Under construction: improving arteriovenous fistula maturation

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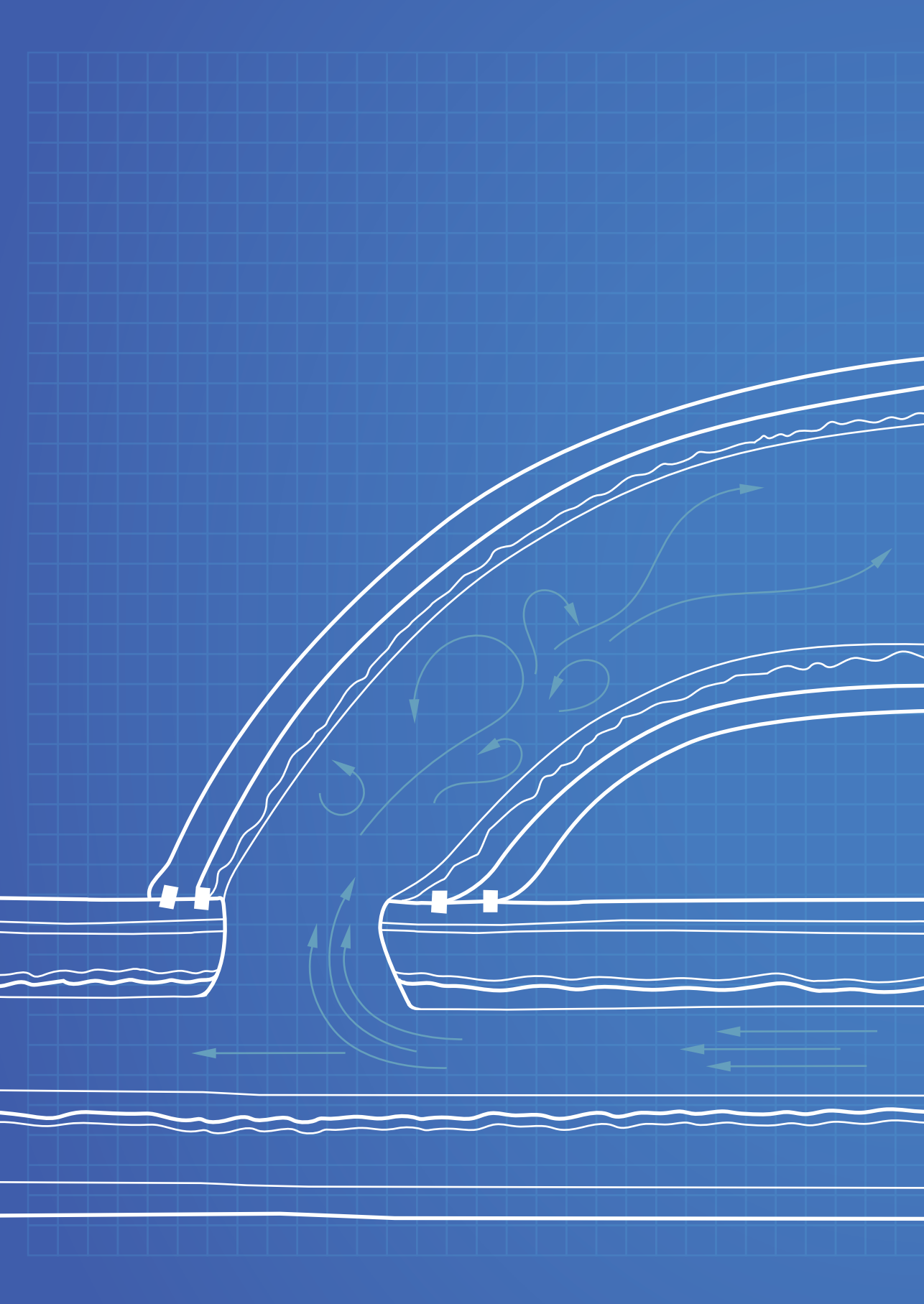

Chapter 1

General introduction

From healthy kidneys to major destruction: End stage kidney disease

The kidneys are the recycling organs of the body: about 180 litres of fluid pass through them every day. The kidneys ensure that only excess water and waste are excreted, while keeping the body hydrated with a stable blood pressure by retaining sufficient fluids, blood cells and minerals. Failure of the kidneys can be acute (AKI: acute kidney injury) or chronic (CKD: chronic kidney disease). In the Netherlands, 10% of the population (1.7 million people) have CKD [1], and yearly 2,000 people are diagnosed end-stage kidney disease (ESKD) [2].

