Under construction: improving arteriovenous fistula maturation

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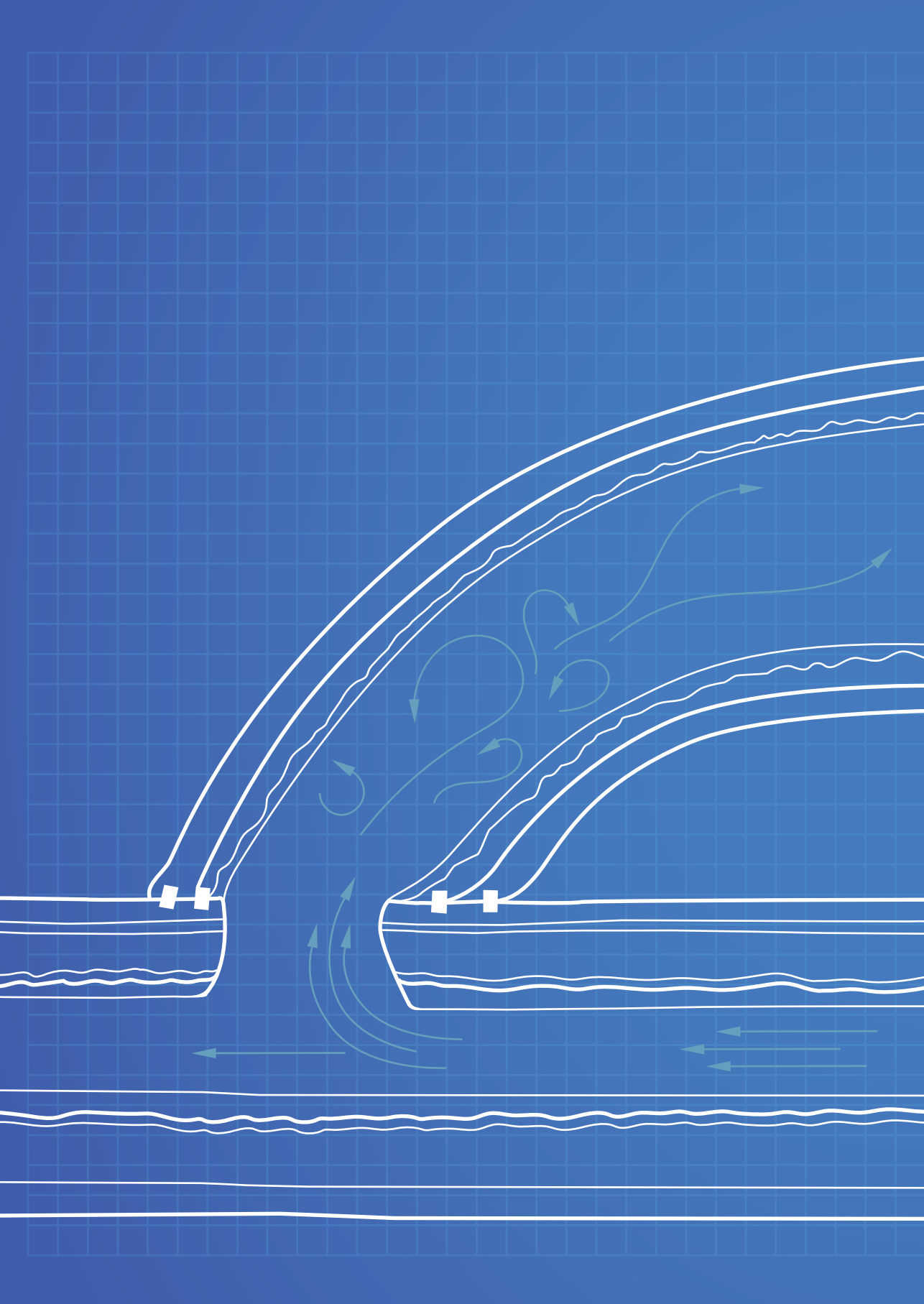

Chapter 7

Summary and discussion

Medical treatment for patients with end-stage kidney disease (ESKD) has come a long way. From the first dialysis machine in 1943 by Willem Kolff [1], to kidney transplantations and the ability to dialyse at home. Notably, the population of ESKD patients has drastically changed since the first patients were treated with hemodialysis (HD). On average, patients are older and have more comorbidities, giving rise to more complications when receiving a vascular access for HD [2, 3]. By having to undergo interventions, this delays the patient to receive HD treatment, and greatly enhances physical discomfort.

