion angiogram.

A

B

Figure 3. EVAS of an isolated CIAA with preservation of IIA flow; A) angiogram at initial procedure, B) completion angiogram.

Procedure-related complications occurred in six patients including major adverse events in three patients (4.2%). Two of these six patients had thrombotic occlusion of one Nellix stent within 30 days of the procedure. These occlusions were treated successfully with thrombectomy and relining of the distal stent lumen with a self-expandable covered stent. None of these two patients had a re-occlusion after reintervention. One patient with pre-existent renal failure (eGFR of 50 mL/min) suffered an infarct of the lower pole of the right kidney due to unintentional coverage of an accessory renal artery. The renal function of this patient remained constant during follow-up. There was one patient with a groin seroma and another patient with a groin hematoma post-procedure. The hematoma was treated by surgical evacuation. One patient died of a haemorrhagic stroke 7 days after the procedure, considered a procedure-related death.

The median follow-up was 11.9 months (9.2-15.6 months) with follow-up imaging involving CT (56%), duplex ultrasound (42.4%) and magnetic resonance angiography (1.6%). No wireform fractures or stent migration occurred during this follow-up period. Late onset (> 30 days) stent obstruction occurred in three patients (4.2%). Two patients (2.8%) had thrombotic occlusion of one Nellix stent occurring at 5 months and 13.5 months post-procedure, respectively. Both occlusions were dissolved by thrombolysis and none of the patients had a re-occlusion of the stent during further follow-up. In addition, in one patient with calf claudication, in-stent stenosis was treated after 3-months by percutaneous transluminal angioplasty (PTA) of the Nellix stent. Angioplasty of a right popliteal artery stenosis was also performed in this patient. The primary patency after 1-years was 95.7% (Figure 4).

Endoleaks were evident in five patients during follow-up (6.9%), and included one type IA endoleak, two type IB and two type II endoleaks. In one patient with an isolated CIAA a type IA endoleak with flow into the aneurysm was observed at CT 9 months post-procedure. This endoleak was not observed on CEUS imaging 3 months later. In another patient a type 1B endoleak was noted in the right CIAA due to a short landing zone in the distal CIA. This endoleak was still present at 17 months post-procedure, but was not treated due to absence of aneurysm growth. Moreover, the perioperative type IB endoleak noted in one patient persisted during 2-year follow-up, and was left untreated in absence of aneurysm growth. The two type II endoleaks were related to retrograde flow from a patent IIA. These endoleaks persisted during follow-up and were left untreated due to absence of aneurysm growth. The 1-year freedom from all type of endoleak was 92.5% (Figure 5). The freedom from reintervention was 92.9% after 1-year.

Figure 4. Kaplan Meier analysis of primary patency after 1-year. The number of patients at risk is displayed at an interval of 6 months.

Over a median follow-up of 12 months the all-cause mortality was 4.2% with two new deaths during follow-up > 60-d. These were due to complications of coronary bypass surgery and fatal stroke, and occurred respectively at 5-months and 8-months post-procedure.

DISCUSSION

The study reports the multi-centre experience of elective treatment of concomitant and isolated CIAA with a sac-anchoring endosystem. Concomitant CIAA associated with AAAs are problematic for conventional EVAR devices where fixation and sealing may be affected by a short and dilated distal sealing zone. The maximum CIA diameter that can be sealed with current EVAR devices is 24 to 25 mm⁵. EVAS with the Nellix endosystem, when used within instructions for use, allows sealing of concomitant CIA aneurysms with a flow lumen diameter up to 35 mm. The stent design allows treatment of concomitant CIA aneurysm without the need for additional stent components, also excluding the risk for type III endoleaks. Moreover, the present study reported a low incidence of type I and

Figure 5. Kaplan Meier analysis of freedom from all type endoleaks after 1-year. The number of patients at risk is displayed at an interval of 6 months.

type II endoleaks, comparable to previous experience on EVAS (7% vs. 6.9% in the present study)¹⁶. The risk of type II endoleaks is likely to be reduced, as the endobags obstruct flow from patent arterial branches, including the IIA if Nellix has to be extended to the external iliac artery. Intraprocedural embolization of the IIA may be less frequent in EVAS than EVAR, because the seal of the endobag in the common iliac artery will prevent backbleeding from the IIA origin into the common iliac artery.

In this study, perioperative embolization of the IIA was performed in 10 patients (13.9%). Most of these cases had aneurysmal disease of the IIA, requiring more extensive embolization. Similar to EVAR, endovascular treatment of a (aneurysmal) dilation of the IIA or growth of the IIA during follow-up after EVAS is complicated due to coverage of the orifice by the endobag. It is appreciated that these cases may benefit from embolization pre-, or during EVAS. Moreover, the risk of a type II endoleak may be higher in cases that involve the iliac bifurcation, whereas the endobag may not adapt to a complex geometry of the flow lumen.

Although outside the IFU, isolated CIAA repair with EVAS allows treatment of CIAA with short sealing zones. Due to the seal of the endobag the minimum length of the non-aneurysmatic common iliac artery (< 24 mm) should be 10 mm. The top stent of the Nellix

endosystem can be positioned partially in the distal aorta, as long as the endobag itself does not protrude in the distal aorta or contralateral CIA. Inflation of a PTA balloon in the contralateral limb during curing of the polymer can be performed to prevent compression of the contralateral limb orifice. In CIAA repair with IBD, a short proximal sealing zone can be addressed by use of the device in combination with a standard modular endograft. This configuration will add time and costs to the procedure and unnecessary stenting of the abdominal aorta and contralateral CIA artery. Moreover, the 1-year estimated primary stent lumen patency of the iliac branch of IBD is moderate (86.4-91.4%)^{7,8}.

The incidence of stent occlusion was slightly higher (5.6%) in comparison to the reported incidence of stent occlusion in literature post-EVAR (3.4-4.1%)^{17,18}. Stent occlusions post-EVAS have been reported in a range of 0-5%^{12,16}. The higher rate of stent occlusions in the present study may be attributed to multiple factors. Early occlusion (< 30 days postprocedure) occurred in one patient with the distal stent in the EIA. Extension to the EIA has been associated with a higher risk of stent thrombosis, and this may explain stent occlusion in this patient^{19,20}. In the other patient with early occlusion the outflow was compromised by an existing stenosis of the EIA, which was not recognized during the primary EVAS procedure. Late occlusion was observed in two patients and may be attributed to other factors that have been associated with stent occlusion, including malignancy (both; N=2) and arrhythmia (N=1).

The incidence of endoleaks was comparable to previous experience with EVAS¹⁶. The type IA endoleak occurred at the level of the proximal common iliac artery in a patient with an isolated CIAA with a maximum flow lumen diameter > 60 mm and no thrombus. Generally it is considered that all endoleaks in combination with aneurysm growth during follow-up require reintervention²¹. Type IA is a predominant cause of late aneurysm rupture post-EVAR²². As such, it is considered that type IA endoleaks should be treated post-EVAS. Reintervention for an iliac type IA endoleak means extension in the aorta, and thus the need for an aorto-bi-iliac solution. Type IB endoleak in this cohort showed no visible flow into the aneurysm sac, and it is yet unknown whether this pressurizes the aneurysm sac. The 1-yr follow-up period may be too short to observe clear aneurysm growth in the patients that suffered endoleaks in the present study. Type II endoleaks from a backbleeding IIA are considered low flow endoleaks, and may therefore have a lower risk to repressurize the aneurysm sac and may resolve overtime.

One of the limitations of the current generation Nellix endosystems is the fact that treatment options of an endoleak are limited, due to the lack of proximal and iliac extenders. Moreover, perioperative type IA, IB and type II endoleaks may be difficult to observe on the completion angiogram due to the large endobag volumes. Completion angiographies with multiple different C-arm rotations are advised to exclude endoleaks. The present study demonstrated use of distal stent extensions in 21 patients (30.6%). Most of the extensions were bare metal stents to better align the distal end of the Nellix stent frame to the common or external iliac artery to avoid kinking and subsequent

stent obstruction. Device sizing is performed by perioperative length measurements with a calibration catheter over a stiff guide wire. The use of a stiff guide wire may straighten the aortoiliac anatomy in curved vessels, making it difficult to assess a good location for the distal landing zone in a straight part of the vessel. Moreover, it is unpredictable whether the aortoiliac anatomy will straighten post-EVAS ²³. The location of the distal landing zone may therefore be unpredictable after withdrawal of the delivery system and stiff guide wire due to tortuosity of the iliac arteries. The relative stiffness of the Nellix stents is considered one of the drawbacks of the current generation device. 3-dimensional preoperative CTA measurements of the device length over the central luminal line may help to better assess the stent length and location of the distal sealing zone. Recently, longer Nellix stents (190 mm, 200 mm) have become available, and this would have avoided a few extensions in the study group also.

Limitations. Complications such as wireform fractures and migration can only be adequately assessed at CTA, and it is uncertain whether these complications have developed in some patients who had ultrasound examinations during follow-up. A prospective study design with standard CTA in all patients during follow-up would have been better to accurately assess these potential complications. No prospective data on ischemic complications like buttock claudication and erectile dysfunction were available, and therefore these complaints could not be assessed accurately, and were therefore excluded from the analysis.

CONCLUSIONS

The Nellix endosystem allows endovascular treatment of concomitant CIA aneurysms up to 35 mm within instructions for use. In this series of 72 patients a low incidence of distal type I and II endoleaks were determined with an acceptable low rate of reinterventions. The incidence of stent graft obstructions is comparable to other commercially available endografts. Long-term follow-up is required to assess the sustained durability of the Nellix endosystem for treatment of CIA aneurysms.

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DISCLOSURES

A Holden, MM Thompson, D Böckler, D Krievins, JM Heyligers, MMPJ Reijnen, JPPM Vries are consultants and members of the scientific advisory board for Endologix.

5

FLOW AND WALL SHEAR STRESS CHARACTERIZATION FOLLOWING ENDOVASCULAR ANEURYSM REPAIR AND ENDOVASCULAR ANEURYSM SEALING IN AN INFRARENAL ANEURYSM MODEL

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ABSTRACT

Introduction. Endovascular aneurysm repair (EVAR) with a modular endograft has become the preferred treatment for abdominal aortic aneurysms (AAA). A novel concept is endovascular aneurysm sealing (EVAS), consisting of dual endoframes surrounded by polymer-filled endobags. This dual lumen configuration is different from a bifurcation with a tapered trajectory of the flow lumen into the two limbs, and may induce unfavourable flow conditions. These include low and oscillatory wall shear stress (WSS), linked to atherosclerosis, or high shear rates that may result in thrombosis. An in-vitro study was performed to assess the impact of EVAR and EVAS on flow patterns and WSS.

Methods. Four AAA phantoms were constructed, including three stented models to study the influence of the flow divider on flow (Endurant, AFX and Nellix). Experimental models were tested under physiological resting conditions and flow was visualized with laser particle imaging velocimetry (PIV), quantified by shear rate, WSS and oscillatory shear index (OSI) in the suprarenal aorta (SA), renal artery (RA) and common iliac artery (CIA).

Results. WSS and OSI were comparable for all models in the SA. The RA flow profile in the EVAR models was comparable to the control, but a region of lower WSS was observed on the caudal wall compared to the control. The EVAS model showed a stronger jet flow with a higher shear rate in some regions compared to the other models. Small regions of low WSS and high OSI were found near the distal end of all stents in the CIA compared to the control. Maximum shear rates in each region of interest were well below the pathological threshold for acute thrombosis.

Conclusion. The different stent designs do not influence suprarenal flow. Lower WSS is observed in the caudal wall of the RA after EVAR and a higher shear rate after EVAS. All stented models have a small region of low WSS and high OSI near the distal outflow of the stents.

INTRODUCTION

Endovascular aneurysm repair (EVAR) has become the standard treatment for infrarenal abdominal aortic aneurysms (AAA). The procedure is related to a lower 30-day mortality rate¹ and shorter rehabilitation period in comparison to open surgical repair (OSR). Most endografts involve a modular bifurcated design in which fixation and seal are provided by radial force in the landing zones and/or proximal fixation with hooks. Stent design varies in the position of the flow divider, the presence of suprarenal fixation and the attachment of the fabric to the stent frame (exoskeleton or endoskeleton). Recently, endovascular aneurysm sealing (EVAS) was introduced, whereby the AAA is sealed by polymer-filled endobags surrounding dual 10-mm cobalt chromium balloon-expandable endoframes. The dual lumen configuration post-EVAS is different from an anatomical or EVAR stent bifurcation with a tapered trajectory of the flow lumen into the two limbs. This difference in stent design may have different implications regarding flow patterns in the aorta and branch arteries proximal and distal from the stents in comparison to standard modular grafts. A potential mismatch area between the native vessel lumen and the EVAS stents may result in flow recirculation at the transition between the stents and the vessel lumen in the aorta and common iliac arteries. Moreover, the transition of the aorta into two 10-mm stents after EVAS may increase vascular resistance, wall shear stress (WSS) and the velocity into renal branches.

WSS is defined as the force per unit area acting parallel to the vessel wall due to the local velocity gradient. Low WSS is associated with atherosclerosis^{2,3} and subsequent atherothrombotic events^{4,5}, and may occur in regions that present flow recirculation. A low WSS has been defined < 1 Pa for arteries in vivo^{6,7}, whereas only extremely low magnitudes (i.e. 10^{-2} Pa) have been associated with development of atherosclerosis and blood coagulation^{2,8}. Moreover, directional changes in WSS throughout a cardiac cycle (i.e. periodic oscillations in WSS) may be found in areas of flow recirculation, and have also been associated with development of atherosclerosis^{2,9}. A high shear rate (> 5000 s⁻¹), referring to the gradient of the local flow velocity near the vessel wall, is associated with acute thrombosis¹⁰.

The study focuses on effects of a dual lumen configuration in the abdominal aorta after EVAS on flow and WSS proximal and distal from the stents, in comparison with two EVAR endografts and an aneurysm control by in-vitro flow visualization.