Kidney failure can be multifactorial and there are many risk factors for developing CKD, such as diabetes, high blood pressure, heart failure, obesity and old age [3]. The 10% prevalence of CKD is expected to rise, as we are an ageing society with an increase in unhealthy food consumption and obesity. CKD is defined by a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 and/or kidney damage for 3 or more months. Eventually, CKD can advance into ESKD, with a GFR < 15 mL/min/1.73 m^2: a state where damage to the kidneys is so severe that treatment is needed to take over the patient's kidney function. Using compartmental simulation modelling, the expected rise in incidence of ESKD disease in the United States of America alone is 11%-18% in 2030, with an 29%–68% increase in prevalence, due to increased survival rates of ESKD patients [4]. Without kidney replacement therapy (KRT), ESKD is fatal. Ideally, patients with ESKD receive a donor kidney, however donor organs are scarce, and sometimes patients are not able to withstand the burden of organ transplantation surgery and immune-suppressing drugs. Therefore, another treatment modality is required to replace the kidneys: this is achieved by dialysis.

Dialysis: substituting the kidney

Dialysis therapy consists of the use of a machine to help patients with kidney failure remove waste from the body. This can occur inside the body by using the lining of the abdomen as a natural filter, called peritoneal dialysis (PD), or outside of the body through hemodialysis (HD). In 2019, 37% of all KRT patients had a donor kidney, while 5% was on PD and 58% received HD [5].

During HD, the blood runs through an extracorporeal dialyser. This treatment can occur at home daily or in-centre, which usually takes place three times a week during four-hour sessions. To receive HD, a vascular access (VA) is needed to connect the patient's blood circulation to the dialyser. A VA is created to provide

an access site to the patients' blood, with enough blood flow to ensure time efficient dialysis. There are several ways to achieve VA.

Vascular access: a lifeline to hemodialysis treatment

When there is acute need for HD treatment, VA is achieved by placing a central venous catheter (CVC). This is quick and gives instant access for HD, however it is not preferred for long term use, as CVCs are prone to central venous stenosis and infections, which can cause sepsis, shock and even death [6, 7]. Instead, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend an arteriovenous vascular access for long term dialysis [8]. This entails a connection between the arterial and venous system, either autologous by creating an arteriovenous fistula (AVF) or through a graft (AVG). This is needed as native blood vessels are not suited to withstand frequent cannulation with needles, and do not have high enough blood flow for efficient dialysis. By creating an AVF or AVG, the high-pressure arterial system is connected directly to the venous system, which ensures a significant increase in blood flow, at a site that can be easily cannulated. This thesis focusses on the AVF.

Construction of an arteriovenous fistula

Dr. Michael Brescia and dr. James Cimino were the first to introduce the AVF in 1966 [9] and provide a stepping stone for vascular access design that provides adequate blood flow for hemodialysis therapy. Currently, there are several modalities of the upper-limb AVF. The first is the radiocephalic fistula, which is created from the radial artery and cephalic vein in the wrist – the Cimino shunt – or the anatomic snuffbox: the snuffbox fistula [10, 11]. The brachiocephalic fistula is situated in the upper arm, where the cephalic vein is connected to the brachial artery. Lastly the brachiobasilic fistula, which is often created in two stages: first the brachial vein is used to create an AVF, which is then transposed at stage two to the basilic artery to ensure superficial accessibility for cannulation.

The first fistulas created functioned well, without complications. Brescia and Cimino reported that only 2 out of 16 AVFs created could not be used for HD, the other 14 AVFs were free of complications [9]. However, since the HD patient population is ageing and has more comorbidities, non-maturation of the AVF poses a problem. Maturation entails both an increase in blood flow and an enlarged luminal diameter of the AVF.

Although AVFs require more planning ahead and time to adapt to the new environment in order to 'mature' to facilitate efficient HD, once this matured state has been achieved AVFs require fewer interventions on the long-term compared to AVGs [12]. In the Netherlands, depending on the patients age, around 60 to 68% of all hemodialysis patients dialyse using an AVF [13].

