Roentgen stereophotogrammetric analysis to study dynamics and migration of stent grafts

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CHAPTER

11

Summary, future aspects and conclusions

Part 1: Surveillance of stent-graft migration after EVAR

Chapter 1 describes the relevance of aortic aneurysmal disease, its treatment and the long term risks of endovascular aneurysm repair (EVAR). One of the major risks of EVAR is stent-graft migration. Migration can lead to repressurization of the aneurysm sac and consequent rupture of the aneurysm. Migration and other forms of device failure are caused by the repetitive strain on the stent-graft caused by the cardiac and respiratory cycle. These device failures can result in aneurysm related death of the patient despite previous EVAR.

Surveillance of EVAR patients is performed regularly to enable early detection of adverse events such as migration and stent fracture. CT Angiography is the current clinical gold standard to determine stent-graft position. However, CT has several disadvantages of which intravascular contrast requirement, cost and logistical burden are the most relevant. Furthermore, CT requires a significant radiation dose.

As an alternative to CT, plain abdominal radiography (AXR) is currently used to determine stent-graft position. Both CT and AXR are methods in which the observer determines the position of the stent-graft relative to a point of reference. Contrast enhanced CT enables the use of side branches as a point of reference. AXR images are analyzed with the vertebral end plate as point of reference. The points of reference are assigned by an observer; the measurements are consequently sensitive to human variance. Both methods have specific disadvantages, which are further discussed in Chapter 1. Furthermore, the accuracy of CT and AXR to detect stent-graft migration has not been described previously.

As a possible alternative to CT and AXR, Roentgen Stereophotogrammetric Analysis (RSA) could be considered as a method to detect stent-graft migration and detect possible stent fracture. RSA is a highly accurate technique to determine marker positions inside the body using calibrated, stereo plain radiography. RSA has a long and successful history in orthopedic surgery in surveillance of joint prosthesis micro-motion. The technical aspects of RSA are discussed in Chapter 2. In short, RSA is based on comparing the two (2-dimensional) images of a stereo roentgen projection to calculate a three dimensional image of the positions of markers in space, i.e. inside the human body. For use in endovascular surgery, RSA requires markers on the graft and in the aortic wall to determine the position of the stent-graft relative to a point of reference. These markers need to be positioned in the patient during surgery. These and several other technical and validation issues concerning RSA as a tool for surveillance after

EVAR were addressed in the first part of this thesis. Furthermore, we assessed the accuracy of CT and plain radiography to measure stent-graft migration.

Validation of RSA to determine stent-graft migration

Static model

In Chapter 3 RSA was validated as a technique to measure stent-graft migration in a static model. In this study, RSA was compared to CT with 3D image reconstruction. The model was constructed from a Plexiglas tube and a Gianturco stent cast in Plexiglas. Markers were added to the stent and the tube for RSA analysis. PTFE inlays in the tube were used to simulate the renal arteries for CT analysis. The stent was "migrated" in axial direction with a micromanipulator, which was used as the standard of reference for the experiment. The initial position and the position after stent-graft migration were imaged with RSA and CT. CT images were acquired with the highest available resolution and 3D image reconstruction was performed using advanced post-processing software with central lumen line reconstruction. This set-up is also used in the current clinical stent-graft surveillance protocol at the Leiden University Medical Center. To correct for inter-observer variability, CT measurements were performed by 3 different, experienced observers.

The results showed that RSA is a feasible method to detect stent-graft migration in a static model, and that it was highly accurate, with a mean error of 0.002mm, SD=0.044mm, maximum error=0.10mm. This was significantly more accurate than CT which had a mean error of 0.14mm, SD=0.29mm, maximum error=1.0mm ($p < 0.0001$). No significant inter-observer variation was found between the CT observers ($p=0.17$).

One of the questions that remained was what the influence of pulsatile motion would be on the accuracy of migration measurement. Theoretically, pulsatile motion of markers can produce errors in RSA measurement. These errors can occur due to marker motion during imaging.

RSA in a pulsatile environment

The question of the influence of pulsatile marker motion on RSA is discussed in Chapter 4. A model was constructed with a fresh thoracic pig aorta fixed to a human cadaver spine. A side branch was attached to resemble the renal artery for CT analysis. The model was connected to an artificial circulation with physiological flow and pressure profiles. A stent was placed inside the aorta. Markers were added to the stent and aortic wall for RSA analysis, including a potential endovascular marker for clinical use. RSA of the stent position without pulsatile

flow was used as the standard of reference for stent-graft migration. RSA and CT imaging were performed of every position of the stent.