METHODS

Flow models

Flow phantoms were fabricated (Figure 1A) based on an inverse negative mold of a 3D-printed AAA model ^{11,12}. Model geometry was based on a straightforward AAA anatomy with an infrarenal neck diameter of 28 mm, infrarenal neck length of 15 mm, and maximum AAA diameter of 55 mm. A summary of the aortoiliac anatomy of the flow model is provided in Table 1. The final design was moulded in transparent silicone (Sylgard 184, Dow Corning, Midland, MI, USA) for optical transparency required for flow visualization. Three different endosystems were implanted: the Endurant II (Medtronic Inc., Minneapolis, MN, USA), the AFX (Endologix Inc., Irvine, CA, USA), and the Nellix (Endologix Inc.). The flow dividers of the Endurant and AFX are situated 5 cm distal to the most caudal RA and at the native bifurcation, respectively. These models were compared to a control (Figures 1A-D). Stent planning, sizing, and deployment in the models were performed following the standard instructions for use (IFU) by experienced vascular surgeons (MR and JV).

Figure 1A-D. Flow models; A) non-stented, control; indicated are the 2D measurements planes where the flow was captured in the centre of the flow lumen. The numbers refer to the three regions of interest; 1. Suprarenal aorta, 2. Right renal artery, and 3. Right common iliac artery B) Endurant EVAR, C) AFX EVAR, and D) Nellix EVAS.

Table 1. Phantom geometries

Suprarenal aorta	
Diameter (mm)	28
Length (mm)	60
Angulation (°)	0
Renal arteries	
Diameter (mm)	6
Length (mm)	
Right	54.7
Left	35.1
Angulation (°)	0
Branching angle (°)	60
Infrarenal aorta	
Proximal neck diameter (mm)	28
Proximal neck length (mm)	15
AAA maximum diameter (mm)	
AP	40
LR	55
Aortic bifurcation diameter (mm)	
AP	28
LR	28
Aneurysm length (mm)	115
Length infrarenal aorta (mm)	130
Angulation (°)	0
Iliac arteries	
Diameter (mm)	
Upper	14
Middle	14
Lower	8
Length (mm)	
Right	86.8
Left	80
Angulation (°)	0
Take off angle (°)	
Right	30
Left	20

AP, anteroposterior; LR, left-right

Flow setup

Flow tests were performed under physiological resting conditions. The setup was based on a two-parameter Windkessel model, including a compliance chamber downstream of the phantom to simulate peripheral vessel impedance¹³. In brief, a pulsatile flow at a rate of 60bpm was generated with a physiologic flow rate in a range of 1.6 L/min (peak flow: 3.6 L/min). The inlet section consisted of a 1.2 m tube to ensure a fully developed laminar flow entering the model. At the start of each flow experiment the setup was initiated at a steady flow rate of 1.6 L/min with an equal outflow to renal and iliac branches

(0.4 L/min) regulated with needle valves, and a mean arterial pressure of 100 mm Hg to equilibrate the system. The relatively larger outflow resistance of the iliac arteries in comparison to the renal arteries was obtained by a larger diameter of the common iliac artery in comparison to the RA. The fluid level in the compliance vessel was maintained constant throughout the flow experiments with an intended peripheral vessel compliance in a physiological range around 1.1 ml/mm Hg. This resulted in a (reproducible) systemic pressure in a range of 120 mm Hg/80 mm Hg.

A blood mimicking fluid (BMF) was used to obtain a fluid with a viscosity comparable to blood¹⁴.

Flow visualization

Laser particle imaging velocimetry (PIV) was used to visualize the flow. Fluorescent PMMA particles (Rhodamine, size 1-20 μm , density 1190 kg/m³, Dantec Dynamics A/S, Skovlunde, Denmark) were added to the BMF. A pulsed laser (LDY300, Litron, Rugby, England) was used to excite the particles in the BMF and was synchronized with a high speed camera (FASTCAM SA-5, Photron Inc., West Wycombe, Buckinghamshire UK,) to capture the fluorescent signal. Images were captured at a frame rate of 1000 fps. Laser light was focused in a sheet of light to illuminate a thin layer of fluid (< 1 mm) within the midplane of the flow lumen. The flow was captured in two dimensions (2D) in the anteroposterior (AP) midplane of the flow lumen in three regions of interest: the suprarenal aorta, right renal artery (RA) and right common iliac artery (CIA) (Figure 1A). The dimensions of a region of interest were approximately 5 cm by 5 cm, which were acquired for 10.5 s (± 10 cardiac cycles) at a frame size of 1024 by 1024 pixels.

Flow analysis

PIV LabTM¹⁵ was used to calculate the average displacement of particles in the BMF. The average displacement was determined with a spatial resolution of 0.6 mm by calculating cross-correlations between subsequent frames. Further processing of the data was performed with MatlabTM (R2015a, Mathworks, Nattick, Massachusetts, USA). In-house built Matlab scripts were used to calculate the flow direction with an average of 10 cardiac cycles, maximum instantaneous shear rate for each region of interest (s^{-1}), and WSS (Pa). Vector plots of the calculated velocity vectors were made with Tecplot (Tecplot 360 RS, Bellevue, WA, USA).

WSS was calculated by multiplication of the first order derivative of the calculated velocity profile near the vessel wall (shear rate; s^{-1}) with the fluid viscosity ($\text{mPa}\cdot\text{s}$). The phantom wall was defined by an automated segmentation algorithm in Matlab, detecting the boundaries of the flow lumen. Subsequently, the algorithm calculated line profiles perpendicular to the vessel wall that cover 50% of the flow lumen length. Natural neighbour interpolation was performed to interpolate the velocity data to a frame size of 1024 by 1024 pixels and velocity data for each line profile was extracted. Subsequently, the shear rate at

the phantom wall was defined on a cubic spline fit of the velocity data based on the best fit determined by the least squares through subsequent velocity points at one velocity vector distance (i.e. 16 pixels) and forced zero velocity at the vessel wall (i.e. no-slip boundary condition). The laser entered to the right of the model, and WSS calculations were therefore performed for the laser-entry side. WSS for each location was calculated by time averaging, referred to as mean wall shear stress in this article, and absolute values were plotted versus distance, defined by the axial distance on the vessel wall. Oscillations in wall shear stress were assessed by the oscillatory shear index (OSI) (equation 1) ⁹.

$$\frac{1}{2} \left(1 - \frac{\left| \int_0^T \tau_w dt \right|}{\int_0^T |\tau_w| dt} \right) \quad (1)$$

The OSI ranges from 0 to 0.5, based on the relative period of negative shear versus positive shear through a cardiac cycle per each location. An OSI close to 0.5 indicates severe oscillations in WSS during a cardiac cycle.

Reproducibility of the measurements was analyzed by comparing the flow rate in the suprarenal aorta at the model inlet between the experiments with the different models. Moreover, the average and standard deviation (SD) of WSS and OSI were assessed for the control model without stent to assess time-variability of measurements.

RESULTS

The average flow rate at the model inlet in the suprarenal aorta, including all four models, was 1.66 L/min (SD: 0.02 L/min). The average and SD of the flow velocity in the central lumen of the suprarenal aorta in the control is displayed in Figure 2. The average WSS and OSI over ten cardiac cycles near the wall at this location were 0.063 ± 0.002 Pa (SD 3.2% of the average WSS), and 0.204 ± 0.001 (SD 0.6% of the average OSI). The maximum suprarenal aortic wall distension was 0.04 mm (0.1% of the total vessel radius) between peak and end systolic phase, and was observed in the EVAS model.

Figure 2. Flow velocity vs. time (ms) in the center of the suprarenal aorta. The average velocity of 10 cardiac cycles is displayed and measurement variability is plotted by two times the standard deviation (shaded error).

Area 1: the suprarenal aorta

Peak-systolic velocity in the center of the suprarenal aorta was comparable for all models with a range of 13.7-14.4 cm/s. In all phantoms, including the control, the BMF was accelerated near the renal orifice during the peak-systolic phase and flow reversal was observed near the suprarenal aortic wall during the end-systolic phase (Video 1, supplementary).

The mean WSS in the suprarenal aorta was similar in all models in a range of 0.05-0.95 Pa (Table 2). The lowest WSS was found in the proximal part of the suprarenal aorta, comparable in all models around 0.05-0.06 Pa (Figure 3A). The OSI was in a similar range for all models (Figure 3B), ranging from minimum 0 in all models to maximum from 0.20 (control) to 0.23 (Endurant) (Table 2).

The maximum shear rate in the suprarenal aorta varied from 186.9 s^{-1} to 352.9 s^{-1} . The highest shear rate was found in the EVAS model near the RA orifice.

Table 2. Minimum and maximum of time-averaged wall shear stress (Pa) and OSI per vessel segment

	Control	Endurant	AFX	Nellix
Suprarenal				
Right lateral				
WSS (Pa)	0.06-0.48	0.06-0.54	0.05-0.43	0.06-0.95
OSI	0-0.20	0-0.23	0-0.23	0-0.20
Renal artery				
Cranial				
WSS (Pa)	0.66-1.23	0.88-1.35	0.12-1.51	0.44-2.27
OSI	0	0	0	0
Caudal				
WSS (Pa)	0.22-1.43	0.66-1.75	0.57-1.58	0.70-2.30
OSI	0	0	0	0
Common iliac artery				
Medial				
WSS (Pa)	0.11-0.54	0-0.63	0.01-0.80	0-0.67
OSI	0.01-0.11	0.01-0.49	0.01-0.43	0-0.46
Lateral				
WSS (Pa)	0.07-0.61	0-0.70	0-0.79	0.01-0.70
OSI	0.02-0.19	0.01-0.50	0.02-0.49	0-0.48

Figure 3. A) Mean wall shear stress and B) OSI at the right suprarenal aortic wall. Distance is defined as the axial distance along the vessel wall. The cranial renal orifice is located at 0 mm.

Area 2: the renal artery

The RA flow profile in the EVAR models was comparable to the control (Video 2, supplementary). A stronger jet flow was observed in the RA in the EVAS model in comparison to EVAR models and control (Video 2, supplementary; Figure 4). In addition, an increase in flow velocity was found in the center of the distal RA for all stented models. The mean WSS in the RA varied in a range from 0.1 Pa to 2.3 Pa. WSS was lower on the cranial wall than on the caudal wall for all models, including control (Table 2). All models including the control showed small regions of lower WSS in the RA on the cranial and caudal wall near the RA orifice (Figures 5A-B). In addition, the EVAR models showed a region of low mean WSS on the caudal wall between 5 to 10 and 5 to 15 mm in the AFX and Endurant, respectively. The OSI in the RA was near zero for all models including the control.

The maximum shear rate in the RA varied in a range from 325.3 s^{-1} to 717.8 s^{-1} . The highest shear rate was found on the cranial wall in the EVAS model.

Figure 4. Peak systolic phase velocities in the right renal artery. A) Control, B) Endurant, C) AFX, D) Nellix. Low velocity regions were observed at the inflow section near the caudal wall of the renal artery for all stented models, which were more apparent for the EVAR models (B,C), and the flow velocity was enhanced at the renal inflow section of the Nellix model (D).

Figure 5. Time-averaged wall shear stress at the right renal artery. A) Caudal; B) Cranial wall of renal artery. The scale is given as the axial distance from the renal orifice at 0 mm.

Figure 6. Velocity during peak systolic phase in the common right iliac artery. A) Control, B) Endurant, C) AFX, D) Nellix. Recirculating flow was observed near the distal end of the stent in all models. The velocity accelerates towards the distal artery in all models, where the limb tapers from 14 to 8 mm.

Area 3: the common iliac artery

A triphasic flow signal was observed in the CIA, with retrograde flow near the vessel wall during the end-systolic phase in all models (Video 3, supplementary). The stented models showed regions of flow recirculation near the distal end of the stents in the CIA (Figure 6), and low mean WSS in those regions in comparison to the control (Figures 7A-B). The regions with low mean WSS ($< 10^{-2}$ Pa) were all < 10 mm for all stented models. In addition, different flow patterns are seen in the CIA with EVAS. An increase in flow velocity was found at the distal end of the stent in the EVAS model in comparison to the other models (Figure 6D). This region was counterbalanced by a region of retrograde flow on the contralateral wall of the vessel. Similar to the control and EVAR models, the flow in this region returned in a positive direction during the end-diastolic phase. An increase

Figure 7. Time-averaged wall shear stress and OSI at the right common iliac artery. A) WSS at the Medial wall; B) WSS at the right lateral wall; C) OSI at the Medial wall; D) OSI at the right lateral wall of the vessel. The start of each curve refers to the distal end of the stent or bifurcation (control), whereas the end of each curve refers to the distal connection of the model in the common iliac artery.

in flow velocity appeared near the distal iliac artery for all models including the negative control (Figures 6A-D), where the model tapers from 14 mm to 8 mm (Table 1). The maximum shear rate in the common iliac artery was comparable for all models, ranging from 324.9 s^{-1} (control medial wall) to 546.5 s^{-1} (AFX lateral wall).

The OSI in the CIA varied in a range from 0 to 0.5. The OSI in the control was at maximum 0.19 (Table 2). In the stented models areas of high OSI (~ 0.5) were found in regions near the distal end of the stents (Figures 7C-D).

DISCUSSION

The present study provides a baseline for flow patterns and WSS for various endograft designs. The studied endografts do not substantially affect flow patterns in the lumen center of the suprarenal aorta. Flow velocity and WSS in this area were comparable to the flow in an aneurysm model. The flow was accelerated near the renal ostium, resulting in a higher velocity in the renal artery in all models. Flow in the renal artery was forward in direction throughout the entire cardiac cycle, presenting physiological flow conditions¹⁶.

