Chapter 1

General introduction and outline of the thesis
Aortic Prosthetic Graft Infection

Prosthetic vascular graft materials are still widely applied in aortic surgery being used to replace an aneurysmal part of the aorto-iliac tract or as a bypass in case of occlusive disease. Introduction of these foreign materials into the human body always carries a potential risk of infection and it has become clear that aortic prosthetic graft infections (AGI) pose a serious clinical problem.\textsuperscript{1-4} Charles Dubost in Paris performed the first successful resection of an abdominal aortic aneurysm with graft replacement on March 29, 1951. He used an extraperitoneal thoracoabdominal approach with resection of the 11\textsuperscript{th} rib. The applied graft was the thoracic aorta taken three weeks previously from a 20-year-old woman. The patient had a normal recovery except for mild jaundice attributed to blood transfusions after which he was discharged three weeks later.\textsuperscript{5-6} Since that time, remarkable advances in graft materials, operative techniques, and anesthesia management have marked progress in the surgical treatment of aortic abdominal aneurysm. After Dubost’s landmark procedure, reports of successful operations appeared in quick succession by Julian,\textsuperscript{7} Brock,\textsuperscript{8} DeBakey\textsuperscript{9} and Bahnson.\textsuperscript{10} In 1952, Voorhees, Jaretski, and Blakemore reported that a tube of Vinyon-N cloth as a plastic artificial substitute for an artery remained open in a dog’s aorta.\textsuperscript{11} This observation was soon confirmed by further research, and although Vinyon-N cloth did not prove to be optimal material, the principle was established. In 1955 Sterling Edwards reported the development of nylon prostheses and also devised a technique of crimping prosthetic grafts. Nylon did not hold, but Teflon\textsuperscript{®} and Dacron\textsuperscript{®} grafts followed in short order.\textsuperscript{12} Half century later, Parodi, Palmaz, and Barone reported the principle of endoluminal stent grafting in 1991, originally as an alternative to open aneurysm repair in high-risk surgical candidates. These developments were the result of a rather rigorous and extensive multi-year preclinical process that included in-depth analysis of physiological characteristics, testing in a flow model, and animal implantations (with 6-month follow-up and detailed studies of the explanted devices). However, in 1985 (in the former Soviet Union) endovascular stent-graft surgery was performed by Professor Nikolay Volodos for the first time in the world.\textsuperscript{13-14} At that time, the technique was termed “remote endoprosthetic repair”. The first patient (aged 66 years) presented with lower limb gangrene secondary to a stenosis of the iliac artery and occlusions of the
superficial femoral and popliteal arteries, with only one tibial vessel extending into the foot. The patient underwent insertion of a self-fixating synthetic endoprosthesis within the stenosed iliac segment (Figure 1) followed by a femoro-tibial bypass using ipsilateral long saphenous vein. The first aortic implantation with such an endoprosthesis was on March 24, 1987, for treatment of a post-traumatic thoracic aortic aneurysm.

Despite the increasing success obtained with endovascular devices, prosthetic grafts made of Dacron® or polytetrafluoroethylene (PTFE) are still being used on a routine basis for open repair of both aneurysmal and occlusive atherosclerotic disease. As said before, one of the possible complications that may occur is infection of the prosthetic material. Several measures can be taken to prevent the development of prosthetic graft infections, such as preoperative hair removal, the use of perioperative prophylactic antibiotics, avoidance of groin incisions, strict adherence to sterility measures, and the use of synthetic prosthetic grafts that have a certain coating (for instance rifampicin-
bonded or silver-coated). Nevertheless, prosthetic grafts remain vulnerable to infection. The incidence of AGI has been reported to range from 0.6% to 3%, with a mortality rate varying from 25% to 88% and an amputation rate ranging from 5% to 25%.

Clinical manifestations of AGI may vary according to the length of time that has elapsed since the procedure. Most infections appear to be caused by bacteria from the patient's skin entering the wound at the time of surgery. The majority (>80%) of prosthetic graft infections are diagnosed more than three months after graft implantation. Early graft infections (<3 months) are generally caused by S. aureus or gram-negative bacteria and frequently originate from failure of primary wound healing. The patient may be systemically toxic with fever and leukocytosis. Bloodstream infection, wound infection, abdominal discomfort and graft dysfunction from recent thrombosis or anastomotic bleeding may also occur. The presentation of late-onset infections (>3 months) tends to be more subtle with non-specific signs and symptoms. Fever is usually absent. These patients are more likely to present with signs of complications of aortic graft infection, such as false aneurysm, gastrointestinal bleeding resulting from erosion of the graft into the gastrointestinal tract, hydronephrosis or osteomyelitis.

