GRAFTWERK

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Summary

A functional vascular access (VA) is the lifeline for patients that rely on haemodialysis to compensate for the loss of kidney function. After all, the VA provides the only access point at which the dialysis machine can be connected to the patient's blood stream and is thus of vital importance to the patient's medical treatment. In approximately 7 %–18 % of all dialysis patients in Europe and the United States, the VA is provided by an arteriovenous graft (AVG). Unfortunately, AVGs are hampered by high complication rates and exhibit short patency durations of typically two years. This graft dysfunction is not only a large burden for the patient, but is also responsible for around 15 %–25 % of all healthcare costs made in the treatment of these patients.

Neointimal hyperplasia (NIH) near the graft-vein anastomosis has been identified as the main cause for AVG dysfunction. NIH is an inward remodelling process that causes stenosis and low flow, ultimately resulting in thrombosis and graft patency loss. NIH development is believed to be triggered by non-physiological haemodynamic conditions near the graft-vein anastomosis after AVG creation, such as oscillating wall shear stress (WSS) or disturbed flow. Consequently, a popular approach to improve graft performance (*i.e.* lowering complication rates and improving graft longevity), is the development of grafts that, by design, result in more physiological blood flow characteristics near the graft vein anastomosis. To develop and evaluate such "haemodynamically optimised" grafts, computational fluid dynamics (CFD) models are typically used to simulate how each graft concept impacts haemodynamics.

The aim of this thesis is twofold. The first aim is to create an *in silico* methodology that allows for optimisation of AVG haemodynamics. For this purpose it is assessed how model assumptions and simplifications impact AVG haemodynamics. Furthermore, a methodology is developed that allows for efficient graft design optimisation. The second aim of this thesis is to evaluate how AVG performance can be improved by graft material selection and geometric design.

Model assumptions

After blood has passed through the dialysis machine, it is returned to the body via a needle on the venous side of the graft. When exiting the needle, the blood forms a high-velocity blood flow jet. In **Chapter 2** it is assessed how haemodynamics in the graft-vein anastomosis are impacted by this dialysis needle flow. It is observed that needle flow can considerably increase disturbed flow and the amount of non-physiological WSS near the venous anastomosis with respect to the situation without needle flow. As such, dialysis needle flow may play an important role in graft dysfunction and should thus, ideally, be considered during graft optimisation. Furthermore, we demonstrate that the negative effects of dialysis needle flow can be minimised by more upstream cannulation of the graft (*i.e.* further from the anastomosis), by ensuring that the dialysis needle tip is located centrally in the graft's lumen and by reducing dialysis flow.

Most CFD AVG optimisation studies make use of highly idealised AVG geometries and/or highly idealised representations of the peripheral vasculature. In **Chapter 3**, a methodology is developed that allows for the creation of more realistic AVG geometries on the basis of available clinical follow-up data and a low contrast-agent dose CTA. Furthermore, realistic boundary condition models are developed to describe the peripheral vasculature. We demonstrate that haemodynamic conditions commonly associated with AVG dysfunction are highly dependent on the use of either idealised or realistic AVG geometries as well as on peripheral boundary conditions. Therefore, the haemodynamic performance of an optimised graft may be significantly misrepresented when evaluated in a highly idealised model. Hence, it is concluded that realistic AVG models and boundary conditions should be used for the haemodynamic optimisation of graft design.

Efficient method for graft optimisation

Graft optimisation requires evaluation of a large number of potentially optimal graft designs. Since CFD models are computationally expensive (>1 day simulation time per graft evaluation), the use of CFD models for optimisation is impractical. In **Chapter 4**, a generalised polynomial chaos expansion (gPCE) algorithm is implemented to create meta-models (*i.e.* a model of a model) that accurately describe the CFD model output response. These models can be evaluated at low computational costs and can thus act as surrogates of the CFD model during an optimisation procedure. The gPCE method requires a number of CFD simulations to be performed and expands the resulting CFD model output into a finite series of polynomials that depend on the model input parameters. To minimise the required number of CFD model evaluations for meta-model creation, an adaptive algorithm is used. For an example CFD problem of the pressure drop over an AVF, the number of required model evaluations for meta-model creation can be reduced by 50 %–90 % with the use of this adaptive approach.

Graft optimisation

AVGs are typically made from expanded polytetrafluoroethylene (ePTFE), which is up to 500 times as stiff as a vein. This mismatch in material stiffness between the graft material and the autologous vein is believed to induce detrimental haemodynamic conditions near the graft vein anastomosis. In **Chapter 5** it is evaluated if graft performance can be improved by the use of a more compliant graft material. More specifically, the haemodynamic performance of a graft constructed from electrospun polyurethane (ePU) grafts is evaluated, since this material can be manufactured such that it's material stiffness approaches that of the veins. It is demonstrated that the use of an ePU graft improves the haemodynamic conditions in the venous anastomosis, but also increases mechanical loading of the vein when compared to an ePTFE graft. We hypothesise that low graft compliance rather than a large graft-vein compliance mismatch is most detrimental to anastomotic haemodynamics. It is concluded that, from a haemodynamic perspective, ePU grafts provide a promising alternative to ePTFE grafts.

Finally, in **Chapter 6** a haemodynamically optimised graft design is developed that efficiently minimises the amount of disturbed flow and the occurrence of WSS metrics related to graft dysfunction. To improve graft performance, the benefit of adding helical features (*i.e.* a helical centreline and/or a helical ridge) to the graft is evaluated. However, the optimisation algorithm can choose to omit any of the helical features if inclusion does not benefit haemodynamic graft performance. To minimise the computational cost of the graft design optimisation procedure, the adaptive gPCE method from Chapter 4 is used to create meta-models of various metrics for graft performance. These meta-models are subsequently used during optimisation to predict graft performance as function of the graft design parameters. After the optimisation procedure is completed, the haemodynamic performance of the "optimal" graft design is finally verified using CFD simulation. The final optimised graft contains both a helical centreline and a helical ridge and considerably improves haemodynamic conditions compared to a regular graft. Hence, it is concluded that the use of grafts with helical features can indeed be used to improve graft performance.

This thesis concludes with a General Discussion (**Chapter 7**) in which we discuss the results and main findings of each chapter and put them in a broader perspective. We elaborate on how graft performance may be improved by optimising graft design. Furthermore, we discuss the limitations of the research and propose directions for future studies.