The acceleration of flow near the renal ostium was larger for EVAS, resulting in a stronger jet flow and higher shear rate in the RA in comparison to the other models, most likely due to transition of the suprarenal aortic flow into the two 10-mm endoframes. Low flow velocity was found in the proximal renal artery of the EVAR models near the caudal wall, presenting an area of lower WSS in comparison to the control. In addition, recirculating flow was observed near the distal end of the stent in all stented models, presenting regions of low mean WSS ($< 10^{-2}$ Pa) and high OSI (~ 0.5) in comparison to the control.

Low mean WSS and severe oscillations in WSS have been associated with atherosclerosis^{2,3}, by initiating endothelial responses that result in intimal thickening of the vessel wall. In the present study the mean WSS in the suprarenal aorta was in a similar range as reported by Moore et al.², and this was fairly low considering values that have been reported for arterial baseline WSS (1-7 Pa)^{6,7}. The regions with low WSS on the suprarenal aortic wall were comparable in axial distance along the wall between the different models including the control. The values found for mean WSS in the renal artery were mostly in accordance with the control, but a region of lower mean WSS (< 1 Pa) was observed in the caudal wall of the proximal renal artery in both EVAR models. This lower WSS may enhance development of atherosclerosis in those areas. Renal stenosis post-EVAR has been scarcely documented and could also be related to a suprarenal stent wire traversing the renal ostium and /or partial coverage of the renal ostium by graft material. The potential additional effects of this area of lower WSS in the caudal wall of the renal artery remain to be investigated. EVAR has been associated with a higher risk of decline in renal function in comparison to open surgical repair mostly during the first postprocedural year¹⁷. Remodelling and adaptation of the vessel to flow alterations post-EVAR are assumed to occur over a longer time period. Moreover, age (> 75 -yr), thromboembolic complications, and use of nephrotoxic contrast have been associated with a decline in renal function post-EVAR^{18,19}, and these factors may explain the poorer outcome of long-term renal function following endovascular repair in comparison to open surgical repair.

In the EVAS model regions of higher velocity and WSS were observed in the RA. The transition of the aorta into the two 10-mm endoframes that are surrounded by the upper margin of the polymer-filled endobags may contribute to the observed increase in peak velocity in the renal artery. In addition, the vascular stiffness is likely to increase compared to the EVAR model. Generally, it is advised to position the endobags immediately below the renal arteries, such that the proximal 4 mm bare stents are at the level of the orifice of one or both renal arteries. The endoframes were positioned with the proximal end of the stent at the proximal edge of the renal artery, and the renal flow profile may be influenced by the covered proximal part of the stent (4 mm from the proximal bare stent), concerning a renal orifice diameter of 6-mm, as the renal ostium was not partially obstructed by the endobag (Figure 4D). Segalova and coworkers performed computational fluid dynamics (CFD) with the proximal bare stent (partially) in the segment of the renal orifice post-EVAS,

suggesting minimal effect of the proximal stent struts on renal flow, whereas the flow velocity and WSS (and shear rate) in the renal artery were comparable to baseline. An increase in WSS was only found close to the stent struts²⁰. An intended lower positioning of the EVAS stents in the present study may have improved the renal flow profile, and this will be subject of a future study. That position, however, could reduce the sealing zone and thus increase the risk on other problems, including migration and type IA endoleak. Maximum shear rates were well below the pathological threshold (max. 717.8 s^{-1} vs. $> 5000 \text{ s}^{-1}$)¹⁰, suggesting that acute events, such as acute thrombosis, are unlikely to be caused by the observed flow alterations after EVAS.

Regions with high OSI (~ 0.5) were observed in the CIA of both EVAR and EVAS models. Flow recirculation in the CIA near the distal end of the stents was most likely caused by the transition between the stent and phantom vessel wall. In addition, the EVAS model showed an increase in flow velocity near the CIA at the distal stent in the EVAS model in comparison to the other models. Increased velocity observed in the present study was mainly due to a pressure drop resulting from transition of the 10-mm stent frame into a 14 mm vessel. This phenomenon may add to a larger area of recirculation and retrograde flow near the lateral wall. Flow recirculation for seconds has been associated with thrombosis²¹. All flow returned in a forward direction during the end-diastolic phase, and there were no areas with stagnant flow, and therefore it is not likely that the risk of limb thrombosis will be increased post-EVAS. So far, no substantial differences have been observed regarding stent graft occlusion for EVAR and EVAS devices. Limited data on post-EVAS follow-up exists. The incidence of limb occlusions after 1-year has been reported around 4%²², and 5% for EVAR and EVAS²³, respectively. Short- and intermediate patency of stent grafts may be more depended on flow alterations in the endograft. Endograft kinking and subsequent stenosis has been found a risk factor for loss both short- and intermediate-term graft patency^{24,25}.

Limitations. A limitation of this study is that flow analysis was limited to a 2D plane in the center of the flow lumen, with potential bias due to out-of-plane motion of the tracer particles. As a result, secondary flow, including recirculation of tracer particles, could not be captured accurately. Moreover, flow visualization was limited to the AP midplane, and differences in flow may be found in another direction (i.e. lateral midplane).

A straightforward anatomy was used to examine the influence of the stent graft only on flow in the regions of interest. The model geometry could be of influence on the measured flow profile, and these effects may be different for the studied endografts. Inclusion of aortoiliac angulation results in lower velocity near the inner curve with potential plaque formation⁵. However, inclusion of angulation in the AP plane makes measurements a true challenge with the current technique. In addition, higher location of one of the branch orifices may result in a larger recirculation zone with lower WSS near the suprarenal aortic wall. Moreover, other in-vitro studies demonstrated a higher WSS (and shear rate) at a

higher heart rate ²⁶, whereas flow experiments in the present study were only performed under (physiologic) resting conditions.

The variation in flow rate between the experiments including all models was low (mean: 1.66 L/min, SD: 0.02 L/min), suggesting that the experiments were reproducible. The slight variations in flow rate may be caused by the different stents in the models. In addition, the slight variations in flow rate may add to slight variations in WSS and OSI between the models in the studied regions of interest.

Flow in the endograft could not be assessed in the present study, as the graft material did not allow optical access, and as a result flow near the bifurcation could not be assessed for the EVAR models. The use of transparent stent grafts ¹² can be used to analyze the flow in these areas with laser PIV. Ultrasound PIV could overcome this problem. In addition, laser PIV of multiple planes in 2D in the flow lumen (e.g. stereo PIV) and / or CFD validated with the results of the present study can aid in an accurate flow characterization in those areas. The end-systolic phase and peak-diastolic phase appeared delayed by 84 ms and 60 ms, resulting in a slightly higher volumetric flow per cycle, and time averaged WSS may be slightly overestimated.

The model compliance was not measured, but only minimal suprarenal aortic wall distension was determined during the cardiac cycle (max. 0.1% of the total vessel radius). The use of a stiff model may be justified due to stiffening of the vasculature in atherosclerosis and elderly ²⁷, however, the results of this study cannot be generalized for all AAA patients. The use of a more compliant model will usually result in lower WSS and lower shear rates ²⁸. The present study demonstrated no (significant) difference in flow between the different models in the studied regions of interest, and a more elastic wall will only result in changes in absolute values. The effects of a more elastic wall on flow, i.e. a lower WSS, will be mainly dependent of variations in (local) wall characteristics between patients.

The glycerol in the BMF is Newtonian, and WSS values may therefore be overestimated. Nevertheless, blood flow in large vessels is supposed to be Newtonian ¹⁶. The concentration of tracer particles in the BMF was small (0.021% of total volume) and it is therefore not likely that these will influence the viscosity of the BMF and WSS calculations. However, the no-slip (boundary) condition may not be accurate for tracer particles near the model wall.

CONCLUSION

The location of the flow divider does not influence suprarenal flow. Low WSS is observed in the caudal wall of the RA after EVAR and an increased shear rate after EVAS, while all stented models have a small area of low WSS and high OSI near the distal outflow of the stents.

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DISCLOSURES

JPPM de Vries is consultant for Endologix and Medtronic. MMPJ Reijnen is consultant for Endologix. DN Ku is consultant for Endologix.

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SUPPLEMENTARY VIDEOS

The videos can be accessed by the URL and password EVAS:

Video 1: Flow in the suprarenal aorta during one cycle. Top left panel: control; top right panel: Endurant EVAR; bottom left panel: AFX EVAR; bottom right panel: Nellix EVAS

<https://vimeo.com/216458254>

Video 2: Flow in the renal artery during one cycle. Top left panel: control; top right panel: Endurant EVAR; bottom left panel: AFX EVAR; bottom right panel: Nellix EVAS

<https://vimeo.com/216458241>

Video 3: Flow in the common iliac artery during one cycle. Top left panel: control; top right panel: Endurant EVAR; bottom left panel: AFX EVAR; bottom right panel: Nellix EVAS

<https://vimeo.com/216458232>

6

THE INFLUENCE OF POSITIONING OF THE NELLIX EVAS ENDOSYSTEM ON SUPRARENAL AND RENAL FLOW: AN IN-VITRO STUDY

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ABSTRACT

Introduction. The transition of the aortic flow lumen into two 10-mm-diameter stents after endovascular aneurysm sealing (EVAS) creates a mismatch area. Flow recirculation may affect local wall shear stress (WSS) profiles and residence time, associated with atherosclerosis and thrombosis. This in-vitro study examined the influence of device positioning and infrarenal neck diameter on flow patterns.

Method. Seven AAA flow phantoms were created, including three unstented controls and three stented models with infrarenal neck diameters of 24 mm, 28 mm and 32 mm. Stents were positioned within the instructions for use (IFU). Another 28 mm model was created to evaluate lower positioning of the stents outside the IFU (28 mm LP). Flow was visualized using optical particle imaging velocimetry (PIV) and quantified by time-averaged WSS, oscillatory shear index (OSI), and relative residence time (RRT), in the aorta anteroposterior (AP) midplane, lateral midplane and renal artery AP midplane.

Results. Flow in the aorta AP midplane was similar in all models. Vortices were observed in the stented models in the lateral midplane near the anterior and posterior walls. In the 32 mm IFU and 28 mm LP model, a steady state of vortices appeared, with a varying location during a cycle. In all models a low time-averaged WSS ($<10^{-2}$ Pa) was observed at the anterior wall of the aorta with peak OSI of 0.5 and peak RRT of 10^4 Pa⁻¹. This region was more proximally located in the stented models. The 24 mm and 28 mm IFU models showed flow with a higher velocity at the renal artery (RA) inflow compared to controls. WSS in the RA was lower near the orifice in all models, with the largest area in the 24 mm IFU model. OSI and RRT in the RA were near zero for all models.

Conclusion. EVAS enhances vorticity in the proximal seal zone, especially with lower positioning of the device and in larger neck diameters. Endobags just below the RA affect the flow profile in a minor area of the RA in 24 mm and 28 mm necks, while a lower stent positioning does not influence the RA flow profile.

INTRODUCTION

Endovascular aneurysm sealing (EVAS) with the Nellix endosystem (Endologix Inc., Irvine, CA, USA) enables treatment of abdominal aortic aneurysms (AAA), based on in situ polymer filling of endobags that surround dual covered cobalt-chromium stents^{1,2}. The two 10-mm-diameter stents provide flow lumens to both limbs. The intended position of the endosystems according to the instructions for use (IFU) is with the proximal edge of the endobags just below the distal edge of the most caudal RA. The stents should therefore be positioned not higher than 4 mm (the portion of uncovered stent above the endobag) across the RA orifice to prevent (partial) coverage of the RA orifice by endobag material. The endosystem was designed with the purpose to reduce reinterventions, mainly for type II endoleaks, that are relatively common following endovascular aortic aneurysm repair (EVAR) with standard modular grafts. The clinical relevance type II endoleak remains unclear and is subject of ongoing debate. Generally, treatment is not performed if aneurysm growth is < 10 mm during follow-up³, but also this threshold had not been validated until now. A low incidence of endoleaks and re-interventions has been reported after 1-year including clinical application of the device in- and outside the instructions for use (IFU)^{4,5}.

The transition of the aortic flow lumen into the two stents induces a mismatched area between the aortic flow lumen and these stents and, in cases where the stents are positioned low in the neck, a cul-de-sac⁶ between the RA and the upper margin of the endobags may form. The design with 10-mm-diameter stents results in an uneven area reduction, especially in a larger diameter aorta (Figure 1). This mismatch area may result in recirculation of flow with vortex formation, and stasis or stagnant flow that has been associated with thrombus formation^{7,8}. Wall shear stress (WSS) is defined as the force acting parallel to the vessel wall and is related to the flow profile. Baseline WSS in arteries has been reported in a range of 1 Pa to 7 Pa in vivo^{8,9}. A very low average WSS, i.e. 10^{-2} Pa, has been associated with enhanced atherosclerosis and blood coagulation^{8,10}, and may be observed in areas with recirculating flow. Moreover, strong oscillations in WSS (i.e. changes in flow and WSS direction) have been associated with an enhanced atherosclerotic lesion formation^{11,12}.

In this in-vitro study, positioning of a Nellix endosystem on flow in the proximal seal zone and renal artery was evaluated, while also comparing different infrarenal neck diameters.

Figure 1. Frontal (A-D) and top views (E-H) of the stented models; 24 mm IFU (A,E), 28 mm IFU (B,F), 28 mm low positioning (C,G) and 32 mm IFU (D,H). The regions of interest are indicated in Figure A, and orientation of the planes in Figure E. The renal orifice is indicated in the top view by a black circle that is drawn around the orifice.

METHODS

Flow phantoms

Seven transparent silicone (Sylgard 184; Dow Corning GmbH, Wiesbaden, Germany) flow phantoms of an infrarenal abdominal aortic aneurysm were created (Figure 2). Transparency was required for optical access for laser particle imaging velocimetry (PIV). The infrarenal neck length was set at 15 mm and maximum AAA diameter was 55 mm. Anteroposterior (AP) aortoiliac angulations were excluded to facilitate 2-dimensional (2D) imaging of the flow at the flow lumen midplane. The infrarenal aortic neck diameter varied between the models to study the influence of the infrarenal neck diameter on flow proximal to the endobags. AAA-models with infrarenal neck diameters of 24 mm, 28 mm and 32 mm were created, including one unstented control and one stented model with stent positioning according to the instructions for use (IFU). Another model with an infrarenal neck diameter of 28 mm was created to study the influence of an intentionally lower positioning (LP) of the endosystem which is outside the IFU, and is referred to as the 28 mm LP model in this study.

