Analysis of new diagnostics and technologies in endovascular aortic aneurysm repair
van Noort, Kim

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Summary, general discussion and future perspectives
How should subtle changes in the endograft position and apposition in the infrarenal neck during CT follow-up be interpreted? (Chapter two)

The illustrated EVAR cases in chapter two show that detection of small changes in aortic neck morphology and endograft position and apposition can be detected with the use of the new, CT-analysis software. Moreover, the cases show how small changes in neck morphology, endografts position and apposition could be detected with the software on follow-up CT scans, months before complications such as type Ia endoleak became apparent according to radiographical readings. The illustrated patients in this chapter with endoleak or migration showed increase in fabric distance, tilt, endograft expansion, or a decrease of apposition surface. Changes occurred on at least one periodic follow-up CT scan before the endoleak or migration was noted at regular CT reports. The patients without complications showed no significant changes in position or apposition during follow-up.

The warnings signs detected by the new CT-analysis software such as an increase in aortic neck surface due to aortic dilatation, a decrease of aortic neck surface due to expanding aneurysm or migration, an increase in fabric-to-renal distances due to migration, an increase in endograft expansion as % of the original endograft diameter due to endograft dilatation and a decrease of shortest apposition length due to expanding aneurysm or migration may be hazardous signs for the occurrence of complications. These signs show that there is aortic dilatation, endograft dilatation, or early endograft migration. The early detection of complications may lead to less invasive and expensive reinterventions.

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 TEVAR the CTA applied software is also applicable, however some changes needed to be made to the software to cope with the larger angulations and surfaces for the thoracic aorta. Moreover, in TEVAR also the distal seal is an important parameter for successful outcome and if complications occur, distal seal failures need different treatment strategies compared to proximal seal failures, especially because the orifices of the visceral arteries should be preserved. The various warnings signs previously described in EVAR may also be applicable for TEVAR. These signs include a decrease in apposition (both surface and length), an increase in shortest fabric distances, and expansion of the endograft toward its original diameter. When the endograft is fully expanded, the radial forces that
have to keep the endograft in place are significantly reduced, and blood may leak along the fabric during peak systole when the diameter of the aorta is at its maximum. A subtle change in apposition, combined with full endograft expansion, may well be the cause of circumferential loss of apposition during the whole cardiac cycle and may result in repressurisation of the aneurysm. Validation showed excellent interobserver agreement for all position and apposition parameters of the new software [ICC between 0.821 – 0.995].

**General Discussion**

Despite ongoing improvements in EVAR and TEVAR devices, still complications such as type Ia endoleaks and migration occur. By assessing only pre-operative risk factors for complications, initial position and apposition of the endograft are neglected as a possible risk factors. The endograft position and apposition in the abdominal and thoracic aorta may change over time, and are the main cause of complications. Thus, early detection of changes in seal may forecast severe complications, and early reinterventions may be less invasive and less expensive. Previously, the CTA applied software was validated for EVAR in a study of Schuurmann et al.¹ Moreover, based on this software a retrospective study was performed to investigate if changes in position and apposition could have predicted type IA endoleaks and migration. Changes in anatomy and endograft dimensions during follow-up were clearly visible in type Ia endoleak and migration groups in CTA scans before the actual seal failure was detected in -regular follow-up.²

If these complications are detected early on, less invasive reinterventions may be performed. Such reinterventions may consist of inserting proximal extensions to reduce type Ia endoleak, or insertion of EndoAnchors to avoid further migration or resolve type Ia endoleaks.

By introducing this methodology into clinical practice a patient-specific follow-up may be achieved. If after one year, no warnings signs are present, a longer interval between the follow-up scans might be needed. Some patient may suffice with follow-up on duplex ultrasound, while others may need an earlier follow-up than one-year post-EVAR/TEVAR, if warnings signs occur on the first postoperative CTA scan. During the follow-up, frequency of follow-up can be adjusted according to the presence of eventual warning signs. However, before introducing the methodology into daily practice cut-off values need to be determined for the warning signs in much larger patient cohort studies.
Future perspective
First of all, a prospective study is needed to define thresholds for the subtle changes in position and apposition to eventual implement the CT-applied software on a large scale. Moreover, for TEVAR a larger prospective cohort needs to be investigated.
Furthermore, only degenerative descending thoracic aneurysms are included. TEVAR after dissections can not be analysed with the software thusfar. Research is needed to determine if the software can be adjusted for dissections. Moreover, the definition of warning signs may be different as the TEVAR device need to meet different criteria’s compared to TEVAR for aneurysms (i.e oversizing of the TEVAR device).
In the end, the software needs Conformité Européenne (CE) and Food and Drug Administation (FDA) approval to be allowed to be to used for clinical decision making. Steps need to be taken to further commercialize and develop the software to meet CE and FDA criteria.

