Chapter 10

Summary, general discussion and future perspectives
Summary and general discussion

Aortic graft infection (AGI) occurs infrequently and its clinical appearance may vary extensively. The natural course of AGI may be devastating and potentially life-threatening.\textsuperscript{1-3} As a consequence, considerable effort is undertaken to decrease the rate of contamination of prosthetic grafts with microorganisms during implantation. Although application of prophylactic antibiotics, avoidance of groin incisions, and adherence to sterility measures have reduced the incidence of prosthetic graft related infection over the last four decades, still a significant number of patients suffer from such infections. The most common bacteria cultured from infected grafts are coagulase-negative staphylococci and \textit{Staphylococcus aureus}, which are believed to be the cause of infection in 50\% of all cases.\textsuperscript{4,5} In our retrospective study of clinical cases of prosthetic infection during a 10-year period of time, coagulase-negative \textit{staphylococcus} was isolated in 27\% of cases and \textit{Staphylococcus aureus} in 18\%. Other less frequent cultured bacteria were \textit{Escherichia coli} and \textit{Pseudomonas} species. The gold standard for identifying a prosthetic infection is a positive culture of prosthetic or peri-prosthetic material, which can be obtained by percutaneous puncture or during surgery.\textsuperscript{6} For AGI, however, to achieve the gold standard, may prove difficult and is one of the reasons why clinical trials are hard to conduct and compare. Furthermore, even if material for culturing can be obtained, a negative culture result does not rule out AGI.

Fundamental tenets of AGI management are removal of the infected device, revascularization (either by an anatomic route, or an uninfected extra-anatomic route), and additional antimicrobial therapy. Conservative treatment for a group of highly compromised patients, such as those who cannot tolerate extensive surgical reconstruction or who have grafts in locations comprehensive to be excised, is associated with high mortality.\textsuperscript{5} Therefore the treatment of infected prosthetic grafts must be tailor-made.

Before treating the patient properly the diagnoses of AGI should be established correctly. As this is not easy; symptoms are nonspecific, even though most patients are symptomatic. Besides, the typical patient with AGI is fragile and has various comorbidities. A reliable imaging tool is essential in the work up for the diagnosis of AGI. A false-negative test result may refrain the patient from proper antibiotic or surgical treatment and may negatively affect the prognosis. A false-positive test may result in unneeded extensive surgical procedures.
After most of the vascular reconstructive procedures for either aneurysmal or occlusive disease, duplex scanning examination is used during follow up. If infection is suspected on duplex images, subsequent CT angiography (CTA) is usually performed. CTA is known to have a high spatial resolution providing a detailed view of perigraft fluid, perigraft soft-tissue attenuation, ectopic gas, pseudoaneurysm, or focal bowel wall thickening. Chapter 2 describes that CTA alone appeared not always sufficient to identify the exact localization of the source of infection and its’ extension. High sensitivity and specificity are in general found in those groups with high-grade infections. In case of a low-grade infection, in particular sensitivity decreased to 55%. Besides, CTA could not distinguish abscessed perigraft from sterile perigraft fluid, and it appeared to have a high false-positive rate, mainly within the first 6 weeks after the primary operation. In the search for more reliable and accurate diagnostic tools, $^{18}$F-Fluorodeoxyglucose Positron Emission Tomography ($^{18}$F-FDG PET) had already proven to be of additional value in the detection of infectious foci, not related to vascular surgery. In Chapter 3 we reviewed previous literature regarding the accuracy of $^{18}$F-FDG PET imaging in the diagnostic workup of AGI. The results were somewhat disappointing as the methodology in these previous papers was only limited available. $^{18}$F-FDG PET scans can be assessed using a descriptive parameter (visual grading scale) or with semi-quantitative parameters (maximal standardized uptake value (SUVmax) and tissue-to-background ratio (TBR)). However, there are no strict guidelines or recommendations available for the interpretation of these PET images in suspected AGI. In a retrospective study (Chapter 4) we assessed the value of $^{18}$F-FDG PET scanning in the diagnostic work-up in patients suspected of vascular prosthetic graft infection. Compared with CTA $^{18}$F-FDG PET revealed a higher sensitivity and specificity of 93% and 70%, respectively. In this study cohort, there was no additional increase in sensitivity or specificity when $^{18}$F-FDG PET images were fused with CTA images, but the study may be liable to a statistical type 2 error, and also it was not set up as a comparative study. AGI remains an uncommon event, and patients with AGI in general exist of a heterogeneous population with different causal microorganisms, different prosthetic materials used and different localizations of infection. After Chapter 3 and 4 we learned that $^{18}$F-FDG PET/CT has a high sensitivity and specificity compared to CTA alone, but no clear recommendations could be stated and the quantitative measures also depended strongly on the evaluating physician. A clear cut-off value of SUVmax, TBR or a combination of these two, to
distinguish infected graft from non-infected graft would be very helpful. A semi-quantitative method has been suggested for the evaluation of thoracic prosthetic graft infections in which a SUVmax >8 in the perigraft area was considered the cut-off value for distinguishing between an infected graft and a non-infected graft.\textsuperscript{18} However, this conclusion was based on a small number of patients and SUV measurement was not corrected properly according to the EARL criteria as formulated by the European Association of Nuclear Medicine (EANM),\textsuperscript{19} which makes it difficult to compare and reproduce in other centers. The various methodologies used to calculate SUVmax and the different equipment makes comparison between studies difficult.

