Analysis of new diagnostics and technologies in endovascular aortic aneurysm repair

van Noort, Kim

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General Introduction

Abdominal aortic aneurysms

Abdominal aortic aneurysms (AAA) are defined as an infrarenal increase in aortic diameter 1.5 times the normal diameter or an absolute diameter of > 3 cm.[1] Loss of elastin, increased inflammation and smooth muscle cell apoptosis appear to be the main causes for dilatation of all layers in the aortic wall, although the precise pathways are still unclear.[2,3] Most important risk factors for developing AAAs are male gender, age, family history, and smoking.[4] Abdominal aortic aneurysm is present in approximately 2% of the global population.

AAAs are mostly asymptomatic and are incidental findings on computed tomography angiography (CTA) or ultrasound. As the diameter of AAAs increases, the risk of rupture raises. Rupture is associated with a mortality rate up to 65-85%, and these ruptures account for a significant part of deaths, especially among men.[5-7] So, intervention is needed when risk of rupture exceeds the risk of the procedure. For AAA this crossover point is roughly estimated at a diameter of 55 mm for men and 52 mm for women, or > 10 mm growth per year.[8] However, every indication for AAA repair should be individually based.

Endovascular Aneurysm Repair (EVAR)

Besides open repair, AAAs can be treated with endovascular aneurysm repair (EVAR). EVAR was introduced by Volodos et al.[9] in 1988, and since then several generations of endografts have been developed to improve the sustainability and decrease the risk of complications of EVAR.

During the EVAR procedure a main body (prepared in a delivery system) is inserted into the left or right common femoral artery and positioned at the landing zone (infrarenal aortic neck). For infrarenal AAAs the landing zone is just below the orifice of the lowest renal artery. Sealing will be achieved by oversizing of the diameter of the endograft compared to the diameter of the infrarenal aorta (radial force), and in the majority of the endografts with anchoring pins in the suprarenal bare stent. If the main body is positioned correctly the delivery sheath is withdrawn, and the endoprosthesis is unfolded and bilateral limbs are inserted through the common femoral arteries into the main body, with distal sealing in the common iliac arteries, thereby excluding the aneurysm from the blood flow.

Compared to open repair, EVAR has been associated with a lower 30-day mortality rate. However, a two-fold higher reintervention rate is required during follow-up compared to open repair.[10,11] Especially type Ia and Ib endoleaks (proximal and distal leakage between aortic wall/ iliac arteries and endograft, respectively), type III (leakage due to inadequate fixation between graft components, or fabric tears) and device migration require reintervention as the risk of rupture increases due

to the persistent pressure in the aneurysm sac.[12] During long-term follow-up 2.3 - 3.1% of all EVAR cases develop type Ia endoleaks. Migration occurs in 1.0 to 5.1% of all EVARs, while type Ib endoleak occurs in 2.3%.[13-17]
Preoperative anatomical risk factors associated with these complications are short infrarenal necks (<1 cm), large supra- and infrarenal angulations (>75°), and large neck diameter (>28 mm).[18-25] Careful pre-operative planning may reduce the risk of post-EVAR complications. However, late type Ia endoleaks and migration are a result of insufficient seal and fixation in the aortic neck, and development of the disease. These factors cannot always be addressed during the procedure, and may arise during follow-up. There is need for a measuring tool that can forecast sealing complications by assessing small changes in sealing and position during follow-up. Ideally, seal failure can be prevented and reintervention can be performed before urgent complications occur. Moreover, this can also be introduced as follow-up imaging tool in thoracic endovascular aortic aneurysm repair (TEVAR).

EndoAnchor implants

If a seal complication has occurred the Heli-FX EndoAnchor System (Medtronic Vascular, Santa Rosa, CA, USA) can be used therapeutically to resolve type Ia endoleaks or prevent persistent migration of the endograft.[26] EndoAnchors can also be used prophylactically in patients with challenging neck anatomy.[27,28] The 4.5 mm long by 3.5 mm diameter helical design of the EndoAnchors ensures safe attachment of the endograft to the aortic wall and the cross bar at the end of each EndoAnchor prevents over-penetration (Figure 1.1).[28] The EndoAnchors increase the fixation strength to that of a surgical hand-sewn anastomosis when they are deployed circumferential into the aortic wall.[29] This can only be achieved when the EndoAnchor implants successfully penetrate the aortic wall with 2 mm.[30,31] Studies have shown good outcomes in both prophylactic and therapeutic use of the EndoAnchors. Large patient cohorts and clinical outcomes were analysed in the ANCHOR registry[26-28,31-34], however, no data is yet available on individual EndoAnchor penetration and the sustainability of these individual penetrating EndoAnchors.

Endovascular Aneurysm Sealing (EVAS)

In 2013 endovascular aneurysm sealing (EVAS) was introduced with the Nellix endosystem (Endologix Inc, Irvine, CA, USA). EVAS as alternative for EVAR may increase the number of patients eligible for endovascular repair, as the instructions for use of EVAS allowed greater morphological variability.[35,36] The

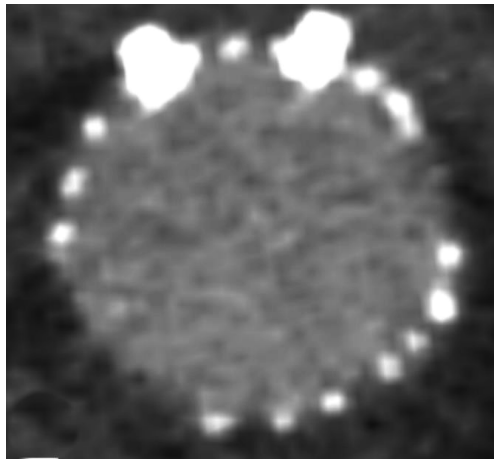

Figure 1.1: Axial view of the aortic lumen with an endograft on a computed tomography angiography scan. Two EndoAnchors (white ovals) are penetrating the aortic wall and endograft.