Part Ib - Technologies for detection and preventions of complications after EVAR

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)
A total of 560 EndoAnchors in 86 patients were investigated of which 29% had maldeployment and were positioned beyond the recommended use; above the endograft fabric or at a gap > 2mm between the aortic wall and endograft. If endoleaks are due to >2mm gaps, EndoAnchor implants alone may not provide the intended sealing and additional devices (like extension cuffs) should be considered. The EndoAnchors are not designed to overcome such a gap. Good penetrating EndoAnchor implants were closer to 90° orthogonal to the aortic wall than the borderline and non-penetrating EndoAnchor implants. Maldeployment may be prevented by careful preoperative planning, by optimizing the intra-operative deployment technique, and an thorough knowledge of the recommended use of EndoAnchors.

What is the sustainability of initial successfully penetrating EndoAnchors during follow-up? (Chapter five)
A total of 54 patients with 360 EndoAnchors were included. All patients had two or more follow-up CTA scans. A total of 187 (51.9%) EndoAnchors had initial good
penetration and 182 EndoAnchors remained good penetrating (97.4%) after 13 [8-23] months follow-up. Four became borderline penetrating and one became non-penetrating without clinical consequence. The sustainability of initial well positioned EndoAnchors is good at one-year follow-up. Preoperative planning and good initial positioning (according to the recommended use) of the EndoAnchor remain the foremost reasons for individual EndoAnchor success.

**General Discussion**
These studies show the importance of EndoAnchor penetration. It emphasises the need for preoperative planning as EndoAnchors may not always be the suitable solution to overcome type Ia endoleaks (both intraoperative and in revision cases). A previous study of Goudeketting et al.\textsuperscript{3} showed aortic neck diameter and neck calcium thickness as independent predictors for individual EndoAnchor failure and a greater number of non-penetrating EndoAnchors was associated with an increased risk for endoleaks. The following factors need to be addressed when planning a procedure to resolve a type Ia endoleak with EndoAnchors;

- Are there large and thick thrombus and calcium loads present in the aortic neck that need to be avoided during the intervention? EndoAnchors will not penetrate calcium, and cannot overcome gaps between between the aortic wall and endograft larger than 2 mm.
- Is there dilatation of the aortic neck and is there no oversizing of the endograft left? If so, the endoleak or gap cannot be resolved solely with the use of EndoAnchors, as the diameter of the endograft is just not large enough to have circumferential seal in the aortic neck. Positioning an extension cuff (i.e with or without chimney grafts for the renal arteries) may be the right minimal invasive solution.
- Does the aortic neck have enough length to position the EndoAnchors? It might be difficult to position the EndoAnchor just below the endograft fabric and EndoAnchors need to be positioned in the sealing part of the endograft. The minimum seal length of the aortic neck should be at least 5 mm. If the EndoAnchor is positioned too low, it does not reach the aortic wall and will only penetrate the endograft and aneurysm cavity.

By addressing these questions before the procedure, better choices can be made and more EndoAnchors may be positioned correctly.

**Future perspective**
For future perspectives, it is interesting to see what the effect of the circumferential distribution of EndoAnchors is on the migration resistance in
clinical setting. If the EndoAnchors are not positioned correctly and do not penetrate, this will also have effect on the migration resistance. These forces have been determined in an in-vitro study set-up. Results of this not yet published data showed a migration resistance of 53.7N for circumferential distribution of 6 EndoAnchors compared to 5.1N without EndoAnchors, and 24.6N for circumferential distribution of 4 EndoAnchors. As this was a in vitro study, these forces should also be determined in a clinical setting (i.e. animal studies).

EndoAnchors are also used for fixation and to resolve endoleaks in the thoracic aorta. It may more difficult to correctly position EndoAnchors in the thoracic aorta, due to the more complex anatomy and difficulties to have the C-arm perpendicular to the applier. It is interesting to investigate if penetration depths and angles are comparable with EVAR.