An important dilemma in clinically suspected AGI is confirmation of definite proof of the graft infection. The commonly used first methods to evaluate and diagnose an AGI are evaluation of elevated infection parameters in peripheral blood samples (erythrocyte sedimentation rate, white blood cell count and C-reactive protein (CRP)), duplex ultrasound scanning and computed tomography scanning (CTA). Ultrasound characteristics of AGI are the presence of pseudoaneurysm, sustained gas (>6 weeks), and purely anechoic fluid collections (>3 months). In addition, ultrasound can distinguish between hematoma and abscess formation. These characteristics make ultrasound a good primary imaging screening modality, in particular for superficial vascular grafts. At the aortic level, the predictive value is limited due to overlying bowel gas and, in some cases, large body habitus. The accuracy of duplex ultrasound for aortic graft infection is therefore questionable, and additional investigations such as CTA, are always indicated to obtain more detailed information on the vascular graft status. To date CTA is considered the reference in diagnosing AGI because of its high spatial resolution providing a detailed view of the vascular structures and perivascular spaces. Several characteristic features of AGI can be visualized with CT. For example, perigraft
air, fluid, and soft-tissue attenuation, ectopic gas, pseudoaneurysm or focal bowel thickening, and discontinuation of the aneurysmal wall can all be used to increase the likelihood of AGI diagnosis. CTA sensitivity and specificity is claimed to be 95% but this high percentage can only be reached in clinically high suspicion for AGI. CTA is much less reliable in case of a low-grade infection, with a sensitivity and specificity of 55% and 100%, respectively.\(^{19-20}\) In particular the false positive results may result in unnecessary surgery or lengthy antibiotic use while the false-negative results may have life or limb threatening consequences. Therefore, novel non-invasive imaging may play an important role in increasing the likelihood of the diagnosis of AGI. \(^{18}\)F-fluorodeoxyglucose positron emission tomography (\(^{18}\)F-FDG PET) imaging has been proposed to visualize infection in patients suspected of AGI. Since 1996, several studies have evaluated the usefulness of \(^{18}\)F-FDG PET in the detection of infectious foci and, including the usefulness in the analysis of suspected AGI. The sensitivity and specificity of \(^{18}\)F-FDG PET varies greatly between 60% and 90% in current literature.\(^{21-25}\) The aim of this thesis is to increase diagnostic accuracy in aortic prosthetic graft infection.

### Outline of the thesis

In **Chapter 2**, a retrospective analysis was performed to evaluate clinical characteristics, diagnostic approaches, treatment strategies and outcomes of AGI and it's treatment thus far at our tertiary referral center. Imaging tools used were examined, also to define the denominator, and predictive factors of mortality were analyzed in this chapter. Several tools had been used during the years of this retrospective cohort, including duplex ultrasound examination and CT-scanning as most commonly used imaging modalities. Clearly, both are able to show some signs of infection but none of them is the holy grail. Although CTA is considered the gold standard, CTA is not able to distinguish abscessed perigraft from sterile perigraft fluid, and it had a high false-positive rate, especially within the first six weeks after the operation. To overcome this problem, we started in **Chapter 3** to fuse \(^{18}\)F-FDG PET images with those from CT-scanning. \(^{18}\)F-FDG PET/CT had been used before in other studies and it seemed a promising diagnostic tool in AGI for the near future. \(^{18}\)F-FDG PET can either be evaluated semi-quantitatively using the maximal standardized uptake value (SUVmax), the tissue-to-background ratio (TBR), and visually using the Visual Grading Scale (VGS). In **Chapter 4** a combination of these
parameters was used in order to increase accuracy of AGI diagnosis. However, the interpretation of $^{18}\text{F}$-FDG PET scan images is mostly based on the nuclear medicine physicians. This is why we decided to search for a new quantitative measure that would decrease inter- and intra-observer variability. FDG distribution pattern analysis could be helpful to achieve this. In the next study, Chapter 5, with patients suspected of AGI, we combined a set of measures, i.e. $^{18}\text{F}$-FDG PET scan derived SUVmax, TBR, FDG distribution pattern and VGS, and assessed it's combined and individual value. In Chapter 6 we focused on heterogeneity pattern of FDG accumulation. As heterogeneous uptake is associated with infection, the distribution of $^{18}\text{F}$-FDG vascular prosthetic activities may help identify AGI with a higher diagnostic precision. A new tool for quantifying this distribution is textural analysis, which may provide valuable information regarding biological heterogeneity in AGI. The concept of textural analysis is generally based on the spatial arrangement of voxels in a predefined volume of interest (VOI) and it has never been tested for AGI. Within the field of clinical oncology, textural analysis already has yielded initial promising results in predicting response by quantifying intra-tumoral heterogeneity.

Obviously, increasing diagnostic accuracy of imaging tools to detect AGI is important, but the avoidance of AGI development even more so. A major cause of AGI is due to surgical site infection, in particular groin infection. As such, specific measures to avoid groin incisions can be taken to prevent the development of AGI. In Chapter 7 a trial was set up to compare percutaneous femoral access against open surgical femoral access (PiERO trial). The PiERO trial is a multicenter randomized controlled clinical trial designed to show the consequences of using percutaneous access in EVAR surgery and focuses on the occurrence of surgical site infections. The result of this trial will be useful to prevent AGI in the future. Another approach to prevent prosthetic graft infection would be to build a barrier within the prosthetic material for microorganisms to settle down and cause infection. Polyethylene oxide (PEO) brush coatings (Pluronic F-127) are introduced as a tool to prevent primary infection related to prosthetic materials. In Chapter 8 we investigated in vitro the feasibility of Pluronic F-127 as a polymer brush coating against adhesion of three bacterial strains, isolated from infected grafts, to commonly used Dacron® and PTFE grafts. Once an infection occurs, several options are available, as also pointed out in our retrospective analysis in the first chapter. It is generally felt that invasive therapy including removal of the infected graft and reconstruction either in situ or extra-anatomical gives the best results. However, due to the
patients’ condition or a hostile abdomen this is not always possible. In Chapter 9 we report a case of AGI after endovascular aneurysm repair due to *Listeria monocytogenes* infection and focus on its treatment in which the endograft was preserved by appropriate antibiotic treatment combined with CT-guided drainage. The general discussion and future perspectives are given in Chapter 10.
References


