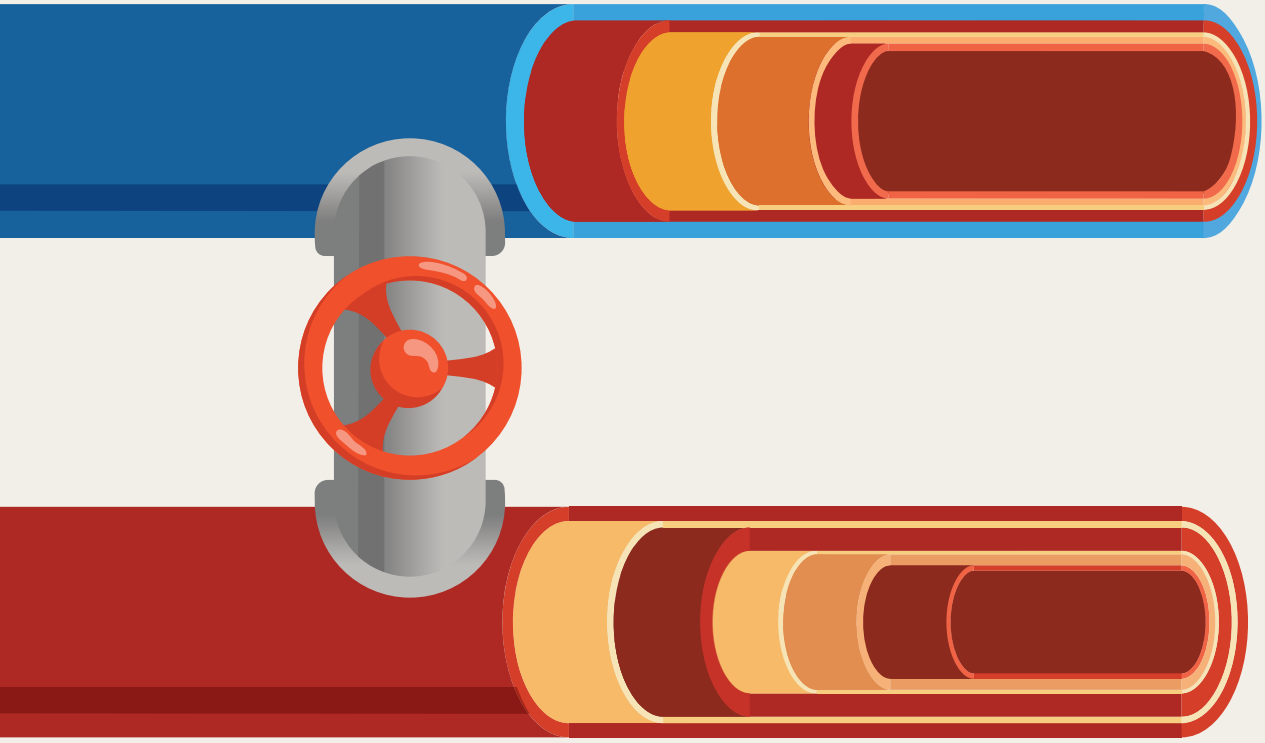
Translational Medical Device Development in Vascular Access for Haemodialysis

Nicholas White



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Translational Medical Device Development in Vascular Access for Haemodialysis

Proefschrift

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Contents

Summary

In patients suffering from end-stage kidney disease the kidneys can no longer adequately filter the body's blood of excess water and waste products. This life-threatening condition is diagnosed in thousands of patients each year in The Netherlands alone, with millions affected globally. Due to a scarcity of suitable donor kidneys, and the difficulties in transplanting them, most of these patients rely on haemodialysis as kidney replacement therapy. In this treatment, blood is taken from the body, passed through an external filter, and then returned. Usually this is performed during 3 sessions of 4 hours per week.

A critical component in haemodialysis is the vascular access (VA), which is necessary to allow sufficient blood to be taken from the body easily and frequently. This is also known as the patients' lifeline. Most often, blood is taken from the arm due to the superficiality of the vessels. However, the typical flow rates in these vessels of ~50mL/min are far too low to supply the dialysis machine of the ~350mL/min it requires for efficient filtering. This challenge is usually overcome by surgically placing an arteriovenous fistula (AVF) in the arm: a vein is cut open and sutured to a hole in the side of an artery. This essentially creates a short circuit in the blood circulation which drastically increases blood flow to enables dialysis. In some cases a synthetic tube is used to create this connection known as an arteriovenous graft (AVG). Directly after placement, the vein starts to adapt to the altered flow conditions and to accommodate a sufficiently high flow for dialysis several weeks later, in a process known as maturation.

Unfortunately the vascular access fails to mature in many patients, and when it does mature, maintaining patency highly uncertain. Patients thus require frequent interventions to restore functionality of their vascular access in order to continue their treatment. In contrast, complications such as aneurysms and high-output heart failure occur when the VA does remain functional. As such, some patients receive their haemodialysis treatment through central venous catheters (CVCs) to bypass the need for a high-flow arteriovenous connection. However, this modality relies on a permanent transcutaneous tube that is placed directly into a central vein. Although immediately usable, these have their own disadvantages such as thrombosis and infection risks.

The inherent drawbacks to all vascular access types highlight the critical need for novel strategies to optimise VA. Due to the mechanical and fluid dynamic nature of vascular access, innovation through medical devices holds significant promise for improving patient outcomes. This dissertation aims to develop and evaluate a novel medical device for improved vascular access for haemodialysis.

Chapter 2 introduces a structured development framework tailored to the European regulatory environment. The Medical Device Regulation (MDR) imposes stringent requirements for high-risk devices, particularly around safety and clinical evidence.

A question-based development strategy is proposed to help guide decision-making, identify knowledge gaps, and improve communication across stakeholders throughout the device life cycle.

Chapter 3 addresses the off-label use of CVCs for power injection of contrast media during imaging procedures. An in vitro study demonstrated that pressures during such injections remained below burst thresholds, suggesting incidental use is unlikely to cause acute device failure. However, evidence of material fatigue and micro-cracks warrants caution. This study highlights how expanding the use of existing devices, even beyond their original intent, may offer clinical benefits if properly evaluated.

A literature review on haemodynamic considerations around arteriovenous VA (**Chapter 4**) revealed that there are currently no modalities available that substantially improve patency. This was further confirmed by a clinical study on a recently introduced external support device, that locks an AVF in an optimal hemodynamic angle (**Chapter 5**). This study concluded that although maturation could be improved, patency did not compared to a historic control group. The constantly supraphysiological flow causes vessel wall damage which ultimately leads to VA failure in or frequent secondary complications in many cases. Yet, patients typically only dialyse during 12 hours per week.

A implantable device was developed that can non-invasively open and close the arteriovenous connection using magnets (**Chapter 6**). This allows flow to be raised sufficiently for dialysis, but the circulation can be normalised otherwise. By removing the supraphysiological flow for most of the time, patency may be improved and complications reduced. Benchtop and cadaver studies showed feasibility of this device in non-invasively controlling the arteriovenous conduit**.** This device was included in a small number of animal studies, that focused on the in vivo development and iterative design improvement (**Chapter 7**). Although some issues remain in the design of the device, these animal studies demonstrated that the implant holds promise for tackling the core issue in vascular access for dialysis. However, future studies are necessary to establish long-term functionality and effects on disease outcomes.

End-stage kidney disease patients will continue to rely on haemodialysis due to limited treatments and donor kidneys. Their VA will remain their lifeline. Therefore, improving clinical outcomes of VA is of critical importance. A proposed device to open the high-flow conduit only during dialysis shows promise but involves significant development risks and long timelines. Interdisciplinary teams are essential to meet all user requirements. Advancing vascular access for haemodialysis requires sustained collaboration to develop, validate, and implement clinically grounded innovations for tangible patient benefits.

Samenvatting

Bij patiënten die lijden aan nierziekte in het eindstadium kunnen de nieren het bloed van het lichaam niet meer voldoende filteren van overtollig water en afvalstoffen. Bij deze levensbedreigende aandoening worden alleen al in Nederland jaarlijks duizenden patiënten gediagnosticeerd en wereldwijd lijden miljoenen patiënten hieraan. Door een tekort aan geschikte donornieren en de uitdaging bij het transplanteren ervan, zijn de meeste van deze patiënten afhankelijk van hemodialyse als niervervangingstherapie. Bij deze behandeling wordt bloed aan het lichaam onttrokken, door een externe filter geleid en vervolgens teruggevoerd. Meestal gebeurt dit tijdens 3 sessies van 4 uur per week.

Een cruciaal onderdeel van hemodialyse is de vaattoegang, die ervoor zorgt dat er gemakkelijk en regelmatig voldoende bloed uit het lichaam kan worden afgenomen. Dit wordt ook wel de levenslijn van de patiënt genoemd. Meestal wordt bloed in arm afgenomen wegens de oppervlakkigheid van de vaten. Over het algemeen stroomt er ~50 mL/min bloed door deze vaten. Dit is echter veel te laag om de dialysemachine te voorzien van de ~350 ml/min die nodig is voor een efficiënte filtering. Dit probleem wordt meestal opgelost door chirurgisch een arterioveneuze fistel (AVF) in de arm te plaatsen: een ader wordt opengesneden en gehecht aan een gat in de zijkant van een slagader. Dit creëert een soort kortsluiting in de bloedsomloop waardoor de bloedstroom drastisch toeneemt, en dialyse mogelijk wordt. In sommige gevallen wordt een synthetische buis gebruikt om deze verbinding tot stand te brengen, die bekend staat als een arterioveneuze graft (AVG). Direct na de plaatsing begint de ader zich aan te passen aan de veranderde omstandigheden en kan enkele weken later een voldoende hoge stroming aan voor dialyse, in een proces dat maturatie wordt genoemd.

Helaas is de maturatie in veel patiënten niet succesvol, en wanneer dit wel lukt is het behoud van functionaliteit, patency, van de vaattoegang zeer onzeker. Patiënten hebben dus regelmatig interventies nodig om de functionaliteit van hun vaattoegang te herstellen zodat ze hun behandeling kunnen voortzetten. Daarnaast treden complicaties zoals aneurysma's en hartfalen vaak op wanneer de vaattoegang wel functioneel blijft. Daarom dialyseren sommige patiënten via centrale veneuze katheters om de noodzaak van een arterioveneuze verbinding met hoge flow te omzeilen. Deze methode gebruikt een permanente slang die door de huid heen steekt en rechtstreeks in een centrale ader is geplaatst. Hoewel deze onmiddellijk bruikbaar zijn, hebben ze hun eigen nadelen zoals trombose- en infectierisico's.

De inherente nadelen van alle soorten vaattoegang benadrukken de kritieke behoefte aan nieuwe strategieën om vaattoegang te verbeteren. Vanwege de mechanische en vloeistofdynamische aard van vaattoegang is innovatie met medische hulpmiddelen potentieel veelbelovend voor het verbeteren van de uitkomsten. Dit proefschrift is gericht op het ontwikkelen en evalueren van een nieuw medisch hulpmiddel voor verbeterde vaattoegang voor hemodialyse.

Hoofdstuk 2 introduceert een gestructureerd ontwikkelingskader dat is afgestemd op de Europese regelgeving. De Verordening Medische Hulpmiddelen (Medical Device Regulation, MDR) stelt strenge eisen aan hulpmiddelen met een hoog risico, met name op het gebied van veiligheid en klinisch bewijs. Er wordt een ontwikkelingsstrategie voorgesteld om de besluitvorming te sturen, hiaten in de kennis te identificeren en de communicatie tussen belanghebbenden tijdens de gehele levenscyclus van het hulpmiddel te verbeteren.

Hoofdstuk 3 behandelt het off-label gebruik van centraal veneuze katheters voor injectie van contrastmiddelen tijdens beeldvorming. Een in vitro onderzoek toonde aan dat de druk tijdens dergelijke injecties op veilige waardes bleef, wat suggereert dat incidenteel gebruik hoogstwaarschijnlijk geen acuut falen veroorzaakt. Er zijn echter aanwijzingen van materiaalvermoeiing en microscheurtjes op het moment van gebruik, waardoor voorzichtigheid geboden is. Deze studie laat zien hoe uitbreiding van het gebruik van bestaande hulpmiddelen, zelfs buiten hun oorspronkelijke doel, klinische voordelen kan bieden als ze goed worden geëvalueerd.

Uit een literatuurstudie naar hemodynamiek rond vaattoegang (**Hoofdstuk 4**) bleek dat er momenteel geen modaliteiten beschikbaar zijn die de patency substantieel verbeteren. Dit werd verder bevestigd door een klinisch onderzoek naar een recent geïntroduceerd extern ondersteuningsapparaat dat de AVF in een optimale hemodynamische hoek fixeert (**Hoofdstuk 5**). Deze studie concludeerde dat de patency niet verbeterde in vergelijking met een historische controlegroep. De constante hoge stroming veroorzaakt schade aan de vaatwand die uiteindelijk in veel gevallen leidt tot falen van de vaattoegang of andere complicaties. Patiënten dialyseren echter meestal maar 12 uur per week.

Er is een implantaat ontwikkeld dat de arterioveneuze verbinding magnetisch kan openen en sluiten (**Hoofdstuk 6**). Hierdoor kan de flow voldoende worden verhoogd voor dialyse, maar kan de circulatie daarna ook worden genormaliseerd. Door de hoge bloedstroming voor het gros van de tijd weg te nemen, kan de patency worden verbeterd en kunnen complicaties worden verminderd. In een testopstelling werd aangetoond dat de implantaat in een gecontroleerde omgeving werkt. Een klein aantal dierstudies met deze implantaat richtte zich op de verdere ontwikkeling en iteratieve verbetering van het ontwerp (**Hoofdstuk 7**). Hoewel er nog enkele verbeterpunten zijn, toonden deze dierstudies aan dat de implantaat veelbelovend is voor het aanpakken van het kernprobleem bij vaattoegang. Toekomstig onderzoek is echter nodig om de lange termijn functionaliteit en de effecten vast te stellen.

Patiënten met nieraandoeningen in het eindstadium zullen afhankelijk blijven van hemodialyse vanwege beperkte alternatieven. Hun vaattoegang blijft essentieel. Daarom is het verbeteren van de vaattoegang van cruciaal belang. De ontwikkelde implantaat die de vaattoegang alleen tijdens de dialyse te opent is veelbelovend, maar brengt aanzienlijke ontwikkelingsrisico's en een lange ontwikkeltraject met zich mee. Interdisciplinaire teams zijn essentieel om aan alle gebruikerseisen te voldoen. Het verbeteren van de vaattoegang voor hemodialyse vereist een duurzame samenwerking om klinisch onderbouwde innovaties te ontwikkelen, te valideren en te implementeren voor tastbare voordelen voor de patiënt.

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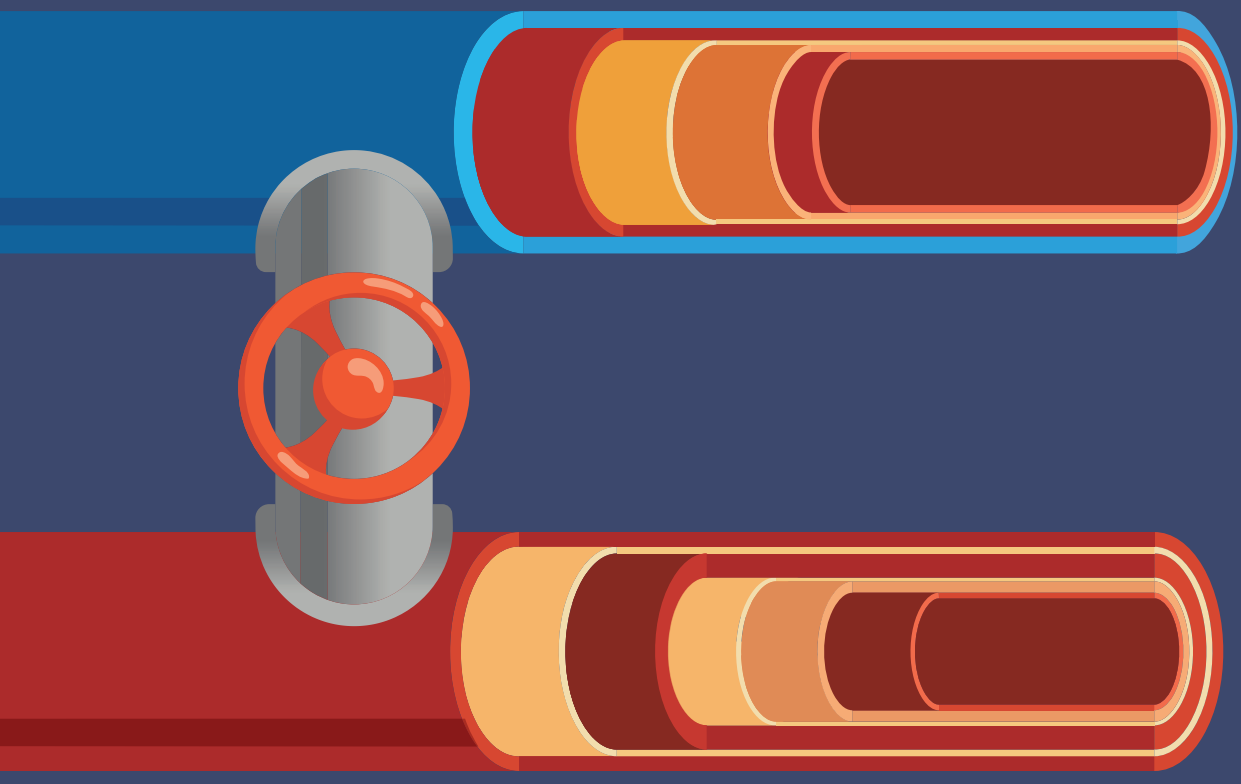

Introduction

1.1 Understanding haemodialysis

End-Stage Kidney Disease

The **kidneys** serve as the body's recyclers, processing roughly 180 litres of fluid daily. They regulate the elimination of excess water and waste while maintaining stable blood pressure by retaining essential fluids, blood cells, and minerals. Due to these essential functions, kidney failure has severe consequences for patients. Kidney failure can manifest as acute or chronic kidney disease. Numerous factors contribute to kidney failure, including diabetes, high blood pressure, heart failure, obesity, and advancing age [1]. The prevalence of chronic kidney disease, currently at 10%, is projected to increase in years to come due to our aging population, unhealthy dietary habits resulting in rising obesity rates [2].

Eventually, chronic kidney disease can progress to end-stage kidney disease (**ESKD**) in which the kidneys are so severely damaged that the patient's kidney function must be supplemented. Without kidney replacement therapy, ESKD is life-threatening because the body can no longer excrete waste products and excess water. In The Netherlands around 2,000 individuals are diagnosed with ESKD annually and receive treatment [3]. Globally it is estimated that the number of patients receiving treatment will double from 2.6 million in 2010 to 5.4 million in 2030 [4], in part due to increasing access of care in developing countries. While receiving a donor kidney is the ideal treatment for these patients, the scarcity of donor organs and the challenges associated with transplantation surgery and immunosuppressive drugs often necessitate an alternative treatment—**dialysis**.

Haemodialysis as a replacement of the kidney

Dialysis involves using a machine to help kidney failure patients eliminate waste from their bodies. This can be achieved intracorporeally through peritoneal dialysis using the abdominal lining as a natural filter, or extracorporeally through **haemodialysis**, depicted in Figure 1-1. Approximately 22% of all ESKD patients receive a donor kidney, 9% undergo peritoneal dialysis, and 69% undergo haemodialysis [4], [5], [6], [7]. Globally this amounted to 2.1 million haemodialysis patients in 2020 [4], [5], [6], [7].

During haemodialysis, blood is filtered through an external dialyser. This treatment can occur daily in a home setting or in a centre, typically in **three sessions of four hours per week** [8]. A high-flow **vascular access** is necessary to connect the patient's bloodstream to the dialyser for haemodialysis and supply sufficient blood to efficiently filter the blood and remove excess water. A dialyser usually requires a supply of ~350 mL/min to and from the machine [9], [10]. Ideally this high flow of blood is easily accessible to connect the patient's circulation to the dialyser multiple times per week.

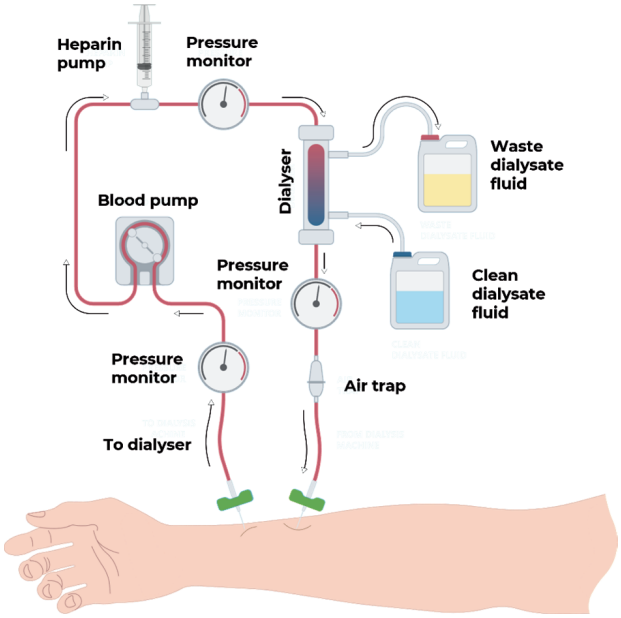

Figure 1-1: a schematic depiction of a haemodialysis circuit for blood filtration outside the body. In this overview, the blood is taken from the lower arm, passed through the dialysis machine, and fed back into the lower arm to complete the circuit.