Using standard tantalum markers, RSA had a mean error of -0.5mm, SD=0.16mm, maximum error= 0.7mm. Using the experimental endovascular marker, RSA had with a mean error of -0.4mm, SD=0.25mm, maximum error= 1.1mm. The marginally lower precision and higher maximum error are probably due to the fact that the endovascular marker is not spherical like the tantalum marker used in standard orthopedic practice. However, both RSA measurements with the different aortic reference markers compared favorably to CT with 3D image reconstruction which had a mean error of -1.1mm, SD=1.17mm, maximum error= 2.8mm.

These results demonstrated that RSA is a feasible and accurate method to detect stent-graft migration in this model despite pulsatile stent-graft motion. Migration measurements using RSA were more accurate than CT. Furthermore, the experimental endovascular marker proved promising with good measurement results.

Further studies were required to test the feasibility of RSA as well as the performance of the endovascular marker in-vivo, before clinical introduction of the technique can be considered. For these reasons, an animal study was undertaken.

RSA in-vivo

In Chapter 5, we describe an experimental study with two large, 100 Kg pigs. A model of a stent-graft was introduced into the thoracic aorta via thoracolaparotomy. Tantalum markers were attached to the adventitia of the aorta as points of reference for RSA. The tantalum marker closest to the stent-graft model was also used as a point of reference for the CT measurements. For RSA analysis, additional Nitinol endovascular clips were inserted in the aortic wall via endovascular technique as aortic reference markers. Stent-graft migrations were measured with CT and RSA.

The standard deviation of the measurements by RSA using tantalum markers was 0.36mm**.** The standard deviation of the measurements by CT with 3D reconstruction was 0.47mm. Radiopacity of the clips was insufficient to allow detection with the RSA software.

The study showed that RSA stent-graft migration measurement in vivo was feasible and very precise despite the physiological motion due to the cardiac and respiratory cycle and the large amount of soft tissue surrounding the markers. Precision of RSA was superior to CT with 3D image reconstruction if a well defined aortic reference marker was applied for CT analysis. It is likely that the precision of migration measurement with CT will decrease if a less well defined point of reference is used, for instance the renal or mesenteric artery, as is current practice. This

assumption seems to be supported by the fact that the variation of CT in the pulsatile model was already larger than the variation of measurement using a well defined reference marker. Therefore, we concluded that placement of an aortic reference marker may facilitate accurate stent-graft migration detection without the need for contrast enhancement. Although this would eliminate a significant disadvantage of CT surveillance, several other disadvantages such as the burden on logistics and cost, and to a lesser extent radiation burden, would remain.

As an aortic reference marker, the nitinol clip needs to be modified to increase radiopacity to enable RSA analysis. Enhancement of the endovascular marker with a gold or platinum ring could fulfill this purpose. Design testing needs to be performed before the marker can be introduced into practice.

Regarding aortic reference markers required for RSA

Apart from the issue of radiopacity, there are several other issues that need to be addressed regarding aortic reference markers. One of these issues is the question which is the appropriate position of the marker relative to the graft.

In the study described in Chapter 4, we found that an increasing distance between the aortic and stent-graft markers due to migration caused a slight increase in the error of measurement in our study, which corroborates with findings as reported in the orthopedic RSA literature. This implies that for the most accurate RSA measurement of stent-graft migration, the aortic markers need to be positioned as close to the stent-graft as possible.

Safety of the nitinol endovascular clip was also studied in the animal study described in Chapter 5. In both pigs the endovascular markers were replaced several times for evaluation purposes without difficulty. At post mortem investigation, the clips had (purposefully) penetrated the aortic wall. No adverse effects were found. It has to be remarked that this is, by nature of the experiment, a limited number of animals with a healthy aorta. Further studies are needed to evaluate the safety of a modified endovascular clip.

Another important question that remained was how many aortic reference markers are needed for accurate stent-graft migration detection with RSA. In orthopedic RSA multiple reference markers are used. As a rule, more markers will result in more accurate measurement with RSA. In endovascular surgery, a reference marker needs to be attached to the aortic wall. This implies that an extra procedure is needed during EVAR. Reducing the number of reference markers to only one would minimize additional risk.

One single reference marker will enable quantification of migration in every direction, except rotational displacement. In contrast to axial, cranio-caudal migration or angulation of the graft

relative to the aortic neck, rotation of an infrarenal stent-graft around its long axis is not a crucial problem since this type of displacement does not affect the sealing zone and should therefore not lead to complications. Furthermore, axial stent-graft rotation as a single phenomenon is not very likely to occur. The impact of reducing the amount of reference markers on the accuracy and precision of RSA migration measurement were unknown.