Given the rising incidence of kidney failure and the subsequent increase in morbidity and costs related to vascular access care, combined with the expectation that hemodialysis will remain the primary kidney replacement therapy in the near future, there is a significant and urgent clinical need to address the current limitations in vascular access for hemodialysis.

To stimulate adequate vascular remodelling of an AVF, it is essential to understand the requirements for a functioning AVF, the biology underlying post-AVF vascular remodelling and how individual patient characteristics might affect AVF patency.

Understanding AVF maturation and strategies to reduce non-maturation

A functional and matured arteriovenous fistula (AVF) is defined as a fistula that can be utilised consistently with two needles for two thirds of HD sessions over four consecutive weeks [4] and depends on adequate vascular remodelling to facilitate the increase in blood flow through the venous site of the AVF.

Adequate vascular remodelling is essential, as an AVF causes high-pressure arterial blood to be redirected into the low-pressure venous system, thereby often increasing blood flow velocity, shear stress, and pressure within the vessel walls. These hemodynamic changes predominantly affect the venous outflow tract, where the altered forces on the vessel wall accelerate inflammation, vascular smooth muscle cell (VSMC) proliferation, and extracellular matrix (ECM) remodelling, collectively contributing to vascular remodelling. Increased shear stress on the endothelial cells (ECs) lining the vessel wall stimulates the release of both vasodilatory and vasoconstrictive factors, as well as growth factors that promote cell proliferation and ECM remodelling. Over time, the vessel undergoes structural changes to accommodate the altered blood flow, such as outward remodelling to accommodate the increased blood flow and restore hemodynamics.

It is essential to identify the plethora of biological processes underlying adequate vascular remodelling in AVFs for functional use. The role of ECs and VSMCs has been studied elaborately. ECs can stimulate angiogenesis and VSMC proliferation but also regulate thrombosis, and vascular tone in the AVF [5-7]. VSMCs are key players in both intimal hyperplasia and outward remodelling, and ECM production [8]. In **chapter 2** we discuss the role of the ECM in AVF remodelling. The ECM forms a scaffold for blood vessels and is involved in AVF maturation by regulating its degradation, followed by deposition of newly formed ECM to enable outward remodelling and strengthening of the AVF. AVF remodelling involves a coordinated interaction of controlled inflammation and regulated cell proliferation. This interplay is essential for promoting re-endothelialisation, thickening of the vessel wall, and OR. The vascular ECM is involved in all these assets of vascular remodelling and poses an effective therapeutic target to modulate vascular remodelling.

A critical protein in the interaction between inflammation, VSMC proliferation and ECs is the von Willebrand factor (VWF). **Chapter 3** delved into VWF's involvement in vascular AVF remodelling, using a VWF-deficient mouse model. Upon stress or stimulation, ECs produce and excrete VWF which can bind platelets and is thereby involved in thrombosis and forms a bed for intimal hyperplasia (IH) formation. Additionally, VWF stimulates inflammation and vascular smooth muscle cell (VSMC) proliferation [7, 9, 10].

Our study hypothesized that VWF would impact thrombosis, IH, and outward remodelling (OR) post-AVF creation. Jugular-carotid AVFs were constructed in wild-type and $vWF^{-/-}$ mice, revealing reduced IH and decreased OR in venous AVF outflow tracts of VWF-deficient mice. This study was the first where our lab measured blood flow through the AVF using ultrasound analysis, giving crucial information regarding the functionality of the fistula. We observed that the significant reduction in IH and the slightly reduced OR still led to diminished flow through the AVF. Furthermore, VWF deficiency increased systemic levels of P-selectin and resulted in reduced recruitment of macrophages in the AVF vessel wall. Supplementing plasma from VWF-deficient mice with human recombinant VWF stimulated VSMC proliferation *in vitro*.