Preoperative imaging may be used for automatic detection of the correct C-arm angle per EndoAnchor. The EndoAnchor should then be positioned in the plane of the optimal C-arm angle for every EndoAnchor. Moreover, overlay techniques may be used to visualize eventual thrombus and calcium plaques during EndoAnchor positioning and may prevent unsuccessful positioning. In some patients and some configuration larger EndoAnchors may be used to overcome gaps. However, this should need careful consideration due to potential damage to surrounding structures like the caval vein or bowels.

Part II - Complications after EVAS

*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)*

In a large part of the aneurysm's intraluminal thrombus is present. If intraluminal thrombus volume decreases after EVAS, due to fluid displacement by compressing the thrombus, this may lead to an unstable endobag configuration, and lead to lateral displacement and/or endoleaks. In this study, 21 thrombi were harvested during open aneurysm repair and inserted into a compression set-up. The compression set-up applied uniform compression on the ILT of 200 mmHg (comparable to EVAS) for 5 minutes. A median of 5.7 mL (interquartile range of 8.4 mL) liquid was displaced. Histologic examination showed reduction of the medial layer of the thrombi, which was the result of compression of the fluid-containing canaliculi. The fluid displacement may have effect on the endobags and stentframe stability.
What influence have different endograft configurations on aortic pulse wave velocity and structural stiffness in an in-vitro aortic model? (Chapter seven)

Three different abdominal aortic endoprostheses (AFX, Endurant II, and Nellix) were implanted in identical silicone aneurysm models. One model was left untreated (control), and another model contained an aortic tube graft (Gelweave). aPWV was significantly lower for the control compared to the AFX, Endurant, Nellix and tube graft models (13.00 ± 1.20, 13.40 ± 1.17, 18.18 ± 1.20, 16.19 ± 1.25 and 15.41 ± 0.87 m s\(^{-1}\), respectively (P < 0.05)). Structural stiffness of the AFX model was significant lower compared to the control model (4718N m\(^{-1}\) versus 5115N m\(^{-1}\) (P < 0.001), respectively), whereas all other models showed higher structural stiffness. Endograft placement resulted in a higher aPWV compared to a non-treated aortic flow model. All models showed increased structural stiffness over the flow trajectory compared to the control model, except for the AFX endoprosthesis.

How accurate can three-dimensional positions of the Nellix stent frame and changes in position be determined? (Chapter eight)

In Chapter eight a methodology is described and validated for the quantification and visualization of 3D displacement of the stent frames of the Nellix endosystem during follow-up. The stent frames of the EVAS device are not only prone to distal migration, they can also displace lateral in the aneurysm, and can also buckle into the aneurysm sac. So the definition of regular distal migration for EVAR is not sufficient for EVAS. The described methodology allows precise 3D determination of the EVAS system and can detect subtle displacement better than standard CTA. Three types of displacement were identified: displacement of the proximal and/or distal end of the stent frames, lateral displacement of one or both stent frames and stent frame buckling. Good inter observer agreement was found for maximum change in stent to stent distance (ICC: 0.750, p <0.05) with a median absolute difference of 0.5 mm [IQR 0.3–0.7 mm]. Perfect inter observer agreement was found for all other displacement parameters (ICC: 0.877–0.958, The median absolute difference ranged from 0.2 mm to 0.7 mm. Moreover, the observed displacement may forecast impaired sealing and anchoring of the Nellix endosystem.

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)

In Chapter nine the initial proximal position and seal of the Nellix endosystem was investigated with the use of CTA applied software. As the EVAS technique is
based on complete sealing of the aneurysm and aortic neck, the non-apposition surface in the infrarenal neck has been calculated. This is the surface between the renal arteries and the endobags that can be used for sealing. Half of the potential seal in the aortic neck was missed due to low positioning of the endograft (4 to 5 mm below the renal arteries). This may be due to the lack of radiopaque markers on the endobags and therefore the stentframes are difficult to position accurately. The low positioning may also be the cause of the higher than expected complication rate after EVAS.

What preoperative anatomical aortic characteristics are predictive for seal failures after EVAS? (Chapter ten)

In order to find risk factors for the occurrence of complications, preoperative anatomical characteristics were identified that predict seal failure after EVAS for 261 patients treated with EVAS in three high volume centres in the Netherlands. Regression analyses showed large neck diameter, short aortic neck length and the ratio between the maximum aneurysm diameter and aneurysm lumen diameter as preoperative anatomical predictors for the occurrence of migration (≥5mm), endoleak (any) and aneurysm growth (>5mm). The optimal cut-off values were 21.3 mm for neck diameter, 18.5 mm for neck length, and 1.35 for the diameter ratio. Moreover, the instructions for use were adjusted in 2016 to reduce the number of complications. However, still 28% of the patients inside IFU 2016 suffered from migration, endoleaks and/or aneurysm growth.