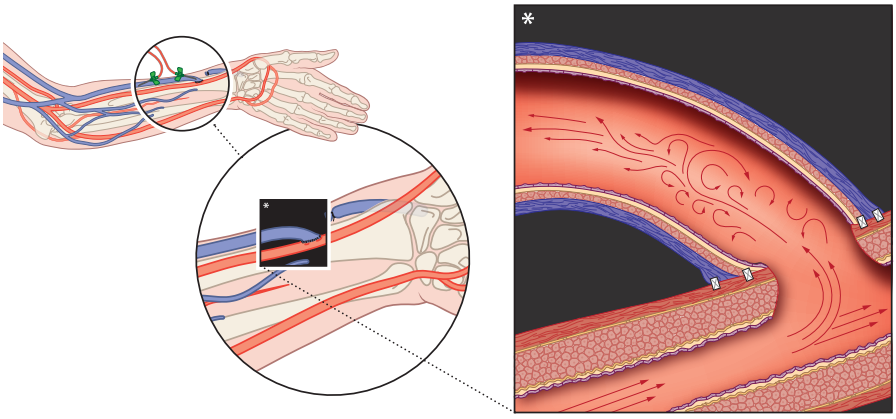

Figure 1: An example of a radiocephalic AVF
An end-to side AVF is created in the wrist, arterial flow is propagated into the venous outflow tract, increasing flow. The AVF with increase in blood flow and a thickened vessel wall can be cannulated to supply the patients' blood to the hemodialysis machine.

Obstruction of the AVF: non-maturation and long-term complications

A functional and matured AVF is defined as a fistula that can be utilised consistently with two needles for two thirds of HD sessions over four consecutive weeks [8]. However, to achieve this has been proven a hurdle in creating a well-functioning VA for HD.

After AVF creation, a non-physiological pressure is created in the venous outflow tract, which differs substantially from the arterial vessel wall. Thus, the venous outflow tract has to undergo arterialisation: the vessel wall has to thicken to endure the increase in pressure and tensile stress and expand its luminal diameter to facilitate both enhanced blood flow and adapt to the increase in shear stress [14, 15]. However, often thrombosis and intimal hyperplasia (IH) occur. IH, together with the degree of enlargement of the vessel diameter, defined as outward remodelling (OR), defines the luminal diameter of the vessel and thereby the ability of the AVF

to facilitate the increase in blood flow [16]. A disruption in this balance due to excessive IH or stenosis or limited outward remodelling leads to AVF failure and hinders efficient dialysis. This can cause primary failure – when an AVF cannot be used for HD – which occurs in about 23% of all AVFs [17]. Within one year after AVF creation, about 60% of AVFs have received an intervention [17, 18].

The blueprint of AVF maturation

Apart from technical surgical failure, non-maturation can be a result of multiple biological factors, such as the response of endothelial and vascular smooth muscle cells to the change in blood flow, or hemodynamics, after AVF creation. These cell types are essential for the successful maturation of an AVF. They work together to promote vessel dilation, prevent thrombosis, and facilitate the structural changes needed to make the fistula suitable for efficient hemodialysis access.

The creation of an AVF alters local hemodynamics: as the venous outflow tract is exposed to arterial pressure, it experiences increased shear stress and turbulent flow [19], which affects the activity of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) [20-22]. ECs line the blood vessel and regulate vascular tone, including vasodilatation to widen the blood vessel, and release factors to regulate angiogenesis, thrombosis and VSMC proliferation, such as the von Willebrand factor and nitric oxide [23-25]. VSMCs are situated in the medial layer of major blood vessels and can switch from a contractile phenotype to a synthetic phenotype, which is more conducive to growth and repair. This phenotypic switch helps the vessel adapt to the demands of hemodialysis by facilitating outward remodelling, arterialisation and synthesising extracellular matrix (ECM) to give support to the vessel and accommodate the increased mechanical stress from higher blood flow rates [26]. There is an interplay between these vascular components in AVF maturation: the ECs, VSMCs and ECM communicate to either stimulate or prevent ECM production, cell differentiation and proliferation. This interplay is discussed further in **chapter 2**, including an overview of the anatomical differences between arteries and veins.