The importance of VWF in successful AVF maturation was supported by the analysis of venous AVF patient samples, showing increased VWF expression in the intimal layer of matured AVFs, as well as more wall thickening and outward remodelling. Extrapolating these findings beyond the role of VWF, our study

reinforced that proliferation of VSMCs is important to promote OR and wall thickening, and outweighs preventing IH, which has been a long-time debate. Therefore, timely stimulating VSMC proliferation could be of added therapeutic value when promoting positive AVF remodelling. However, since VWF has a multifaceted role in thrombosis and inflammation, other VSMC stimulating agent might be more suitable.

Hurdles post-AVF maturation

When an AVF is created and successfully used for hemodialysis, it can still give rise to various complications, such as stenosis or aneurysms. Stenosis narrows the vessel and thereby restricts blood flow. This could be due to IH, thrombosis, trauma to the vessel wall due to repeated needling for HD, infection or pre-existing vascular disease. In an aneurysm on the other hand, excessive OR weakens the vessel wall and makes it prone to bursting under the increase in blood flow [11].

Both excessive AVF flow and stenosis hindering AVF blood flow can cause strain on the cardiac output, induce pulmonary hypertension or steal syndrome [12]. The latter occurs when arterial blood, intended to supply the distal limb, is 'stolen' by the AVF, causing ischemia. Therefore, it is important to not only study how to enhance AVF maturation, but also the possible complications that arise after AVF surgery due to too much AVF flow, excessive vascular remodelling or changes in flow pattern and forces.

In **chapter 4**, we explored the impact of altered hemodynamics that occur post-AVF surgery on VWF structure and functionality. The creation of an AVF induces a shift from laminar to turbulent blood flow at the anastomosis site [13], thereby affecting shear stress and subsequently influencing EC function. ECs secrete the multimeric protein VWF in an inactive globular form, as high molecular weight multimers (HMWMs) [14, 15]. Shear stress can modulate the conformation of VWF by elongating it and exposing its cleavage site and platelet-binding collagen domains. This exposure facilitates platelet binding and interaction with the subendothelial matrix, as well as the binding of metalloprotease ADAMTS13 (A Disintegrin and Metalloproteinase with a Thrombospondin Type-1 Motif, Member 13) for cleaving HMWMs into smaller subsets. A delicate balance of multimeric structures is crucial for maintaining haemostasis, as the functionality of VWF multimers depends on their molecular weight. Excessive VWF cleavage is a characteristic of acquired von Willebrand syndrome (aVWS), in which patients

show increased bleeding tendency. Sudden turbulent flow can induce aVWS, as has been shown in patients treated with an arterial extracorporeal membrane oxygenation (ECMO) device, or in patients with stenosis of the aortic valve. Luckily, aVWS is reversible when flow patterns are restored [16-18]. We aimed to investigate the effect of AVF creation on systemic VWF levels and functionality using patient-matched plasma samples from two-staged brachiobasilic AVF surgeries, allowing us to perform pair-matched analysis of pre- and post-AVF induced flow to assess HMWM cleavage. We observed that ESKD patients had high levels of low molecular weight multimers both before and after AVF surgery, possibly affecting haemostasis. AVF-induced hemodynamic changes did not have a clear effect on VWF configuration or function. As we did not have data on the flow velocity nor flow pattern in these patients, no correlation could be made between the individual HMWM ratio response and patient-specific blood flow data. Lastly, almost all patients received HD treatment, affecting VWF levels and multimers.

As the mice in our *in vivo* studies do not receive hemodialysis, in future studies the direct effect of AVF-flow on VWF functionality could be assessed by multimer assays using mouse plasma samples obtained before AVF surgery and after. This would also enable us to study the effect of uremia and loss of kidney function by comparing mice with healthy kidney function to mice with Autosomal Dominant Polycystic Kidney Disease (ADPKD).

Understanding how patient characteristics influence AVF maturation: autosomal dominant polycystic kidney disease

As every patient is unique, every AVF has a different vascular remodelling process. This underscores the importance of tailoring AVF management strategies to individual patient profiles, paving the way for more targeted interventions and improved clinical outcomes. By exploring how variations in patient-specific factors influence AVF maturation, we can enhance our understanding of the complex interplay between physiological dynamics and vascular remodelling.