1.2 Vascular access for haemodialysis

The vascular access is crucial to perform haemodialysis, and is therefore considered the lifeline of the patient. Without a functional vascular access, the patient cannot receive dialysis. Without dialysis, waste product and excess fluids cannot be removed from the body, and the patient will fairly quickly die from autotoxication. There are currently 3 types of vascular access most often used for haemodialysis: Arteriovenous Fistulae (**AVF**s), Arteriovenous Grafts (**AVG**s), and Central Venous Catheters (**CVC**s). Each has its merits, but also its pitfalls:

AVFs

In the US, 60% of patients receive an AVF [11], which involves surgically connecting a vein and artery in the arm to create a high-flow circuit for dialysis, depicted in Figure 1-2a. Two large cannulas or needles are placed in the vein for blood flow to and from the dialyser. This repeated puncturing can cause vascular stenosis, weakening the access site. Proper technique and regular assessment are vital for minimizing complications. AVFs are functional when at least 500 mL/min of blood flows through the vein and they have a diameter >4 mm, but this **maturation**, or luminal expansion, can take up over 6 weeks [12].

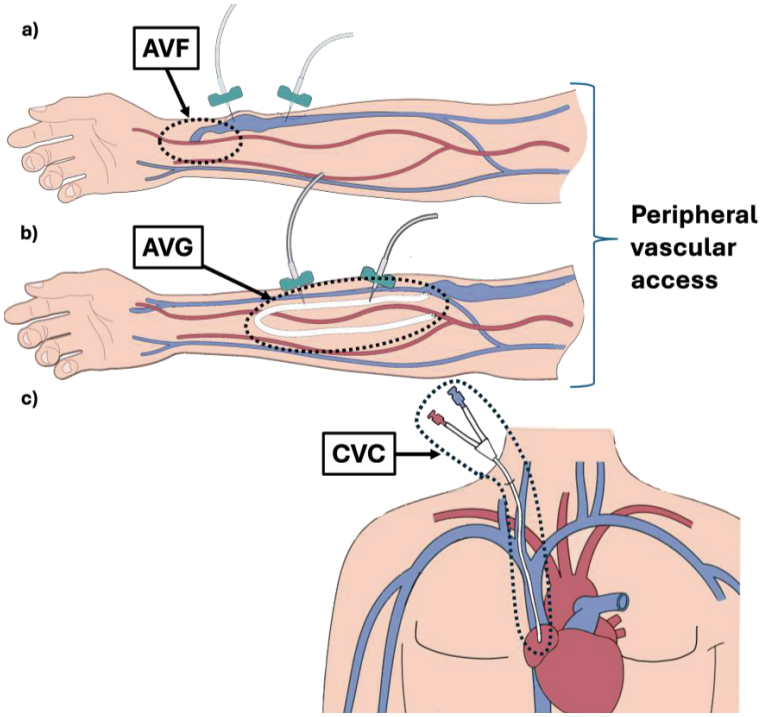

Figure 1-2: The most commonly used types of vascular access for hemodialysis. These accesses provide a proximal and distal access port to the circulation to enable the filtration of blood in an external dialysis machine. a) a surgically created arteriovenous fistula (AVF), b) a surgically created arteriovenous graft (AVG), and c) a permanently central venous catheter (CVC) which permanently protrudes the skin.

While AVFs are the gold standard with the fewest long-term interventions [13], they carry risks such as hematoma, infection, thrombosis, aneurysms, and nerve injury. The high flow introduced by the connection can lead to complications such as stenosis, thrombosis, Steal syndrome, and aneurysms, and increase the risk of heart failure due to the constantly elevated cardiac output necessary to sustain the supraphysiological vascular access blood flow [14].

AVGs

Similarly to AVFs, AVGs connect a vein and artery, but use a graft made from synthetic or biological material to connect the blood vessels, as shown in Figure 1-2b. Together, AVFs and AVGs are known as **peripheral vascular access**. AVGs are used by 15% of US patients [11]. They typically offer a quicker time-to-use (2 weeks) and fewer cannulation-related complications compared to AVFs, but carry a higher risk of infection and more often require surgical maintenance [8]. These make AVGs less suitable for long-term use.

CVCs

Shown in Figure 1-2c, CVCs are used by 25% of patients in the US [11] and involve inserting a catheter into the central vein near the heart, where flow rates are sufficiently high for dialysis

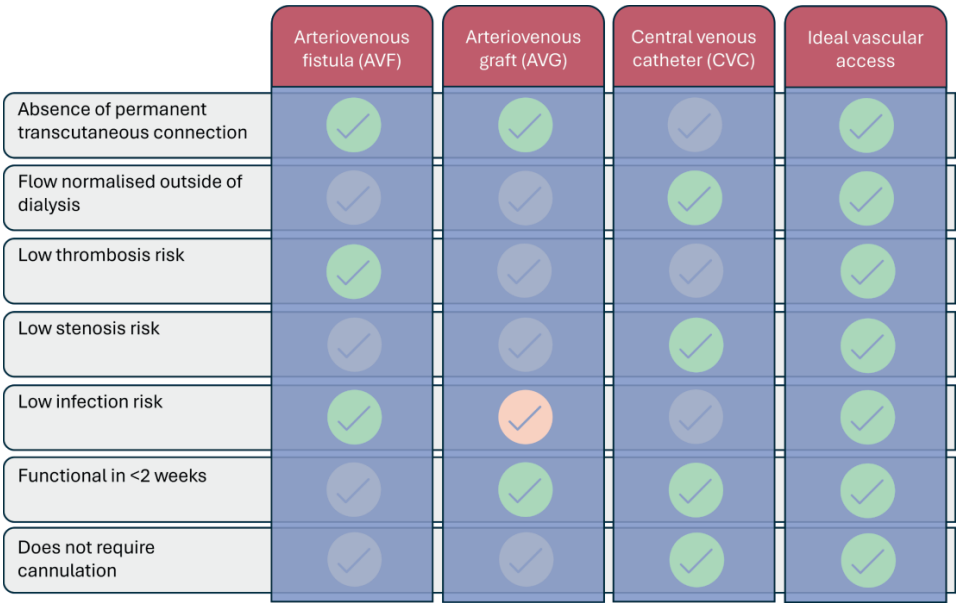

Figure 1-3: pros and cons of the different types of vascular access used for haemodialysis.

and no arteriovenous connection is required. They are typically used in acute settings, as they are immediately functional, or when peripheral vascular access is not possible. However, they pose a significant infection risk due to the permanent external connection, and the lack of flow when inactive increases the risk of clotting [8]. Flushing can reduce, but not eliminate, this risk.

The (Non-)Ideal Vascular Access

Given the types of vascular access used, and the benefits and drawbacks of each, it can be assumed that an ideal vascular access (Figure 1-3):

- only has a transcutaneous connection when dialysing, and
- only elevates cardiac output during dialysis,
- does not thrombose,
- remains functional for the remainder of the patient's life without intervention,
- has a low infection risk,
- is immediately functional, and
- does not require cannulation for use.

Unfortunately, none of the types of vascular access meet all these specifications. Clinical guidelines state that the choice remains a trade-off tailored to each patient, e.g. to minimise complications or time-to-use [8]. Although the AVF is by far the most commonly used, outcomes are very far from optimal. Loss of access patency is the primary risk of the durability of AVF [12], [14], [15]. The altered blood flow causes luminal narrowing (stenosis) of the venous outflow tract near the AVF, ultimately leading to thrombosis [16]. The less than

optimal patency rates lead to an average of 1.5 surgeries per patient per year to maintain functional vascular access, with associated healthcare costs at on average around USD 15k per patient per year [17], [18]. Next to vascular access surgeries, the cardiac burden, steal syndrome and aneurysms also require maintenance surgeries. Vascular access survival is typically lower and interventions more frequent in AVGs and CVCs [13]. There is a clear clinical need for a durable arteriovenous conduit which can limit primary and secondary dialysis-related conditions and thereby reduce healthcare costs.

1.3 Vascular access innovation

Since the introduction of dialysis in 1947 and AVF in 1966 [19], a lot of research into improving vascular access has been conducted. Although understanding of the mechanisms behind maturation and failure has improved significantly in the past decades, the outcomes have not. Methods such as improving geometry and monitoring of the vascular access, prescribing medication, lifestyle changes improved surgical materials only show limited benefits.

Due to the mechanical and fluid dynamic nature of vascular access, innovation through **medical devices** holds significant promise for improving patient outcomes in haemodialysis. The altered flow conditions necessary to perform dialysis, e.g., cause mechanical stimuli to the blood vessels leading to remodelling and often complications, or cause coagulation [16]. Therefore, in more recent years, numerous innovations in medical devices for haemodialysis have been developed, with the goal of reducing complications and improving the quality of treatment. For instance, some devices are designed to enhance patient comfort [20], reduce the risk of complications such as infection and thrombosis [21], or extend the longevity of access sites [22]. However, there are also potential downsides, such as device-related complications, including malfunction, migration, or thrombosis.

Using devices in a clinical setting poses significant safety challenges due to the associated risks to patient wellbeing that may be introduced during malfunction, particularly in implanted devices, which are often necessary for vascular access. Legislation, such as the recently introduced European Medical Device Regulation (**MDR**) [23], plays a crucial role in balancing innovation and safety. While these regulations ensure the quality, safety, and performance of medical devices, they can also introduce barriers to market entry and hinder rapid innovation due to the rigorous testing and compliance requirements. Thus, navigating the regulatory landscape of medical devices requires careful consideration of both patient needs and regulatory standards to foster responsible innovation in vascular access technology.

Finally, the transdisciplinary nature make the design and development of medical technologies inherently challenging. These technologies often require the integration of insights from various specialized fields, including engineering, medicine, biology, as well as patients, which do not always naturally converge. Moreover, the introduction of new medical technologies can create challenges in training healthcare professionals, integrating devices into existing clinical workflows, and ensuring patient acceptance. This complexity arises from

the need to balance numerous factors—such as clinical need, mechanical functionality, biological compatibility, and long-term sustainability—as the requirements of various stakeholders can vary considerably. Finding alignment is not always easy, but is essential in ensuring that innovations improve clinical outcomes and enhance patient well-being.

1.4 Aim and outline

This dissertation aims to develop and evaluate a novel medical device for improved vascular access for haemodialysis. This is done by examining the interplay between clinical demands, scientific knowledge, technological advancements, and regulatory requirements.

In **Chapter 2** the regulatory requirements relating to the development of medical devices are characterised, specifically for clinical investigations in vascular access devices. A framework for tackling this complex network of rules and procedures is proposed, which is followed in subsequent chapters.

Chapter 3 focuses on the expansion of use cases in currently marketed devices in the legal and developmental framework proposed in Chapter 2. The safety for off-label use of central venous catheters for contrast fluid injection in angiography is determined to potentially mitigate the need of creating additional incisions during the procedures.

A literature study on surgical and technical peripheral vascular access modalities in **Chapter 4** discusses the high flow haemodynamic conditions presented by peripheral vascular access. An overview of existing modalities to modulate these conditions favourably is provided, and the most important pitfalls are determined.

Chapter 5 examines the clinical performance of optimising the surgical procedure of radiocephalic AVF placement by including several of the modalities introduced in Chapter 4 in a retrospective clinical study.

Following the findings of Chapter 4, **Chapter 6** introduces an implantable device that creates a novel type of peripheral vascular access, aiming to tackle the core issue present in currently available solutions.

Chapter 7 discusses the further development of the implantable device from Chapter 6 by integrating the framework for clinical development introduced in Chapter 2. Initial in vivo studies in animals are reported and future studies towards clinical application are described.

Finally, **Chapter 8** gives an overall summary of the research described in this dissertation and discusses future prospective on vascular access devices to improve outcomes in vascular access for haemodialysis.

This dissertation comprises five studies, presented across five chapters, each based on papers published in peer-reviewed scientific journals. As self-contained publications, each chapter includes its own introduction, discussion, and reference list, which inevitably results in some redundancy between chapters.

Finally, the research and results presented in this dissertation generously received financial support from Delft Health Initiative. This aim of this body is aligned with this dissertation: to break down barriers between technological solutions and clinical application, to improve sustainability, reduce interventions and complications, and improve patient care.

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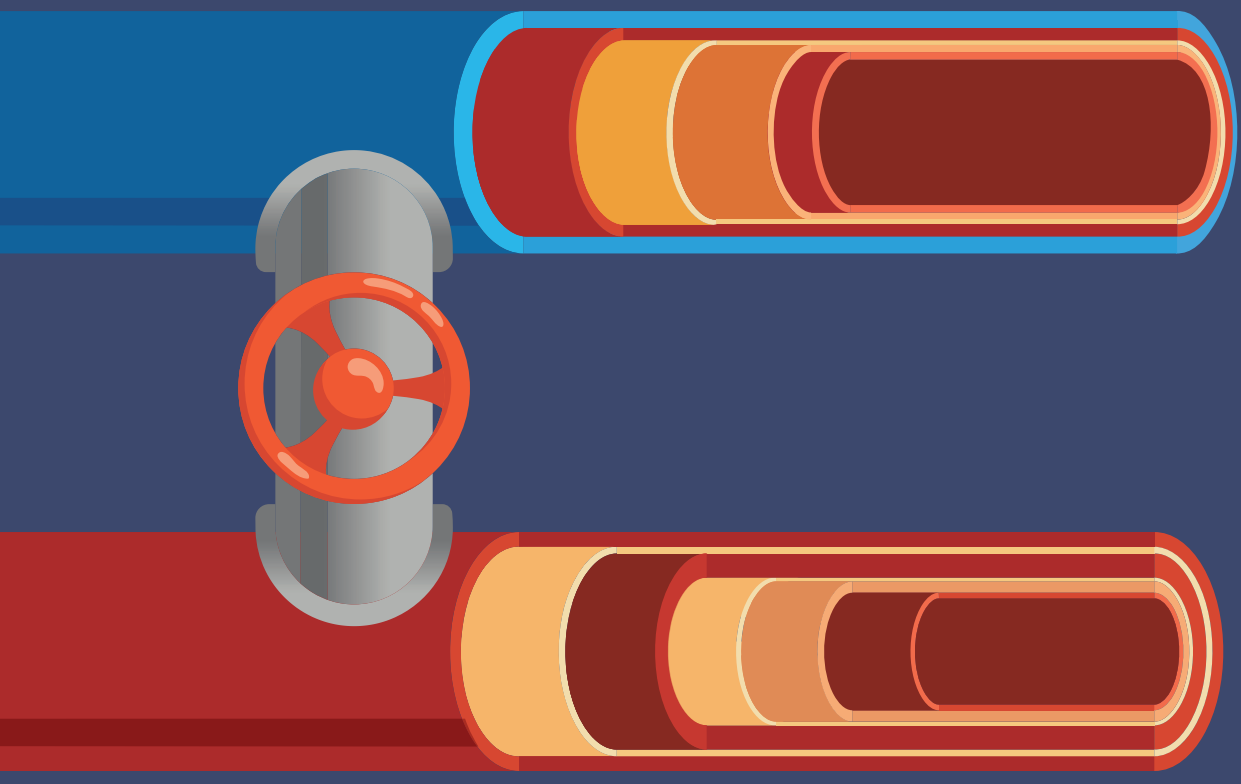

Question-based development of high-risk medical devices: A proposal for a structured design and review process

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This chapter explores the question-based development framework for high-risk medical devices, which aligns with this dissertation's aim of evaluating structured approaches to regulatory science and innovation in medical technology. By critically examining this framework, the chapter contributes to the broader discussion on optimizing evidence generation and decision-making throughout the medical device lifecycle.

Abstract

The recent introduction of the European Medical Device Regulation poses stricter legislation for manufacturers developing medical devices in the EU. Many devices have been placed into a higher risk category, thus requiring more data before market approval, and a much larger focus has been placed on safety. For implantable and Class III devices, the highest risk class, clinical evidence is a necessity. However, the requirements of clinical study design and developmental outcomes are only described in general terms due to the diversity of devices.

A structured approach to determining the requirements for the clinical development of high-risk medical devices is introduced, utilizing the question-based development framework, which is already used for pharmaceutical drug development. An example of a novel implantable device for haemodialysis demonstrates how to set up a relevant target product profile defining the device requirements and criteria. The framework can be used in the medical device design phase to define specific questions to be answered during the ensuing clinical development, based upon five general questions, specified by the question-based framework.

The result is a clear and evaluable overview of requirements and methodologies to verify and track these requirements in the clinical development phase. Development organizations will be guided to the optimal route, also to abandon projects destined for failure early on to minimize development risks.

The framework could facilitate communication with funding agencies, regulators and clinicians, while highlighting remaining 'known unknowns' that require answering in the post-market phase after sufficient benefit is established relative to the risks.

2.1 An introduction to the Medical Device Regulations

Throughout history magical curative properties of some medicines have been advertised that were later found deleterious. This led to the first legislation that regulated the marketing of these products in 1938: the Federal Food Drug and Cosmetic act. In later years this was followed by further US legislation, specifically defining and regulating high risk medical devices. In the USA both medicines and devices have always been regulated by the FDA, that recognizes the strong overlap between medicinal products and devices [1]. However, it is suggested that 80,000 deaths and 1.7 million injuries were attributed to medical devices in the past decade, potentially linked to inadequate regulation of those products and their manufacturers [2]. In Europe the development of these regulations went in separate directions and took place much later, with the EU Active Implantable Medical Device Directive (AIMDD) introduced in 1990 [3], and Medical Device Directive (MDD) in 1993 [4]. The directives outline certain goals which the devices must meet and are subsequently selectively integrated in national laws. These goals are then controlled by national authorities and local notified bodies. This changed in 2017 with the adoption of the EU Regulation 2017/745 on medical devices, the Medical Device Regulation (MDR) [5] and the ending of the transition period in 2021, when all existing European directives on medical devices were replaced by this single binding law covering all medical devices in all member states. The conformity assessments in each EU country should now use similar standards as set out in the new legislation, which forces manufactures to change the development processes used in the past [6]. The requirements regarding clinical study design, necessary for devices considered high-risk, and outcomes during the development are described only in general terms in Chapter VI of the EU MDR due to the enormous diversity of medical devices that fall under the regulation [5]. This regulation does place an increased focus on safety and performance, which should benefit patients [7]. Unfortunately, this often conflicts with the interests of manufacturers as it poses substantial hurdles and financial risks [8], and eventually increases costs of devices which hinders penetration of certain markets [7]. However, these interests should be synergistic as safe and well-performing devices should also encourage adaptation, thus creating more revenue, while recalls of poorly functioning devices has bankrupted companies [9]. Efforts exist to bridge this gap, although consistent structured approaches for such development programs are scarce [8].

The development of new medical devices is in many aspects analogous to new medicines; the device has an assumed mechanism of action, and a designed profile with a potential positive value for health but may also generate risks. The MDR now requires that these properties are also formally determined for devices; a much larger focus has been placed on safety and mapping of side-effects, further increasing overlap and making the evaluation process more similar to drugs. The program of clinical investigations for new medicines has been well-established since 1998 (5) and is supported by an extensive set of guidelines issued by both the FDA and EMA. This is not the case for medical devices within the MDR.

A structured approach to the development of clinical trial programs would therefore be useful for industry, researchers and regulators. Now more than ever, the knowledge and expertise from the field of clinical pharmacology could be valuable in the development of medical devices due to the aforementioned similarities in challenges. Conversely, clinical pharmacologists will be increasingly involved in the development of, e.g., products that are combinations of medicinal molecules and devices. For pharmaceutical drugs, the ICH E8 guideline on clinical development [10] states succinctly *"The essence of clinical development is to ask important questions and answer them with appropriate studies. The primary objectives of any study should reflect the research questions and be clear and explicitly stated."* The concept of Question-Based Drug Development originated from this statement [11], [12], [13], [14] and utilises a set of 5 or 6 generic questions to be answered during the clinical development of drugs to properly design the clinical evaluation plan. In this paper we propose a structural approach to the development of high-risk medical devices based on the question-based development method for drugs as a means to dealing with the clinical MDR requirements. An example of a novel vascular access device will be utilised to demonstrate the application of this approach. To support the development of this method for use in the MDR, a more in-depth section is provided to understand the background and implications of the new regulation. All references to specific sections of the MDR are shown as hyperlinks to get immediate access to the regulation. An overview of definitions of the terms in *italic* can be found in Supplemental File 1 (online).

The Medical Device Regulation

Of patients receiving a specific breast implant in the early 2000s, over a third showed rupture of at least one of the silicone implants in a 10 year follow-up – far higher than most other breast implants [15]. In retrospect, the material used did not pass biocompatibility tests, posing significant risks to patients. In 2010 this resulted in a recall of this medical device legally marketed in the EU [16]. Additionally, in 2011 a faulty hip prosthetic was recalled from the European market after it became apparent metal particles resulting from wear of the device made their way into surrounding tissue. The revision rate for this implant was 49% at 6 years, where others were at 12-15% after 5 years. In some patients the implant caused permanent disability. Investigation revealed that clinical evidence that should have shown this before market approval was largely absent [17].

Both these examples of unnecessary suffering demonstrated shortcomings of the European legislation on medical devices at the time and contributed to the introduction of a new EU-wide regulation: on the 26th of May 2021 the MDR has fully replaced MDD and AIMDD in the EU. An important change of the MDR is the stronger focus on clinical evidence required to the demonstrate the safety and performance of a medical device. The safety of the device must be continuously monitored after market introduction, in the form of *post-market surveillance* and *periodic safety and update reports*.