Renovating the AVF: the need to optimise AVF maturation

Non-maturation greatly decreases quality of life for ESKD patients, as AVF complications and subsequential interventions cause physical discomfort and delay the use of the AVF for HD treatment. Furthermore, it puts a burden on both health care costs and requires additional interventions from health care providers.

In the Netherlands, dialysis costs around 80 to 120 thousand euro's each year [2]. Analysis of USA Medicare data shows that AVFs that require an intervention within the first year after surgery are 2.3-fold more expensive than AVFs that do not require an intervention within the first year, and AVFs that were not used within the first year cost four-fold more [27]. Moreover, in 2013 12% of all ESKD treatment costs was due to vascular-access related services [27]. Considering the increasing incidence of kidney failure, and the accompanying rise in morbidity and expenses associated with vascular access-care, as well as the expectation that hemodialysis will continue to be the primary method of kidney replacement therapy in the near future, there is a notable and pressing clinical requirement to tackle the existing constraints in vascular access for hemodialysis.

Individual characteristics set the foundation for AVF maturation

Several individual patient characteristics are known risk factors for non-maturation or AVF failure, such as ethnicity, female sex and age [28-30]. Thus, an individualized approach when deciding on the type of VA and subsequent interventions are a necessity: looking at both the biological key-players in AVF maturation and the individual characteristics of the patient. ESKD patients can have a diverse cause of kidney failure. Despite the widely known fact that kidney failure and cardiovascular morbidity go hand in hand, little is known if the cause of the underlying kidney diseases affects cardiovascular processes such as AVF maturation differently.

The focus of this thesis is to understand arteriovenous fistula dysfunction and maturation failure as to design novel therapies to optimize AVF maturation. Therefore, we aimed to uncover whether the type of kidney failure affects AVF outcomes in **chapters 5 and 6** of this thesis.

Scope of this thesis

Some major pitfalls for AVF failure are known, however there is more to discover how individual factors influence components of AVF failure, or novel ways how ECs, the ECM and VSMCs can interact to achieve in AVF maturation. In this thesis I aim to further unravel what happens during AVF maturation, but also which complications occur after VA creation.

In **chapter 2** we dive further into the process of AVF maturation and give an overview of differences in the arterial and venous vessel wall. We emphasise the importance of the extracellular matrix in AVF maturation, and studying this aspect of vascular remodelling post-AVF surgery. Lastly, we discuss potential therapeutic targets to enhance AVF maturation through ECM modulation.

In **chapter 3** we unravel the role of the von Willebrand Factor (VWF) in AVF maturation. VWF is produced by ECs and affects both VSMCs and macrophages. We hypothesized that VWF plays a role in vascular remodelling after AVF creation. We performed an *in vivo* study with VWF-deficient mice who received an AVF, and measured AVF functionality by using Doppler ultrasound to measure blood flow through the AVF. Subsequently, we analysed whether VWF deficiency affected vascular remodelling and the composition of the venous wall in the AVF outflow tract.

As VWF functionality is affected by hemodynamics, in **chapter 4** we assessed whether the functionality of systemic VWF is affected by the turbulent flow that arises after AVF creation. It is known that turbulent flow can cause cleavage of VWF into less functional subunits, leading to increased bleeding risks. Therefore, we assessed if AVF flow can also cause VWF cleavage, by comparing VWF subsets in patient-matched plasma of ESKD patients obtained before AVF surgery, and after AVF surgery.

In **chapter 5** we investigated the effect the most common genetic kidney disease: Autosomal Dominant Polycystic Kidney Disease (ADPKD) on AVF outcomes. ADPKD encompasses 9% of all patients on KRT in Europe, of which 69% is treated with hemodialysis (HD) [31]. Besides loss of kidney function, ADPKD also leads to early hypertension and an increased incidence of aneurysm formation [32-34], hinting at a possible altered vasculopathy. In a retrospective cohort study using clinical data we evaluated whether ADPKD affects AVF/AVG patency and compared this to other ESKD patients receiving an AVG or AVF. We found no effect on patency rates. Therefore, in **chapter 6**, we proposed ADPKD as the first clinically relevant model to study the effect of CKD on AVF maturation *in vivo*. In this model we also touch upon the role of the ECM in AVF maturation.
Finally, **chapter 7** gives an overall summary of the research described in this thesis and discusses future prospectives on vascular access for hemodialysis to enhance AVF maturation and reduce complications in VA use.

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