The life cycle of the vascular access: from creation to ligation

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Chapter 1

General introduction

Treatment of end stage kidney disease patients

The kidneys are the organs responsible for the removal of waste products and excess fluid. Furthermore, they are part of the regulation of blood pressure, red blood cell formation and bone formation. The kidneys consist of an intricate network of blood vessels, tubules and associated cells. Diseases such as hypertension, diabetes or autoimmune diseases can reduce kidney function by damaging one or more of these compartments of the kidney. Some patients reach end stage kidney disease (ESKD), a state in which the kidney function has irreversibly deteriorated to the point where, if no action is taken, the patient will die due to the accumulation of waste products or fluid in the body, or a combination of both.

If a patient is expected to reach ESKD, treatment options are a conservative approach, renal replacement therapy or kidney transplantation. At the end of 2019, in the Netherlands a total of 17,933 ESKD patients received either renal replacement therapy (6,292) or were alive with a functioning kidney transplant (11,641) [1].

Vascular access for hemodialysis

In hemodialysis (HD), the blood passes a filter in close proximity to a clean fluid, the dialysate, allowing the waste products and excess fluid to be removed from the body and enter the dialysate. An artificial filter is used external to the body. To pass through this filter, the blood must flow from the body to the filter and then flow back into the body. To efficiently dialyze a patient in a reasonable amount of time, blood flow rates around 300 milliliters per minute are typically used. These flow rates cannot be provided by simply cannulating a vein with a needle repeatedly. A vascular access must be created specifically for this purpose. An ideal vascular access can be created quickly and used instantly, provides a high blood flow, can be reliably used repeatedly, has a low incidence of complications and required few maintenance procedures during its' lifetime.

Several types of vascular access are available. The central venous catheter (CVC) consists of a tube with two lumens approximately 3 to 3.5 mm in diameter and is typically placed in the jugular vein, although other sites can be used as well. Benefits of a CVC are that it be inserted quickly at the bedside, and insertion can be delayed until the patient actually starts HD. For maintenance HD, there are several disadvantages of CVCs. As CVCs are relatively long tubes with a relatively small diameter, they provide resistance to blood flow, limiting the blood flow which can be provided to the HD machine. By having a foreign body inserted into the body at all times, the

patient is exposed to a significant risk of infections. CVCs are also associated with thrombosis and occlusion of the veins they are inserted into.

Arteriovenous conduits, in which a high-pressure artery is connected to a low-pressure vein to create a high-flow conduit, tackle some of the problems of CVCs. In the 1940's Alwall pioneered the creation of glass arteriovenous conduits, and in 1960 Scribner created a vascular access consisting of a metal plate and a curved Teflon tube between the radial artery and a forearm vein, located outside the body [2,3]. The tube could be connected to the HD machine repeatedly. Currently, arteriovenous grafts (AVGs) consisting of a subcutaneously placed artificial tube are used. Although these conduits provide an adequate flow for HD, infections and thrombosis often occur.

In 1966, the Brescia, Cimino, et al pioneered the creation of the native arteriovenous fistula (AVF), in which the radial artery is directly connected to the cephalic vein in a small surgical procedure, without the use of artificial graft materials [4]. After creation of this radiocephalic AVF (RCAVF), the vein was observed to dilate and thicken and the blood flow increased. This vein could then be cannulated repeatedly during HD sessions. The AVF was shown to be reliable and because no artificial materials were introduced, infections were uncommon.

Maturation of arteriovenous access

Immediately after a high-pressure artery is connected to a low-pressure vein, blood flow through the newly created AVF increases and a process of maturation of the vein is initiated [5]. Due to active outward remodeling, the diameter of the lumen increases. Conversely, excessive intimal hyperplasia formation may decrease the lumen. If the balance between these processes is tilted towards outward remodeling, a vein with a proper diameter and blood flow may be obtained. If the balance is tilted towards more intimal hyperplasia, the AVF may be stenosed and fail. Typically, an AVF is considered mature and suitable for HD if it meets the 'rule of sixes': a diameter of 6 mm, a flow of 600 ml/min and a length of at least 6 cm suitable for cannulation at a depth of no more than 6 mm, at 6 weeks after surgery. Less strict criteria have also been shown to be clinically useful [6]. Unfortunately, a large proportion of AVFs does not mature successfully, with maturation rates at 6 months in literature ranging from only 26% to 40% [7,8]. These patients require additional procedures to assist maturation, or the AVF may be abandoned altogether and the patient will be burdened with creation of another VA. In **Chapter 2** the topic

of clinical nonmaturation will be discussed and in **Chapter 3** we will look into the long-term functional outcomes of vascular accesses.