*Table 2-1: An overview of medical device classification of the Medical Device Regulation (MDR) and the conformity assessment route. *Unless necessary for the general safety and performance requirements (to be determined by the manufacturer) PMCF = post marketing clinical follow up. PSUR = periodic safety update report. Further explanation of the terminology in italic can be found in supplemental file 1 (online).*

Classification and main characteristics	**Examples of Medical Devices**	**Conformity Assessment Route (see art. 52)**	**Documentation Requirements**	**Clinical trials required**
Class I e.g., non-invasive or short-term invasive under direct control of the operator	Surgical gloves Bandages Wheelchair Scalpel blades Examination lamps Surgical instruments	Conformity Assessment by Manufacturer (by notified body in specific cases, sterility etc.)	*Base technical documentation* (includes *PMCF*)	No*
Class IIa Active and non-invasive or non-active but in contact with bodily fluids	Needles Syringes ECG MRI scanner Hearing aid Contact lenses	Chapters I and III of Annex IX, assessment of technical documentation **By notified body**	*Base technical Documentation*+ *PSUR* every 2 years	No*
Class IIb Active and invasive devices or invasive devices that cause a direct hazard during malfunction (Annex VIII, rule 12)	Devices involving ionizing radiation Vascular closure devices Dialysis system Ventilator Infusion pump IC monitoring software Vascular grafts and stents	Chapters I and III of Annex IX, assessment of technical documentation (Chapter II, part (4), Annex IX) (alternatively, annex X coupled with annex XI for implantables) **By notified body**	*Base technical Documentation*+ *PSUR* every 2 years, or every year for implantables	Yes for implants (see exceptions art. 52(4)), otherwise no* Optional expert consultation prior for devices associated with medicinal products (Annex VIII, rule 12)
Class III Implants and invasive devices in contact with vital anatomies	Neuroendoscopes Cardiovascular catheters Prosthetic heart valves Intra-aortic balloon pump Breast implants Joint replacements Drug-eluting stents	Annex IX, assessment of technical documentation (alternatively, annex X coupled with annex XI) **By notified body**	*Base technical Documentation*+ yearly *PSUR*	Yes with optional expert consultation prior through notified body. (see exceptions art. 61(4))

The classification of the device (class I, IIa, IIb and III) is an indication of the risk of the device to patients (class III being the highest risk), but more importantly, determines the assessment route for market introduction and thus the level of technical and clinical evidence required (Table 2-1). The classification is determined by a set of classification rules as part of the MDR (Annex VIII, MDR). When compared to earlier directives, the MDR also increased the classification level of specific medical devices to the highest device class such as devices that are in direct contact with the central nervous system and the central circulatory system. As a result, an important change is that the amount and quality of clinical evidence necessary for market approval has increased. For most devices the conformity assessment is required through a notified body. These are bodies appointed by the relevant national governments of EU member states for the purpose of assessing conformity of certain products to applicable legislation prior to receiving CE marking and market approval.

A *benefit-risk analysis* and clinical evaluation (MDR Annex XIV, part A) are integral parts of the *base technical documentation* of any medical device. The clinical evaluation must include all the relevant clinical information needed to demonstrate conformity with the *general safety and performance requirements* of the device that are determined by the developer, which should ensure suitability for intended use while remaining safe. In certain cases, *clinical evidence* is necessary to demonstrate conformity to these requirements prior to market approval, and the manufacturer must provide an overview and rationale of suitability of clinical evidence. *Equivalence* with prior data can be used as a means of providing clinical evidence, and may mitigate the necessity of *clinical investigations*.

As for medicinal drugs [10], clinical evidence from clinical investigations is always required for implantable and class III, or high-risk devices (MDR art. 61(4)). The exception is when it can be demonstrated that the drug or device is equivalent to other existing safe drugs [10] or devices (MDR art. 61(4)). Prior to clinical evaluation or investigation, developers may consult an expert panel to review their clinical development strategy. The developer must document the findings in a clinical evaluation report, included in the technical documentation. Suitability of this data is evaluated by the notified body and appointed experts, which in turn prepare a clinical evaluation assessment report. For class III implantable devices and class IIb devices intended to administer or remove medicinal products, the conclusion is transmitted to the European Commission for additional assessment of the document by an expert panel. When conformity to the MDR is adequately achieved and the notified body provides a positive response, a declaration of conformity and the CE-marking are granted, and the device may be marketed in member states.

The potential necessity of clinical investigations is apparent from the MDR. However, the structure and goals of the clinical trials and the amount of clinical evidence required to demonstrate conformity with the general safety and performance requirements is not clearly defined and left to the developer. As the function of clinical trials is to show conformity with the general performance and safety requirements, these requirements to some extent dictate what is to be investigated. However, for devices as with medicines, the design of the clinical

trials also plays a part in the definition of the requirements, as they must be able to provide certain data (e.g., from biomarkers) with which the requirements can be objectively verified, are subjected to ethical assessments, and patients must consent to participation. This interplay can be complex, but guidance to structure a program to demonstrate safety and efficacy, while minimising risks and costs, is currently still absent for devices, contrary to medicines. To facilitate development, a framework for a structured approach could be beneficial for developers, regulators, and ultimately patients.

Clinical development of devices-a proposal for structure

A structured program for clinical development serves several functions. Most importantly the strategic aspects of the development are made explicit in clear terms that can be approached experimentally. In listing the "known unknowns" and how these can be dealt with, the risk of development becomes transparent. Such a structured program is also best suited for expert consultation. The MDR appears to give only general indications that a device should have proven efficacy and safety as could be determined in a confirmatory Phase III trial for a medicine. The reality is more complex in practice, because neither for a medicine nor for a device can such a trial be performed without preliminary studies that should logically lead to this confirmation in Phase III. The MDR provides little guidance about what to do. In this section we attempt to provide further structure to this programme of studies.

The importance of defining proper questions and studies can, for example, be highlighted by the recent introduction of an aspiration-thrombectomy catheter in the US market [18]. During the clinical study, the researchers primarily focused on the difference in ventricular diameters in a broad target population and found positive results. However, if they had focused more on clinical outcomes, such as risk of death or better functional status, while enrolling participants from more accurate target population, the results may have differed significantly and changed the course of development. Unfortunately, only after numerous patients had already been treated with this device it became apparent that this expensive treatment offered no clinical benefit to the patient. A more structured and properly defined clinical evaluation plan can lead manufacturers to abandonment of a project at a much earlier stage and save a lot on investments into a product destined for failure.

The system of question-based drug development proposed for drugs is based upon the classification of questions to be answered about the product under certain headings [14]. This system provides a clear and evaluable overview of the "known unknowns" of the product and the methodology to resolve these. Unresolved questions obviously determine the development risk of the product and the system can be used for modelling the financial value of a product using real options decision techniques [11]. Due to the increased focus on the demonstration of safety through clinical evidence in the MDR, this framework can now also pose a solution for the development of high-risk medical devices, similarly to how it is used in the development of medicines. The question-based approach is preceded by an analysis of the target product profile.

2.2 Target Product Profile and Question-Based Evaluation

Table 2-2: Suggested topics for a Target Product Profile of a medical device ([1] and MDR Annex I).

Commercial	- **Intended markets** - **Target price** - **Development costs**
Technical/Engineering (MDR Annex I, Chapter 2)	- **Biological properties** - **Robustness** - **Technical Safety** - **Manufacturing** - **Contamination** - **If active: Supply and transmission of energy**
Medical (MDR Annex I, Chapter 2)	- **Patient indication** - **Target population: age, gender, etc.** - **Safety** - **Efficacy** - **Adverse events**
Intellectual Property	- **Patentability** - **Competitor interference**
Patient Perspective	- **Outcomes** - **Cost of treatment** - **Quality of Life**

Determination of a target product profile (TPP)

According to the World Health Organization (WHO), TTPs "*aim to inform product developers, regulatory agencies, procurement agencies and funders on R&D and public health priorities. They describe (1) the preferred and (2) the minimally acceptable profiles for vaccines, therapeutics, diagnostics or medical devices criteria. They also provide information for funders and developers on the performance and operational characteristics expected of products if they are to meet WHO's needs.*" [19]

When used in drug development, the purpose of a target product profile is to clearly define what the product should accomplish in a fixed document that clearly defines a desired state and the minimally accepted profile. Preferably, the document is supported by literature, research, properties of competing products and above all by the requirements of the patient. At the same time, it facilitates communication between developers and regulators; it provides structure and clarifies the goals and expectations in the drug development process, as well as the type of clinical studies and end-points necessary [20]. In general, a TPP specifies the medical need by including the current state of the art, includes a section on efficacy and safety and can be constructed analogous to the structure as suggested by Tansey [21] for medicines. The MDR states that a set of general performance and safety requirements must be set for a device to ensure the clinical condition or safety of patients is not compromised. When such a guarantee is not possible, these risks must be minimised. Thus, these are the minimum requirements a device must meet in order to be safe and of benefit, analogous to a minimally accepted profile in a drug TPP. By defining a desired "target" state with a number of

criteria, design choices can be made to most closely approximate this state. Determining these elements in this fashion forces the manufacturer to consider scientific reasoning for these measures alongside measures that can be objectively evaluated. Thus, the elements of the TPP can already summarize what is necessary to achieve a marketable product that is of benefit to patients. It should be set up prior to the design stage as it defines how the device is to perform, while forming the basis of the technical documentation for the MDR at an early stage. As such, defining such a profile should also be of benefit in the development of medical devices. However, it must be noted that the TPP is a living document that is to be updated as more information becomes available throughout the development cycle, for example after conducting pre-clinical studies or other treatments or devices enter the market.

The content of the TPP is dependent on the type of product and its intended use, but a medical device in the EU should usually at least cover the points shown in Table 2-2 to be considered safe and of clinical benefit ([21] and MDR Annex I). The TPP can highlight which targets will require clinical data to be verified, but also those which can be verified non-clinically or pre-clinically. For example, certain targets may be studied and verified through in vitro studies, animal studies, in silico modelling and simulation or meta-analytical approaches (e.g. literature review), which could help avoid costly and slow clinical studies. At the start of clinical development of a high-risk device the TTP should be updated with all non- and pre-clinical data, and only targets requiring clinical data should remain. The clinical program has to be supported by, e.g., adequate studies of mechanical properties of the device, toxicology, or model studies in phantoms or animals. Clinical trial simulations should also be considered as a tool for the optimisation of clinical trial design and evaluation of the potential effect of interindividual variability. In this paper we concentrate on structuring the clinical development program as the development risks and often high costs of clinical trials make properly designing these trials to optimally verify the targets crucial.

Design of a question-based clinical evaluation program

The TPP includes verification methods of the targets. Thus, prior to the design stage a development plan must also be determined for the evaluation of the device. In the case of high-risk devices, clinical investigations must form an integral part of this plan, and logically should provide objective data demonstrating safety and performance according to the MDR. For drugs, the question-based model of clinical development [11], [12], [13], [14] has been developed in which important questions are asked and answered with appropriate studies to demonstrate safety and clinical benefit. Technical stability of the product is a prerequisite leading to a set of specific questions that is generated based on a predefined set of 5 or 6 generic questions, as shown in [14]. When combining this system with a TPP, answering the questions should also provide data on remaining, unanswered TPP targets that call for clinical data. Together with the TPP, the questions can be identified at an early stage to provide insight into the information that needs to be collected [22]. When the appropriate questions have been defined, answering all of these should determine if benefits outweigh the risks. To enable objective assessment, effective and measurable clinical endpoints, and minimally accepted values must be determined prior to commencing the studies. The endpoints dictate

which biomarkers need to be measured, while the availability and qualification of biomarkers guides endpoint selection [23]. The endpoints translate to TPP targets, thus the TPP dictates the methodology and vice-versa.

Depending on the situation, one question may be answered with multiple studies, but one study can also answer multiple questions. In many cases it can be wise to maximize the amount of data generated to answer as many questions as possible, bearing in mind the possible biomarkers and potential interactions between them. The system of question-based development then assumes that estimates of costs and probability of success can be made from either expert opinions or historical data [13]. These studies are implemented in a real options decision tree, and after each study a decision between abandonment and continuation is taken. When a study is successful, value will have been added to the project. When not successful, losses will have been minimised, which limits the risk of development [11]. Developmental risks are made apparent and can be managed by determining the optimal sequence of studies that minimises losses when results are not favourable. This will vary for each device and is dependent on the risks and costs of the studies necessary [11], [13]. The highest risk questions should receive focus at an early stage to abandon drugs that will not be successful as quickly as possible to minimise losses. This optimal sequence can guide the development strategy in which risks and associated costs are be minimised, while making the central issue in drug development explicit rather than implicit; whether all relevant questions have been asked and answered adequately to demonstrate safety and performance can then be objectively assessed [13].

With the introduction of the MDR, necessitating more clinical evidence, the need for a well-defined and structured clinical evaluation program has become more evident. Due to the increased parallels between devices and drugs mentioned, as well as the lack of guidance, the question-based approach can now also pose as a framework for the clinical evaluation plan for high-risk devices imposed by the MDR. Implementing this framework prior to the design stage and throughout the development should maintain a focus on devices being safe and of clinical benefit in the relevant context. In the case of Class III and Class IIb devices intended to administer or remove medicinal products, this clinical development plan may be shared with an expert panel through the notified body for evaluation, prior to commencing the clinical development (art. 61(2)). In other cases the notified body is not legally obliged to provide such feedback. Thus, the success is dependent on the knowledge and expertise of the developers in which a structured approach is thought to be beneficial. Figure 2-1 shows a diagram of the question-based framework adapted for high-risk medical devices.

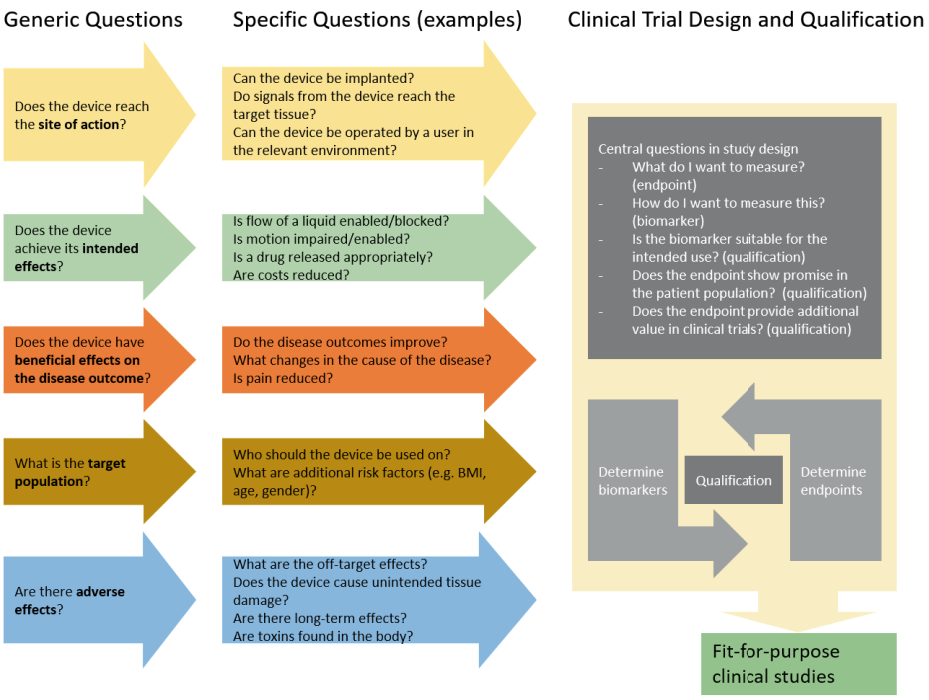

Figure 2-1: A diagram of the structure of a question-based development plan of a high-risk medical device. It shows how generic questions are raised for specific to a device in question. These specific questions are to be answered through clinical studies. The design of the clinical studies is determined based on the endpoints to be measured and the available biomarkers. The biomarkers need to be suitable and qualified for the intended purpose. All questions are answered in a certain population with regard to, for example, age, genetics, and genomics, and the methods to stratify the population (especially genomic or biochemical methods) also require validation and fit-to-purpose qualification. Adapted from References [2]] and [3]] with permission.

Post-market surveillance to answer remaining unknowns (as phase IV studies)

At the end of the clinical investigations for MDR conformity, a number of unknowns, or risks that have not yet been fully quantified such as unexpected complications, will be apparent to the manufacturer. These will most likely remain a “known unknown”. More challenges arise when very small patient populations or rare diseases are involved, which pose similar challenges for devices as seen in the development of drugs: low statistical power, difficulty in patient recruitment and lack of randomized control trials. As such, it would make sense to utilise the same approaches as recommended in the EMA guidelines for such cases [24]. There has to be a transparent plan for monitoring any long term complications and the situation is analogous to the risk management plans as outlined in the EMA pharmacovigilance guidance [25]. However, this is outside the scope of this paper.

When sufficient clinical data has been collected to clearly demonstrate the potential benefit of the use of the device outweighing the risks, these risks may be considered acceptable. There is a likelihood that new and unexpected long term complication occur and these will generate an unknown risk that can only be monitored. The MDR requires manufactures to conduct *post-market clinical follow-up* and provide a plan to proactively monitor safety and efficacy prior to market approval from the notified body. For Class IIa, IIb and III devices *periodic safety and update reports* must be shared in order to continuously monitor these unknown risks and update the risk-benefit analysis accordingly. For devices such long term effects may be more important than for medicines and require long term monitoring through registries [26], [27].

Clearly, spontaneous reporting of adverse events that coincide with the use of a device require evaluation of causality to interpret them as side effects. The associated problems are evident but not different for devices, medicines, or food and this discussion is beyond the scope of this paper.

2.3 The question-based framework applied

Figure 2-2 shows a generalised flowchart of the process from detection of a clinical need to application to a notified body and market approval as described in previous chapters.

Practical example: A Class III novel vascular access device

Medical device manufacturers are developing a novel implantable device for haemodialysis patients that can open and close a tubular anastomosis between a vein and artery, shown in Figure 2-3, and consider this as Class III. This example does not cover Class IIb devices, but the regulations and requirements are similar, i.e. technical documentation including the same elements and clinical evidence demonstrating performance and safety, as well as a post-market clinical follow-up plan. The practical execution of clinical evidence generation therefore follows the same general approach from definition of targets and questions, to the evaluation thereof. A major difference is that not all clinical development plans of Class IIb devices may receive an expert consultation through the notified body. This absence even emphasises the need for a well-structured approach. The case presented is based upon ongoing development work by our departments and serves for illustration only. Supplemental File 2 (online) includes more explanatory images showing part of the development process.

Haemodialysis is performed by taking blood from the body, filtering it in an external dialysis machine, and then returning the clean blood to the body. For this, a vascular access site is necessary in which the circulation can easily be accessed, and a high flow of blood is present. These patients usually receive an arteriovenous fistula in the arm, in which a vein is ligated on one side and connected to an adjacent artery. The pressure drop between the vein and artery stimulates a large increase in flow through these vessels, enabling dialysis. This high flow is

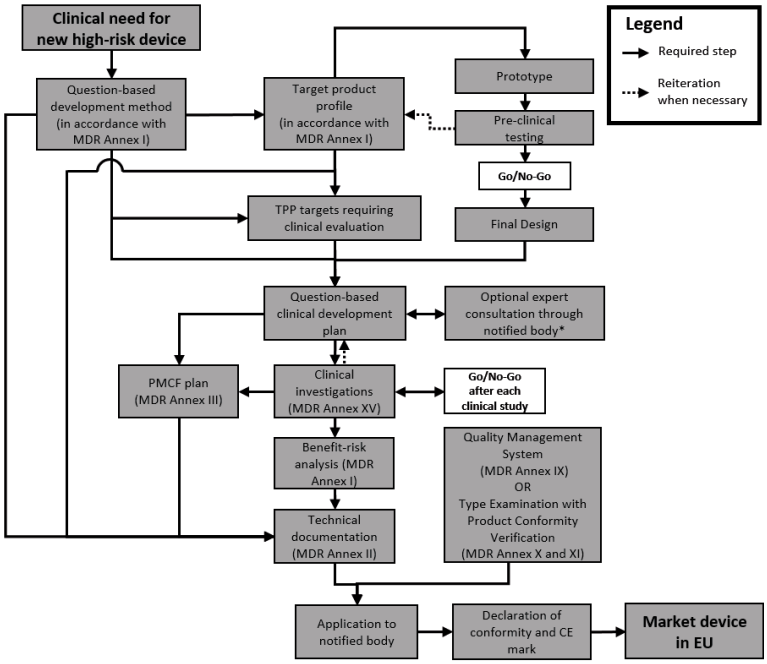

*Figure 2-2: A flowchart illustrating the generalised process from the detection of a clinical need for a high-risk medical device to the application to a notified body utilising the Target Product Profile (TPP) and Question-Based Development method as described in this paper for the Medical Device Regulation (MDR). PMCF = Post-market clinical follow-up. *The MDR allows developers to request an expert consultation for their clinical development plan through the notified body in the development of Class IIb devices intended to administer and/or remove a medicinal product and Class III devices (MDR Art. 61(2)).*

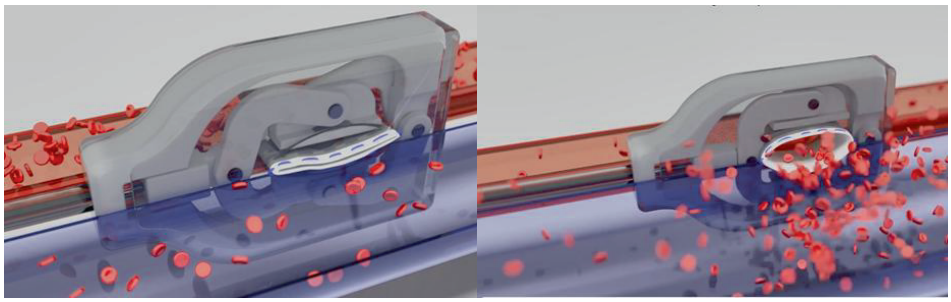

Figure 2-3: A conceptual depiction of a novel implantable device for haemodialysis that can open and close a tubular anastomosis placed between a vein and an artery to control the flow through these vessels. This device is considered a Class III device under the European Medical Device Regulation On the left the anastomosis is closed and the circulation is normal. On the right, the anastomosis is opened and the flow is increased to enable haemodialysis.

usually also very turbulent and is present all the time. Patients very frequently suffer from complications related to the fistula, most of which can be attributed to this constantly present high and turbulent flow. However, patients rarely require dialysis more than 12 hours a week. The manufacturers aim to develop a device that can open and close this fistula to enable control of the high and turbulent flow between the artery and vein being connected. The researchers argue that by removing the high anastomotic flow outside of dialysis sessions, complications related to the presence of the fistula, such as stenosis and thrombosis, should decrease greatly, while dialysis remains possible when opening the fistula. However, as such an implant will likely have moving components that interact with their surroundings, complex energy transmissions can be expected between tissues and implant components.