Two Nellix Endosystems with a length of 150 mm (NX 10-150) were implanted. Implantation was performed with an intended fill pressure of 180 mm Hg. The proximal edge of the endobag was positioned at the distal margin of the most caudal RA (Figures 1A, 1B and 1D). In the 28 mm LP model the top of the stent was positioned at the distal margin of the

most caudal RA, approximately 4 mm lower than the other configurations (Figure 1C). The implantation of the stents was performed by a team of two physicians experienced with the EVAS endosystem (JV, MR). After deployment the models were flushed with warm water (approx. 37 degrees Celsius) to mimic in-vivo conditions required for polymer curing. The phantoms were stored in a 0.9% saline solution and isolated from direct light sources to optimize conditions for polymer preservation for two-three weeks until the flow studies were completed.

Figure 2. Flow phantom of abdominal aortic aneurysm.

Flow characteristics

The flow setup was based on a two-element windkessel¹³. Both renal and iliac branches have a dedicated peripheral resistance settings to adjust the outflow. The Windkessel conditions were only applied to the iliac outflow, as the kidneys are a low-compliance part of the system showing very limited backflow in vivo. The compliance of both iliac arteries was combined into one compliance and one peripheral resistance. The difference in resistance between the renal arteries and iliac arteries was established by a larger diameter of the iliac artery (8 mm) in comparison to the renal artery (6 mm) at a comparable flow per branch (400 mL/min). The flow tests were performed under physiologic resting conditions with a heart rate of 60 beats per minute, a blood pressure of 120/80 mm Hg and a peripheral compliance of 1.1 mL/mm Hg. The inflow waveform was based on previous reported in-vivo duplex ultrasound (DUS) measurements with an average flow rate of 1.6 L/min (peak flow 3.6 L/min)¹⁴. A blood-mimicking fluid (BMF) was used with a dynamic viscosity comparable to blood (dynamic viscosity of 4.3 cP; density of 1.2 g/mL)¹⁵. The flow passed through a 1.2 m long tube before it entered into the model, ensuring a fully developed laminar flow at the model inlet.

Flow visualization

The flow was visualized with laser particle imaging velocimetry (PIV), based on imaging of fluorescent particles that accurately follow the fluid stream. Fluorescent Poly Methyl Methacrylate (PMMA) particles (Rhodamine, size 1-20 μm , density 1190 kg/m³, Dantec Dynamics A/S, Skovlunde, Denmark) were dissolved in water, and the solution was mixed with the BMF. A continuous wave laser (5W DPSS laser, 532 nm, Cohlibri, Lightline, Osnabruck, Germany) was used to illuminate a 2-dimensional (2D) layer of fluid (< 1 mm) in the midplane of the flow lumen. The flow was captured in three planes, the AP midplane upstream of the proximal seal zone, the lateral midplane upstream of the proximal seal zone and the AP midplane of the right RA. To visualize the lateral plane, the model was turned by 90 degrees. The regions of interest and orientation of the planes are indicated in Figure 1A and 1E, respectively. Full frame (1024 x 1024 pixels) images were captured with a high-speed camera (FASTCAM SAX-2, Photron Inc., West Wycombe, Buckinghamshire UK) at a frame rate of 1000 frames per second for a period of 10 s. The imaging plane dimension was approximately 5 cm by 5 cm, and this resulted in a spatial resolution of 0.04 mm.

In-house built Matlab (R2016a, Mathworks, Natick, Massachusetts, USA) scripts were used for automated wall detection to segment the flow lumen with fluorescent particles in the PIV images. PIVlabTM (open source toolbox, Matlab)¹⁶ was used to calculate the average displacement of particles in the fluid by calculating cross-correlations between subsequent frames. Velocity vectors were averaged over 10 cardiac cycles and displayed in Tecplot (Tecplot 360 EX 2016 R1, Bellevue, WA, USA). In addition, the average vorticity (s^{-1}) over a cardiac cycle was calculated to display regions of flow recirculation. The

magnitude represents the amount of recirculation in a region, and the positive or negative sign represent the direction of the flow, counter clockwise and clockwise, respectively.

WSS calculations

Flow was quantified by time-averaged WSS (TAWSS; Pa), the oscillatory shear index (OSI; dimensionless)¹⁷ and relative residence time (RRT; Pa⁻¹)¹⁸. These parameters were calculated for the lateral and anterior aortic wall, which were both on the laser entry side for the different 2D imaging planes (AP and lateral), and therefore had the most reliable signal.

WSS was calculated by multiplying the viscosity of the BMF with the shear rate, defined by the velocity gradient parallel to the vessel wall (equation 1). The calculations of the velocity gradient near the vessel wall included the flow velocity profile over a distance of 50% of the flow lumen length, and a forced zero velocity at the vessel wall. Time-averaged WSS was calculated by averaging the WSS in a single point at the wall over one cardiac cycle. The OSI (equation 2) is defined by the ratio of positive and negative WSS area under the WSS vs. time curve during one cardiac cycle and is therefore a measure for the oscillatory behaviour of the flow. OSI is 0 when WSS is unidirectional during the cardiac cycle. The maximum OSI is 0.5, indicating equal positive and negative WSS area under the WSS vs. time curve, referred to as high oscillatory shear. OSI can indicate areas of flow reversal, however, WSS magnitude is not taken in to account. Strong oscillatory flows can exhibit the same OSI as very slow flows with the same waveform. The relative residence time (RRT) was introduced to incorporate the level of WSS and its oscillatory behaviour¹⁸. The relative residence time is a measure for residence time of particles near the vessel wall. With the given equation (equation 3) OSI modifies the effect of the WSS on the relative residence time and near wall interactions. Relatively high values present potential regions with flow recirculation compared to regions with a RRT near zero. WSS, OSI and RRT were plotted versus the axial distance along the vessel wall to identify regions with unfavourable flow conditions associated with an enhanced atherosclerosis and thrombosis, i.e. low time-averaged WSS, peak OSI (0.5) and peak RRT.

$$\frac{1}{T} \int_0^T |\tau_w| dt \quad (1)$$

$$\frac{1}{2} \left(1 - \frac{\left| \int_0^T \tau_w dt \right|}{\int_0^T |\tau_w| dt} \right) \quad (2)$$

$$\frac{1}{(1-2 \cdot \text{OSI}) \cdot |\text{TAWSS}|} \quad (3)$$

RESULTS

Suprarenal aorta

The peak systolic velocity in the central lumen of the suprarenal aorta was comparable for the controls and respective IFU models. The (peak) velocity was lower in models with a larger aortic diameter compared to a smaller diameter (around 16, 14, and 12 cm/s, respectively, for the 24 mm, 28 mm and 32 mm models and respective IFU models). The flow profile in the AP midplane was comparable between the controls and IFU models; flow from the infrarenal aorta or stents recirculated into the renal arteries during the end-systolic phase, and retrograde flow was observed near the lateral suprarenal aortic wall (Videos 1-3, supplementary). Also, in the 28 mm LP model the flow profile in the AP midplane was comparable to control (Video 4, supplementary).

The controls and IFU models showed a different flow profile in the lateral midplane. The controls showed a retrograde flow near the anterior and posterior aortic wall (juxtarenal and suprarenal) during the end-systolic phase. In the IFU models, retrograde flow was also present, but additional vortex formation was observed proximal to the endobags near the anterior and posterior walls. In the 24 mm and 28 mm IFU models the vortex intensity decayed at the end of a cardiac cycle (Video 5 and 6, supplementary), whereas in the 32 mm IFU model (Video 7, supplementary) the vortices appeared to have a steady state, although changing location during the cycle. The average vorticity over a cardiac cycle is displayed in Figure 3. The vorticity proximal to the endobags was larger in the 32 mm IFU model compared to the 24 mm and 28 mm IFU models and controls. In addition, the vorticity proximal to the endobags was larger in the 28 mm LP model (Figure 4), in which also a steady appearance of vortices was observed near the anterior and posterior wall which was not the case in the 28 mm control and 28 mm IFU model (Video 6 and 8, supplementary).

Figure 3. The average vorticity near the anterior and posterior wall in the (left) lateral midplane. The left figures show the unstented controls, and right figures the respective models with EVAS endosystem implanted: A) 24 mm control, B) 24 mm IFU model, C) 28 mm control, D) 28 mm IFU model, E) 32 mm control, F) 32 mm IFU model. The black dashed circle indicates the renal artery orifice

Figure 4. The average vorticity near the anterior and posterior wall in the (left) lateral midplane (IFU vs. low positioning of the stents); A) 28 mm control, B) 28 mm IFU, and C) 28 mm LP model. The renal orifice is indicated with a black circle.

WSS in the suprarenal aorta varied in a range from 0 Pa to 1.2 Pa; both the controls and IFU models showed areas of low time-averaged WSS at the anterior wall. In the control this region was juxtarenal, while in the IFU models, the location was transferred proximally (-0.4 cm to -0.8 cm) and proximal to the endobags in regions of enhanced vorticity (Figure 5). In the 28 mm LP model, the location of low WSS was also more cranial compared to the control at -0.4 cm distance from the RA orifice (Figure 6). The OSI and RRT in the aorta were in a comparable range for the controls and stented models. The OSI in the aorta varied from 0 to 0.5, and RRT varied from 0 Pa⁻¹ to 10⁴ Pa⁻¹. The locations of peak OSI and peak RRT in the suprarenal aorta were in the same location as the regions that showed the lowest WSS. The axial distance of the regions was in the order of millimetres and was the largest in the 32mm IFU model (0.2-0.3 cm).

Figure 5. WSS, OSI and RRT on the anterior wall of the suprarenal aorta (IFU comparison). The renal artery orifice is located between 0 cm - 0.6 cm.

Figure 6. WSS, OSI and RRT on the anterior wall of the suprarenal aorta (IFU vs. low-positioning of the endosystem). The renal artery orifice is located between 0-0.6 cm.

Renal artery

The 24 mm and 28 mm IFU models showed a stronger jet flow at the RA orifice with a higher peak velocity compared to controls (Figure 7; Video 9, supplementary). The maximum velocity in the RA was 85 cm/s in the 28 mm IFU model compared to 50 cm/s in the respective control. The 32 mm IFU model and 28 mm LP model showed a comparable flow profile and velocity in the RA flow compared to controls (Figure 7E,F and 8A,C).

WSS in the renal artery was in a range of 0-2.3 Pa, with regions of lower WSS near the RA orifice in all models including controls (Figures 9). This region was largest on the caudal wall in the 24 mm IFU model with 0.5-1 Pa over a distance of 2 mm from the RA orifice (Figure 9B). The 28 mm LP model showed no areas of lower WSS in the RA. The OSI and RRT in the RA were near zero in all models including the controls.

Figure 8. Flow in the renal artery during the peak systolic phase (IFU vs. low positioning of the endosystem); A) 28 mm control, B) 28 mm IFU, C) 28mm low positioning

Figure 9. WSS of the renal artery plotted vs. the longitudinal distance along the vessel wall (IFU comparison); Top: cranial wall, Bottom: caudal wall. The renal artery orifice is located at a distance of 0 cm.

DISCUSSION

In the present study we have shown that both positioning of the Nellix device in the infrarenal neck and infrarenal neck diameter affect flow profiles in the aorta above the seal zone and in the renal artery. Although EVAS had only minimal influence on flow profiles and WSS on the lateral suprarenal aortic wall, vorticity, with lower WSS and higher OSI and RRT was observed on the anterior wall proximal to the endbags. The vortices had a steady state in the 32 mm IFU model and 28 mm LP model, in contrast to the 24 mm and 28 mm IFU models where they resolved at the end of a cycle. In the 32 mm IFU model, the enhanced vorticity may have been caused by the larger mismatch area at the transition between the aortic flow lumen and the stents. The observed peak velocity was lower in the 32 mm IFU model compared to the 24 mm and 28 mm IFU models, due to its larger diameter. The lower velocity may have also contributed a steady state of vortices. Lower positioning of the stent in the 28 mm LP model lead to prolonged flow recirculation proximal to the endbags, and was potentially associated with the creation of a cul-de-sac volume between the RA and the endbags. The flow is likely to be redirected by the endbags, causing recirculation of flow, potentially leading to the formation of vortices.

The vorticity in the vessels is usually increased near branches and bifurcations where flow separation occurs, but usually without steady state ^{19,20}. Vortices that sustained over one cardiac cycle (> 1 s) were only observed in the 32 mm IFU and 28 mm LP model. Absolute residence times in the order of seconds have been associated with thrombus formation ^{21,22}. The RRT does not provide an absolute time for the presence of particles in regions of flow recirculation. The pulsatile inflow signal causes a varying location of the vortices that could prevent tracer particles from residing proximal to the endobags for seconds. It is unknown what the effect of a (stationary) vortex proximal to the endobags will be. Very few events of thrombus formation have been reported post-EVAS. Remodeling of the infrarenal neck with thrombus has been reported in only one case on CTA 30-d post-EVAS ⁶. A recent study of 50 patients one-year after EVAS showed no thrombus formation in this area (unpublished data). Distal embolization has been reported in very few cases after EVAS ²³, and other factors could be involved (i.e. arrhythmia). In two patients distal embolization was associated with anatomic causes, in one patient there was no clear focus. A relation with suboptimal stent expansion, or pillowing of the covering material, thus reducing the flow lumen might have been involved. Remodeling of the infrarenal neck with thrombus may also function protective by neutralizing flow recirculation and preventing embolization.