In **chapter 5** we explore vascular access outcomes of patients with autosomal dominant polycystic kidney disease (ADPKD) compared to other patients receiving an AVF or AVG (arteriovenous graft). ADPKD is a leading hereditary cause of ESKD. In Europe, ADPKD accounts for 9% of all patients undergoing kidney replacement therapy, with a majority receiving hemodialysis (HD) through an AVF [19, 20].

ADPKD patients may also exhibit extrarenal manifestations, including arterial aneurysms, and hypertension occurring before the onset of kidney failure. Polycystins, the proteins that are affected in ADPKD, are expressed in ECs and VSMCs, and play a crucial role in ECM production and vessel wall support, as well as in mechanosensation [21-23]. This could indicate altered vascular reactivity when an AVF/AVG is constructed.

We aimed to create a representative cohort of patients with ADPKD and conducted a retrospective cohort study using data from the Swedish Renal Registry spanning AVFs/AVGs created between 2011 and 2020, with follow-up until 2022. This study included 496 ADPKD patients and 4321 propensity-score matched controls.

We observed no significant differences in primary, post-cannulation primary, secondary, or functional patency between ADPKD and non-ADPKD patients, however, more VAs were ligated in ADPKD patients. Additionally, ADPKD patients underwent more surgical primary interventions to re-establish flow. However, overall patients with ADPKD had fewer interventions per year of functional patency than non-ADPKD controls. In conclusion, this suggests comparable AVF/AVG patency rates between ESKD patients with or without ADPKD.

Studying AVF maturation in a new pre-clinical model of chronic kidney disease

As we did not observe differential outcomes between arteriovenous conduits in patients with ADPKD when compared to patients with other kidney diseases, we proposed that ADPKD could serve as a clinically relevant model to study AVF maturation in a chronic kidney disease (CKD) setting.

To date, when AVF maturation is studied in animal models that mimic kidney failure, researchers use diet-induced kidney failure, perform nephrectomies or induce hypertension [24-29]. However, these models are an inaccurate representation as they are caused by acute kidney injury without the progressive vascular damage characteristic of ESKD and the often-present co-morbidity of hypertension. These are significant clinical traits observed in patients who receive an AVF, which can greatly affect vascular reactivity and remodelling.

Therefore, in **chapter 6** we investigated the use of a previously established murine ADPKD model [30] to elucidate the effect of CKD on vascular remodelling following AVF surgery. The aforementioned CKD characteristics were present in

our model: Pkd1$^{nl/nl}$ mice with aberrant Pkd1 splicing experienced hypertension and increased blood urea levels, indicating uraemia, compared to their wildtype littermates.

When assessing the AVF of Pkd1$^{nl/nl}$ mice, they had increased blood flow over the three weeks post-AVF creation compared to controls. In this study, we were able to obtain 3D luminal volumes from our ultrasound analysis. This is a significant improvement from our previous OR analysis based on histology of harvested AVFs, which lack the wall tension and distensibility that is present *in vivo* due to blood pressure. At the endpoint of our study (three weeks post-AVF surgery), ADPKD mice had a 1.3-fold increase in luminal AVF volume.

When performing RNA sequencing it showed decreased processes of ECM regulation during early AVF remodelling. When assessing the venous AVF wall, Pkd1$^{nl/nl}$ mice had decreased deposition of collagen, however there was no decrease in the presence of collagen (αSMA or vimentin-positive) producing cells. The increase in AVF flow and venous outflow tract volume could be due to better vessel distensibility, indicated by reduction of collagen in the venous outflow tract. When studying cephalic veins, which are used for about 60% of AVFs, veins of ESKD patients also showed irregularly organised collagen fibres, and more VSMC phagocytosis of collagen and elastin than healthy controls [31].

In conclusion, the murine ADPKD model is a clinically relevant CKD model that recapitulates essential characteristics of the patient population receiving AVFs, showing the importance of ECM regulation in AVF maturation.

Future perspectives

We have come a long way in understanding the multifactorial process of AVF maturation. The research outlined in this thesis aims to expand upon this knowledge and tackle several crucial aspects crucial for optimizing AVFs.

However, there is still a variety of unknown parameters in AVF maturation. One being disturbances in hemodynamics leading to maladaptive remodelling of the vessel wall, resulting in AVF failure. To address this, it is important to monitor patients before AVF creation and post-AVF surgery, to survey the vascular access, including local shear stress and flow patterns. The degree of shear stress is associated with specific patterns of vascular remodelling, with the notion that low shear stress can induce IH while high shear stress can induce OR [32, 33].