Target Product Profile and pre-clinical studies

First, relevant specific questions are raised, based on the main category question-based development questions. These questions are translated to TPP targets, and the TPP is amended with elements that have been identified from the relevant parts of Annex I of the MDR, cross-referenced with the TPP components as described by Tansey [21] (Table 2-2). A number of example targets are shown in Table 2-3. The developers consider these targets requirements for this device to be safe and of added value. The minimal viability requirements form the design requirements of the device, and the categories “technical”, “medical” and “patient perspective” translate to the general performance and safety requirements as specified by the MDR. The target measures translate to design criteria aimed at guiding the manufacturers in design choices. Moreover, these targets may result in more design-specific requirements, for example relating to maximum dimensions and force transmissions, and often need to be verified prior to commencing clinical studies. These must also be included in the technical documentation in the application to the notified body.

Figure 2-4 shows the interaction between the question-based scheme, TPP and pre-clinical studies in the haemodialysis device example. By preceding the TPP with the question-based scheme, the questions form the basis of the non- and pre-clinical study design. However, targets are not always easy to properly define at an early stage, and may change depending on the outcomes of studies. Clinical expertise is crucial in translating readouts to clinical use cases, indications and risks in this learning process, and they can be fed back into the question-based scheme and TPP. Hereafter, performance and safety of amended targets and questions will require confirming. If confirmation fails, discontinuation may be necessary. Defining questions and seeking preliminary answers in a non-clinical setting resulted in the revision of the TPP of the haemodialysis device throughout the development. This has been further elaborated in Supplemental File 2 (online).

The question-based clinical development plan

The remaining targets that cannot be fully verified during pre-clinical studies require clinical evaluation. Table 2-4 shows an example of a question-based plan for the development of the vascular access device from Table 2-3. The clinical development roadmap can be determined

Table 2-3: Some examples of Target Product Profile targets for a novel implantable vascular access device.

	Target profile	Motivation	Measure	Target value	Minimal viability req.	Compar. data	Differentiation
Commercial	Market share	To be commercially viable, a sufficient market share is necessary	Number of implantations	5% of market share 5 years after introduction	2% of vascular access market years 5 years post-introduction	Haemodialysis patients	If worse abandon
Commercial	Development cost	To be able to receive sufficient funding and develop a marketable product, the costs for development cannot be excessive	Developmental costs	Development costs 7 mln euros to reach EU market approval	Development costs 14 mln euros to reach EU market approval	Similar vascular access devices	Reassess development program
Technical	Operation	The device can be operated non-invasively with a correct user input to prevent excessive discomfort to the patient.	Pain scale	0 on the Numeric Pain Rating Scale	3 on the Numeric Pain Rating Scale	n/a	Redesign if not compliant
Technical	Fully close anastomosis	The core of the issues with fistulae lies in the elevated and turbulent flow. The aim of the device is to improve outcomes by removing this flow outside of dialysis sessions and returning circulation to normal.	Shunt flow, measured by duplex	Shunt flow in closed position is 0 mL/min	Shunt flow in closed position is 0 mL/min	n/a	Redesign if not compliant
Technical	Open anastomosis	To enable dialysis a shunt flow of at least 600mL/min is necessary, with higher flows being linked to complications. Ideally, the shunt flow can approximate this value as closely as possible	Shunt flow, measured by duplex	Shunt flow in open position is 600 mL/min	Shunt flow in open position is greater than 600 mL/min	AVF data	Redesign if not compliant
Technical	Robustness - remains functional	To prevent the necessity of frequent intervention, the device must remain functional for a suitable time.	Percentage of patients with functional device	Device outlives 90% of HD patients, functional after 11 years	Device outlives 50% of HD patients, functional after 3 years	Traditional AVF/AVG patients	Redesign if not compliant
Technical	Contamination	Introducing foreign materials into the body poses a risk of, e.g., infection. It is thus necessary to sterilize implantable medical devices.	Surface micro-organisms after sterilisation	Theoretical probability of micro-organisms on surface <10e-6	Theoretical probability of micro-organisms on surface <10e-6	Conform to ISO standard 10993	Redesign or alternative sterilization if not compliant
Medical	Target population	To be of added value to dialysis patients and to justify the integration into health systems, a significant percentage of patients must be eligible to receive the device.	Percentage of eligible dialysis patients	80% of haemodialysis patients eligible	50% of haemodialysis patients eligible	Dialysis patient indications etc.	If worse negative for continuation
Medical	Adverse events	Adverse events occur very frequently in VA patients. This device aims to target the main cause of these adverse events, thus decreasing them is a major criterion.	Rehospitalisation rate	Rehospitalisation decreased by 50%	Rehospitalisation decreased by 20%	Traditional AVF/AVG patients	If worse negative for continuation
Medical	Clinical outcomes	Patency rate of vascular access is generally too low and results in the necessity of surgical intervention. The device should improve this significantly to be a viable solution	Shunt patency rates	1 year patency rate increases by 10%	1 year patency rate remains the same	Traditional AVF/AVG patients	If similar or worse negative for continuation
Pat.perspective	Quality of Life	As end-users of the device, the quality of life of the patients should improve in order to be desirable and adopted by patients	Relevant quality of life index	Quality of life improved by 5%	Quality of life remains the same	Traditional AVF/AVG patients	If worse negative for continuation

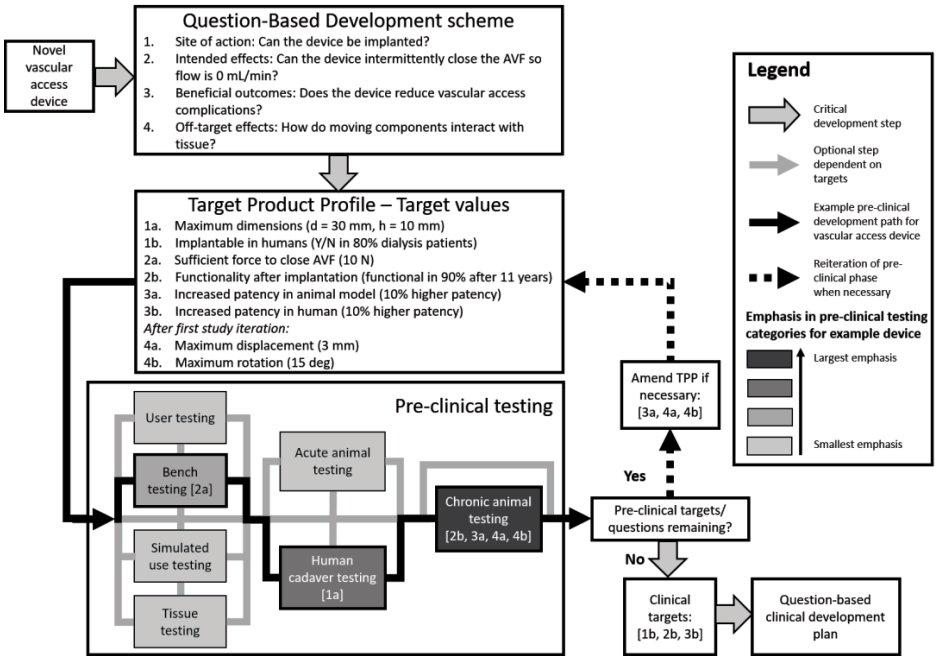

Figure 2-4: The clinical development framework for the novel vascular access device synthesized from the results of the question-based development scheme. The pre-clinical testing scheme has been adapted from [4]. The black line indicates where the main emphasis lies in the pre-clinical testing used to demonstrate the safety and performance of the vascular access device. The numbers in brackets refer to the targets assessed at each study category. The shade of the category box indicates how resource intensive each category is for this example. AVF = Arteriovenous Fistula

analogously to the method described in [11]. The data collected by answering these questions should then further supplement the example TPP from Table 2-3 to the point of either (near) completion or abandonment. As demonstrated, a main category question is associated with one or a number of TPP targets described previously, and conducting these studies will thus amend the TPP further. The parallels with clinical development of drugs allow valuation and determination of the optimal clinical study sequence similarly to the method described in [28], in which estimates of costs are determined through historical data and experts, e.g. from clinical pharmacologists. Similarly, a go/no-go decision point including a detailed benefit/risk analysis follows each clinical study.

The targets that remain after completing the clinical development plan are the "known-unknowns". Additionally, some questions and targets may not be fully answered and merely have an initial estimate. For example, if 90% of devices remain functional after 2 years it is probably likely that >50% will be functional after 3. However, the clinical data can already be adequate to show sufficient benefit over the risks to be considered a viable option to patients to allow market approval.

Table 2-4: A simplified example of the question-based framework for a novel implantable vascular access device illustrating how generic questions are used for the generation of specific questions relating to the TPP targets, and how the methodology could originate from here. Generally applicable considerations for each generic question are provided.

Generic Questions	Considerations	Specific Questions	TPP Targets	Methodology
Does the device reach the site of action?	The specific questions generated here can to some extent be assessed prior to clinical studies. However, clinical verification remains necessary due to differences between (e.g. animal or cadaver) models and the actual working environment.	Can the device be implanted as a fistula in the arm as intended? Does the device stay in the correct location? Can the vascular access be adequately controlled non-invasively the operator?	- Pain score does not exceed 3 on the Numeric Pain Rating Score - Open non blinded study with descriptive statistics only	Clinical pilot in which the device is implanted into a small number of patients requiring haemodialysis. Follow-up of several months to verify the device remains operable with the correct user input during this period and pain is acceptable.
Does the device achieve its intended effects?	These questions usually relate to the main working principle of the device. Again pre- and non-clinical evaluation can provide a lot of preliminary data that can be used for optimisation, but models can never completely mimic the real working environment so verification is required. Moreover, clinical trial design and evaluation of the potential effect of interindividual variability may be optimised through e.g. in silico methods.	Can the device control the flow of blood to 0 mL/min and at least 600 mL/min with the correct user input?	- Anastomotic flow >600 mL/min when open - Anastomotic flow 0 mL/min when closed	Single-centre study in which the device is implanted into a larger number of patients. On a regular interval, these patients will receive echography with duplex measurement to determine the anastomotic flow in different positions.
Does the device have beneficial effects on the disease outcome?	In most cases these questions should primarily focus on the clinical outcomes in general terms. Selection of correct biomarker(s) and endpoint(s) is crucial and rarely straightforward, and multiple studies may be necessary.	Does the device improve vascular access outcomes in haemodialysis patients?	- 1-year vascular access patency rate remains at least the same - Quality of life of haemodialysis patients remains at least the same	A large cohort multi-centre study in which the device is implanted into various patients with different indications. Follow-up of 12 months in which Quality of life and vascular access patency is recorded and compared to traditional fistula patients.

Table 2-5: continued

Generic Questions	Considerations	Specific Questions	TPP Targets	Methodology
What is the target population?	The aim of target population studies are to gain insight into the patient populations in which benefits can outweigh the risks. This includes analysis of eligibility (e.g. anatomical), but also of contra-indications in which risk is increased. These studies may be combined with off-target effect studies. Studies of small populations or rare diseases are very challenging and methodology must often be adapted.	Age, gender, BMI, indications and contra-indications? How to determine for which patients this is acceptable? For which patients are the on-target effects (not) likely?	- At least 50% of dialysis patients eligible	• A multi-centre study in which is recorded whether clinicians consider haemodialysis patients eligible to receive the device. When patients agree and have the device implanted, patient characteristics are recorded together with patency, rehospitalisation, quality of life etc. Correlations between characteristics and outcomes are analysed.
Are there off-target effects?	These studies should generally focus on quantifying expected adverse events but also on monitoring unexpected adverse events. However, unexpected adverse events, such as mechanical deterioration of the device, can take several years in certain cases. It can however be difficult to assess all these (potentially infrequent) events, in the pre-market phase for such long periods if benefits are shown to outweigh risks. "Unknown unknowns" are likely to remain and must be monitored in the post-market phase, for which good systems and methodologies must be set up.	What are the off-target effects? Are there long-term effects? How are moving components in the device influenced by fibrosis formation?	- Device outlives at least 50% of HD patients, functional after 3 years - Rehospitalisation rate decreased by at least 20%	A large cohort multi-centre study in which the device is implanted into various patients. Follow-up of several years in which device functionality, adverse events and rehospitalisation are recorded and compared to traditional fistula patients.

Upon completion of the clinical investigations, the TPP and question-based development process can form the basis of the technical documentation required by the MDR for application for approval at a notified body. The TPP clarifies the general performance and safety requirements set, and the values found, while the question-based plan clarifies the clinical development steps taken to facilitate objective assessment of the data and decisions made. The final, critical step is a benefit-risk analysis showing that the benefits of using the device outweigh the risks and the device is safe for use. This can be an integration of all TPP values found during development.

Key learnings

Applying this framework to the vascular access device in an early stage provided several learnings to the manufacturers:

- The question-based framework forced the developers to focus on the greater context with a stronger focus on clinical benefit and safety, and set up TPP targets focused on clinical endpoints rather than technical requirements. Technical requirements to achieve these outcomes could be drafted consequently;
- As an example, utilising the question-based framework it became evident that there were uncertainties regarding the concept of intermittently adjusting a fistula and how vessels would respond. Asking this question early on resulted in the rapid development of a cheap device that was intended to assess a fundamental developmental question in a chronic animal model rather than an end-product. Conducting such a study to collect this information earlier than planned prevented time-consuming and costly prototyping when it was unclear if the concept was feasible;
- Additionally, the question-based framework revealed uncertainties relating to the interaction of moving components with surrounding tissue, which could also be assessed in this initial chronic animal study. Findings could be incorporated into the TPP (Figure 2-4). It was also a starting point of a broader research area of moving implantable devices to be studied in the future;
- Amending the TPP with targets relating to management of fibrosis around moving components in this stage changed the design of the device to accommodate these essential requirements early on rather than after a larger and later study. Paired with the initial confirmation of functionality potentially reduces total development time and costs;
- It clarifies the current achievements and necessary milestones to reach the market, e.g., clinical trials and endpoints (Figure 2-4). This provided a clear and evaluable step-by-step overview that supports greater planning, both useful for the developers and appreciated by investors. In our case, the clear development plan has led to financial support for the manufacturer to develop the device further.

2.4 Discussion

In this paper we have presented a structured generic approach for the design and subsequent performance of a clinical development program for medical devices. The vascular access device case was used to gain practical insights into the relation between the question-based framework and the TPP. The definition of questions at an early stage showed that many unknowns were present, and a proper TPP could not be created without in vivo data. This data was consequently collected at an earlier stage than initially planned with a prototype which was not intended to function perfectly. Not only did it show that the concept was feasible, much more insight into the biological responses and interaction between moving components and tissue was gained which helped guide further development. Each study aimed to provide initial answers, and estimate uncertainties and potential risks, which could amend the question-based scheme and TPP. This process should always precede continuation of studies, as amendments could require assessment in subsequent (clinical) studies, changing the development plan. As development progresses, results and uncertainties from detailed benefit-risk analyses or safety and performance monitoring may similarly be incorporated into the development plan and addressed in following studies or post-market surveillance where necessary.

This question-based approach is analogous to the development of medicinal substances. Both medicines and devices are heterogeneous, cover a wide range of indications and have varied concerns regarding efficacy and safety. This would suggest that a generic approach is impossible, and all plans will be on a case-by-case basis. Although the clinical development will have widely varying aims and methodology, our case study showed that it can still be represented in a structured manner that transparently displays the considerations that form the basis of a clinical research program. Such programs must be assessed by companies, researchers, ethics committees regulators and even investors and all would benefit from a generally accepted structure to facilitate communication and quantification. When the clinical program is completed, the results can also be evaluated against this program, improving the review process by standardising it. Additionally, the structured approach highlights validation deficits in measures used to answer the questions. Finally unanswered questions define the development and commercial risks of a device.

Analogies between clinical pharmacology and clinical development of high-risk medical devices have been made clear. However, some differences remain, the biggest of which being the ability to modify a device more easily than a molecule. Therefore, the possibility of redesign as a method to circumvent problems that occur in the course of the development has to be a more prominent part of the planning and the evaluation. The question-based framework is aimed at optimising the clinical development path, of which a result is early abandonment of unsuccessful drugs. However, this is more easily avoided in devices; devices are often more easily redesigned than drugs because of their modularity, and “modification”, of one of its components may be an option. In drugs, often a project may need to be abandoned because a small failure requires modification of the complete molecule which

can be a very costly process. When significant changes to the device are necessary, it may be required to change the TPP and/or redo the studies previously conducted, but when these are minor the failed study can be repeated while preserving the validity of results previously obtained through equivalency. Not only does this diminish some of the associated development risk, it also reduces the need for abandonment and the time-to-market of the device. In the case of modification at a decision point, an estimate of redesign costs should be made, along with re-evaluation of risks and costs in the following studies to verify the development plan is still optimal.

Finally, the general performance and safety requirements from Annex I of the MDR primarily focus on the demonstration that the device functions as expected and is safe. The benefit-risk analysis must show that the risks have been minimised and are acceptable with regard to the intended use, taking into account the relevant state of the art. However, the MDR has no hard requirements relating to beneficial clinical outcomes – as long as the risks are low – while the adaptation of novel medical devices in the clinic does for a large part depend on efficacy relative to the current standard of care; clinicians and healthcare payers will be reluctant to adapt novel devices without proven benefit to patients. The framework currently proposed is focused on the clinical assessment according to the MDR. The exact assessment route and clinical requirements may vary per regulator (e.g. FDA, MHRA, PMDA) which can be reflected in differences in the TTP. However, safety and clinical benefit are essential in the widespread adaptation of medical devices. The framework proposed here forces the developer to place a greater focus on the patient and clinical outcomes in the development plan. As a result, more appropriate care should reach patients, and adapting this approach should then logically also be of greater value to the manufacturer, potentially reaching further than just the EU.

Limitations and future work

The development of all medical interventions is usually iterative, highly complex and dynamic [11]. A structured question-based program has been used in drug development in many forms and shown to be useful although no consensus has been reached on how this should be applied in a harmonised manner. Similarly to in the MDR, this is left up to the manufacturer. Moreover, as the MDR has only recently come into effect, experience with the clinical evaluation with respect to the new regulations is limited. The framework described here aims to guide medical devices developers in the development process. It has been tested extensively in the field of drug development, but it has not yet been utilised sufficiently for devices so it awaits application in a wider practice. The developmental results obtained depend largely on assumptions made [11], which will be less accurate for devices than drugs because of this lack of experience. Thus, even more caution is required when interpreting and defining the optimal development path. The field of devices is ever diversifying [1] without centralised controlling agencies, so we believe that this calls even more for a structured approach. A review of the limitations and gaps in current clinical protocol designs for high risk medical devices should be conducted, that should be carefully considered or modified given the new regulation. This should offer clear insight into the issues medical device evaluation

faces. It will become evident if the proposed implementation offers a more efficient approach, and whether the generic questions suffice to ensure effective compliance with the MDR.

Currently it cannot be claimed that our approach is effective as this would require some sort of control situation for comparison. To do this would require at least a fully completed development program, but that could only be evaluated in hindsight. The approach described could improve the development process of medical devices by both focusing on performance and safety, and reducing development time and costs. It was valuable in the non-clinical development of the example device provided and helped focus attention on important safety and performance endpoints in the clinical stages. However, at the time of writing non-clinical investigations are still ongoing. The approach has not been formally evaluated, and a formal evaluation of the clinical development stage will likewise not be straightforward due to the long development timelines and the large differences between innovation projects. It remains a proposal and should be interpreted as such.

2.5 Conclusion

The question-based framework for medical device development proposed in this article can support developers starting from the initial device design stage in overcoming the obstacles and ambiguity of clinical development presented by the newly introduced MDR. The framework could guide manufacturers in setting up the clinical development plan, but it also potentially has the added benefits of showing clear relations between design and validation steps and thus may contribute to the “learn and confirm” cycle that forms the basis of any intervention development [29]. This can assist further research into the adequacy of the development process and help to responsibly dismiss risky technology at an early stage and introducing effective innovations more quickly with lower costs. Our proposal has not been formally evaluated and this can only be done in practical use.