Accuracy of RSA using one aortic reference marker

In Chapter 6, we described the renewed analysis of the images of the model with pulsatile circulation and the animal experiments. Instead of using a cluster of reference markers for RSA analysis, we now only used one single aortic reference marker.

In the in-vitro model, the measurement error of RSA using multiple markers was -0.5 ± 0.16mm. Using only one single reference marker, the error of RSA was -0.73 ± 0.12mm. In-vivo, RSA using one reference marker had a pooled mean error of 0.17 ± 0.65mm as compared to standard RSA.

Our data showed a very accurate detection of stent-graft migration with RSA using a single reference marker. Therefore, it appears that one single aortic reference marker is sufficient for stent-graft migration surveillance after EVAR.

Clinical applicability of AXR for migration surveillance

Currently, plain abdominal radiography (AXR) is advocated by some to determine stent-graft position and detect migration. AXR has several advantages over CT. Because of these advantages, AXR is an attractive and readily available alternative to CT surveillance of stent-graft migration. The accuracy of AXR to measure position change has been reported to be 2mm in an experiment by Hodgson et al. with a static model using a standard protocol for image acquisition and analysis. Inter-observer variability and clinical precision have not been studied.

In AXR, the spine is used as the point of reference to detect stentgraft migration in sequential examinations. Cranio-caudal stent-graft motion during the cardiac cycle has been described up to 3 mm in a small number of patients, making a wider range of motion likely. Further more, in the clinical pilot study described in Chapter 9, we found cranio-caudal stent-graft motion of up to 5,8mm. Because of this motion of the graft, the use of bony points of reference seems to be hazardous in terms of measurement accuracy. Furthermore, with increased experience and new generation stent-grafts, the minimum acceptable aneurysm neck length continues to decrease, approaching 5mm. This requires increased accuracy of our tools for migration surveillance.

In Chapter 7, we report on a study that compared migration measurement using AXR to that of RSA. We performed in-vitro and in-vivo studies. Stent-graft migration was simulated in a static model of an aorta with stent-graft. Migration was measured by five different observers in AXR images with image acquisition and analysis according to standardized protocols. The results were compared to RSA as the standard of reference. This way, accuracy and precision could be determined in-vitro. Next, to determine the precision of AXR in-vivo, the observers measured stent-graft migration in two consecutive AXR images of four patients after EVAR.

The mean pooled error of AXR as compared to RSA was 3.0 ± 2.4 mm (range 0.01-13.1 mm, n=114). Of all AXR measurements, 16% had an error larger than 5mm. In-vivo, the pooled mean variation was 3.0 ± 4.5mm (n=76). The maximum difference between measurements in one patient was 33.0 mm. There was no significant inter-observer variability in the in-vitro and in-vivo groups.

The fact that a large portion of the measurements had an error or variation that was larger than 5mm is worrisome, especially in view of the ever diminishing accepted aneurysm neck length for endografting. In-vivo, the standard deviation of 4.5mm would yield a 95% confidence interval of 9mm in measuring stent-graft migration. It might be safe to use AXR in patients with an aneurysm neck length of more than 3cm. However, this is only a very small portion of the patient population.

Apart from the issue of accuracy and precision of measurement, there is the problem with the bony point of reference used in AXR. Changes in the vertebral column, e.g. due to osteoporosis or fractures, and possibly changes in neck angulation due to AAA shrinkage can influence (the relation to) this point of reference.

These results showed that the accuracy and precision of plain radiography for detection of stent-graft migration after EVAR is insufficient for clinical use, especially when early and accurate identification of minimal migration is required like in patients with short aneurysm necks.

Future aspects of RSA in endovascular surgery

RSA has several advantages over CT for its use in stent-graft migration surveillance: no nephrotoxic contrast requirement, ease of use for physicians and patients, low cost, low burden on hospital logistics, and low radiation dose. Furthermore, RSA seems to be more accurate than CT in measurement of stent-graft migration. This is an aspect that will be increasingly important in the near future since there is a strong tendency towards shorter accepted aneurysm neck length in EVAR and therefore increasing risk of complications due to slight stent-graft migrations.

There are still a lot of unanswered questions in the field of stent-graft migration that might be answered if accurate migration detection is routinely introduced. With more rigorous surveillance, more migration seems to be found. One of the questions concerns the pattern of migration. Does migration continue to occur once it takes place? If this is the case, early detection is even more crucial and could reveal a high risk subgroup of patients. Alternatively, migration may occur at first and stabilize thereafter. Is there a graft specific pattern of migration?

