GRAFTWERK

A functional vascular access (VA) is of vital importance for patients that receive haemodialysis (HD) since it provides the only location where the dialysis machine can be connected to the patient. Autologous arteriovenous fistulas (AVF) are the preferred type of VA due to superior patency and lower complication rates compared to alternatives. However, creation of an AVF is not always feasible due to, for instance, insufficient blood vessel quality. In these cases VA is preferably established by using a synthetic arteriovenous graft (AVG). Unfortunately, VA related complications are the main cause for hospitalisation of patients with either an AVF or an AVG [1]. Furthermore, typical VA life-span is limited to only a few years (2 years for AVGs), which necessitates regular creation of a new VA in many patients. Consequently, it may not come as a surprise that VAs are not only considered the "lifeline", but also the "Achilles' heel" of dialysis [2].

AVG dysfunction is mainly caused by neointimal hyperplasia (NIH) near the venous anastomosis. Disturbed flow and non-physiological wall shear stresses (WSS) after AVG creation are believed to be the main trigger for NIH development. Consequently, it is believed that AVG performance and longevity may be increased by ensuring that haemodynamic conditions after AVG surgery are similar to those observed under physiological circumstances. The aim of this thesis was: 1) to develop an *in silico* strategy that allowed for optimisation of AVG haemodynamics and 2) to propose a haemodynamically optimised graft design.

In this chapter the valorisation opportunities of the work in this thesis will be evaluated. First, it will be evaluated how society and the academic field may benefit from the work in this thesis. Next, clinical relevance of the work will be assessed. Finally, it will be evaluated how the research in this thesis may lead to the development of new products or services.

Academic and Societal relevance

The knowledge and techniques developed in this thesis are, or will be, published in academic journals related to the fields of biomedical engineering and vascular surgery. As such, this knowledge and these techniques will become available to a large audience of scientists and may be used in future studies.

The work in this thesis was performed using 3D computational fluid dynamics (CFD) or fluid structure interaction (FSI) models of AVGs. Since haemodynamics are heavily dependent on geometric characteristics of the AVG model, it is of importance that the 3D models used are geometrically representative of the *in vivo* situation. Hence, a (largely) patient-specific modelling approach is often desired. The requirement for a realistic 3D geometry also applies for various other (if not all) cardiovascular haemodynamics applications, such as AVF flow [3] or coronary artery flow [4]. Unfortunately, imaging modalities that may be used

for the reconstruction of patient-specific 3D models, such as magnetic resonance imaging (MRI) or computed tomography angiography (CTA), often rely on the admission of contrast agents. Since admission of high doses of contrast agents is not desired (particularly in ESRD patients), many CFD studies use highly idealised 3D geometries that may not be able to accurately reproduce *in vivo* haemodynamics. Development of techniques that allow to accurately reconstruct a realistic model with no or minimal amounts of contrast agents would thus be a valuable asset to the academic field. In **Chapter 3** an algorithm is created to reconstruct a realistic AVG geometry from (routinely obtained) clinical follow-up data for monitoring AVG function, combined with CTA scans that are obtained using a protocol that requires minimal amounts of contrast agents to be administered. Such an approach may also be used for geometric reconstruction of other vascular geometries, thereby facilitating the general use of more realistic geometries in CFD and FSI studies.

Vascular grafts (including AVGs) are generally made from expanded polytetrafluoroethylene (ePTFE), which is much stiffer than any autologous vessel. It has been hypothesised that at least part of the relatively poor performance of ePTFE grafts can be attributed to the mismatch in mechanical properties between the graft and native vessels, since this compliance-mismatch may induce non-physiological flow. Consequently, more compliant vascular grafts are actively being developed. Though these more compliant grafts show similar, if not better patency rates compared to ePTFE grafts [5], it is unclear whether the benefit of these grafts can be solely attributed to haemodynamic improvements. In **Chapter 5** we have applied an FSI model and demonstrated that the use of a more compliant graft indeed improves overall haemodynamic conditions in the case of an AVG. Though our research focussed specifically on the use of electrospun polyurethane (ePU) as an AVG material, similar FSI models may be used to evaluate a large range of graft materials. Moreover, the application of these FSI models is not limited to only the field of dialysis grafts, but can also be applied to, for instance, arterial bypass grafts. Finally, the models developed in **Chapter 5** may also be used to inform material scientist during optimisation of the mechanical properties of the graft material, or when optimising graft wall thickness.