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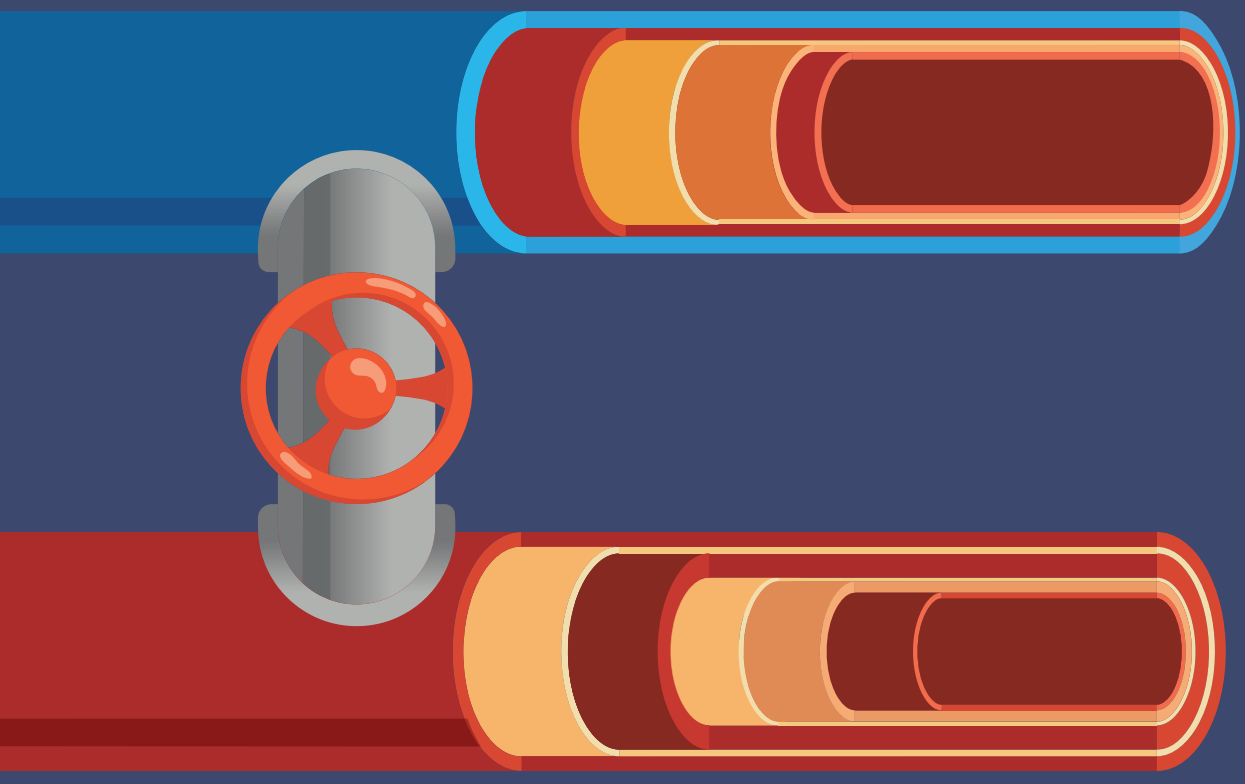

In vitro safety of power injection of contrast media through central venous haemodialysis catheters

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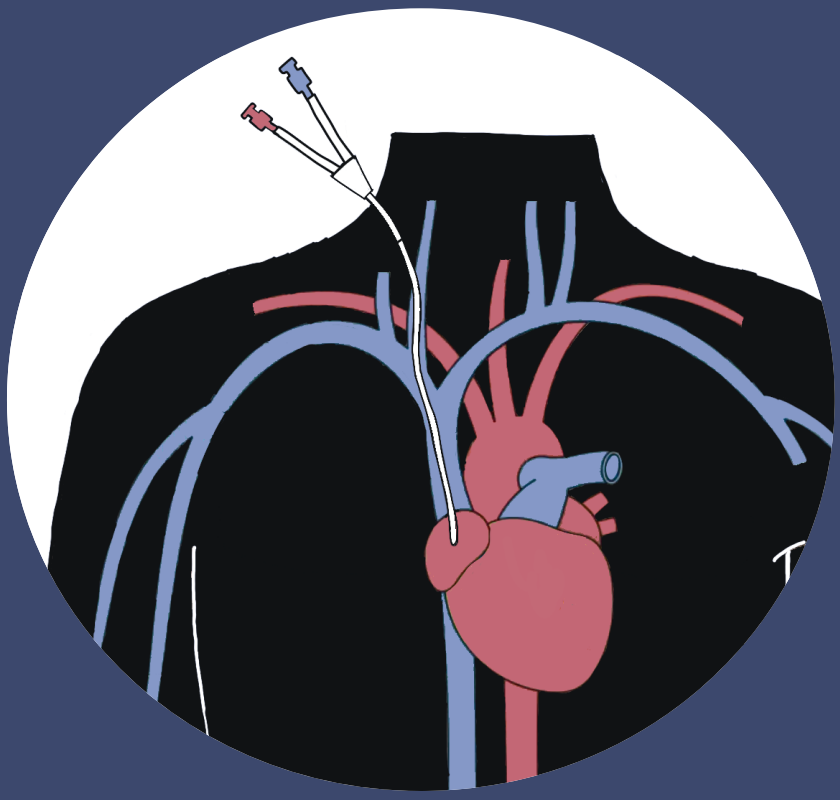

This chapter presents an in vitro study investigating the safety of power injection of contrast media through central venous catheters (CVCs) used in haemodialysis patients. Although this use is currently off-label, it is occasionally employed in clinical practice to avoid placing additional peripheral intravenous lines in patients with limited vascular access. The findings contribute to the broader theme of this dissertation by illustrating how existing medical devices might be safely repurposed to improve patient comfort, reduce procedural burden, and avoid unnecessary interventions.

Abstract

Central venous catheters (CVCs) provide direct access to the central circulatory system, commonly used in hemodialysis and intensive care units for drug administration. Although uncertified for the procedure, CVCs are sometimes used for power injection of contrast medium (CM) during CT scans to avoid peripheral intravenous catheter placement. Previous studies suggest this practice is safe, but incidents are reported. This study aims to measure intraluminal pressure during CM injection through CVCs and assess its impact on the luminal surface to guide responsible clinical use.

An experimental in vitro test setup was developed. Four samples each of three different types of unused CVCs were used. Strain gauges were applied to the exterior walls of either the inflow or outflow lumen of the CVC. These gauges measured material deformation due to intraluminal pressure during CM injections at rates of 4.5 and 8 mL/s, each performed five times. Strain data were calibrated against known pressures in a static system. Three CVCs of each type were then pressurized until bursting, and one was subjected to microscopic analysis of the luminal surfaces.

Intraluminal pressures measured (97–545 kPa or 14–79 PSI) were below the burst pressure (779–1248 kPa or 113–181 PSI) in all instances. Strain regression analysis shows a statistically significant ($p < 0.01$) trend over 10 injections in all CVCs tested except one, indicating material fatigue. Surface microscopy revealed surface micro-cracks from repeated injections, suggesting material damage.

The intraluminal pressures from power injections of CM are sufficiently low to prevent CVC bursting. While incidental use for CM injection appears safe, repeated use may cause material damage.

3.1 Obstacles in contrast media injection through dialysis catheters

Haemodialysis patients frequently utilize a central venous catheter (CVC) as vascular access to transport blood to and from the dialysis machine. Similar CVCs may also be used for administration of drugs to patients in intensive care units. For diagnostic purposes, these patients may need CT scans with radiopaque contrast medium (CM). Bolus intravenous injection of CM using a power (pressure) injector is the preferred method for CM administration for CT examinations of the neck, chest, and abdomen [1], [2]. This is usually achieved with an intravenous needle in the forearm, with typical CM flow velocities around 3-6 mL/s [3], [4], [5]. However, haemodialysis patients often have poor peripheral veins, necessitating preservation for future arteriovenous access surgery. Studies have indicated safe in vitro pressure levels for CM injection through various types of CVCs [6], [7], [8], [9], [10], [11], [12], and some clinical evidence of safe use [13], [14], [15]. Concerns remain about catheter-related complications due to high pressures in these devices that are often not certified for this usage, with several incidents of rupture and tip displacement reported [16], [17], [18]. Clinical guidelines remain limited [19].

Clinically, power injector pressures are capped at 2000-2250 kPa (300-325 PSI), but it cannot be claimed that the pressure is constant throughout a dynamic, flowing system. There must be a pressure gradient for fluids to flow. The pressure gradient depends on many variables, including viscosity, flow velocity, friction of the tube surface, and geometry. Although the pressure displayed on the power injector thus overestimates the pressure downstream, (e.g., in a CVC), the non-uniform geometry of CVCs could cause local increases in pressure and wall stress [20]. It is crucial that pressure is measured at the correct location to obtain the most accurate data on intraluminal pressure in CVCs during CM injection to properly assess safety.

Moreover, pressure transducers in a flow circuit interfere with the flow, often requiring a three-way connection that introduces static fluid dead space. This dead space can impede accurate pressure measurement due to its lack of direct pressure response to fluid flow and the flow distortions it introduces. In systems with rapidly changing flow rates, dead space can dampen fluid oscillations and distort pressure readings, contributing to significant pressure measurement differences in previous studies (14-483 kPa (2-70 PSI) at 4.5 mL/s with similar catheters) [6], [7], [11], [12]. As a non-invasive method to measure pressure without the intrinsic drawbacks of pressure transducers, strain gauges may pose a solution.

The present study aims to equip healthcare professionals with the knowledge required to make informed decisions regarding the usage of commonly used CVCs for power injection of

CM by presenting a comprehensive study of intraluminal pressure during injection, material fatigue, bursting pressures, and surface analysis.

3.2 In vitro pressure measurement setup

Central venous catheters

Each CVC type has an inflow lumen, used for transport of fluid to the body, and an outflow lumen, for fluid transported out of the body. Figure 3-1a shows the differences in cross-sections. Four samples each of three different types of new, unused CVCs were collected and tested:
13F, 250mm GamCath Dolphin Protect High Flow Double Lumen straight catheter (Baxter, Deerfield, IL, USA)

- 13F, 250mm GamCath High Flow Triple Lumen straight catheter (Baxter, Deerfield,IL, USA)
- 15.5F, 200mm Jet Medical Short-Term Free Flow pre-curved catheter (Jet Medical SA, La Chaux-de-Fonds, Switzerland)

Experimental setup

The CVCs are tested by repeated injection of CM and recording the response with strain gauges. The strain gauges are then calibrated with a pressure transducer in a closed system with static pressure in which pressure is equal everywhere and in all directions. Calibration is performed after the CM injection; the pressure necessary to properly calibrate the sensors must exceed the pressure induced by the CM, and therefore may damage the CVCs and distort the pressure recordings if performed prior to the power injections. Finally, the CVCs are either burst or dissected for microscopic surface analysis. The experimental setup is displayed in Figure 3-1.

The working principle of a strain gauge is shown in Figure 3-2. Deformation of the material on to which the gauges are placed results in deformation of the thin wires. This in turn results in a change in resistance which can be accurately measured. Materials deform predictably when stress is applied. Intraluminal pressure introduces such stresses in the wall of the CVCs, so strain gauges may be utilized to measure this deformation. The strain can thus be related to an intraluminal pressure when calibrated with a pressure transducer in a static closed system. Additionally, such strain gauges are typically used to determine material wear and fatigue over time. As such, they may provide information relating to such effects occurring in the CVC material with CM injection.

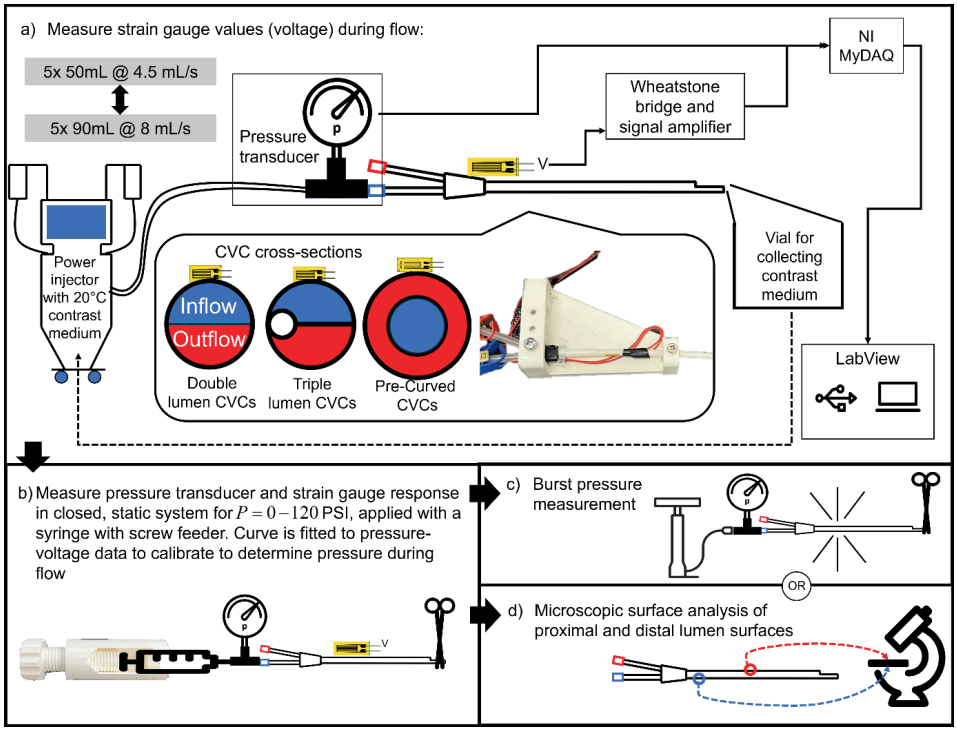

Figure 3-1: The experimental setup for testing the central venous catheters (CVCs): a) the catheters with strain gauges are clamped and connected to a contrast medium injector with a pressure transducer placed at the inlet of the catheter. CVC cross-sections are also shown. Blue indicates the inflow (flow to the body) lumen, and red indicates outflow (flow from the body). b) The strain gauges are then calibrated through static pressure. The pressure transducer values are stored together with the strain gauge voltages. Next the pressure transducer and strain gauge voltages are processed, and a curve fit is generated. Intraluminal pressure during injection is determined through this curve fit. c) catheters are finally pressurized until burst; or d) microscopic surface analysis is performed on the lumina of 1 sample of each catheter types tested.

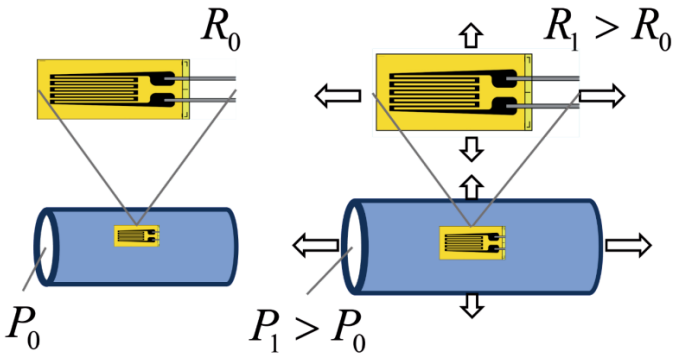

Figure 3-2: Working principle of a strain gauge. The strain gauge is placed on a surface and the resistance R is continuously measured, of which the value is R0 at rest with intraluminal pressure P0. When the material stretches, e.g. due to a higher intraluminal pressure P1, the strain deforms with the material. The resistance of the deformed gauge R1 will increase due to the increase in length and decrease in cross-sectional diameter of the wire. This can then be measured as a voltage change when amplified in a Wheatstone bridge.

A GFLAB-3-70 Low Elastic Strain Gauge (Tokyo Measuring Instruments Laboratory Co., Tokyo, Japan) was fixed on the inlet side of each CVC. This position was chosen because it is where the pressure is expected to be highest. Placing the strain gauge on the inflow lumen (blue, shown in Figure 3-1a) was preferred as this lumen is typically used for administration of fluids. Standard strain gauge cyanoacrylate adhesive (Tokyo Measuring Instruments Laboratory Co., Tokyo, Japan) was used. The strain gauge was placed in a Wheatstone bridge to amplify the voltage change and correct the signal for effects such as temperature change. To achieve temperature compensation, the other gauges in the bridge were placed on an additional, unused CVC made of the same material. Application of pressure to the CVC, caused a resistance change in the strain gauge, resulting in a change in voltage over the bridge. This voltage signal was further amplified by a CPJ Strain Gauge Conditioner (Scaime, Juvigny, France) and read in LabVIEW through a NI MyDAQ (National Instruments, Austin, TX, USA). Each tested CVC sample was fixated at two points (Figure 3-1a) to ensure no deformation of the catheter occurs, other than induced by pressure.

The inflow lumen of each CVC was connected to a FlowSens® syringeless soft bag CM injector (Guerbet, Paris, France) with standard consumable tubing and with a PU5405 pressure transducer (ifm GmbH, Essen, Germany) fastened with a three-way stopcock just proximal to the CVC connector. The system was flushed with saline and primed so that there was CM iobitridol 350 mgI/ml (Xenetix, Guerbet, Paris, France) in the CVC prior to starting measurements. The test setup and all fluids used were operated at room temperature as strain gauges are sensitive to temperature changes. Since viscosity decreases as temperature rises, higher pressures are required at lower temperatures. This represents a

worst-case scenario where the fluid is administered without prior heating [21]. The CM exiting the tip of the CVC was collected in a vial and reused.

Flow measurement

First, 50 mL of CM was injected into each CVC at 4.5 mL/s over 11 seconds [6], [7], [11], [12], and both the pressure transducer and strain gauge values were recorded. Due to the viscoelasticity (i.e., non-direct strain response) of the material, a 5-minute resting time is needed prior to commencing the next measurement. This process was repeated 5 times. Next, 90 mL was injected at 8 mL/s over 11 seconds, corresponding to the protocol with the highest flow rate used in our center. The same 5-minute resting time was applied, for 5 measurements. The maximum pressure in the power injector was also recorded. For half of the samples, the order was reversed, with 90 mL injections performed first, followed by 50 mL injections. Finally, the CVCs were flushed with saline.

Pre-curved CVCs

The pre-curved CVCs do not have the same “double-D” cross section, but an inner (inflow) and outer (outflow) lumen (Figure 3-1a). Due to this geometry it was not possible to directly attach a strain gauge to the wall of the preferred inflow lumen. Instead, the strain gauges were secured to the wall of the outflow (outer, red) lumen, and measurements were taken through this lumen. However, this lumen is not typically used for administration of fluids. Therefore injection with the power injector was repeated with both lumina and maximum injection pressure was recorded for both lumina. This provides an indication of pressure differences between these lumina. The measurement of the inner lumen was performed in 3 of the 4 samples. The inner lumen in the remaining sample was spared for microscopic surface analysis.

Sensor calibration and data processing

After completing the flow measurements, the tip of each catheter was clamped and the power injector was disconnected. A syringe filled with room temperature water and a screw feeder was connected to the three-way stopcock to create a closed and static system. The strain gauge was calibrated by gradually increasing the pressure to ~800 kPa (~120 PSI) over 2 minutes three times per CVC, and recording the strain gauge voltage together with transducer values. This data was processed in MATLAB (MathWorks, Natick, Massachusetts), in which the calibration data was zero-shifted, and a 3rd-order polynomial was fitted. The maximum intraluminal pressure of each measurement was determined by inserting the zero-shifted maximum gauge value into the curve fit of the respective CVC. To assess material fatigue (permanent strain) and damage of the CVC material after CM injection, the resting voltages

were recorded of the strain gauge after the 5-minute relaxation periods. Linear regression was applied to these values to assess for a non-zero linear coefficient with 95% confidence.

Burst pressure test

Three samples each of the 3 different CVC types were then connected to a high-pressure manual bicycle pump with a calibrated Gems 3300 1600 kPa pressure transducer (Gems, Plainville, CT, USA) fastened through a three-way stopcock just proximal to the CVC connector. The catheter was filled with room temperature water and the tip was sealed with a medical clamp. Pressure was increased until burst.

Microscopic analysis

The remaining CVCs were dissected. Surface samples from the inlet ends of the lumina subjected to power injection of CM were collected and sectioned. The samples from the unused, outflow lumina of the same CVCs were also taken as control. The samples were mounted on Scanning Electron Microscopy stubs with double sides carbon stickers. Before imaging, all samples were sputter-coated with a layer of Gold/Palladium. Images were recorded in a GeminiSEM 300 Scanning Electron Microscope (Zeiss, Oberkochen Germany), operated at 5 kV.

3.3 Intraluminal pressures and surface analysis

Calibration

All CVCs were successfully tested and calibrated by fitting a curve to the pressure and strain data. These curves were used to determine the intraluminal pressure from the strain gauge values during CM injection. As an example, Figure 3-3a shows the calibration data, curve fit and 95% confidence bounds of this fit in of a double lumen CVC tested. Supplemental Figures S1-S3 (online) show the raw strain gauge data. The complete set of calibration figures can be found in Supplemental Figures S4-S6 (online).

Power injection of contrast medium

Figure 3-3b-d display the pump pressures, intraluminal strain gauge pressures (determined with the fitted calibration curves), pressure transducer values at injection velocities 4.5 mL/s and 8 mL/s, and the lowest recorded burst pressures of the 3 different CVC types. Pressure transducer measurements were lower than intraluminal pressures measured with the strain gauges in all instances. The intraluminal pressures were always lower than the pressure exerted by the pump. Intraluminal pressures always remained below the lowest burst pressure measured.