Nevertheless, in a next study including a larger cohort of patients (Chapter 5) an attempt was made to define cut-off values for both SUVmax and TBR. The cohort derived from two large tertiary referral hospitals. Relatively high values of SUVmax and TBR (8 and 6, respectively) were needed to ensure an accurate positive predictive value (PPV). This, however, was associated with a low negative predictive value (NPV). These results reflect the difficulty of FDG PET with standard semi-quantitative measures to diagnose AGI adequately. As a consequence, at this moment, the value of \textsuperscript{18}F-FDG PET in the diagnosis of AGI is limited. This initiated our further research for better measures to describe the uptake observed on \textsuperscript{18}F-FDG PET images. From previous literature it appeared that a heterogeneous \textsuperscript{18}F-FDG uptake is associated with infection. As a consequence the distribution pattern of \textsuperscript{18}F-FDG activities could be helpful to identify AGI with a higher diagnostic precision. A tool for quantifying FDG distribution is textural analysis. Texture analysis is an important property commonly used for image classification in the field of pattern recognition, which may provide valuable information regarding biological heterogeneity. The concept of textural analysis is generally based on the spatial arrangement of voxels in a predefined volume of interest (VOI). Spatial heterogeneity can be depicted from different spatial interrelationships on \textsuperscript{18}F-FDG PET scans. Within the field of clinical oncology, textural analysis already has yielded promising initial results in predicting response by quantifying intra-tumoral heterogeneity.\textsuperscript{20-25} In Chapter 6, textural features were used to characterize FDG uptake heterogeneity and some of them appeared to be of value in predicting AGI. In contrast, the performances of SUVmax, TBR, and VGS measurements were all limited. These results encourage further research to facilitate implementation of automated textural analysis algorithms into clinical practice. Further research regarding the construction, refinement, and validation
of prediction models in larger prospective cohorts is required before it can be implemented in the clinical decision-making process.

**Future perspectives**

Obviously, it is better to prevent prosthetic infection than to cure it. To this respect, there have been some interesting developments in material and coatings. The so-called poly(ethylene oxide) (PEO) brush-coating is a recently developed coating technology. In an unpublished pilot study (Chapter 8), we achieved to adhere PEO coating to the most commonly materials used in vascular surgery. The coating could theoretically prevent biomaterial-centered infections, as it creates a barrier between the surface and approaching microorganisms and proteins. The treated segments of Dacron® and PTFE showed reduction of bacterial adhesion of 71% and 53%, respectively, compared to non-treated segments. However, additional research in the clinical setting is needed to confirm the benefit of this graft coating in prevention of AGI. Surgical site infection (SSI), after aortic intervention is another point that needs attention. In the Percutaneous femoral access in Endovascular Repair versus Open femoral access trial (PiERO) we compared surgical cut-down and percutaneous access of the common femoral artery in a single patient during endovascular aneurysm repair (Chapter 7). The trial was a multicenter randomized controlled clinical trial designed to show the consequences of using percutaneous access in EVAR surgery, when considering surgical site infections. In addition, patient comfort, estimated hospital stay and other wound complications were taken into consideration. No significant differences were found between the two groups in terms of surgical site infections and other postoperative complications.

Despite prevention matters, prosthetic grafts remain sensitive to infection, and as said before, the clinical dilemma in suspected graft infection is how to obtain a reliable, non-invasive proof of infection. Increased ¹⁸F-FDG uptakes may occur in postsurgical inflammatory changes, scar tissue, and native veins. Within the first 6 to 8 weeks after surgery a physiological ¹⁸F-FDG uptake within the graft can result in a false-positive scan. The presence and patterns of ¹⁸F-FDG uptake for uninfected vascular grafts largely overlap with those of infected vascular grafts.²⁶ This questions the value of these ¹⁸F-FDG patterns alone in identifying infected grafts. Although in our study fusion of ¹⁸F-FDG PET images with CT did not increase sensitivity and specificity, other studies did, either with
CT or MR images. Fusion of $^{18}$F-FDG PET with MRI provides anatomic information but with much higher soft tissue contrast and without the additional radiation dose from CT. $^{18}$F-FDG PET/MR resulted in more definitive imaging interpretations with high accuracy in the field of oncology. However, clinical studies are required to show the areas of patient care for which PET/MR has advantages over other diagnostic methods.\(^{27}\)