Lower values for baseline WSS have been reported for the abdominal aorta in a range of -0.17 to 0.14 Pa ¹¹. The locations with the lowest WSS were found near the aortic bifurcation and (near zero) correlated well with the locations with enhanced atherosclerosis measured by intimal thickness. In the present study the regions that presented a very low time-averaged WSS ($< 10^{-2}$ Pa) were small in both controls and stented models. Additionally, both controls and stented models showed a peak OSI of 0.5 and increase in RRT in some areas in the suprarenal aorta, although the location was more cranial in the suprarenal aorta in the stented models compared to the controls. Small regions of low WSS and high OSI (0.5) were found in areas on the infrarenal aortic wall of healthy subjects (i.e. juxtarenal), and it is unknown whether these will enhance atherosclerosis ²⁴. A recent review by Peiffer et al. ²⁵ demonstrated that a discrepancy persists regarding the role of low shear and high OSI in the development of atherosclerosis. It is still unknown what the effects of low WSS and high OSI after EVAS will be. The area of lower WSS in the renal artery in the 24 mm and 28 mm IFU models (< 1 Pa) was small (< 2 mm) but still atherosclerosis may be enhanced or vascular remodelling may occur in this region. The stronger jet flow and higher velocity in the RA in the 24 mm and 28 mm IFU models may be caused by excessive endobag material in the neck or by partial coverage of the RA orifice due to proximal stent positioning. Positioning variability of the stents in EVAS may be caused by minor changes in stent position during injection of the polymer, as the stents should be held in position by one of the operators. In vivo, aortic movement may also be involved.

The 28 mm IFU model showed the largest increase in peak velocity around 70% compared to the control. This phenomenon was also observed in a previous flow study on EVAS including the 28 mm IFU model²⁶, showing that maximum shear rate associated with this increase in peak velocity in the RA is well below the pathological threshold for acute thrombosis, which is therefore not expected²⁶. The computational fluid dynamics study conducted by Segalova and coauthors have demonstrated that the proximal bare stent had almost no influence on the renal flow profile when positioned across the RA orifice²⁷, and it is not likely that the proximal bare metal stent will cause large disturbances in RA flow profile. An intended positioning with the bare metal stent across the RA ostium (proximal 4 mm) should be a safe margin for positioning of the endosystem with reference to the RA orifice. This positioning will lead to an optimal use of the available infrarenal neck and maximize the seal zone in this area.

The present study showed that the endobags had a different morphology in all models and a different location of the proximal stents in the aorta in all configurations (Figure 1A-D). It therefore seems that there is also variability in positioning of the endosystems, especially when considering the large variance in human anatomy. Future developments should focus on reducing variability of the proximal expansion of the endobag and avoiding excessive endobag material in the infrarenal neck. In EVAR, the proximal sealing zone is clearly marked by radiopaque markers on the stent fabric or frame, and this is supposed to enable a more predictable positioning of proximal stent with reference to the most caudal RA.

Study limitations

A drawback of a two-element Windkessel model is that pressure and flow are out of phase. A three-element Windkessel model may also be applied, however, this mainly benefits the relation between blood pressure and blood flow. This is important, but of less interest in the present study, where we focused on flow dynamics.

A straightforward anatomy was used to study positioning of the EVAS endosystem on flow in the suprarenal aorta and renal artery. A different geometry, i.e. inclusion of aortoiliac angulations, asymmetric location of renal artery orifice, and inclusion of other branches (SMA) could have led to other flow profiles. Thus, the results of this study cannot be generalized for all patients that undergo EVAS. Moreover, the flow was examined at physiologic resting conditions (60 bpm), whereas other in-vitro studies have shown that flow changes can be expected at a higher heart rate¹². It is presently unknown how a higher heart rate (and blood pressure) will affect flow post-EVAS. Moreover, the flow rate was similar in all flow tests, which clinically might not be the case. A patient with a larger aortic diameter might have a larger cardiac output compared to a patient with a smaller aortic diameter. The abdominal aortic flow rate of 1.6 LPM at rest was used in a previous in-vitro study¹⁴. This flow rate was close to the lower boundary of physiologic flow at rest, corresponding to a cardiac output of 4 LPM. A lower flow rate was selected

as the cardiac output usually decreases in elderly. This study demonstrated that at low flow rates stationary vortices occur proximal to the endobags in a 32 mm aorta. It is supposed that a larger flow rate in a 32 mm aorta will lead to an even higher degree of flow recirculation, as the Reynolds number increases. It is unknown how long individual particles will reside proximal to the endobags in the 32 mm IFU and 28 mm LP model. Particle tracking velocimetry, may allow tracking of individual particles and calculation of absolute residence times, and may provide a better understanding of the risk for thrombus formation proximal to the endobags. A dye injection to visualize (individual) fluid streams could be an alternative approach to study the (absolute) particle residence time²⁸. Recent updates to the Nellix IFU were made, excluding treatment of AAA with an infrarenal neck diameter > 28 mm.

Blood has been demonstrated as Newtonian for flow in large vessels. But, it has a shear-thinning behaviour for flow in small vessels (< 6 mm). WSS in the RA may therefore be slightly overestimated in comparison to the in-vivo situation. In addition, a no-slip boundary condition was used with zero velocity at the vessel wall for the calculation of the shear rate, and may have added to a steeper velocity gradient near the wall, resulting in an overestimation of WSS. The assumption of using a rigid model during the flow tests may be justified by stiffening of the vasculature in atherosclerotic disease.

CONCLUSIONS

The EVAS endosystem enhances vorticity in the suprarenal aorta, mostly in larger diameter necks and when the stents are positioned low. A positioning of the endobags just below the RA affects the flow profile in a small area of the RA in 24 mm and 28 mm diameter necks while a low positioning of the stents does not influence the RA flow profile.

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DISCLOSURES

JPPM de Vries and MMPJ Reijnen are consultants for Endologix Inc.

SUPPLEMENTARY VIDEOS

The videos can be accessed by the following URL and password:

<https://vimeo.com/channels/1241561>

Password: EVAS

Supplementary Video 1: Flow velocity 24 mm control and 24 mm IFU model

Supplementary Video 2: Flow velocity 28 mm control and 28 mm IFU model

Supplementary Video 3: Flow velocity 32 mm control and 32 mm IFU model

Supplementary Video 4: Flow velocity 28 mm control and 28 mm LP model

Supplementary Video 5: Flow vorticity 24 mm control and 24 mm IFU model

Supplementary Video 6: Flow vorticity 28 mm control and 28 mm IFU model

Supplementary Video 7: Flow vorticity 32 mm control and 32 mm IFU model

Supplementary Video 8: Flow vorticity 28 mm control and 28 mm LP model

Supplementary Video 9: Flow in the renal artery during one cycle (IFU comparison)

Supplementary Video 10: Flow in the renal artery during one cycle (IFU vs LP)

7

BENCHTOP QUANTIFICATION OF GUTTER FORMATION AND COMPRESSION OF CHIMNEY STENT GRAFTS IN RELATION TO RENAL FLOW IN CHIMNEY EVAR AND EVAS CONFIGURATIONS

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ABSTRACT

Introduction. The chimney technique has been successfully used to treat juxtarenal aortic aneurysms. The two main issues with this technique are gutter formation (GF) and chimney graft (CG) compression, which induce a risk for type IA endoleaks and stent thrombosis, respectively. In this benchtop study the geometry and renal artery flow of chimney Endovascular Aortic Repair (ch-EVAR) configurations was compared to chimney configurations with the EndoVascular Aneurysm Sealing (ch-EVAS) system.

Methods. Seven flow phantoms were constructed, including one control and six ch-EVAR (Endurant and AFX) or ch-EVAS (Nellix) configurations, combined with either balloon-expandable (BE) or self-expanding (SE) CGs with an intended higher positioning of the right CG in comparison to the left CG. Geometric analysis was based on measurements at 3-dimensional (3D) CT angiograms, and included gutter volume and CG compression, quantified by the ratio between maximal and minimal diameter (D-ratio). In addition, renal artery flow was studied in a physiological flow model and compared to the control.

Results. The average gutter volume was $343.5 \pm 142.0 \text{ mm}^3$ with the lowest gutter volume in the EVAS–Viabahn combination (102.6 mm^3) and the largest in the AFX–Advanta-V12 configuration (559.6 mm^3). The maximum D-ratio was larger in SE CGs than in BE CGs in all configurations (2.02 ± 0.34 vs. 1.39 ± 0.13). The CG compression had minimal influence on renal volumetric flow (right: $390.7 \pm 29.4 \text{ mL/min}$ vs. 455.1 mL/min ; left: $423.9 \pm 28.3 \text{ mL/min}$ vs. 410.0 mL/min in the control).

Conclusion. The present study showed that gutter volume was lowest in chimney-EVAS in combination with a Viabahn CG. CG compression was lower in configurations with the Advanta-V12 than with Viabahn. Renal flow is unrestricted by CG compression.

INTRODUCTION

Endovascular aortic aneurysm repair (EVAR) has become the standard treatment for abdominal aortic aneurysm (AAA) because of an improved 30-day outcome and a shorter rehabilitation period compared to open repair¹. EVAR has proven long-term durability when used on label². Applicability of EVAR is mostly limited by unfavorable proximal neck characteristics, including short (< 15 mm) or severely angulated (>60°) infrarenal necks, and dilations that involve the juxtarenal aorta, present in around 20% of patients³. These characteristics are associated with a substantial risk for adverse events post-EVAR, including migration and type IA endoleaks^{4,5}. Fenestrated endovascular aortic repair (FEVAR) has been demonstrated an alternative treatment option for this group of patients, with good short- and intermediate term outcomes^{3,6}. However, anatomic characteristics may preclude the use of custom-made devices, the construction is expensive, and the technique is unsuitable for ruptured AAA repair, due to 4 to 6 weeks of manufacturing^{7,8}. Moreover, these devices are not globally available.

Chimney endovascular aortic repair (ch-EVAR), in which a standard modular graft is combined with chimney, or parallel, stent graft(s) (CG) to maintain flow in side branches (i.e. renal arteries, superior mesenteric artery, and celiac trunk), provides an off-the-shelf solution in patients with a juxtarenal AAA⁹ with a 30-days mortality rate comparable to FEVAR^{7,10}. ch-EVAR however has been associated with a higher incidence of stroke and early type IA endoleaks in comparison to FEVAR⁷. Moreover, a difference in stent geometry and architecture (i.e. material stiffness) of standard modular and chimney grafts may result in gutter formation, and induce a risk for (early) type IA endoleaks. In addition, compression and/or kinking of the CG may be caused by the radial force of the endograft that occurs from oversizing of the endograft in the aortic neck. CG compression is supposed to influence renal flow (i.e. volumetric flow rate, flow profile), and changes in flow profile may induce a risk for thrombosis.

Endovascular aneurysm sealing (EVAS) is an alternative technique for AAA repair, obliterating the aneurysm sac by polymer filling of endobags that surround dual cobalt-chromium endoframes¹¹. EVAS was designed to reduce the incidence of migration and endoleaks and according to the instructions for use, AAA with an infrarenal neck length of > 10 mm can be treated with EVAS¹². Its potential has also been demonstrated in combination with chimneys (ch-EVAS) in several case reports in both an elective and acute setting¹³⁻¹⁵. The endobags potentially allow a better conformation to the chimney graft geometry following ch-EVAS, which could reduce the incidence of gutters and subsequent type IA endoleaks in comparison to ch-EVAR. In addition, after curing of the polymer, the filled endobags will no longer compete with the radial strength of the CG, in contrast to the situation post-ch-EVAR.

In this benchtop research the geometry of several ch-EVAR and ch-EVAS configurations was studied, including CG compression and gutter formation (GF). In addition, volumetric flow for each chimney stent graft was measured.

METHODS

Flow phantoms and stents

Flow phantom geometry was based on an average aortoiliac anatomy of 25 elective juxtarenal AAA patients, performed at preoperative CT-scans, including a short proximal neck (aneurysm starting at a distance of 10 mm), and branches of the SMA, renal arteries and common iliac arteries (Table 1). The infrarenal neck morphology was reversed tapered with an infrarenal neck diameter of 26 mm, and a linear increase to 38 mm over a distance of 15 mm. The manufacturing of 7 juxtarenal AAA flow phantoms was conducted by Elastrat (Elastrat Inc., Geneva, Switzerland). One model was used as a reference without stents, and the others were used to implant 6 different chimney stent graft configurations, including EVAR (Endurant II (ETBF 32 16 C 166 EE; ETLW 16 16 C 124 EE), Medtronic Inc., Minneapolis, MN, USA) and AFX (BA28-70/116-30; A34-34/C100-020V), Endologix Inc., Irvine, CA, USA) and EVAS (Nellix [Nx-10-150], Endologix), combined with either balloon-expandable (BE) (Atrium AdvantaV12 (known as iCast in the USA) (6 mm x 58 mm), Atrium Medical Corporation, Hudson, NH, USA) or self-expanding (SE) (Gore Viabahn (6 mm x 38mm), W. L. Gore & Associates, Inc., Flagstaff, AZ, USA) chimney grafts. The proximal graft diameter of the EVAR devices was 32 mm and 34 mm for the Endurant and AFX, respectively. This size resulted in 23.7% and 30.7% oversizing for the Endurant and AFX endograft, respectively.