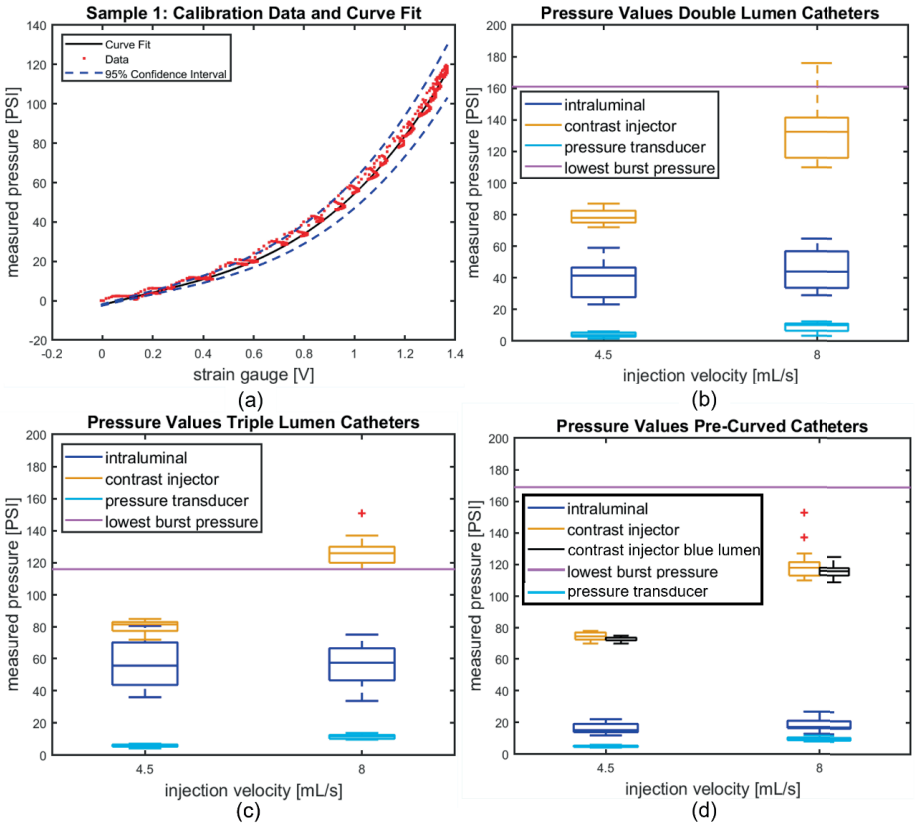

*Figure 3-3: a) The calibration data, fitted 3rd-order polynomial and its 95% confidence bounds of catheter sample 1, used to determine intraluminal pressure with the strain gauge. b-d) Boxplots of the pump pressures, intraluminal strain gauge pressures and pressure transducer values at injection velocities 4.5 mL/s and 8 mL/s, and the burst pressures of b) the double lumen catheters; c) the triple lumen catheters; and d) the pre-curved catheters. n=4 applies to (b-d) *Only 3 samples were tested*

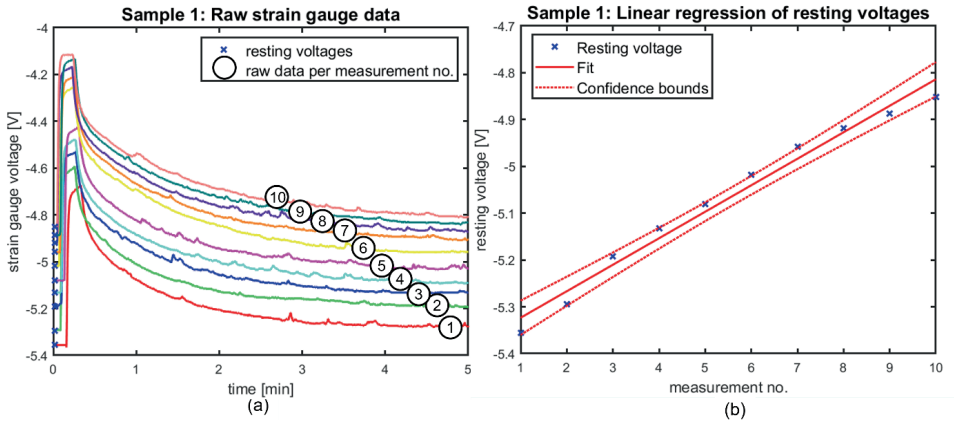

Figure 3-4: Representative regression plot of catheter 1 showing the trend in resting voltages throughout the measurements. Patterns are similar throughout the tested catheters. a) shows the raw strain gauge data over the 5-minute testing period of measurements 1 through 10 in catheter 1, as indicated by the numbers in the graph; and b) displays the regression analysis of the resting voltages as indicated in a).

Material fatigue

Material fatigue, or permanent strain of the CVC, is assessed for each sample tested. Linear regression is applied to the strain gauge voltage at rest, which corresponds to the material strain at rest and fatigue. A non-zero regression coefficient thus corresponds to permanent strain of the material. The linear regression coefficients are non-zero ($p < 0.01$) in every CVC tested, except sample 2 (double lumen, $p = 0.53$). As an example, Figure 3-4 displays the raw strain gauge data of the first CVC measured together with the linear regression analysis performed on the resting voltages of this CVC. Figure S7 displays the linear regression analysis of CVC sample 2. The complete set of linear regression analyses is found in Supplemental Figures S7-S9 (online).

Burst pressure

All CVCs failed at one of the locations displayed in Figure 3-5 during burst pressure measurement. Burst pressures and the failure location at burst pressure are also recorded in Table 3-1.

Microscopic surface analysis

Magnification was chosen to best illustrate the differences in the surface in each CVC. The microscopic surface analysis of the 3 CVCs examined is depicted in Figure 3-6. With the unused lumina as control, the pictures of the tested lumina show an increase in size and density of micro-cracks in the double and triple lumen CVCs. These micro-cracks present themselves as clear black lines in the microscopy images. However, this contrast is less

apparent in the pre-curved CVC, where the lumen was larger (15.5F versus 13F) and intraluminal pressures were lower.

Table 3-1: Testing regime, burst pressure and failure location for each catheter tested. Failure locations are shown in Figure 5.

Sample no.	CVC type	Testing regime	Burst pressure [kPa] ([PSI])	Failure location
1	Double Lumen	5x4.5mL/s; 5x8mL/s	1179 (171)	Inlet tube burst
2	Double Lumen	5x4.5mL/s; 5x8mL/s	N/A	N/A
3	Double Lumen	5x8mL/s; 5x4.5mL/s	1158 (168)	Inlet tube burst
4	Double Lumen	5x8mL/s; 5x4.5mL/s	1110 (161)	Inlet tube burst
5	Triple Lumen	5x4.5mL/s; 5x8mL/s	862 (125)	Inlet tube burst
6	Triple Lumen	5x4.5mL/s; 5x8mL/s	917 (133)	Inlet tube burst
7	Triple Lumen	5x8mL/s; 5x4.5mL/s	N/A	N/A
8	Triple Lumen	5x8mL/s; 5x4.5mL/s	800 (116)	Inlet tube burst
9	Pre-Curved	5x4.5mL/s; 5x8mL/s	1165 (169)	Connector dislocation
10	Pre-Curved	5x4.5mL/s; 5x8mL/s	1248 (181)	Connector dislocation
11	Pre-Curved	5x8mL/s; 5x4.5mL/s	1220 (177)	Connector dislocation
12	Pre-Curved	5x8mL/s; 5x4.5mL/s	N/A	N/A

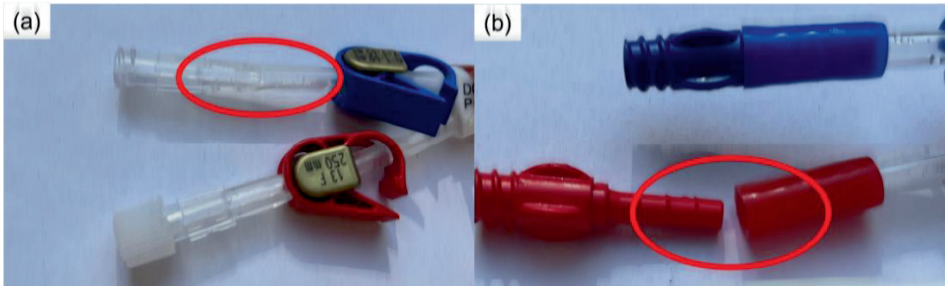

Figure 3-5: Failure modes of the central venous catheters at burst pressures: a) failure of the inlet tube resulting in rupture; and b) dislocation of the inlet tube connector.

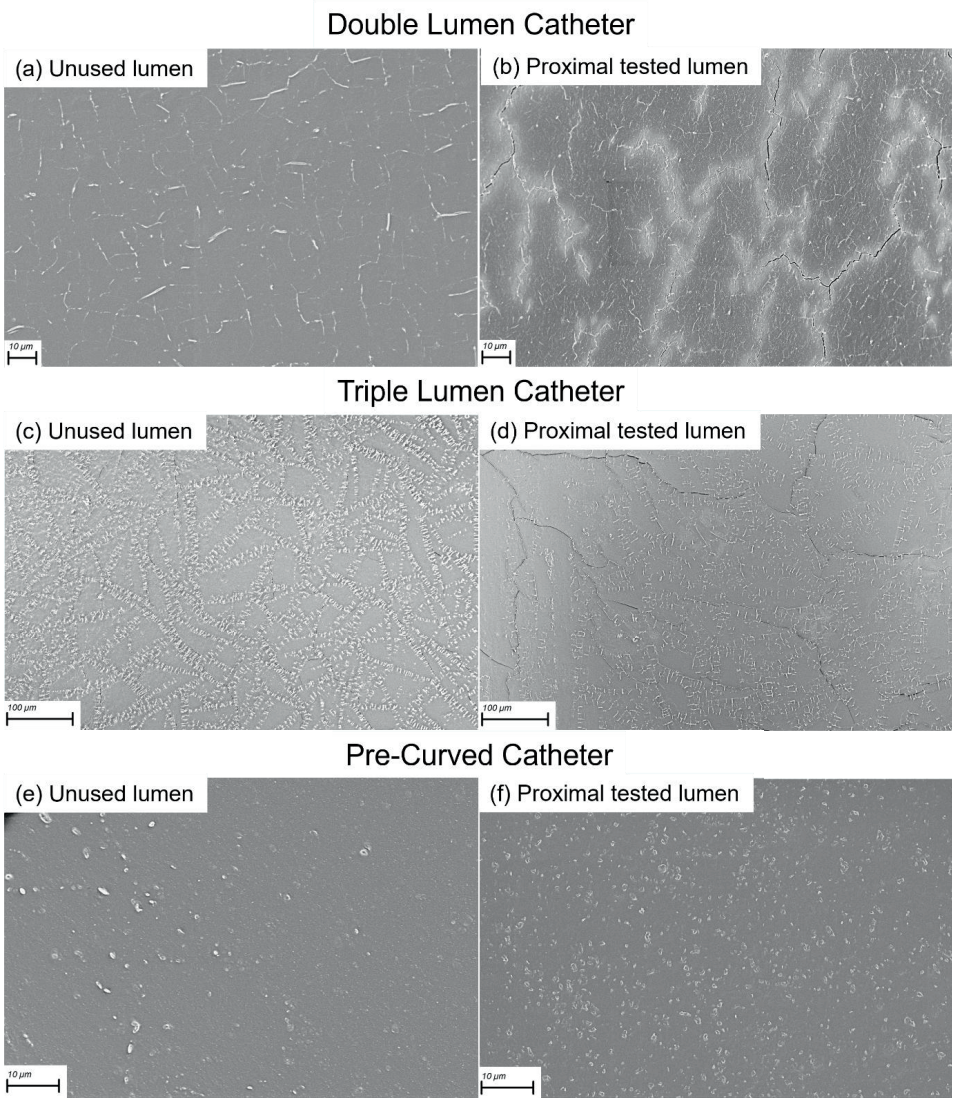

Figure 3-6 Surface analysis through scanning electron microscopy of: a) unused lumen, and b) part from the inlet side of the tested lumen, of the double lumen catheter; c) unused lumen, and d) part from the inlet side of the tested lumen of the triple lumen catheter; e) unused lumen, and f) part from the inlet side of the tested lumen, of the pre-curved catheter. Small white dots and lines visible in all images are identified as pores in the material. The black lines are indicative of micro-cracks. There are notable differences in the luminal surfaces across the various types of catheters. The magnifications used were selected to best illustrate the surface changes in each catheter type before and after exposure to contrast medium injection.

3.4 Discussion

In this study it was observed that intraluminal pressures during power injection of CM remain well below burst pressure. By using strain gauges and a pressure transducer in the flow circuit, the data suggest that strain gauges provide a more accurate measurement of intraluminal pressure. Moreover, the strain gauges showed that material fatigue and damage can occur to the CVCs with repeated use. Surface analysis of the CVCs was performed to assess microscopic damage to the material, in which a greater incidence of micro-cracks was noticed after testing. This data can guide clinicians in responsible use of CVCs for CM power injection.

As in literature [6], [8], [9], [10], [11], [12], the measured pressures were well below bursting pressure. Bursting pressures were also comparable [6], [10]. The CM injector pressure was higher than the intraluminal pressure, which is necessary to overcome the frictional losses in the tubing and CVCs. Given that the injection pressures through CVCs are comparable to those in standard angiography catheters [21] and are applied for only a short duration, the risk of vascular or cardiac tissue damage is expected to be minimal.

The outliers in the injector pressure may be explained by the injector exerting an increased pressure on the fluid bag when almost empty, which was a constant trend. The intraluminal pressures also show a substantial variation in values, explained by the sensitivity of the gauge to environmental factors and the measurement error in the calibration.

Contrarily to the injector pressures, the intraluminal pressures in the different types of CVCs show some discrepancy, likely because the lumina have dissimilar cross-sections. The highest intraluminal pressures correspond to the smallest cross-sectional area. Despite the geometrical differences between the lumina of the pre-curved CVCs, the injector pressures were similar through both when injecting at the same velocity. This suggests pressures are also similar in both lumina.

Although the CM injector exerted greater pressures at higher injection velocities, the intraluminal pressures appear more similar. An explanation could lie in the frictional losses of the fluid flowing through a substantial length of tubing before entering the CVC. Frictional losses are greater at higher velocities and small diameters, which explains considerable pressure losses. Additionally, the three-way stopcock present in the flow circuit may have introduced more turbulence in the flow which could have resulted in a slight drop in pressure and affected the measurements downstream.

The pressure transducer placed further upstream should measure a higher pressure than the strain gauges. Therefore, it is an interesting finding that the pressure measured by the pressure transducer was noticeably lower than the pressures measured by the strain gauges. However, a three-way connection is placed to connect the pressure transducer which introduces dead space in which fluid is static. This likely interferes with the flow, as these stagnant zones act as reservoirs of pressure, exerting localized effects that can distort the

overall pressure profile in such locations. Turbulent eddies may form in regions of abrupt flow constriction or expansion, causing fluctuations in pressure and velocity. In systems with rapidly changing flow rates, the presence of dead space can thus impede the propagation of pressure waves and dampen fluid oscillations, leading to distorted pressure transducer readings [20]. This dead space will thus not always show a direct pressure response to fluidic flow, which impedes accuracy of the measurement. These phenomena may contribute to the rather large differences in measured pressures throughout previous in vitro studies (2-70 PSI at 4.5 mL/s velocities with similar catheters) [6], [7], [11], [12]. As the strain gauges do not interfere with the flow and they measure pressure directly at the location of interest, the pressures they measured are more likely to be valid.

The fatigue analysis of the strain values implies that material damage accumulates throughout the repeated measurements. Consistency in peak amplitudes suggests that the adhesive interface between the strain gauge and CVC remained intact. In all CVCs, except one, this coefficient is statistically significant. In CVC sample 2 the non-significant coefficient appears to result from the last 2 measurements having a far higher resting voltage. This likely occurred through accidental interference with the CVC during testing, and registered by the high sensitivity of strain gauges. It is likely that higher CM volumes or flow rates will accelerate the fatigue process.

The microscopy shows an increase in size and density of micro-cracks between the unused and tested luminal surfaces in the double and triple lumen CVCs. These cracks seem to propagate along what appear to be small pores in the material. Propagation is likely induced by the pressure of the CM injection. Electron microscopy in literature of similar dialysis CVCs, exposed to normal use and explanted from patients, do not show such clear micro-cracks [22], [23], suggesting the CM injection caused the damage. These micro-cracks could potentially promote bacterial adhesion and biofilm formation. This study does not address such risks, but proper handling and flushing remains crucial.

In the pre-curved CVCs, no such micro-crack formation is clearly visible. This could be due to the intraluminal pressures in the pre-curved CVCs being lower due to the larger cross-sectional area of these lumina, thereby causing less damage.

As the CVC material appears to stretch after CM injection, permanent stretching and offset may have occurred prior to calibration. The validity of calibration data can thus be questioned. Although most regression coefficients are significantly non-zero, the actual changes in resting voltage are relatively small compared to the amplitude of the voltage peaks. Moreover, the amplitudes of the voltage peaks remain fairly constant throughout the 5 measurements at the different injection velocities in all CVCs. The effects on the determined intraluminal pressure values are therefore expected to be limited.

Failure of the CVCs at bursting pressure always occurred at the inlet, which in clinical use will remain outside the body. However, the stretching of the material and increase in micro-crack

size and density suggested damage accumulates with repeated CM injection. The micro-cracks may increase thrombus risks but this remains to be studied. With the velocities tested, incidental use likely carries little risk.

The relatively small number of CVCs used does pose issues with drawing statistically significant conclusions, and statistical analysis has therefore been omitted. However, the burst pressures measured were always at least a factor 2 higher than the intraluminal pressures measured which does illustrate a substantial margin of safety. Burst pressure measurement was only performed on three CVCs of each type, but they do resemble values previously found in literature [6], [10]. The electron microscopy on single samples holds no statistical value, but does support the findings on pressure and fatigue in all the CVC types tested, and aids in understanding effects of repeated use. Future studies should include larger sample sizes.

This study has several limitations. Intraluminal pressures were measured in vitro, not fully simulating in vivo conditions, and the CVCs are not subjected to normal clinical handling which may impact device integrity. Although CVC pressures during dialysis typically do not exceed arterial pressure, the CVCs were new and not subjected to normal dialysis use. They were also not maintained at body temperature. Testing at body temperature could have increased flexibility of the material. Contrarily, rigidity, and thus pressure, could increase due to fibrous tissue forming on the CVC in the body. Venous pressure at the tip was absent, which may have increased intraluminal pressure. However, venous pressure is typically far lower than the pressures measured in the system. Moreover, intraluminal pressure is only measured at one location in the catheters. Although pressure close to the inlet is expected to be highest, the pressure and stress profile throughout the entire CVC is not examined. Therefore stress or pressure concentrations that could occur are not considered. Additionally, a lower temperature than typically used in patients was used with a high-concentration CM (350 mg/mL iodine) which will have considerably increased the viscosity [21] and resulting pressures will therefore have been overestimated. It has been found that higher concentrations up to the typical maximum of 400 mg/mL may further increase pressures by ~15% [21]. Any changes in fluid composition due to evaporation or deposit on the luminal surface during reuse of the CM are not considered. However, this will likely only have increased the concentration of the CM, and thus further overestimated in-use pressures. Moreover, the fatigue analysis suggests that stretching of and damage to the material occurs after repeated use. However, it is not known how material fatigue relates to material strength, and to which extent safe use may be maintained. In vivo factors and fatigue should receive attention in future safety studies.

Finally, CVCs are medical devices regulated under the European Medical Device Regulation in the EU[24] and the FDA in the US [25]. Manufacturers must meet performance and safety requirements for market approval [24], based on the device's intended use. Expanding use cases thus requires additional evidence, leading manufacturers to limit intended uses to reduce costs. Despite reports of safe in vitro use with higher velocities [6], [7], [8], [9], [10],

[11], [12] and clinical application [13], [14], [15], incidents of rupture have been reported [16], [17], [18]. Unexpected tip displacement was found to increase thrombus risk, which may be addressed with adequate flushing.18 Guidelines for CM injection through CVCs are limited [19] and most standard CVCs remain uncertified for CM injection. This likely causes hesitance in their use for such procedures, in which liability is shifted to the healthcare professionals. Clinical use of CVCs for this purpose has previously been shown to be safe with sufficient image quality, provided adequate protocols with pressure limits are in place [14]. However, caution must be taken and caretakers must understand that liability is shifted away from the manufacturer when using such CVCs for CM injection.

The findings presented highlight that while incidental use of CVCs for CM injection does not pose immediate risks, repeated use could compromise catheter integrity over time. This research underscores the importance of cautious, informed application of CVCs for CM injections in clinical settings, guiding practitioners toward safer, evidence-based decisions to prevent potential complications.