Nellix endosystem contains of two balloon-expanding cobalt-chromium stent frames which are 10-mm in diameter.[36] These stent frames provide blood supply to the iliac arteries and are surrounded by endobags which are filled with polyethylene glycol (PEG) during the EVAS procedure. The PEG polymerizates in 3-5 minutes after insertion into the endobags, occupying the aneurysm cavity and therefore excluding the aneurysm from the blood flow. For determination of the volume of PEG used to occupy the aneurysm cavity, the aneurysm diameter, length and the volume of intraluminal thrombus (ILT) should be accounted for. ILT is present in 75% of the AAAs.[37] The proximal uncovered stent of the stentframes must be deployed 5 mm above the lower border of the orifice of the lowest renal artery, for total seal of the endobags in the aortic neck. This sac-anchoring system is thought to reduce endoleaks and migration. The early results were promising, but limited to 30 days and one-year results.[38-40] At mid-term follow-up differences in clinical outcome have been observed, questioning the durability of the EVAS device as endoleaks and migration occurred.[41,42] Further insight is needed in the behaviour and sustainability of the Nellix endosystem in the abdominal aorta. Moreover, risk factors that cause complications need to be defined.

Objective of the thesis

The overall goals of this thesis are to investigate technologies for improved detection and prevention of EVAR complications and to investigate the occurrence of complications after EVAS. The thesis consists of two parts:

Technologies for detection and prevention of complications after Endovascular Aneurysm Repair (EVAR):

- Part IA; The first objective of the thesis is to introduce a new 3D methodology for determination of the position and apposition of endografts in the abdominal and thoracic aorta.

- Part IB; The second objective is to associate positional EndoAnchor characteristics with successful penetration of EndoAnchors.

Complications after Endovascular Aneurysm Sealing (EVAS):

- Part II; The third objective is to associate complications after EVAS with mechanical behaviour of ILT, arterial stiffness and positioning of the Nellix endosystem. Moreover, predictive anatomical characteristics for the occurrence of complications are determined.

Outline of the thesis

In Part IA the newly developed 3D methodology to identify patients at risk for sealing complications after EVAR is introduced (**Chapter two**). The new software is also validated for TEVAR in **Chapter three**. The new methodology is used for precise determination of the position and the apposition of EVAR devices. By monitoring these locations and surfaces early changes in endograft position and seal may forecast late complications.

These chapters focus on answering the following questions:

- How should subtle changes in the endograft position and apposition in the infrarenal neck during CT follow-up be interpreted? (**Chapter two**)
- How should subtle changes in the proximal and distal sealing zones in thoracic endograft position and apposition during CT follow-up be interpreted? (**Chapter three**)

In Part IB individual EndoAnchor deployment success is studied thoroughly. EndoAnchors are designed to increase migration resistance and apposition of endografts in the aortic neck. In **Chapter four**, 560 individual EndoAnchor

implants are investigated regarding penetration depths as well as angles and circumferential distribution over the aortic circumference after therapeutic use to treat type IA endoleaks. In **Chapter five** the sustainability of these EndoAnchor implants is investigated.

These chapters focus on answering the following research questions:

- What is the association between EndoAnchor deployment and successful resolving of type IA endoleaks, considering their distribution along the circumference of the neck, penetration depth into the aortic wall, and angle of penetration? (**Chapter four**)
- What is the sustainability of initially successfully penetrating EndoAnchors during follow-up? (**Chapter five**)

Part II focusses on causes of complications after EVAS. First (**Chapter six**), a study was performed on fluid displacement during compression on intraluminal thrombus. It is hypothesized that during pressurization the volume of intraluminal thrombus may decrease, due to squeezing liquid out of the thrombus. This may have negative effects on the stability of the endobags of the Nellix endosystem. In this study freshly harvested ILT was inserted into a compression set-up, to investigate the fluid displacement under pressure.
Aortic pulse wave velocity (aPWV) is a measure for arterial stiffness, which is associated with increased cardiovascular risk.[43] In **Chapter seven** the aPWVs for an EVAS configuration, two EVAR configurations, and a tube graft in an in-vitro aortoiliac trajectory were calculated, to investigate the influence of different aortic endoprostheses on aPWV and structural stiffness. **Chapter eight** introduces a method to investigate the EVAS stentframe displacement over time within the aneurysm. In **Chapter nine** the non-apposition surface was introduced in a study on the accuracy in positioning the EVAS system, as the surface over the aortic wall between the renal arties and the top of the endobags. Ideally this non-apposition surface is zero. The endobags of the EVAS system do not have radiopaque markers on the endobags, therefore, positioning the endobags just below the renal arteries may be difficult. In **Chapter ten** the anatomical characteristics of 261 EVAS patients treated in three high volume EVAS centers are determined and used in a regression analysis to find anatomical predictors for complication after EVAS.

Part II focusses on answering the following research questions:

- What is the quantity of fluid displacement from freshly harvested intraluminal thrombus when uniform compression is applied in an in vitro compression set-up? (**Chapter six**)
- What influence do different endograft configurations have on aortic pulse wave velocity and structural stiffness in an in-vitro aortic model? (**Chapter seven**)
- How precise can three-dimensional positions of the Nellix stent frame and changes in position be determined? (**Chapter eight**)
- What is the accuracy of initial position and seal of the Nellix EVAS system in the aortic neck using a novel measurement methodology? (**Chapter nine**)
- What preoperative anatomical aortic characteristics are predictive for seal failures after EVAS? (**Chapter ten**)

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Part Ia