Table 1. Model geometries

Suprarenal aorta		
Diameter (mm)		26
Length (mm)		65
Angulation (°)		0
Superior mesenteric artery		
Diameter (mm)		8
Length (mm)		120
Take-off angle (°)		60
Renal arteries	Right	Left
Diameter (mm)	5	5
Length (mm)	120	120
Take-off angle (°)	111	115
Infrarenal aorta		
Diameter (mm)		
Infrarenal neck		26
Baseline		26
Baseline + 15 mm		38
Maximum AAA		50
Aortic bifurcation		26
Length (mm)		105
Angulation (°)		0
Common iliac arteries	Right	Left
Diameter (mm)	12	12
Length (mm)	130	130
Take-off angle (°)	27	23

Implantation in the models was performed by two experienced vascular surgeons (JV, MR). The intended position of the endograft was at the distal edge of the SMA (proximal end of the bare stent at the proximal edge of the SMA in the EVAS configurations). The intended position of the proximal end of the right and left chimney were at the top- and mid SMA, respectively, to study the influence of positioning on CG compression and GF (Figure 1 and 2). CGs were deployed in advance of the endograft main body/EVAS endobags to allow maximal expansion before potential compression by the endograft. The proximal fixation zone of the EVAR devices was postdilated with a compliant balloon (Reliant, Medtronic) to minimize GF in these configurations, with 6 mm balloons in the CGs inflated. Similarly, polymer filling of the endobags was performed with balloons inflated in the CGs. Polymer fill volume of the EVAS endobags was 150 ml and 145 ml, respectively, for the Advanta-V12 and Viabahn configurations, with an intended fill pressure of 180 millimeters of Mercury (mm Hg) (186 mm Hg and 190 mm Hg). After stent deployment the models were flushed with water with a temperature of ± 37 degrees Celsius to allow maximal expansion of the nitinol stents. In addition, the EVAS configurations were stored in a 5% sodium solution to prevent degradation of the polymer.

Figure 1. Anteroposterior view of the in-vitro chimney stent graft configurations; A) EVAR Endurant with Advanta V12; B) EVAR AFX with Advanta-V12; C) Nellix EVAS with Advanta-V12; D) EVAR Endurant with Gore Viabahn; E) EVAR AFX with Gore Viabahn; F) Nellix EVAS with Gore Viabahn.

Figure 2. Lateral view of in-vitro chimney stent graft configurations; A) EVAR Endurant with Advanta-V12; B) EVAR AFX with Advanta-V12; C) Nellix EVAS with Advanta-V12; D) EVAR Endurant with Gore Viabahn; E) EVAR AFX with Gore Viabahn; F) Nellix EVAS with Gore Viabahn.

Geometry analysis

Measurements of the stent configurations were performed with 3Mensio™ Vascular (Pie Medical, Bilthoven, the Netherlands) in 3-dimensions (3D) at CT angiograms. High resolution CT-scans were acquired with a 256-slice CT scanner (Brilliance iCT, Philips Healthcare, Eindhoven, The Netherlands). Scan parameters included a tube voltage of 120 kV, tube current time product of 250 mAs, increment of 0.75 mm, pitch of 0.25 and collimation of 12.5 mm × 0.625 mm. CT-scans were reconstructed with a slice thickness of 0.67 mm. The models were scanned without filling with contrast to enhance the contrast between the endobags and flow lumen in the EVAS models.

Gutter was defined as the volume between graft fabric and aortic wall in the aortic neck (15 mm distance between the distal edge SMA to 10 mm from lowermost RA). Gutter volume (mm³) was calculated by the sum (i.e. integral) of gutter area (mm²) determined at subsequent CT-slices at 2 mm distances. The start of the sealing zone was determined by the proximal stent markers for the EVAR configurations and 1 cm from the proximal stent strut for the EVAS configurations where the endobags actually fill with polymer. Measurements of gutter area were conducted using the functionality *polygon region of interest* (ROI) in the software, including a surface calculation based on an interpolation algorithm between user-defined spline points to mark the boundaries of a gutter. Measurements were conducted in the plane perpendicular to the flow lumen, established by a center luminal line (CLL) through the endograft flow lumen or the center of the endobags in the EVAS configurations (Figure 3A).

CG compression was determined by the maximal deformation of the graft lumen calculated by the ratio between major and minor axis of the graft luminal area (diameter-ratio or D-ratio). The D-ratio is equal to 1 in case of a circular lumen area and becomes larger when eccentricity of the stent luminal area increases (i.e. describes an ellipse). Major and minor axis of the graft luminal area were determined from the CG luminal area perpendicular to the flow lumen of the chimney graft (Figure 3B). Measurements were taken at subsequent CT-slices at 2 mm distance. In addition, maximum CG angulation (°) was determined with use of digital calipers over the central luminal line (*tortuosity* in 3Mensio) of the CG (Figure 3C). The measurements were performed two times, by two experienced users to determine repeatability of measurements (J.T.B., R.S.). The outcomes were displayed by mean and standard deviation.

Figure 3. Measurements in 3Mensio. A) Gutter area measurement in plane perpendicular to the endograft flow lumen. The gutter areas are displayed in blue B) CG luminal area measurements in plane perpendicular to CG flow lumen. The red arrows indicate the minor and minor axis of the luminal area C) maximum angulation of CG measured with use of digital calipers over the central luminal line with the tortuosity tool.

Flow measurements

The flow setup reported by Groot Jebbink and coauthors was used to perform the flow experiments, including an additional connector for the SMA ¹⁶. The model was based on a second order Windkessel, including a compliance chamber to include peripheral artery impedance. Flow tests were conducted at physiologic rest conditions, including a volumetric flow rate of 2 liters per minute (LPM) at 60 beats per minute (bpm) (peak flow 3.9 LPM), and an intended systemic pressure in a range of 120/80 mm Hg ¹⁷. The outflow of each branch was controlled by needle valves with an equal outflow of 400 mL/min to each branch, including connections for the SMA, right and left renal artery, and one connection for the common iliac arteries. A baseline resistance for each branch was determined by an equal branch flow for the aneurysm model, and this resistance was sustained throughout flow tests with the stented models. The volumetric flow rate was recorded with ultrasonic flow sensors (Cynergy3, type UF8B, Cynergy3 Components Ltd., Dorset, UK) two times for a duration of 30 seconds (s). The average flow, based on two recordings, was calculated for each branch and compared to the baseline. A blood mimicking fluid (BMF), based on a ratio of 56% and 44% of glycerol and water contents was used to obtain a fluid viscosity comparable to blood ¹⁸.

Statistical analysis

The statistical analysis was performed with IBM SPSS Statistics (SPSS Version 21, IBM Corporation, Armonk, New York, USA). Interobserver agreement of CT measurements was assessed with an interobserver reliability test, based on a two-way mixed model and absolute agreement between single measurements. The intraclass correlation coefficient (ICC) and 95% confidence interval (CI) were displayed for all measurements, and an ICC > 0.7 was considered as good agreement between the observers.

RESULTS

Geometry analysis

Measurement outcomes for each CG configuration are displayed in Table 2. The average gutter volume was $343.5 \pm 142.0 \text{ mm}^3$, and gutter volume appeared larger in the configurations with the Advanta-V12 ($367.6\text{--}559.6 \text{ mm}^3$) than in the configurations with the Viabahn ($102.6\text{--}319.4 \text{ mm}^3$). The lowest gutter volume was found in the EVAS configurations with Viabahn stents (102.6 mm^3) and the largest in the AFX configurations with Advanta-V12 stents (559.6 mm^3). In both EVAR and EVAS configurations, the CG compression was larger for Viabahn stents in comparison to Advanta-V12 CGs (average D-ratio of 2.02 ± 0.34 vs. 1.39 ± 0.13). CG compression of the Advanta-V12 stents was similar between EVAR and EVAS configurations, while the compression of the Viabahn was less in the EVAS configuration in comparison to the EVAR configurations (Figures 4A-B). The largest D-ratio over the entire stent length was found in the right chimney of the AFX model with Viabahn stent grafts (maximum D-ratio of 2.48), and the lowest D-ratio was found for the right CG in the AFX configuration with Advanta-V12 stents (maximum D-ratio of 1.16). Maximum angulation of the CG appeared comparable between the different configurations (Right: $25.7 \pm 8.3^\circ$; Left: $27.7 \pm 7.3^\circ$), with a lower maximum angulation of BE CGs in comparison to SE CGs (BE: $23.2 \pm 5.7^\circ$; SE: $30.2 \pm 8.0^\circ$). All measurements showed good inter-observer agreement (Table 3), all presenting an ICC > 0.7.

Table 2. Geometry analysis

	Endurant Advanta V12	Endurant Viabahn	AFX Advanta V12	AFX Viabahn	Nellix Advanta V12	Nellix Viabahn
Gutter volume (mm ³)	367.6	220.0	559.6	319.4	382.2	102.6
Right CG geometry						
Maximum D-ratio	1.55	1.83	1.16	2.48	1.45	1.63
Maximum angulation (°)	21.0	15.0	20.0	37.0	29.0	32.0
Left CG geometry						
Maximum D-ratio	1.37	2.03	1.35	2.36	1.43	1.76
Maximum angulation (°)	30.0	29.0	15.0	36.0	24.0	32.0

Gutter volume (mm³) is displayed for each chimney stent graft configuration. In addition, the maximum diameter-ratio and angulation (°) are shown for right and left chimney graft (CG).

Figure 4. D-ratio of chimney grafts for the different configurations; A) Right chimney, B) Left chimney. The start of each curve refers to the proximal graft end in the suprarenal aorta.

Table 3. Interobserver variability of the CT measurements

	Intraclass Correlation Coefficient	95 % Confidence Interval	
		Lower	Upper
Diameter (N= 312)	0.937	0.845	0.967
Area (N = 312)	0.915	0.492	0.970
Angulation (N = 12)	0.953	0.848	0.986
Gutter Volume (N = 6)	0.930	0.804	0.977

Flow

The average volumetric flow at the model inlet was in a physiologic range around 1.92 ± 0.05 LPM, as was the system pressure for all flow tests with a system pressure in a range of 115-135 mm Hg. The baseline flow through the SMA was lower than intended in the aneurysm model (292.4 mL/min on average vs. intended branch flow of 400 mL/min), while the flow of the other branches was higher (RRA: 455.1 mL/min; LRA: 410.0 mL/min; CIA: 949.2 mL/min). Right renal flow decreased on average in the chimney configurations (390.7 ± 29.4 mL/min vs. 455.1 mL/min in the control), while left renal flow shows an increase (423.9 ± 28.3 mL/min vs. 410.0 mL/min in the control). The average branch flow (SMA, renal and common iliac arteries) for each configuration is provided in a supplementary Figure. In addition, the SMA and common iliac arteries flow appeared comparable between the unstented and stented configurations (on average 335.3 ± 36.4 mL/min vs. 292.4 mL/min and 900.3 ± 44.8 mL/min vs. 949.2 mL/min of flow through the SMA and CIA in comparison to the control).

DISCUSSION

In the present study we have shown that gutter volume is lowest in ch-EVAS in combination with Viabahn as CG, probably due to good conformability of the endobags to the CG and vice versa. The maximum D-ratio was larger for self-expanding than balloon-expandable CGs, indicating a higher compression rate. This difference is most likely caused by a difference in stent architecture between the Viabahn and Advanta-V12 stents (nitinol vs. stainless steel stents). Self-expanding stents usually have more resistance to radial compression than balloon-expandable stents and could therefore be more prone to stent deformation between the endograft and the aortic wall, however, they might conform better to the anatomy. A lower deformation of the Viabahn in the ch-EVAS configuration in comparison to the Viabahn ch-EVAR configurations may be due to an ongoing outward force of the EVAR device, which is not present in EVAS, after curing of the polymer. In addition, the angulation of the CG could cause stent deformation and a diameter reduction, as may squeezing of the stent between the proximal bare metal struts in the EVAR configurations. Flow to visceral branches (SMA, renal arteries and common iliac arteries) remained nearly unchanged. Slight changes in flow between right and left chimney may be due to a slightly larger maximal luminal area reduction of the right chimney in comparison to the left chimney in all configurations.

To date limited evidence is available concerning the outcome of various combinations of EVAR devices and CGs for treatment of juxtarenal AAA and the ideal combination is yet unknown. Decision making is mostly based on local experience with the various devices and preference of the surgeon. Benchtop research of chimney graft configurations may help to differentiate between favorable and less favorable combinations of stents, and

to assess which combinations lead to potentially unfavorable geometries, such as CG compression and GF, which could lead to complications and subsequent re-interventions. GF was larger in configurations with balloon-expandable stents than in the configurations with self-expanding stents, which confirms results of previous benchtop studies ¹⁹⁻²¹. Absolute values for GF unfortunately are incomparable between studies, since different methods were used to measure the gutter, including 2D measurements of gutter area at multiple levels and 3D measurements of gutter volume, including the entire volume of the gutters. The method that was used in the current study demonstrated good inter-observer agreement, and was comparable to the method that was used by Niepoth and coworkers ¹⁶. The results of the current study showed lower gutter volumes in the ch-EVAS configurations in comparison to the results from Niepoth et al. (440-530 mm³ vs. 102.6-382.2 mm³). This difference is most likely to the proximal sealing zone of the endobags defined at 10 mm from proximal stent strut in the present study vs. 5 mm by Niepoth et al. The present study demonstrated larger compression of Viabahn compared to the Advanta-V12 stents in both ch-EVAR and ch-EVAS configurations. This has also been shown by others, examining geometry of CGs in ch-EVAR with the Endurant and Gore Excluder (W. L. Gore & Associates) endografts ^{19,20}. In contrast, Niepoth and coworkers demonstrated less compression of the Viabahn in comparison to the Advanta-V12 in chimney EVAS configurations (42% vs. 22%) ²¹. Tran et al. showed that the diameter reduction in CG is consistently 10-15% larger at the junctional area than in other regions of the CG (proximal and distal) ²². In the present study the maximum angulation of the CGs was fairly low for Advanta-V12 and Viabahn EVAS configurations, and a more parallel configuration with a sharper curve of the CG as presented by Niepoth et al. may have resulted in larger deformation in the Advanta-V12 in comparison to the Viabahn. The Viabahn may allow better conformation and may be more flexible to conform to more complex trajectories, including severe angulations.