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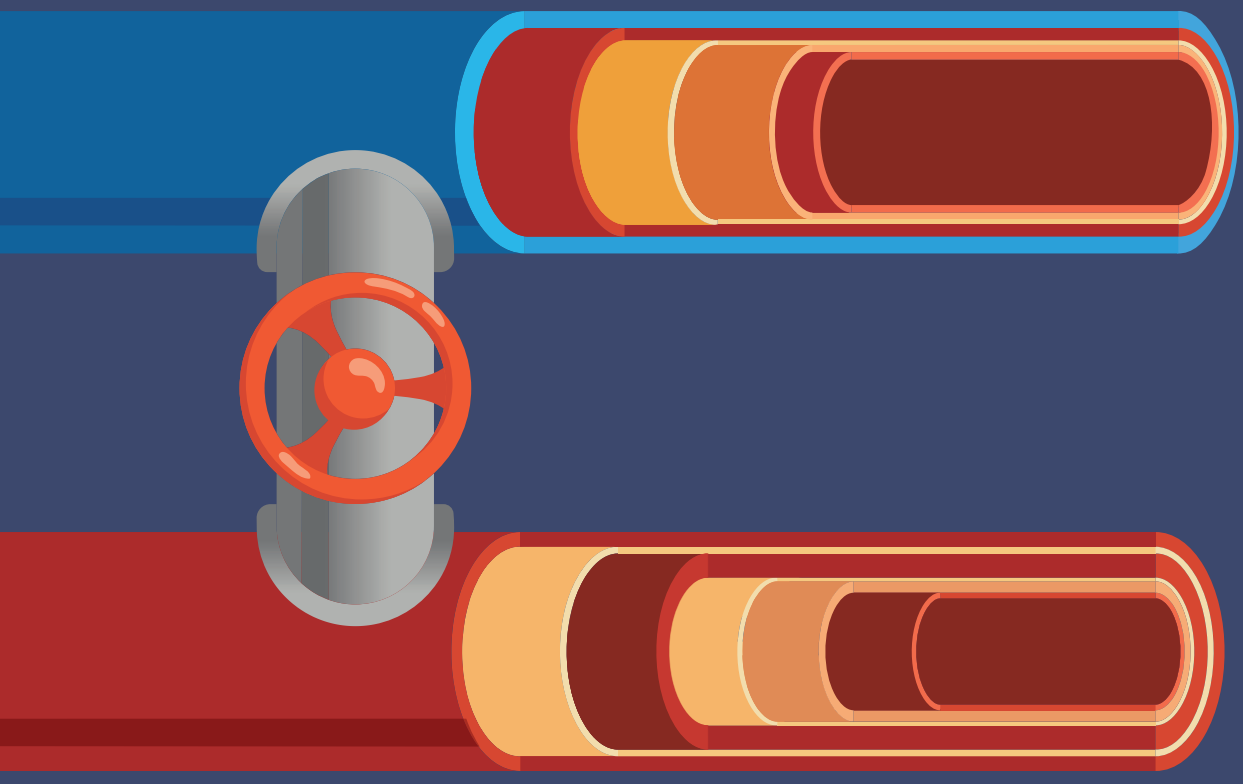

Haemodynamic considerations in arteriovenous vascular access modalities for haemodialysis

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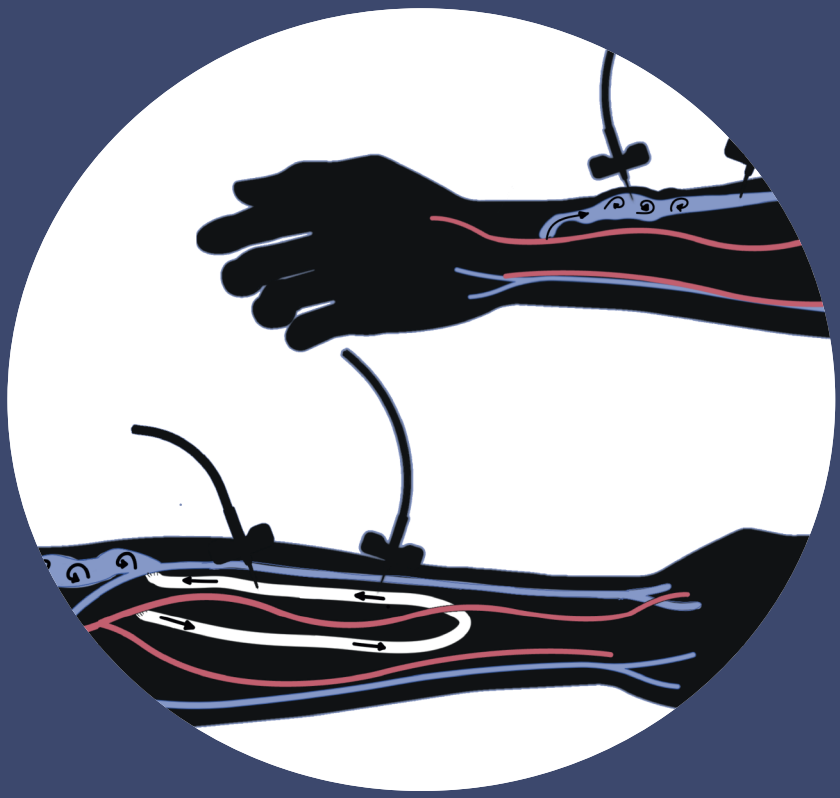

This chapter reviews the haemodynamic factors underlying complications in arteriovenous vascular access (VA) for haemodialysis. By examining how access configuration, flow dynamics, and vascular remodelling contribute to VA failure, the chapter provides essential background for understanding why persistent supraphysiological flow remains a key target for innovation. These insights directly inform the rationale for developing flow-modulating technologies such as the Dynamic AVF, discussed in subsequent chapters.

Abstract

Arteriovenous fistulas and arteriovenous grafts are the most commonly used vascular access for hemodialysis in patients with end-stage chronic kidney disease. However, both methods face significant challenges due to the hemodynamic disturbances induced by the arteriovenous anastomosis. This causes changes in vascular structure and blood flow velocity near the anastomosis site after the fistula/graft surgery, and introduces abnormal wall shear stress and cyclic stretch. This leads to endothelial cell dysfunction, vascular smooth muscle cell proliferation, and adverse remodeling. The resulting effects include low patency rates due to vascular stenosis caused by intimal hyperplasia and insufficient outward remodeling. Additionally, the high flow conduit has been linked to adverse cardiac remodeling. To address this, various strategies have been explored to correct these localized hemodynamic abnormalities, aiming to improve long-term patency rates. In this review, an overview is provided of the current surgical techniques, anastomosis types, anastomosis angles, external scaffolds, modified fistula designs, and types of grafts. It evaluates the impact of these approaches on local hemodynamics in the access conduit and their potential effects on patient outcomes.

4.1 Haemodynamics of peripheral vascular access

End-stage kidney disease (ESKD) patients often rely on haemodialysis as renal replacement therapy. The arteriovenous (AV) vascular access is the lifeline for these patients. Introduced in 1966, the radiocephalic arteriovenous fistula (AVF) [1] in the wrist provides a reliable means of vascular access for repeated cannulations for chronic haemodialysis. This innovation laid the groundwork for the widespread adoption of chronic haemodialysis as a viable long-term treatment option, transforming the prognosis for patients with renal failure. Vascular access outcomes and durability have improved over the decades with, advancements in surgical techniques, arteriovenous grafts (AVGs), and central venous catheter (CVC) technology.

The AV access remains the preferred vascular access for chronic haemodialysis, with the radiocephalic AVF the most commonly used type [2]. Despite considerable progress, the creation and maintenance of functional arteriovenous vascular access continue to present significant challenges [3]. 1-year primary failures rates of AVFs are poor, at 40% [4]. The primary complications affecting the longevity and efficacy of AV access include stenosis induced by intimal hyperplasia (IH), thrombosis, infection, and aneurysm formation [5]. This contributes to a high burden on the patient, healthcare systems and society [6].

Although underlying mechanisms are not yet fully understood [7], current knowledge suggests that local haemodynamic factors, introduced by the arteriovenous conduit, play a crucial role in the success and failure of AV access [8]. A key factor is the difference in pressure between the arterial and venous system, which enables the high flow through the arteriovenous conduit as the blood flows through the path of least resistance. An AV access is typically considered suitable for cannulation when the flow exceeds 500 mL/min [9], but many fistulae have far higher flow rates, reaching up to 3000 mL/min [10]. This is especially the case in AVFs in the upper arm such as the brachiobasilic AVF, where vessel diameters are typically larger. Together with the pressure differential and anatomical bifurcation created, turbulence is introduced in the blood flow. These disturbed flow patterns and shear stress variations at the AV access drive IH, and often result in inward remodelling (i.e. a decline in the luminal diameter of the vessel), and eventually stenosis [7].

In addition to local vascular complications, arteriovenous conduits for haemodialysis can have systemic effects on the cardiovascular system. The high flow introduced by the AV access results in increased cardiac output, and can cause changes to blood pressure, left and right ventricular hypertrophy and may contribute to a decline in cardiac function over time, including congestive heart failure and pulmonary hypertension [10], [11]. This can exacerbate pre-existing cardiovascular conditions and risks such as hypertension and chronic heart failure, commonly found in haemodialysis patients [12]. The hyperdynamic circulation induced by the AV access can also lead to higher incidences of sudden cardiac death [13], underscoring the need for careful monitoring and management of these patients. Conversely, cardiac output and blood pressure also have a significant impact on the haemodynamic profile of the AV access.

As flow profiles are a significant factor in the outcomes of AV access [14], it is crucial to understand the effects of different modalities on the local and systemic haemodynamics. The presented study aims to provide background information into the local and systemic haemodynamic factors of AV access, a review of arteriovenous access modalities in scientific literature, and determine their local and systemic haemodynamic effects. The focus will remain on types of surgical procedures and devices for AVFs, and types of AVGs. The ultimate goal of this review is to describe strategies to enhance design and management of AV access to improve the outcomes for haemodialysis patients.

Local haemodynamic factors and effects

The haemodynamic profile of AV access – laminar or disturbed – is dependent on geometry, flow velocity, density and viscosity. Laminar flow is present in most of the cardiovascular system, and is smooth and orderly. However, disturbed flow is chaotic and increases the risk of uneven and multidirectional flow patterns [15]. In the context of AV access, disturbed flow is common due to the abrupt changes in vessel geometry, blood flow velocity at the anastomosis, and potentially inflow from distal veins and arteries. Vascular endothelial cells (ECs) and smooth muscle cells (SMCs) in the intima and media layers of blood vessels are affected by mechanical forces resulting from this disturbed blood flow and the increase in flow rate. The most well-studied mechanical factors are wall shear stress (WSS), and circumferential cyclic stretch [16], [17], [18], [19].

WSS is the frictional force between blood flow and the vessel wall surface. Both the magnitude and direction of WSS affect EC function [16], [17]. In straight vessels under physiological conditions, unidirectional WSS with normal value maintains vascular homeostasis by downregulating proinflammatory and proliferative markers in ECs. However, at the site of the anastomosis, flow patterns become unstable, leading to disturbed flow characterized by low and multidirectional WSS on the inner wall of the vein [18]. The common haemodynamic parameters for describing disturbed flow are:

- Time-averaged wall shear stress (TAWSS), the average value of WSS throughout one cardiac cycle, which is low in the disturbed flow region [19];
- The oscillatory shear index (OSI), a parameter quantifying the degree of flow reversal along the main flow direction, and
- relative residence time (RRT) representing the residence time of blood near ECs, which is high in disturbed flow locations [20], [21].

This disturbed flow is crucial in upregulating proinflammatory and proliferative markers in ECs, potentially promoting IH [7], [22], [23]. Notably, when blood flows through the anastomosis, it induces relatively high WSS on the outer wall of the vein. When the blood flow is particularly high, the extremely high WSS can lead to endothelial damage and vascular calcification [24], which can stiffen arteries and impair normal blood flow.

CS refers to the periodic expansion and contraction of the vessel wall caused by differences in systolic and diastolic blood pressure. Physiological cyclic stretch ranges from 10-15% and

varies among vessel types, and is important for maintaining the contractile phenotype of VSMCs in the tunica media [25]. Abnormal cyclic stretch induces a switch in VSMCs from a contractile to a proliferative phenotype [26], [27]. The contractile phenotype is essential for vascular contraction and blood pressure regulation, inhibiting VSMC proliferation and excessive extracellular matrix (ECM) synthesis [28], [29]. Conversely, proliferative VSMCs increase ECM synthesis and vessel wall thickness, with some migrating from the media to the tunica intima, contributing to IH along with other inflammatory cells [30], [31].

The unnatural vibrations with high-frequency pressure fluctuations, often occurring due to transitional flows found in anastomoses, can reach frequencies up to hundreds of Hertz [32]. More recent studies suggest that such vibrations in AVFs are linked to the haemodynamic and structural changes post-creation [32], [33]. They are predominantly found at the anastomotic heel and the inner curvature of the vein, areas prone to vascular remodelling and stenosis development. The vibrations are believed to stimulate mechanobiological processes within the vascular wall, contributing to adverse remodelling and stenosis.

These factors are modulated by the local haemodynamics of the AVF, and are critical in the outcome of the AVF. Before AVF surgery, blood flow in the cephalic vein is very low, resulting in low uniform WSS, cyclic stretch and vibration. After creating the anastomosis, blood flow velocity and pressure increase dramatically and instantaneously. The abnormal anastomosis angle exacerbates local disturbed flow. Although vessels adapt by outward remodelling and luminal expansion to reduce WSS to a reasonable range, the disturbed flow near the anastomosis and abnormal cyclic stretch continuously stimulate local ECs and VSMCs. Activated ECs and VSMCs with a proliferative phenotype are key factors in the development of IH. Finally, the locally modified haemodynamics have been linked to aneurysm formation in the venous outflow through modification of the vessel wall [34]. Therefore, improving haemodynamics in the juxta-anastomotic region could inhibit IH and increase AVF patency.

Systemic haemodynamic factors and effects

Chronic kidney disease is a significant risk factor for cardiovascular morbidity and mortality [12]. The creation of a high-flow arteriovenous vascular access site for haemodialysis further amplifies these risks by introducing substantial alterations in systemic haemodynamics. Immediately after AV access creation, cardiac output (CO) increases significantly due to reduced systemic vascular resistance, heightened sympathetic activity, and increased stroke volume and heart rate [10], [35]. This rise in CO is necessary to accommodate the increased blood flow through the AV access.

Persistent high flow through the AV access can lead to adverse cardiac remodelling [36]. The chronic volume overload from increased blood volume and CO promotes the development of eccentric left-ventricular hypertrophy (LVH), characterized by enlarged cardiac chambers and increased left ventricular mass [11].

A major risk associated with AV access is high-output heart failure, defined by an elevated cardiac index and symptoms such as dyspnoea and enema. Continuous volume overload and

myocardial structural changes drive this condition [13]. The increased CO also elevates pulmonary arterial flow and pressure, potentially leading to pulmonary hypertension. Furthermore, the diversion of blood flow through the AV access can result in organ hypoperfusion. Vascular access-related hand ischemia, or steal syndrome, can occur in the distal limbs [37], but is most often limited to the ipsilateral hand. The heart can suffer from coronary steal, which may lead to congestive heart failure with inadequate organ perfusion and pulmonary congestion [38]. Cerebral hypoperfusion may occur, exacerbating cognitive impairment, already common in haemodialysis patients [39].

Blood pressure management is crucial in this scenario. AV access creation can cause significant fluctuations in systolic and diastolic blood pressure. Initially, blood pressure may rise due to the increased CO and volume overload. However, during haemodialysis sessions, hypotension is common due to ultrafiltration and the blood diversion through the AV access. These fluctuations can cause symptoms like dizziness and fatigue, and persistent variability increases the risk of ischemic events and further cardiovascular instability [40].

Subclavian vein stenosis and arterial stenosis are also potential complications associated with AV access. Ipsilateral venous subclavian stenosis can result from the high flow rates and increased venous pressure similarly to local stenoses, leading to venous hypertension, arm swelling, and impaired access function [41]. Arterial subclavian stenosis, although less common, can cause significant reductions in arterial inflow, exacerbating distal ischemia and potentially compromising the viability of the AV access [42]. Both types of stenosis can further aggravate the cardiovascular burden on dialysis patients and complicate the management of AV access.

Finally, the cardiovascular conditions introduced by the VA also significantly impact the fitness and well-being of dialysis patients. Kidney transplant patients with a prior AVF typically report a lower quality of life than a control group that received peritoneal dialysis before transplantation [43]. Moreover, proximal, high flow AVFs were associated with a lower quality of life than distal, low flow, AVFs [43]. These findings suggest that the AVF, and more specifically the high flow, are negatively associated with quality of life, although prospective trials need to be performed to confirm this potential causative relation. Managing these haemodynamic changes is essential for improving the long-term outcomes and well-being of dialysis patients.

4.2 Haemodynamic modalities in arteriovenous fistulas

The structure of AVFs significantly impacts haemodynamics, and surgical techniques directly influence this structure. Therefore, various surgical methods and configurations have been explored in attempts to optimize haemodynamic profiles and AVF patency.

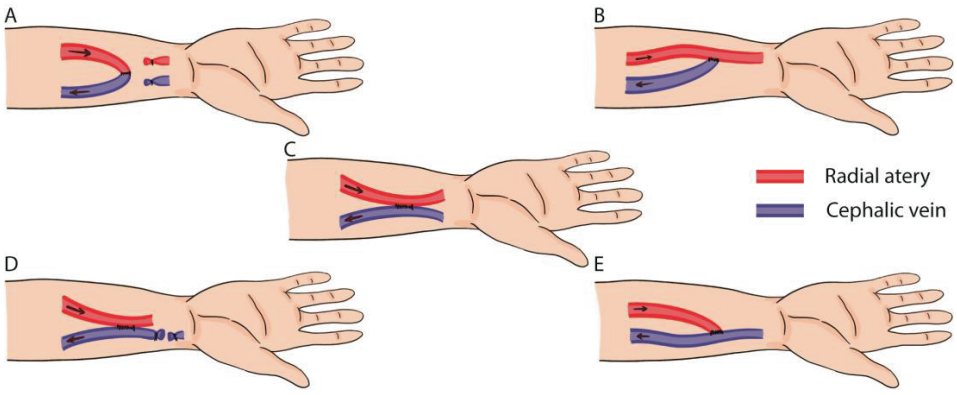

Figure 0-1: arteriovenous fistula configurations: a) end-to-end anastomosis; b) end-to-side anastomosis; c) side-to-side anastomosis; d) modified functional end-to-side anastomosis; e) radial artery deviation and reimplantation anastomosis.

Location and type

The location of the AVF in the arm has been found to affect local haemodynamic profiles significantly, with upper arm AVFs typically having higher flow rates corresponding to improved maturation rate and functional patency. However, secondary complications are also more prevalent as a result of the increased flow. Importantly, more proximal locations remain available for creating an AVF is distal fistulae fail, so guidelines recommend placing fistulas as distal as possible, provided sufficient vessel diameters [2].

Since the inception of autogenous AVF surgery, anastomosis techniques include end-to-end (ETE), end-to-side (ETS), side-to-side (STS), and modified functional ETS anastomoses (Figure 0-1a – 1e, respectively). ETE involves anastomosing the cut ends of an artery and vein, while ETS connects a severed venous end to the side of an artery. STS involves creating sections in both vessels and anastomosing the edges of sections, whereby the distal vein functionality and inflow remains. Though the ETE AVF can avoid the bifurcation, computational fluid dynamics (CFD) simulations still showed disturbed flow occur in the outflow tract where IH is common [44], additionally, due to higher complication rates and the risk of distal limb ischemia, ETE is being replaced by ETS and STS [45]. Although the venous inflow remains in STS AVFs, CFD simulations find varying results on its effects on flow disturbances and multi-directionality of WSS [46], [47], which is linked to an increase in IH. A meta-analysis found similar patency rates between ETS and STS anastomoses, but also a significantly increased occurrence of arterial steal syndrome with STS AVFs [48]. However, this may have been due to the more proximal placement of the STS AVF.

Modified functional ETS is a variation of STS where the distal end of the vein is ligated when constructing the anastomosis. Post-anastomosis, arterial blood flows into the low-pressure venous system, significantly increasing venous blood flow to meet haemodialysis needs. A meta-analysis of 16 studies, including 6 RCTs, showed that traditional ETS had higher six-month patency rates than STS but lower 12-month rates than functional ETS [49]. Researchers

utilized computational fluid dynamics (CFD) to compare haemodynamics in functional ETS and traditional ETS, finding that functional ETS provided higher venous blood flow and more uniform wall shear stress (WSS), potentially explaining its better outcomes [46]. Although more surgeons are opting for the functional ETS, there is currently no proof that improved haemodynamics have a direct impact on prognosis. More individualized haemodynamic studies are needed to confirm the clinical benefits of functional ETS.

Endovascular AVFs

The endovascular AVF (endoAVF) allows the creation of a vascular conduit through catheterisation into the vessels, thus without necessitating surgery. The WavelinQ™ (Becton, Dickinson) and Ellipsys™ (Medtronic) are the most commonly used systems for endovascular AVF creation, using radiofrequency and a combination of heat and pressure, respectively, to create the anastomosis. The minimally invasive nature creates less vessel trauma which may lead to decreased maturation time and preferable EC activation. Both devices are used to create a STS in the deep mid-forearm vessels.

The haemodynamic profile in endoAVFs is dissimilar to that of standard STS AVFs due to the deepness of the site. The primary advantages result from the mid-forearm location, which is typically different compared to creation with standard surgical techniques. Flow rates in the mid-forearm are typically higher than in the wrist but lower than in more proximal locations [2], and 6-month secondary patency was found to be 94% [50]. Therefore, low incidence of distal ischemia, aneurysm, and cardiac overload may be achieved even when wrist AVFs are not possible. However, interventions on endoAVFs are typically larger due to the deep location of the anastomotic site, and the effect of the learning curve of the devices cannot be excluded from results in literature.