General Discussion

Part II shows the difficulties of treating patients with a rigid endograft, while the environment in which it is inserted is dynamic. Intraluminal thrombi cannot be addressed as a rigid structure and may deform due to pressure, or even by the inflammatory process of the thrombi. The Nellix endobags may therefore displace into the thrombi, while it actually needs support from the surrounding tissue.

In addition to deforming thrombi, the sudden decrease in flow diameter after EVAS (from normal aortic neck diameter to 2x10mm diameter), may lead to extra forces applied on this configuration. Moreover, the two stentframes are not attached to each other or to the aortic wall. All these factors may lead to an unstable EVAS configuration in the abdominal aorta.

In the regression analyses, migration was specified as distal migration, while lateral displacement and buckling were not assessed. More patients might have stentframe displacement while they were not yet observed as distal migration ≥5mm.
Interestingly, during the first two years the EVAS configuration seems stable, and show good early outcomes. After two year almost 30% of the patients suffer complications. Perhaps this is due to the ongoing process of aortic wall degeneration. As the disease progresses, the EVAS configuration may not be stable with all the dynamic forces applied to Nellix configuration. Moreover, previous studies showed that when migration occurs it is unlikely to stop due to the lack of suprarenal fixation into the aortic wall.

In conclusion, EVAS should only be used inside the IFU. Moreover, not only the proximal seal of the EVAS configuration is important, the stability of the whole configuration needs careful consideration during follow-up and should be determined in patients who have had an EVAS procedures in the past. Furthermore, long-term results are needed before applying this technique on a large scale. For now, caution is needed when treating patients with EVAS, or better, it should be stopped at least temporarily with the current generation device.

Future perspective
More knowledge is needed of the effect of the dynamic environment in the abdominal aorta on the current generation Nellix endosystem configuration. As ILT cannot be addressed as a rigid structure, more research is needed on the variety of ILTs. Moreover, it should be analysed if structural information of ILTs can be quantified on imaging modalities pre-EVAS. If the structure can be correlated with for example the amount of fluid displacement during pressurization of the endobags, a more substantiated choice can be made if a patient can be treated with EVAS or not.

Interestingly, the EVAS configuration showed a lower aPWV than one would expect, due to stiffness of the endobags. As this was an in vitro study, this research should be extended to investigate differences in aPWV of different configurations in animals.

As migration is the most common complication, a fixation method into the aortic wall needs to be considered. Only sac-anchoring may not be sufficient enough due to the dynamic environment. Most EVAR devices contain forms of suprarenal fixation into the aortic wall. This should also be incorporated in the EVAS design. Besides, stronger stentframes may aid to the migration resistance as kinking may be reduced, however this may cause larger aPWV. For more secure positioning, filling of the endobags should be visualized to determine their position relative to the orifices of the renal arteries. These features should be incorporated in a new
EVAS designs and investigation is needed if this aids to the positioning and sustainability of the EVAS configuration.
Software to determine the stentframe displacement and non-apposition may aid in decision making during EVAS follow-up. This should be further analysed in larger cohorts.

**Final conclusions**
Subtle changes in EVAR and TEVAR positioning can be detected with the studied dedicated CT-analysis software. The early detection of endograft changes may lead to less invasive and expensive reinterventions before severe complications occur. Moreover, it may add to a more patient-specific follow-up scheme. Almost 30% of the EndoAnchor implants for treatment of acute or late endoleaks are maldeployed. In the majority of these cases this is due to the use of EndoAnchors beyond the recommended use. For that reason careful preoperative planning and optimization of the intra-operative deployment technique need to be performed. If however, the EndoAnchors are positioned correctly durability is good.
For EVAS, large neck diameter, short aortic neck length and the ratio between the maximum aneurysm diameter and aneurysm lumen diameter were found to be preoperative anatomical predictors for the occurrence of migration (≥5mm), endoleak (any) and aneurysm growth (>5mm). Despite adjusting of the IFU, in still 30% of the patients complications occur at mid-term follow-up. These complication may be a result of unstable configuration of the current generation of the Nellix endosystem in the abdominal aorta. Long-term data is needed to determine the durability and future of the current Nellix endosystem. Until then, the use of EVAS should temporarily be stopped.
References