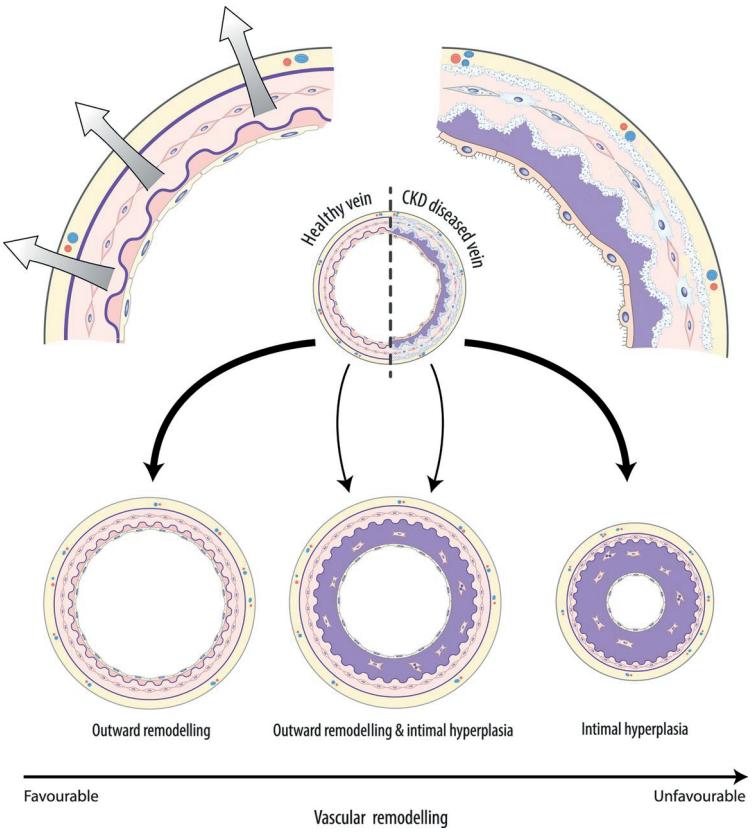

Figure 1 The balance between outward remodelling and intimal hyperplasia [5].

Pathophysiology of nonmaturation

The typical lesion of nonmaturation is that of a juxta-anastomotic stenosis, a narrowing of the vessel near the connection between the artery and vein, limiting the blood flow through the entire AVF and preventing further maturation. The formation of intimal hyperplasia responsible for this stenosis involves an inflammatory response which may be triggered by surgical trauma or the increased blood flow after AVF creation [9]. In human arterial disease, modulating inflammation with doxycycline increased aneurysm growth [10]. Prior work by our group demonstrated that in mice, AVF maturation could be improved by inhibiting inflammation using liposomal prednisolone, a locally-acting drug that targets sites of inflammation. In **Chapters 4**

and 5 the design and results of a clinical trial of liposomal prednisolone to improve AVF maturation in humans will be discussed.

Cardiac effects of an arteriovenous access conduit

The presence of an arteriovenous conduit poses a burden to the cardiovascular system due to the additional blood flow which gets 'added' to the systemic circulation, increasing the cardiac output. In the vulnerable HD population, this may have unfavorable effects on cardiac structure and function had been dubbed 'AVF toxicity' in literature [11]. In **chapter 6** we performed a review of literature on the cardiac effects of arteriovenous conduits and in **chapter 7** we performed a survey to investigate physicians' opinions on how to act if an access remains patent after kidney transplantation.

Scope of this thesis

Our group previously investigated the pathophysiology of AVF maturation failure and developed an animal model in which to test pharmacological interventions aimed at improving maturation. This thesis focuses on the clinical aspects of the life cycle of the AVF. The first part, chapters 2 and 3, describe the current outcomes of vascular accesses in a retrospective study. In the second part, chapters 4 and 5, outcomes of a novel intervention aimed at improving AVF maturation are presented. In the third part, chapters 6 and 7, a side-effect of a well-functioning AVF is described and we investigate opinions in the field on how this should be approached.

In **Chapter 2** we investigate the outcomes of maturation of AVFs and initial functional outcomes of AVGs in the Netherlands in a multi-center retrospective cohort from 8 hospitals, and we aimed to create a model predicting nonmaturation. **Chapter 3** focuses on the patency outcomes and long-term side-effects and maintenance of the vascular accesses in this cohort.

Chapter 4 presents the rationale and design for the Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study, a randomized controlled trial in which we investigated if liposomal prednisolone improves RCAVF maturation in humans. **Chapter 5** presents the results of this trial.

Chapter 6 introduces the problem of AVF toxicity and provides a review of literature investigating the effect AVF creation and closure have on on cardiac parameters. In **Chapter 7** we aimed to measure the opinions of physicians on how to approach an AVF after kidney transplantation.

Finally, in **Chapters 8 and 9** we discuss and summarize the findings from this thesis.

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