For the next few years, a further introduction of bio-optical imaging in various biomedical disciplines is to be expected. It is anticipated that bio-optical imaging will become an important technique in the study of biomaterial-associated infection and the development of clinically effective antimicrobial coatings. Bio-optical imaging have found their way into animal research on cancer, atherosclerosis and infectious diseases.\(^{28-33}\) Two different types of bio-optical imaging related to infections have been described in the literature. Bioluminescent and fluorescence imaging. Bioluminescent imaging is based on production of the enzyme luciferase, which needs a specific substrate named luciferin, to produce light. Using bacterial strains genetically modified to produce luciferase, bioluminescent imaging can be used to monitor (biomaterial-associated) infection induced by these strains in live animals. Fluorescence is based on specific probes with attached fluorophores acting as reporters on specific processes as occurring in the course of infection or inflammation. These processes are detected by fluorescent imaging, which is accomplished by transillumination or reflection at single or multiple excitation wavelengths. Image analysis software is able to distinguish different fluorescent reporters by spectral unmixing and eliminating autofluorescence. Bioluminescence technologies offer the opportunity to observe the in vivo course of biomaterial-associated infection in small animals without the need to sacrifice animals at different time points after the onset of infection. The ability to detect pathogens non-invasively through the course of infection will provide new information about the disease process in real time. Bio-optical imaging may play an important role in diagnosing AGI as obtaining bacterial culture is not always possible from suspected AGI.\(^{33,34}\)

When AGI has been diagnosed, the next step is to choose an optimal treatment strategy. However, consensus about the best treatment strategy is lacking. Traditionally, excision of the infected aortic grafts, and restoring lower limb perfusion placing an extra-anatomic bypass through a non-infected part of the body is widely accepted as gold standard. However, initial results were disappointing because of high mortality rates, mostly due to aortic stump
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blowout and failure of the extra-anatomic graft because of thrombosis and reinfection.\textsuperscript{35,36} It is therefore not surprising that antibiotic bonded grafts and antiseptic-coated grafts (e.g. silver coated) became the study focus for various research laboratories. Acceptable results have been described with silver grafts for \textit{in situ} reconstructions, and later on with silver grafts bonded with rifampicin. Rifampicin soaked grafts have not only been used to reconstruct the aorta in case of infection, but also in elective aortic reconstruction as a prophylaxis against future infection. Outcomes from case series of rifampicin soaked grafts are difficult to interpret because of the heterogeneous presentation of aortic infections. Thirty-day mortality ranges from 7\% to 21\% and morbidity from 2\% to 60\%. Reinfections of the rifampicin grafts are seen in 4\% to 22\% of patients, and 5-year survival is approximately 50\%.\textsuperscript{37} A limitation of rifampicin soaked Dacron\textsuperscript{®} grafts for aortic reconstructions includes the increasing prevalence of virulent organisms resistant to rifampicin. Improvements in alternative conduits, such as cryopreserved allografts, may diminish the use of antibiotic-soaked grafts, but it will remain a useful tool in the vascular surgeon armamentarium. Autologous vein could be a good alternative. In particular, the use of an autologous vein is claimed to be most effective in avoiding reinfection according to a meta-analysis comparing the clinical outcomes associated with four treatment modalities for aortic graft infection, including extra-anatomic bypass, rifampicin-bonded prosthesis, cryopreserved allograft, and autologous vein.\textsuperscript{2} However, autologous vein is not always available and harvesting the femoral vein after previous deep venous thrombosis is contraindicated.

Recently, a new graft has been developed named No-React\textsuperscript{®} BioVessel, which is composed of bovine pericardium sutured into a single or bifurcated conduit of variable diameters. This graft is intended for use when there is a need for a biocompatible and infection resistant graft for the replacement of infected prostheses or to treat patients at high risk of (re)infection. The bovine pericardial No-React\textsuperscript{®} BioVessel has demonstrated anti-infective properties to prevent (re)infection and the structural and biological properties for long-term durability.\textsuperscript{38} The No-React\textsuperscript{®} BioVessel is an effective replacement for infected grafts and in cases of high infection risk when a homograft is not available. At the very least, its performance matches the “gold standard” homografts.\textsuperscript{38} The exact role of No-React\textsuperscript{®} BioVessel in treatment of AGI should be investigated.

To optimize results of AGI diagnosis and treatment, a multidisciplinary approach involving vascular surgeons, anesthesiologists, intensive care specialists, radiologists, nuclear medicine physicians and microbiologists seems
mandatory. To ensure adequate diagnostic and therapeutic experience for the treating team, patients with suspected AGI should best be treated in specialized centers only, using strict diagnostic protocols and individualized therapies. In the absence of large-scale studies, clinical guidelines should be developed concerning the definition of AGI. The European Society of Vascular Surgery has just formed a committee to achieve consensus, which will result in a prosthetic infection guideline, which is scheduled to appear mid-2018. Consensus on standard diagnostic work up is essential in order to compare and pool results from future studies. The many different treatment options will further continue to interfere with the comparison within and between hospital results. The low incidence rates of AGI will continue to limit this issue. Therefore, there is a strong need for a national and international collaboration for the management of AGI.

In conclusion, AGI remains a challenging complication for the vascular surgeon. Mortality and morbidity rates associated with AGI remain high despite all preventative measures. There is still no consensus on diagnostic work up and therapeutic strategy. The role of $^{18}$F-FDG PET scan is becoming increasingly important in the detection of AGI; however, an accurate assessment of the uptake and pattern, including a cut-off value is warranted.
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