The largest gutters were observed in the AFX configurations. In EVAR sealing is obtained by oversizing of the graft with reference to the aortic wall. Mestres et al. highlighted importance of proper sizing of the endograft to minimize gutter formation, and to obtain the best possible sealing in ch-EVAR ¹⁹. The best outcomes in terms of GF and CG compression were obtained by oversizing the endograft with 30%, although this is influenced by the number of required CGs. The oversizing of the main body was in a range of 20-30% for the ch-EVAR configurations. In addition, wall apposition and GF in ch-EVAR may be influenced by unpredictable deployment of the CGs due to interaction with the proximal bare metal stent extension. The AFX has a greater number of proximal bare metal stent struts and this may provide less space to accommodate the CGs in comparison to the Endurant, in particular when combined with balloon-expandable CGs (Figure 1). However, the configurations were studied at static CT acquisitions, excluding the AFX active seal design feature with the graft material on the outside, which potentially may reduce the risk on type IA endoleak in case of GF. This phenomenon could not

be evaluated in the current study design. Gutter volume was the lowest in the Viabahn ch-EVAS configuration, with probably good conformability of both endosystem and CG. In ch-EVAS sealing and potential GF is dependent on proper filling of the endobags in the proximal neck and conformation to the chimney stent grafts. Moreover, additional balloons are required for balloon inflation of the CG during curing of the polymer and CG compression was higher with Viabahn. Accordingly, the configurations with Endurant-Advanta-V12 and EVAS-Advanta-V12 may have acceptable GF.

The present study showed gutter formation in all configurations and this may be inherent to the chimney technique. However, it is supposed that not all gutters will lead to type IA endoleaks in-vivo. In clinical practice most gutters may be missed due to poor scan quality, and poor filling of the gutter with contrast. A small gutter with adequate sealing below the CG may exhibit a low risk for type IA endoleaks after both ch-EVAR and ch-EVAS, and may resolve over time by filling with thrombus. A longer gutter, originating at the proximal sealing zone and continuing until the aneurysm sac, may have a higher risk to cause a type IA endoleak ²³.

The observed CG compression ratios for self-expanding and balloon-expandable stents only had a minimal influence on the measured renal artery volumetric flow. However, it is assumed that CG compression should be intended as low as possible, since a complex shape (i.e. asymmetric) of the CG luminal area may lead to unfavourable flow profiles, and may induce a risk for stent thrombosis. The diameter of the RA branch was 5 mm, and therefore a

CG stent graft with a diameter of 6mm was used. A larger CG diameter may result in more CG compression ²⁰.

Another serious limitation of the chimney technique is a significant higher incidence of stroke compared to standard EVAR and FEVAR procedures where fenestrations can be managed through femoral access. The reported incidence for stroke has been 3.2% for ch-EVAR vs. 0.3% for FEVAR ⁷. Also, the incidence of early type IA endoleaks is higher with the ch-EVAR technique in comparison to FEVAR (10% vs. 4.3%) ⁷.

Limitations. The used phantom had a relatively short proximal sealing zone, as the distance between the distal edge of the SMA and the lowest RA was only 12 mm. This length was considered as healthy aortic neck, and the stent sizing was based on the aortic diameter in this part. Accordingly, based on a minimum oversizing of 20 % for proper endograft fixation in the aortic neck, the total length of sealing zone was at maximum 15 mm, as the aortic diameter starts to increase below the renal arteries. The positioning accuracy of the stent grafts was not assessed in the present study, and a lower positioning may cause differences in gutter formation and CG compression, in particular in a short neck anatomy. Moreover, deployment of the chimney stent before deployment of the endobags may result in inaccurate positioning of the main graft. However, it is yet unknown what will be the optimal sequence of steps regarding CG and endograft deployment.

A longer proximal sealing zone could have improved proximal graft apposition in the studied configurations, but the chosen geometry was based on real-life CT scans and thus clinically relevant. However, the average anatomy of 25 elective AAA patients was fairly straightforward, and results cannot be generalized for the entire population either undergoing ch-EVAR or ch-EVAS. The formation of gutters and compression of CG is likely influenced by a different geometry and a phantom geometry including (severe) aortoiliac angulations and an asymmetric origin of branches would have been interesting to examine including the studied configurations. A patient specific analysis, also including clinical outcomes, may be useful to assess clinical relevance of the findings.

In addition, geometry changes that may occur during the cardiac cycle were excluded, whereas the configurations were studied at static CT acquisitions. The flow distribution to branch vessels differed slightly from the intended flow, and also the systemic pressure was somewhat higher than the normal rest range, but flow distribution and pressure were still within a physiologic range. The models were fabricated from an elastic silicone. The models in this study may therefore be more elastic compared to in-vivo, whereas aneurysms are usually stiffer because of a larger volume of collagen and less volume of elastin and muscle cells ²⁴.

CONCLUSION

The present study showed that gutter volume is lowest in ch-EVAS with Viabahn stents. CG compression was lower in all configurations with Advanta-V12 in comparison to Viabahn stents, but renal flow was unrestricted by CG compression. Further research is required to assess clinical implications of these findings concerning the incidence of type IA endoleak and CG patency.

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MMPJ Reijnen and JPPM de Vries are consultants for Endologix Inc. JPPM de Vries is also a consultant for Medtronic Inc.

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SUPPLEMENTARY MATERIAL

Supplementary figure. The average branch flow in the superior mesenteric artery (SMA), renal arteries, and common iliac artery for each configuration.

8

GENERAL DISCUSSION, CONCLUSIONS AND RESEARCH RECOMMENDATIONS

DISCUSSION AND CONCLUSIONS

The EVAS therapy is currently in a phase where it is being improved and refined. In this thesis, several features of EVAS therapy were studied, providing answers to some preclinical and clinical questions. Yet, long-term results of EVAS are still missing. In this chapter, the most important conclusions to the studies in the thesis and relevant remaining challenges are identified and discussed.

Chapter 2. What is the reproducibility of preoperative CTA aortoiliac volume measurements of aortoiliac flow lumen and precision in estimation of perioperative (pre)fill volume of the endobags?

In chapter 2 the reproducibility and precision of preprocedural CTA aortoiliac volume measurements in estimating fill volume of the endobags was studied. Preoperative CTA measurements of aortoiliac flow lumen showed a good interobserver agreement (intraclass correlation coefficient of 0.98), but underestimated prefill volume of the endobags (-11.3 ± 9.9 mL). Pre- and postprocedural measurements of aortic aneurysm and thrombus volume showed a reduction of thrombus volume after implantation of the Nellix endosystem that was associated with the difference in CTA calculations and actual fill volume of the endobags ($R=0.39$, $p=0.01$). It was suggested that fluid in the luminal layer of the thrombus can be displaced when applying a pressure of 180 mm Hg, which was demonstrated in in-vitro research by Van Noort et al. ¹. Currently, a study into imaging of layers inside the intraluminal thrombus (ILT) of AAA specimen is being conducted.

Imaging of different layers inside the thrombus can be useful to select patients for EVAS. Recent changes to the Nellix instructions for use exclude treatment of patients with a large thrombus volume due to stent migration. However, there may be patients suitable for EVAS that are now excluded for treatment. In addition, visualization of ILT layers can be useful to detect unremodelled parts inside the ILT after EVAS that may contribute to stent migration during follow-up. Magnetic resonance imaging can be used to visualize different layers within the ILT ², but is not part of the standard clinical workflow of EVAS. Currently, a study into the feasibility of dual energy CT in differentiating between different layers inside the thrombus is being conducted.

Chapter 3. What are the changes in aortoiliac anatomy at the 30-day follow-up CTA concerning infrarenal neck and aneurysm diameter, aortoiliac length, aortic neck angulation, and aneurysm and thrombus volume?

In chapter 3 changes in aortoiliac anatomy were analysed to study the conformability of the Nellix endosystem to a patient anatomy. Similar to the findings in chapter 2, there was a reduction of thrombus volume pre- and post-EVAS (-3.2 mL). In addition, there appeared straightening of the aortoiliac anatomy, including a reduction in aortic and common iliac artery length (-2.6 mm and -2.3 mm) and maximum common iliac artery angulation (right:

5.2°; left: 5.5°). The straightening could cause displacement of maximum common iliac artery angulation distal from the stent. It is therefore important to check the outflow in anteroposterior and lateral orientations on the procedural angiography to detect a potential outflow obstruction during the primary procedure, and to avoid acute stent occlusion. The other parameters that were studied showed no changes compared to baseline. The displacement of maximum angulation distal from the stent suggests that the endosystem is relatively stiff compared to the vasculature. The analysis included the first 27 patients treated by a single centre, including patients with a relatively straightforward anatomy. Further research should focus on evaluation of tortuous anatomy.

Chapter 4. What is the rate of stent migration, stent occlusion, endoleak and reinterventions of endovascular aortic sealing (EVAS) with the Nellix endosystem in treatment of concomitant and isolated common iliac artery (CIA) aneurysms after one year?

In chapter 4 the rate of migration, stent occlusion, endoleak and reintervention was studied for EVAS in isolated and concomitant iliac artery aneurysms (CIAA). The results were promising with 0% stent migration, 4.2% stent occlusion, 6.9% endoleak, and 6.9% reinterventions after 1-year follow-up. However, all endoleaks were left untreated and some may require reintervention during follow-up. Type I endoleaks can be considered high flow endoleaks and induce a risk for secondary rupture.

Krievins *et al.*³ demonstrated that inadequate CIAA exclusion causes aneurysm growth during long-term follow-up. The internal iliac artery (IIA) can only be preserved if there is a sealing zone available in the CIA distal to the aneurysm of at least 10 mm per IFU. In case of a missing seal zone the stent should be extended to the EIA to stay on IFU. Further research should focus on the evaluation of graft apposition in the distal seal zone on the first postoperative CT-scan and long-term clinical outcomes of EVAS in CIAA. In addition, positioning variability of the stent in the distal landing zone should be investigated with regard to an intended position of the distal bare metal stent ring across the IIA orifice in case of a short distal seal zone to preserve IIA branch patency. (Partial) obstruction may affect IIA branch patency during follow-up.

An advantage of the Nellix endosystem in treatment of isolated CIAA compared to other techniques might be the ability to conform to varying diameters in the proximal and distal landing zone. However, shorter Nellix stents should become available to cover a broader range of anatomies, as the length of the CIA is usually shorter than 90-100 mm.

Chapter 5. What is the influence of a dual lumen configuration after EVAS on flows recirculation in the suprarenal aorta and common iliac artery, and flow in the renal artery compared to two EVAR stents and an aneurysm control under physiologic resting conditions?

In chapter 5 the influence of a dual lumen configuration on flow recirculation proximal and distal to the endobags was studied and compared to two EVAR stents and an aneurysm control. No changes were observed in flow in the anteroposterior midplane of the suprarenal aorta in the stented models compared to the aneurysm control. Flow in the renal artery was influenced in the EVAR models and EVAS model, including a region of lower wall shear stress (WSS) in the EVAR models and higher shear rates in some regions in the EVAS model compared to the control. The alterations in flow profile were most likely due to the proximal bare metal stent covering the renal artery orifice or excess of endobag material in the EVAS model. The clinical consequence of the observed changes in renal flow profile and wall shear stress after EVAR and EVAS require further research. The stented models showed an area of backflow near the distal stent compared to the control. The EVAS model showed the largest region of flow recirculation distal from the stent, but all flow returned in a forward direction at the end of a cycle. Accordingly, there is no increased risk of embolization expected after stent placement.

The complex flow patterns distal from the EVAS stent were also observed in vivo and reported by different groups ^{3,4}.

A limitation of this study was that flow was only studied in the anteroposterior midplane of the flow lumen, and this may be insufficient to capture complex flow patterns in multiple directions. In chapter 6 the flow fields were visualized in two planes.

Chapter 6. What is the influence of positioning of EVAS on flow recirculation proximal to the endobags, and flow profile in the renal artery under physiologic resting conditions?

In chapter 6 the influence of positioning of the Nellix endosystem on flow proximal to the seal zone was studied, while comparing various infrarenal neck diameters. A larger infrarenal neck diameter enhances vorticity near the anterior and posterior suprarenal aortic wall. Stationary vortices appear when the endosystem is positioned in a 32 mm infrarenal neck, and in a 28 mm infrarenal neck with the proximal end of the stent aligned with the most caudal renal artery.

Stationary vortices may result in formation of thrombus. Thrombus formation post-EVAS has been reported in literature, including remodelling of the aorta with thrombus proximal to the endobags at the 30-d postoperative CT-scan ⁴, and distal embolization in some patients, however, with an anatomical cause ⁵. It is likely that other patient specific factors are involved. In this context it would be interesting to compare outcomes (i.e. remodelling of the aortic neck and distal embolization) of EVAS in patients with different positioning of the stents with reference to the renal artery and different aortic neck diameters.

Positioning of the stent with the proximal uncovered stent ring across the renal artery orifice does influence the renal artery profile in a 24-mm and 28-mm infrarenal neck, including a jet flow at the inflow, and regions of lower WSS at the inflow in the 24-mm model. The changes in renal artery flow profile may be attributed to positioning variability of the stents or endobags, while the position of the uncovered stent ring distal to the renal artery does not influence the renal artery flow profile. On the other hand, a lower positioning reduces the potential seal zone.

It would be interesting to study clinical outcomes (i.e. renal functioning) between patients with IFU positioning and a low positioning of the stents outside the IFU.

Chapter 7. How large are gutter volume and chimney stent compression in chimney EVAR and chimney EVAS configurations, and what influence does chimney stent compression has on renal volumetric flow compared to a juxtarenal aneurysm control, studied in an in-vitro setup under physiologic resting conditions?