A popular approach for improving AVG performance is development of a graft that, by its geometric design, improves haemodynamics. In the field of vascular surgery this approach is not unique since, for instance, geometrically optimised vascular stent designs have also been proposed [6]. Unfortunately, to obtain an "optimal" device geometry, evaluation of numerous sub-optimal device geometries with computationally expensive computer models (*e.g.* CFD models) is often a requisite. In **Chapter 4** an algorithm was developed that can be used to create a meta-model of the original 3D model. Since such a meta-model is much more light-weight than the 3D model, computational costs of graft optimisation studies can significantly be reduced, as successfully demonstrated for the optimisation of

a helical graft in **Chapter 6**. The usefulness of the optimisation algorithm presented in **Chapters 4 and 6** is not limited to the optimisation of helical graft designs. In fact, it may be applied for a large range of optimisation problems and, as such, be even of use for research outside the realm of (bio)medical engineering.

Finally, the methods developed in this thesis may be used to inform *in vivo* or *in vitro* experiments for studying the physiological principles underlying graft dysfunction. For instance, the model outcomes of **Chapters 3 and 5** have been used to define boundary conditions for *in vitro* studies conducted at the Eindhoven University of Technology regarding the biological response to haemodynamic wall shear stress and mechanical strain.

Clinical relevance

The computer models used in this study can be used to evaluate and inform clinical procedures. More specifically, in **Chapter 2**, we demonstrated how the negative effects of dialysis flow may be mitigated by optimal selection of the dialysis flow rate and needle positioning. Ultimately, such insights may translate to clinical guidelines, which, when in place, may result in better anastomotic haemodynamic conditions during dialysis and, consequently, increased graft longevity.

Development of new products or services

VA related complications are not only a large burden on the patient, but also result in high health insurance costs. For AVGs it has been estimated that VA related costs are between $1025–$2250 per patient per dialysis month, which constitutes around 15 %–25 % of all costs required for dialysis treatment [7]. These costs may be reduced considerably by using haemodynamically optimised grafts. The work presented in **Chapters 5 and 6** can be used to develop a graft design with increased haemodynamic performance compared to regular grafts. However, to facilitate development of such a graft, haemodynamic modelling is only one of many steps. Other important factors that need to be considered are, for instance, graft manufacturability, *in vivo* graft performance and biological response to the graft material. Consequently, to develop a marketable graft, it is of utmost importance that a smooth interaction is achieved between, amongst others, clinicians, engineers, materials scientists, biologists and industry. For the project in which also the work in this thesis was performed, all these fields of expertise were united in the Chemelot InSciTe XS-GRAFT project, which aimed to, jointly, improve AVG performance by development of a novel ePU graft. Such initiatives are an important step to increase the economic and societal impact of academic research.

References

1. Ng, L. J., Chen, F., Pisoni, R. L. *et al.* Hospitalization risks related to vascular access type among incident US hemodialysis patients. *Nephrology Dialysis Transplantation* **26,** 3659–3666 (2011).
2. Riella, M. C. & Roy-Chaudhury, P. Vascular access in haemodialysis: strengthening the Achilles' heel. *Nature Reviews Nephrology* **9,** 348–357 (2013).
3. Grechy, L., Iori, F., Corbett, R. W. *et al.* The Effect of Arterial Curvature on Blood Flow in Arterio-Venous Fistulae: Realistic Geometries and Pulsatile Flow. *Cardiovascular Engineering and Technology* **8,** 313–329 (2017).
4. Berthier, B., Bouzerar, R. & Legallais, C. Blood flow patterns in an anatomically realistic coronary vessel: influence of three different reconstruction methods. *Journal of biomechanics* **35,** 1347–56 (2002).
5. Ferraresso, M., Bortolani, E. M. & Amnon, G. A two-year experience with a rapid access, self-sealing, polycarbonate urethane nanofiber vascular access graft for hemodialysis. *Journal of Vascular Access* **17,** 210–214 (2016).
6. Zeller, T., Gaines, P. A., Ansel, G. M. & Caro, C. G. Helical centerline stent improves patency: Two-year results from the randomized mimics trial. *Circulation: Cardiovascular Interventions* **9,** 1–8 (2016).
7. Nordyke, R. J., Reichert, H., Bylsma, L. C. *et al.* Costs Attributable to Arteriovenous Fistula and Arteriovenous Graft Placements in Hemodialysis Patients with Medicare coverage. *American Journal of Nephrology* **50,** 320–328 (2019).