Part 2: Stent-graft dynamics

The second topic of this thesis is development of a method to study 3-Dimensional stent-graft motion after EVAR. The cardiac and respiratory cycle, in conjunction with tissue properties, result in repetitive stent-graft dynamics. Knowledge of cyclic stent-graft motion after EVAR is limited due to the limitations of current imaging modalities. This limited knowledge results in unintended stent-graft construction errors and, unavoidable, insufficient pre-clinical testing. These forms of device failure can lead to death of the patient. Detailed knowledge of stent-graft motion after EVAR is mandatory to further improve stent-graft durability.

Currently, dynamic studies of stent-graft motion can be performed with cinematographic (or cine-) CT and MRI. These methods have specific disadvantages to the patient in terms of intravascular contrast requirement, radiation dose (for CT) and limitation in analysis of stainless steel stent-grafts (MRI). Furthermore, there are technical difficulties in ECG gated analysis. The images that are produced represent a temporal reconstruction of an average stent-graft motion over several cardiac cycles.

The main disadvantage of cine-CT and cine MRI is that reconstruction of images is limited to one single plane. Therefore, quantification of out-of-plane motion is impossible with the current techniques. This thesis describes the development, validation and clinical introduction of Fluoroscopic Roentgen Stereophotogrammetric Analysis, FRSA. FRSA is a combination of existing RSA software and technique, and new digital imaging hardware.

In Chapter 2 we describe the technical aspects of FRSA. Contrary to RSA to detect long term stent-graft migration, FRSA does not require additional aortic reference markers to enable analysis of stent-graft dynamics. Stereo images are acquired with a Siemens digital bi-plane imaging system used for percutaneous cardiac intervention. The images are analyzed with a re-programmed version of Model-based RSA software by Medis Specials BV. The re-programming mainly consisted of enabling the calibration of the set-up without a calibration box being present in the image with the stent-graft, as is the case in standard RSA. The calculation of marker positions was unchanged.

In contrast to cine-CT and cine-MRI, there are no limitations in terms of direction of motion, type of graft, length of time of image acquisition or ECG changes.

Validation of FRSA

In Chapter 8 we describe a validation study of FRSA. The accuracy and precision of the set-up were validated with the use of a static and a pulsatile model of an aorta with stent-graft. Afterwards, three-dimensional stent marker motion was analyzed with a frame rate of 30 images per second, including three-dimensional marker position (change), diameter change and motion of the center of circle (center of the top end of the stent).

The results showed that the flat panel detectors did not distort the images, contrary to image intensifier images. The mean error of FRSA measurement of displacement was 0.003 mm (SD: 0.019 mm; maximum error: 0.058 mm). A very high precision of position measurement was found in the pulsatile model (SD: 0.009-0.015 mm). During pulsatile motion, the position (changes) of the markers could be assessed in the x, y, and z directions, as well as the stent diameter change and center of circle position change.

The radiation dose of FRSA was determined in a separate experiment by our clinical physicists. The radiation dose is approximately 0.1 mSv for a 3 second study, which corresponds to 4 cardiac cycles at a heart rate of 80 bpm. This compares very favorably to the 17 mSv dose of triple phase CT scan used for EVAR follow up.

Specifically distinguishable markers on commercially available stent-grafts, like welding points and positioning markers, can be used for stent-graft dynamics analysis with FRSA. Because there is no need for additional markers, FRSA could be introduced in a clinical pilot study.

FRSA in clinical stent-graft dynamics analysis

In Chapter 9 we describe the first results of a pilot study in two patients. Stent-graft motion was studied in a patient after thoracic EVAR and in one after abdominal EVAR. The motion of the grafts was calculated by quantification of the motion of the standard (commercially applied) markers used to position the stent-graft during EVAR, as well as welding points of the hooks to the top stent of the device. Stent-graft motion was measured during the cardiac cycle with respiratory arrest. In addition, stent-graft motion due to respiratory action was measured in the patient after abdominal EVAR.

Three dimensional stent-graft dynamics could be quantified at 30 (stereo) frames per second in both patients without difficulty. The thoracic stent-graft showed a motion pattern of stent dilatation and a center of mass motion of the top stent in caudal-ventral-right hand side

direction relative to the patient, followed by an over-compensation in opposite lateral and cranial direction and a gradual return to the starting position with reduction of diameter of the graft. In other words, at the start of the systole, the graft moves toward the heart. If this motion is assessed in a single plain as is the case with cine-CT or cine-MRI, the initial segment of the aorta as viewed in the first image would be out of the reconstruction plane almost all the time. Only at the end of the diastole will it return to the initial position in the image reconstruction plane. Therefore, FRSA is much more powerful than current cinematographic imaging using CT and MRI as it enables quantification of the true changes of three-dimensional stent-graft position and configuration.