In chapter 7 the geometry of chimney EVAR and EVAS configurations was studied in-vitro in relation to renal flow. All configurations showed gutters. The lowest gutter volume was found in chimney EVAS with Viabahn chimney stent grafts (102.6 mm³), while the largest volume was found in the chimney EVAR configuration with AFX and Advanta-V12 chimney stent grafts (559.6 mm³). The Viabahn showed more deformation than the Advanta-V12 in all configurations (2.02 vs. 1.39), which is in accordance with previous in-vitro studies ^{6,7}. Chimney stent graft compression did not influence renal flow, indicating that there was no severe outflow obstruction at the compression ratios that were found in this study (maximum diameter-ratio of 2.5). These numbers should be validated in a clinical setting, including (long-term) outcomes on type Ia endoleak and occlusion of chimney stent grafts. In addition, a model with a straightforward anatomy was used in this study, and there could be different outcomes for these combinations of stent grafts in patients with severe neck angulation (> 60 degrees). Moreover, a different number of chimney grafts and sizing may influence gutter volume.

RESEARCH RECOMMENDATIONS

Long-term clinical outcomes are needed to demonstrate whether EVAS is a durable solution for treatment of AAA. Besides the clinical outcomes, some other issues require further research. In chapter 6 of this thesis positioning variability of the endobags has been demonstrated in-vitro, and this was also observed on follow-up CT-scans.

Non-apposition of the endobags in the landing zones may result in gutter formation and type I endoleak. The endobags are not visible on angiography, while the markers on the fabric of a regular EVAR graft clearly mark the seal zone. It is questionable whether a clear visibility of the endobags on angiography would allow more accurate positioning of

the endosystems, whereas adequate aneurysm sealing will depend on proper filling of the endobags in the landing zones.

According to the IFU, a landing zone with a length of at least 10 mm is required in the proximal and distal landing zones, suggesting that aneurysm sealing is obtained within 10 mm of the start of the endobag. It is yet unknown what sealing length is required for successful aneurysm exclusion, and if circumferential graft apposition is obtained within 10 mm from the start of the endobags. Apposition of the endobags on CTA has not been studied so far in a clinical setting and can be challenging due to poor contrast between the endobags and the flow lumen. Merging of a contrast and non-contrast CT can assist in detecting endoleak ⁴, and non-apposition of the graft in the infrarenal neck. In addition, the influence of thrombus in the landing zones on sealing of the aneurysm is yet unknown. Krievins and coauthors ³ studied aneurysm growth in patients with common iliac artery aneurysms, and found aneurysm growth during follow-up in patients without complete aneurysm exclusion. They hypothesized that intraluminal thrombus (ILT) in the landing zone can cause growth during follow-up by transmitting pressure, which suggests that landing in extensive ILT should better be avoided. The role of ILT in the proximal and distal landing zones warrants further research. In addition, positioning variability of the stent frames could affect seal.

Proper filling of the endobags is also important for adequate fixation of the stents inside the aneurysm due to lack of active fixation in the proximal and distal landing zones (> 10 mm in diameter). It is important to know what factors are involved in stent migration. Fixation inside the aneurysm sac may not be stable due to potential remodelling of ILT and the aneurysm sac during follow-up. In addition, air inside the endobags that dissipates during follow-up may affect stent positional stability during follow-up. This has also been observed at CTA. Potential factors that cause migration can be studied at the postoperative CT-scans.

In addition to long-term clinical outcomes, positioning variability and positional stability of the endosystem inside the aneurysm require further research to study applicability of EVAS.

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9

SUMMARY (DUTCH)

VALIDATIE VAN ENDOVASCULAR ANEURYSM SEALING VOOR DE BEHANDELING VAN EEN ABDOMINAAL AORTA ANEURYSMA

Een abdominaal aorta aneurysma (AAA) is een pathologische verwijding van de lichaamsslagader tot meer dan twee keer de normale diameter. Naarmate de diameter toeneemt, wordt het risico op een ruptuur groter, waardoor een levensbedreigende situatie ontstaat. Behandeling gebeurt steeds vaker via een endovasculaire procedure, waarbij er via een incisie in de lies een stent in het bloedvat wordt geplaatst om het zieke gedeelte te ondersteunen. Bij een standaard endovasculaire procedure, endovascular aortic repair (EVAR), wordt de stent proximaal en distaal van het aneurysma gefixeerd. De EVAR stent komt vast te zitten door een grotere diameter stent in te brengen dan de diameter van het bloedvat. Een relatief nieuwe techniek is Nellix endovascular aneurysm sealing (EVAS), waarbij het aneurysma in zijn geheel wordt afgesloten van de bloedstroom. Het EVAS endosysteem bestaat uit twee parallelle stents met daaromheen een zogenaamde “endobag”, een zak die wordt opgevuld met polymeer om het aneurysma en de stents in het aneurysma te fixeren.

Een juiste hoeveelheid polymeer is belangrijk om de stents goed te fixeren in het aneurysma en het risico op een zogenaamde “endoleak”, lekkage van bloed langs de endobags, met daarbij weer druk op het aneurysma, te verkleinen. In hoofdstuk 2 van dit proefschrift is onderzocht wat de reproduceerbaarheid en precisie is van preoperatieve computertomografie (CT) volumemetingen van het aorta flow lumen in het bepalen van het vulvolume van de endobags. Preoperatieve CT-metingen van het aorta flow lumen zijn reproduceerbaar met een intraclass correlation coefficient van 0.98, maar onderschatten het werkelijke vulvolume van de endobags (-11.3 mL). Dit is geassocieerd met een afname van het volume trombus in het aneurysma na het plaatsen van de EVAS stents ($R=0.39$, $p=0.01$).

In hoofdstuk 3 van dit proefschrift is de anatomie voor en na implantatie vergeleken om te weten te komen hoe goed het EVAS endosysteem zich aanpast aan de anatomie, hetgeen belangrijk is voor een goede plaatsing. Hiervoor zijn diameter, lengte, angulatie en volumemetingen verricht van de aortoiliacale anatomie op de preoperatieve en 30-dagen postoperatieve CT-scans. Net als in hoofdstuk 2 wordt er een afname van het trombusvolume in het aneurysma gevonden na implantatie (-3.2 mL). Een andere bevinding is dat de maximale hoek in het iliacaaltraject in sommige gevallen verplaatst wordt naar distaal van de stent, wat kan leiden tot een outflow obstructie. De overige parameters die zijn onderzocht laten geen veranderingen zien tussen de preoperatieve en 30-dagen postoperatieve CT-scan.

In hoofdstuk 4 van dit proefschrift is onderzoek gedaan naar stent migratie, stent occlusie, endoleak en reïnterventies bij EVAS in gecombineerde en geïsoleerde iliacaal aneurysmata over een gemiddelde follow-up periode van 1 jaar. De uitkomsten na 1 jaar laten een lage incidentie zien van stent migratie (0%), stent occlusie (4.2%), endoleak

(6.9%) en reïnterventies (6.9%). De lange termijn moet uitwijzen of EVAS ook een duurzame oplossing is voor het endovasculair behandelen van patiënten met een a. iliaca communis aneurysma.

De EVAS stents worden standaard met de endobags vlak onder de nierarterie geplaatst zodat een maximale lengte van de beschikbare infrarenale aorta nek wordt geseald. Een configuratie met flow lumina naar beide benen, op het niveau van de nierarteriën, kan invloed hebben op de hemodynamiek in de aorta proximaal van de EVAS stents en geassocieerde parameters, zoals wall shear stress (WSS) en de oscillatory shear index (OSI), welke geassocieerd zijn met het ontstaan van atherosclerose. De EVAS stents voor klinisch gebruik hebben standaard een diameter van 10 mm, wat niet goed aansluit op het flow lumen van de aorta. Hierdoor kan het zijn dat bloed moeilijker wegstroomt en er kunnen complexe vloeistromen (o.a. vortices) ontstaan in de aorta boven de stent, met het risico op het vormen van stolsels.

In hoofdstuk 5 is in vitro onderzoek beschreven naar complexe vloeistofstromen in de aorta onder fysiologische condities in rust. Hierbij is een aneurysma model met Nellix stent vergeleken met twee conventionele EVAR stents met een bifurcatie meer dan 5 cm onder de nierarteriën en een aneurysma controle model. De vloeistofstromen zijn in beeld gebracht met laser particle imaging velocimetry (PIV) in de suprarenale aorta, de nierarterie en de a. iliaca communis, en gekwantificeerd op basis van WSS en de OSI. Er zijn geen verschillen in recirculatie, WSS en OSI in de suprarenale aorta tussen de modellen met stent en het aneurysma model. De modellen met EVAR stent laten een gebied met lagere WSS zien in de nierarterie, terwijl het EVAS model een regio met hogere WSS laat zien ten opzichte van de controle. Ten opzichte van het aneurysma controle model is er bij de modellen met stent in de a. iliaca communis een groter gebied met recirculatie van vloeistof te zien met lagere WSS en maximale OSI waarden. Aan het eind van een hartcyclus is alle flow wederom weer in een voorwaartse richting in het controle model en stent modellen.

Hoofdstuk 6 beschrijft in vitro onderzoek naar vloeistofstromen in de aorta boven de EVAS stents in modellen met verschillende aorta diameters, waaronder modellen met een 24, 28 en 32 mm infrarenale nek diameter. Een grotere aortadiameter leidt tot meer terugstroom van vloeistof boven(op) de endobags, evenals een lage plaatsing van de stents ten opzichte van de nierarterie in een model met een 28 mm infrarenale nek. Vervolgstudies zijn nodig om te kijken of de verschillen in hemodynamiek, die zijn gevonden, leiden tot een verschil in klinische uitkomst. EVAS in een 24-mm en 28-mm infrarenale nek laat een toename zien van de stroomsnelheid en WSS in de nierarterie. Dit wordt mogelijk veroorzaakt door de proximale ongecoverde stent ring of een overmaat aan endobag wat gedeeltelijk voor het ostium van de nierarterie ligt.

Behandeling van een juxtarenaal aneurysma met een zogenaamde “chimney” EVAR geeft een risico op het vormen van zogenaamde “gutters” en het risico op een type Ia endoleak. Daarbij kan radiale compressie van de chimney stent door de EVAR stent

leiden tot een outflow obstructie en een risico op occlusie. De behandeling van juxtarenale aneurysmata met chimney stents is ook mogelijk in combinatie met EVAS (ch-EVAS).

In hoofdstuk 7 van dit proefschrift is in vitro onderzoek gedaan naar het vormen van gutters en compressie van chimney stents bij verschillende chimney EVAR en EVAS configuraties in relatie tot de volumeflow in de nieren. Gutters waren zichtbaar in alle configuraties met het kleinste volume in de ch-EVAS configuratie met een “self-expanding” chimney stent in de nierarterie (102.6 mm³). De self-expanding chimney stents laten meer compressie zien dan de “balloon-expandable” chimney stents (diameter-ratio van 2.02 tegenover 1.39 gemiddeld over alle configuraties), maar dit leidt niet tot een significante outflow obstructie.

Uit de literatuur volgt dat er sprake is van goede resultaten wanneer EVAS binnen de juiste klinische en anatomische indicaties wordt toegepast. Lange termijn klinische resultaten zijn nodig om aan te tonen dat de oplossing ook duurzaam is voor het behandelen van een AAA. Hetzelfde geldt voor niet reguliere toepassingen, zoals het behandelen van een geïsoleerd iliaaal aneurysma. In vitro onderzoek heeft een aantal verschillen in beeld gebracht tussen de situatie voor en na stentplaatsing voor verschillende toepassingen (EVAS en ch-EVAS). Deze bevindingen vereisen nu verdere klinische validatie.

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ADDENDUM

LIST OF ABBREVIATIONS

AAA	Abdominal aortic aneurysm
AP	Anteroposterior
BE	Balloon-expandable
BMF	Blood mimicking fluid
CEUS	Contrast-enhanced ultrasound
CG	Chimney graft
Ch-(EVAR/EVAS)	Chimney-
CI	Confidence interval
CIA	Common iliac artery
CIAA	Common iliac artery aneurysm
CLL	Centre lumen line
CTA	Computed tomography angiography
DUS	Duplex ultrasound
D-ratio	Diameter-ratio
EIA	External iliac artery
EVAR	Endovascular aortic repair
EVAS	Endovascular aortic sealing
FEVAR	Fenestrated endovascular aortic repair
GF	Gutter formation
ICC	Intraclass correlation coefficient
IFU	Instructions for use
IIA	Internal iliac artery
IQR	Interquartile range
LP	Low positioning
OSI	Oscillatory shear index
PIV	Particle imaging velocimetry
RA	Renal artery
RRT	Relative residence time
SA	Suprarenal aorta
SD	Standard deviation
SE	Self-expanding
SMA	Superior mesenteric artery
TAWSS	Time-averaged wall shear stress
WSS	Wall shear stress

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Validation of preoperative EVAS endobag fill volume measurements. Leipzig Interventional Course (LINC). 2016 Jan. Leipzig, Germany.

RESUME

Jorrit Boersen studied Technical Medicine at the University of Twente (Enschede, the Netherlands) from September 2007 to March 2015. His 1-year master of science specialization internship during the last year of his studies was in Endovascular Aneurysm Sealing (EVAS), and was performed at the vascular surgery department at the St. Antonius Hospital (Nieuwegein, the Netherlands). After his graduation he continued with research on EVAS, involving collaborative studies with Rijnstate Hospital (Arnhem, the Netherlands). Parts of his work have been published in peer reviewed scientific journals on vascular surgery and presented at international vascular conferences.

His personal motivation in doing clinical research is to provide physicians and medical device companies with evidence and consult on research & development, in the process working on better healthcare. In addition to the work for his PhD, he reviewed the anatomy and procedure of 350+ Dutch EVAS patients for the Dutch Endovascular Aneurysm Sealing study (DEVASS), a multicenter study of three Dutch centres (St. Antonius Nieuwegein, Rijnstate Arnhem, St. Elisabeth Tilburg) on the outcomes of EVAS. Jorrit is passionate about sports, in particular running, cycling, swimming, skiing and soccer. He finished three marathons and cycled in one day six times Alpe d'Huez for a fundraising event for cancer research. Other interests include photography, architecture, music, travelling and innovation.

VALIDATION OF ENDOVASCULAR ANEURYSM SEALING

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