Devices to aid in regulating favourable hemodynamics after AVF surgery, such as the VASQ, are being applied and tested thoroughly [34, 35]. However, it may not be a predetermined threshold of shear stress levels that initiates OR in AVFs, but rather a specific change (delta) in shear stress between different time points, such as the local difference observed before and after AVF surgery. Leveraging the effects of shear stress could be advantageous in promoting AVF maturation, as has been shown in mice through modulation of endothelial nitric oxide synthase (eNOS) [36]. Possibly, patients prone to IH could benefit from AVF anastomosis with an adjusted angle to induce higher shear stress levels. However, in other settings excessive shear stress may lead to detrimental outcomes, including disproportionate OR and aneurysm formation. Additionally, underlying vascular pathology and patient-specific factors can influence AVF maturation and its response to hemodynamic changes. Therefore, it is of importance to characterise every patient.

Besides vascular surgeons optimising the anastomosis angle to create a favourable hemodynamic environment, biomedical researchers should aim to develop local therapy with a timely active therapeutic drug to promote AVF maturation. Applying local therapeutics minimises both the risk of undesirable systemic effects and reduces the therapeutic burden on an already fragile patient population. Local delivery can be achieved by using targeted nanoparticles, or a slow-releasing gel applied during AVF construction. To intervene successfully, it is important to know the optimal time frame and remodelling process to target.

In human pair-matched brachiobasilic AVFs, ECM proteins ranked highly among the genes with differential expression when compared to the venous samples taken prior to AVF creation [37]. Pathway enrichment analysis revealed a significant increase in collagen remodelling, both degradation and production. Furthermore, failed and matured AVFs could be categorised by distinct clusters of differentially expressed ECM components. AVF maturation arguably follows phases of ECM degradation, followed by reorganisation of the collagen and elastin scaffold and deposition of ECM proteins [38]. We also found altered ECM deposition in mice, including disruption of arterial elastic laminae and venous collagen on the long-term, resulting in increased luminal volume of the AVF. As ECM degradation facilitates OR, which happens first during AVF remodelling, therapeutics aimed at intervening ECM regulation could have high potential. Several *in vivo* studies have shown promising results in inhibiting elastin and collagen crosslinking [39, 40]. Again, it is important to exercise caution when encouraging excessive degradation

of the ECM or promoting overly aggressive OR, as this can weaken the vessel, increasing its susceptibility to aneurysm formation.

We firmly believe that our new mouse model presents a clinically relevant depiction of a significant portion of patients undergoing AVF procedures and should be employed to further study the potential of ECM interventions to promote AVF maturation. Nonetheless, it's crucial to acknowledge and prioritise ethics and animal welfare in our research endeavors. While the CKD model offers valuable insights, researchers must carefully assess the necessity of impacting the well-being of research animals. When performing *in vivo* studies, it is important to implement non-invasive and preferably longitudinal study methods, as to minimize the discomfort imposed on these animals and the number of animals needed. One promising research method is non-invasive imaging, as we have performed using Doppler ultrasound AVF imaging, to get valuable data and follow-up in time, comparable to what is performed in the clinic. It is essential to balance this consideration with the availability of alternative methods such as *in vitro* models. However, given the intricate nature of AVF maturation, *in vivo* studies remain indispensable for gaining a comprehensive understanding of the complex interplay of factors.

Conclusion

In this thesis, the aim was to add knowledge to multiple facets of AVF functionality. Given that preventing kidney failure entirely, and thereby the need for HD and an AVF, might be an overly ambitious goal at present, I propose that individual patient characteristics should be thoroughly screened prior to AVF surgery, to possibly characterise factors that aid AVF maturation, and provide personalized therapy for the widely diverse array of individuals receiving AVFs. Interventions could be provided through modulating wall shear stress, or the ECM, which can facilitate outward remodelling and thereby shear-stress restauration and AVF maturation. This interdisciplinary topic necessitates a collaborative approach involving experts from various fields, including biomedical researchers, engineers, vascular surgeons, and nephrologists, all working together as islands in the AVF stream.

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