We found a significant motion of the abdominal stent-graft due to respiratory action of almost 6mm in caudal direction. When using plain abdominal radiography to detect stent-graft migration as discussed in part 1 of this thesis, these dynamics due to respiratory action could result in under- or over-reporting of migration in individual cases due to the change of position of the stent-graft as compared to the reference point, the vertebral column.

These studies clearly demonstrate that fluoroscopic Roentgen stereophotogrammetric analysis (FRSA) is a clinically feasible, non-invasive tool to quantify real time 3-D stent-graft dynamics after EVAR in detail. The results of this pilot are very promising in the fact that quantification of 3D motion including rotational dynamics is now possible for the first time.

Future aspects of FRSA in endovascular surgery

The images of this non-invasive technique were of very high quality in terms of spatial and temporal resolution and measurement accuracy. Currently, the only limits are that specific markers are required to detect their position in consecutive images and that the field of view is limited by the detector size. As an alternative to marker detection, automated pattern recognition of the stent-graft could be used to facilitate measurements without the need for markers. These aspects of FRSA are subject to further evaluation at our institution.

Further, detailed, knowledge of stent-graft motion during the cardiac cycle is required to better understand in-vivo behavior of stent-grafts after EVAR. New stent-grafts can be evaluated, as well as existing grafts. With this knowledge, virtual mechanical modeling becomes possible and assessment of the failure modus of the stent-graft, such as failure due to metal fatigue is facilitated. Based on clinically acquired, detailed knowledge of stent-graft motion, forces acting on the stent-graft during the cardiac cycle can be calculated more accurately. Pre-clinical bench testing can be verified for adequacy. Bench testing itself will be improved according to in-vivo measured clinical data. One could argue that assessment of the dynamics

of a new stent-graft should be mandatory in the period of first clinical introduction to possibly detect unexpected motion in an early phase to determine if adequate bench testing has been performed and predict possible failure by fatigue modeling according to clinical motion data. Devastating complications and withdrawal of a graft from the market due to mechanical defects that arise after widespread introduction could be prevented with better bench testing and early detection of unexpected graft motion.
The medical ethics committee of the LUMC approved an initial pilot study for further research into the specifics of motion of different grafts in the thoracic and abdominal aorta.

Addendum
Risk of radiation exposure due to imaging in EVAR

Medical imaging with ionizing radiation is performed during endovascular abdominal aortic aneurysm repair (EVAR), preoperative planning and postoperative surveillance. Cumulative patient dose is relatively high and causes concern about radiation induced malignancies. In Chapter 10, the patient dose and excessive relative risk of cancer mortality is calculated for typical patients aged 55 to 85, using the BEIR VII model for age-, gender- and site-specific solid cancer mortality. The results showed that the number of radiation induced deaths per 1000 EVAR patients was 12, 8, 4 and 1 for patients treated at ages 55, 65, 75 and 85 years, respectively. The number of AAA related deaths per 1000 EVAR patients was: 126, 91, 67 and 47, respectively. The average radiation induced reduction of life expectancy was 40, 21, 8 and 2 days for patients treated with EVAR at 55, 65, 75 and 85 years of age respectively. Corresponding AAA related reduction of life expectancy was respectively 739, 387, 197 and 82 days. Therefore, we conclude that the impact of the considerable dose of ionizing radiation on patients after EVAR is small, especially when compared to the reduction of life expectancy related to vascular disease.

Final Conclusions

- Roentgen stereophotogrammetric analysis is a feasible and accurate method to detect stent-graft migration in-vivo.
- One single aortic reference marker is sufficient for accurate stent-graft migration detection with RSA and should be placed as close to the stent-graft as possible to ensure maximum measurement accuracy.

- Plain abdominal radiography has insufficient accuracy and precision to detect stent-graft migration, this is especially dangerous in patients with a shorter aneurysm neck (shorter than 2-3cm).
- Application of a reference marker to the aortic wall will facilitate more accurate detection of stent-graft migration with CT, without requiring intravascular contrast enhancement.

- FRSA has proven to be a method with very high accuracy and temporal resolution to measure real time three-dimensional stent-graft dynamics in a pulsatile environment. Measurement of 3-D stent-graft motion has become feasible in patients after EVAR.

- Radiation exposure accumulates rapidly for patients undergoing EVAR. However, associated radiation risks are modest and much smaller compared to AAA related risks.