Radial artery deviation and reimplantation (RADAR)

To address abnormal haemodynamics and reduce surgical injury at the anastomosis, the RADAR technique, where the artery is ligated and the end is anastomosed to the side of the vein, has shown promising clinical results [51], Figure 0-1e. Short- and long-term follow-ups indicated higher primary (6 months: 93% vs 53%; 12 months: 72.2% vs. 48.1%; 36 months: 62.1% vs. 37.6%) and secondary patency rates (6 months: 100% vs 89%; 12 months: 98.4% vs. 72.1%; 36 months: 94.9% vs. 66.8%) and fewer reinterventions (6 months:10% vs 74%) with RADAR compared to traditional methods [52], [53]. CFD and animal studies suggest RADAR reduces pressure and high WSS at the anastomosis rather than improve low and oscillatory WSS, potentially mitigating intimal hyperplasia. Hypertension, diabetes mellitus, and anemia are common combinations in ESKD patients, affecting blood flow velocity, vessel wall stiffness, and blood viscosity. Integrating these variables into CFD, other research found that RADAR reduced disturbed flow and flow velocity at the anastomosis as well as the extremely high WSS at the anastomosis toe, decreasing the risk of juxta anastomotic intimal hyperplasia [54].

Although a higher incidence of distal ischemia (steal syndrome) may be expected due to the distal ligation of the artery, this does not appear to be an issue [52]. An explanation may lie in the presence of retrograde flow in conventional ETS AVFs in which distal hypoperfusion is exacerbated as the anastomotic site draws blood from the hand through the artery, whereas in RADAR the proximal inflow is merely diverted into the vein.

Finally, the RADAR AVF may pose additional challenges in patients suffering from diabetes mellitus and microangiopathy due to increased stiffness of the artery. However, due to the limited amount of literature on this technique, no evidence exists suggesting unsuitability of the RADAR technique for these patient populations.

Vessel diameter and anastomotic angle

Another aspect of the AVF structure is anastomosis angle which is also crucial in AVF haemodynamics. Researchers seek the optimal anastomosis angle to improve local haemodynamics and AVF outcomes (Figure 0-2). CFD analysis revealed that low and oscillatory WSS occurred primarily in the inner wall of juxta-anastomosis vein and the outflow tract vein, correlating with clinical stenosis locations, suggesting disturbed flow contributes to AVF intimal hyperplasia [55], [56]. Then, the distribution of low and oscillatory WSS were simulated in AVF models with anastomosis angles of 30, 45, 60, and 90 degrees, with 30 degrees showing the least abnormal WSS distribution at juxta-anastomosis indicating the sharper angle may have a better AVF outcomes. Another study collected PTA data and AVF configuration from 27 patients with juxta anastomotic stenosis on their radiocephalic AVF, using patient-specific 3D vascular models and CFD found that the anastomosis angle was closely related to the blood flow velocity at the stenosis site, and ROC curve analysis suggested that patients with anastomosis angle greater than 46.5° had a significantly lower stenosis ratio and disturbed flow when compared to patients with an angle less than 46.5° [57].

Significant correlations have been established between anastomotic angle and vessel diameter, and the distribution of disturbed haemodynamics in AVFs. CFD studies suggested that the blood flow velocity and WSS at the anastomosis site increased when the venous diameter was smaller than the arterial diameter, leading to a larger area of disturbed flow and a higher risk of thrombosis. In this scenario, the anastomosis angle had little effect on local haemodynamics. Conversely, when the venous diameter was larger than the arterial diameter, increasing the anastomosis angle reduced the area of disturbed flow and normalized WSS [58]. To further investigate the impact of larger anastomosis angles on AVF haemodynamics, the concept of obtuse angle anastomosis has been proposed. CFD studies indicated that the obtuse angle ETS AVFs significantly reduced disturbed flow and lowered abnormally high WSS compared to traditional anastomosis techniques. However, clinical studies did not show that obtuse anastomosis angle could improve primary, assisted primary, or secondary patency compared to sharp angle anastomosis [59], [60].

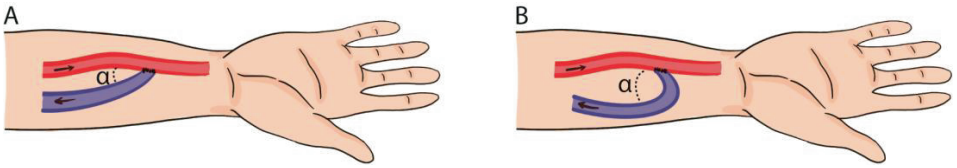

Figure 0-2: anastomotic angle "α" used for arteriovenous fistulae. a) sharp anastomotic angle; b) obtuse anastomotic angle.

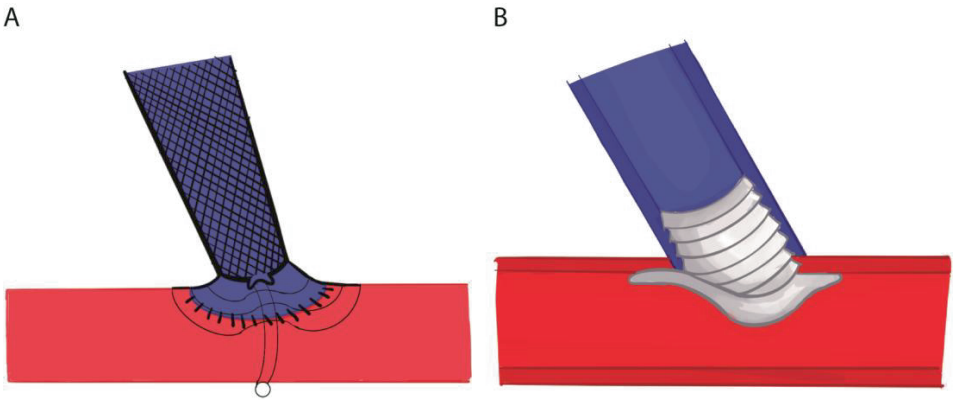

Figure 0-3: External and internal devices used to standardize and lock the anastomotic angle of an arteriovenous fistula. a) VasQ™ external vessel support; b) OptiFlow™ internal vessel support.

In summary, functional ETS and RADAR show potential advantages over traditional methods, though direct evidence linking improved haemodynamics by functional ETS and RADAR to better clinical outcomes is lacking. Reducing low and oscillatory WSS may protect endothelial function and prevent intimal hyperplasia, while addressing high WSS could also lower stenosis rates.

External vessel support devices

The VasQ™ (Laminate Medical Technologies) external vessel support device is designed to enhance the performance and longevity of AVFs (Figure 0-3a). It has two distinct features: it provides rigid support to the venous wall to reduce tension, and it fixes the anastomotic angle at 38° and tapers outwards in the outflow vein to beneficiate flow conditions in the juxta-anastomotic region.

Although sample sizes were small, a longitudinal study using high-fidelity CFD simulations based on 3D patient-specific models showed that the device helps stabilize blood flow velocity and reduce disturbed flow and shear stress metrics over time [61]. The largest difference in flow patterns and remodelling between the group receiving the external support device and the control group appeared to be at the intermediate timepoint at 3 weeks, at which the study group showed far less remodelling, more laminar flow patterns and low WSS. Moreover, the velocity profile in the control groups was more indicative of high frequency

vibrations. The morphological changes, flow patterns and WSS appeared more similar between the groups at 1 year after the surgery with statistically significant differences between the groups diminishing.

Multiple clinical studies have been conducted with the VasQ™, which typically report high maturation, and primary and secondary patency rates with the device. Lower primary failure (29.4% vs. 6%, p=0.0251) and higher 6 month primary patency rates (79% vs. 53%, p = 0.04) were found compared to a control group in a single centre study [62]. Moreover, a decreased brachial artery flow rate (0.71L/min intervention group vs. 0.81L/min control, p=0.05) and cardiac output were found (4.5L/min intervention group vs. 5.6L/min control, p=0.05) at 6 months [63], although other studies found a higher, but non-significant increase in venous flow with the VasQ™ [64]. High patency rates, exceeding 70%, are also reported at 18 months [65] and 36 months [66]. This may in part be attributed to the improved haemodynamic profile induced by fixating the anastomotic angle, decreasing WSS, and offering venous support which may reduce excessive outward remodelling and wall vibrations. However, the long-term studies offer no valid control. Only one RCT (20 vs. 20 patients) has been conducted with the VasQ™ in literature. Although patency rates were higher, this did not always translate to a statistically significant difference due to underpowering. Such an improvement was only noted in functional patency at 6 months (p=0.01) [64].

The longitudinal flow study [61] suggests turbulence is not fully addressed, and WSS, cyclic stretch and resulting remodelling are decreased, but not mitigated. The negative consequences of these haemodynamic factors are thereby most likely merely delayed. Consequently, the device appears to primarily aid in AVF maturation and could be particularly advantageous for patients with an imminent start to dialysis. This underscores the necessity for longer-term randomized controlled trials to better establish any long-term clinical benefits of the VasQ™ device.

Internal vessel support devices

An alternative method to fixating the anastomotic angle is the Optiflow™ (Bioconnect Systems), which is a cylindrical silicone insert placed inside the ligated outflow vein with a flange that is placed into the artery to create an ETS AVF with a predetermined angle of 60° [67] (Figure 0-3b). Due to the insert there is no contact between the blood and the vessel walls at the arteriovenous bifurcation. Some support to the vessels is provided by the insert, although less than in the VasQ™ due to reduced stiffness of silicone compared to the metal in the external support device.

The first-in-human study in 10 patients noted a sufficient increase in venous diameter in all patients at 6 weeks with no adverse effects [67]. The only prospective and controlled study, including 41 patients receiving the insert, reported unassisted maturation rates of 76%, 72%, and 68% at 2, 6, and 13 weeks, respectively, with no statistically significant differences to the control group [68]. Flow rates also did not differ significantly. The larger diameter Optiflow™ had a higher maturation rate at both 6 and 13 weeks (p = 0.04 and p = 0.01, respectively), which is typically expected with larger vessel diameters.

In a case report a patient is described with multiple occurrences of significant stenotic lesions just distal to the device at the transition from the silicone to the native wall, thought to be the result of IH induced by flow dynamics [69].

Limited data exists to support the benefits in maturation and decreased stenosis using the Optiflow™. Although the endothelium at the anastomotic bifurcation is not exposed to flow, downstream IH still occurs. The case report may be a sign that the transition from the device material to the native vessel even induces more local flow disturbances as overall maturation and patency shows no improvement. This transition zone might also be susceptible to kinking, which can further increase IH risks. The device is currently no longer marketed, as funding constraints caused termination of development [70].

Suturing techniques

The piggyback Straight Line Onlay Technique (pSLOT) is a surgical method designed to prevent IH and enhance AVF maturation by eliminating torsional stress in the outflow vein and reducing haemodynamic stresses resulting from the torsion [71]. Torsional stress can create local flow disturbances, which may disrupt EC functionality, promote EC activation, and thereby contribute to stenosis formation [72]. In pSLOT, the cephalic vein is dissected to ensure a straight-line outflow, minimizing torsional stress. An anastomosis is created by placing the ligated vein in a "piggyback" position over a deep artery and suturing it in place, ensuring proper alignment and avoiding twisting.

The first clinical study found a significantly decreased rate of venous stenotic lesions with a 36 month follow-up in pSLOT compared to an ETS control (29% vs 11%, p=0.04), with no significant differences in flow rate between the groups [72]. Further long-term outcomes from an observational study showed that AVFs created using pSLOT achieved high functional patency rates at 12, 24, and 60 months, with primary patency at 42.8%, 31.6%, and 20.8%, and secondary patency at 81.8%, 77.6%, and 71.7%, respectively [73]. Another study confirmed that the pSLOT technique decreases the incidence of early stenotic problems and maturation failure, supporting its potential to improve long-term outcomes for AVF patients [71].

Similarly, the diamond-shaped anastomosis technique is another method for creating AVFs, aimed at ensuring long-term patency and functionality. This technique involves a geometrically precise creation of a diamond-shaped arteriotomy, which is matched with a corresponding venotomy [74], [75]. The diamond shape facilitates a more uniform distribution of stresses in the vessel wall and reduces turbulence, which is critical for maintaining fistula patency. Although clinical data is very scarce, one study has shown that the diamond-shaped anastomosis technique results in high early-stage patency rates, reporting an 89% patency rate at six months post-surgery [76].

This low IH found throughout the studies suggests that either or both WSS and EC activation are decreased as a result of reducing wall stress in the outflow vein. However, the limited

amount of data does not allow a distinction to be made between contributions of these effects to the improved outcomes.

4.3 Haemodynamic modalities in arteriovenous grafts

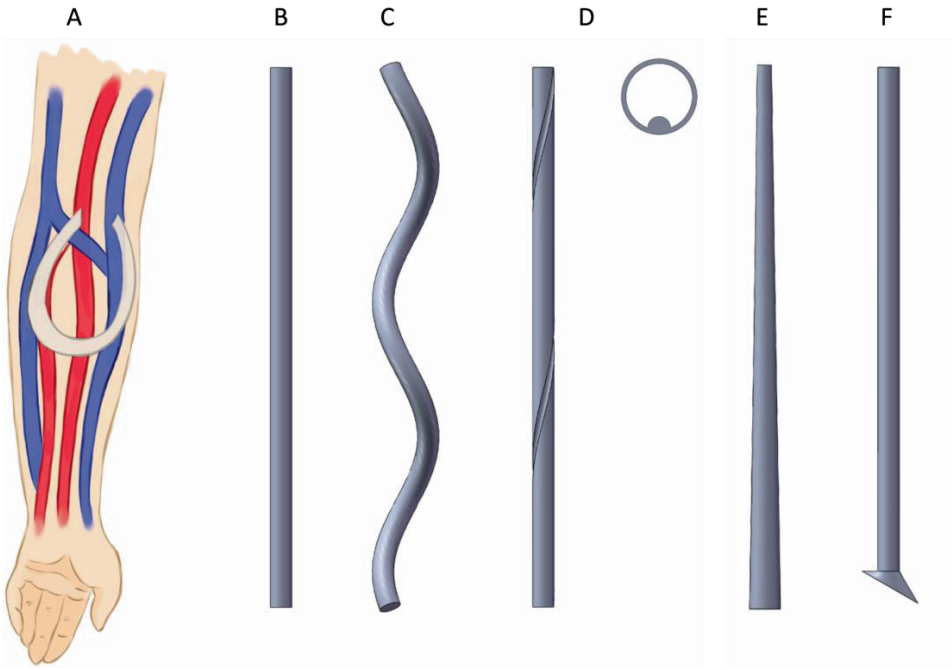

Figure 0-4: Different types of AVG used to modify haemodynamics. a) AVG in the arm; b) standard graft; c) swirling graft; d) spiral graft and its cross section; e) tapered graft, with an increased diameter on the venous side; f) cuffed/patched graft;

Arteriovenous grafts (AVGs) use synthetic or biological materials to connect arteries and veins, providing an alternative site for needle insertion during haemodialysis when native arteriovenous fistulas (AVFs) are deemed unsuitable (Figure 0-4a, b). Although native AVFs are the preferred type of access for most patients, AVGs are considered predominantly in patients with poor vascular conditions and a high risk on non-maturation [77], [78]. Notably, the early cannulation AVG allows incident haemodialysis patients to be cannulated within 48-72h, reducing the need for CVCs and are therefore gaining popularity [79]. The KDOQI guidelines now suggest that the choice between AVF and AVG should be individualized, considering patient and physician circumstances as both options offer similar primary and secondary patency rates [2]. Despite these advantages, AVGs are more prone to stenosis near the venous anastomosis compared to AVFs, often requiring more frequent interventions [2], [80]. The primary cause of stenosis is IH induced by disturbed flow and the compliance mismatch between the graft material and vessel. Since the grafts must first be manufactured,

either synthetically or biologically, their design can be modified to improve haemodynamics. Synthetic materials, most often expanded tetrafluoroethylene (ePTFE), have been used for decades. However, more recently tissue-engineered blood vessels have gained attention, as they require less or no foreign material to be implanted [81], [82]. Haemodynamically, the primary differences lie in the frictional coefficient of the graft which may marginally effect flow velocities in the graft and outflow vein.

Helical flow graft

Helical flow, a physiological pattern that resists atherosclerosis, is characterized by axial and circumferential components induced by the curved and non-planar geometry of the vascular structure [83]. Helical flow reduces vortex and recirculation, lowers endothelial cell exposure to low and oscillatory wall shear stress (WSS), and decreases monocyte and platelet adhesion [84], [85], [86], [87], [88]. Researchers have explored altering AVG designs to induce helical flow at the anastomosis, potentially mitigating intimal hyperplasia. Swirling and spiral grafts are two such designs. Swirling grafts feature non-planar geometry, Figure 0-3c, while spiral grafts have an internal spiral ridge, Figure 0-4d. By adjusting the helical pitch, curvature radius, and ridge shape, these designs can enhance helical flow [89], [90], [91], [92], [93]. Although CFD-based designs suggest improved outcomes, there are few animal or human trials. In a porcine model, researchers found that spiral ePTFE grafts induced helical flow but did not reduce intimal hyperplasia compared to standard grafts after 14 days implantation [94]. Another study implanted swirling grafts in 20 CKD patients, reporting six-month primary, assisted primary, and secondary patency rates of 57.9%, 84.4%, and 100%, respectively, indicating potential improvements in assisted primary and secondary patency rates, but larger clinical trials are further needed [95].

Tapered grafts

Tapered grafts, designed with a smaller arterial end and larger venous end, were initially developed to reduce distal limb ischemia by decreasing inflow with a small diameter and reducing flow velocity and the outflow with the increased diameter [96], Figure 0-4e. Further research showed that tapered grafts also affect haemodynamic conditions at the venous anastomosis, reducing disturbed flow and high WSS downstream, thus potentially lowering IH and thrombosis [97]. However, a meta-analysis of five studies including >4000 patients found that tapered grafts did not significantly reduce the risk of steal syndrome or infection and had comparable primary and secondary patency rates to standard grafts [98]. An explanation may lie in the venous diameter dictating the venous flow conditions, and therefore effects such as WSS and cyclic stretch in the venous outflow.

Cuffed and patched grafts

Cuffed and patched grafts are other designs aimed at improving local haemodynamics at the venous end. CFD simulations suggest that cuffed grafts lower indicators of disturbed flow such as wall shear stress gradient, wall shear stress angle gradient, and radial pressure gradient at anastomosis toe [99], [100], [101], reduce abnormally high WSS in the host artery

[102], while enhance helical flow in the distal outflow tract [99], [103], Figure 0-4f. Patched grafts also improve local disturbed flow patterns but have a smaller impact on distal helical flow compared to cuffed grafts [99]. Clinical studies comparing these grafts are limited. A meta-analysis of eight studies (six cuffed and two patched) involving 414 patients indicated that cuffed grafts improved one-year primary and secondary patency rates and reduced stenosis rates, whereas patched grafts did not offer these benefits [104].

In conclusion, various modified types of AVGs have been designed to improve haemodynamics and reduce complications. While some designs show promise haemodynamics in CFD models but small-scale studies show benefits in reality, larger clinical trials are necessary to confirm their efficacy and long-term benefits.

Stents

Bare metal stents can be used as internal vessel support to treat aneurysms and stenoses in VA outflow and cephalic arch. The deployment of these stents is intended to provide a sustained mechanical force to keep the vessel lumen open and resist inward remodelling [105]. Often these stents include a membrane on the inner side – covered stents – to prevent thromboses forming on the stent material, because the stent's structure can create areas of altered shear stress, which may influence EC behaviour and vessel wall remodelling. The membrane also provide a more uniform surface which would limit the occurrence of flow disturbances.

Covered stents are primary used in treating stenoses. A meta-analysis including 8 RCTs found that a higher patency could be maintained by using covered stents in AVG patients compared to using percutaneous transluminal angioplasty alone [106]. Although good patency could be achieved in AVF patients [107], no significant results were found, possibly due to the relatively small number of patients. Similarly cephalic arch stenosis treated with covered stents also show positive outcomes compared to other treatments in a meta-analysis with 19 clinical studies, with a 73% patency rate at 12 months [108].

Although direct effects on anastomotic and systemic flow are limited in the application of stents and covered stents, these findings do suggest that membrane stents typically perform better than the bare metal variety. An explanation may lie in the exposure of the bare metal to blood, which could induce thrombus formation. However, the flow disturbances resulting from the non-uniform surface of the stent could promote IH formation. Finally, the clinical benefit of freedom from target lesion reintervention may be questionable, especially when including the increase in cost from placing a device, for which studies are necessary.

4.4 Discussion

Despite its many sub-optimal clinical outcomes, AV access remains the access of choice for haemodialysis patients. Although it is difficult to deny that the altered haemodynamics introduced by creating a permanent arteriovenous connection play a significant role in these

negative outcomes, modalities aimed at improving haemodynamics most often show only limited benefit over the traditional radiocephalic AVF introduced 60 years ago.

Computer modelling and simulations, such as CFD, have gained interest in recent years, with the quality of the studies improving. Through CFD studies on arteriovenous access conduits, our understanding of the local haemodynamics has advanced. Moreover, techniques that can model the AV access in vivo and examine haemodynamic conditions exist, such as ultrasound vector volume flow and 4D flow quantification MRI. This allows monitoring and modelling of the AV access haemodynamics in vivo by creating a digital 3D model of the anastomosis and applying CFD. However, these imaging modalities are currently most often limited to use for research purposes, and less often in clinical care. Unfortunately, these techniques have not yet resulted in modalities that improve the outcomes, despite haemodynamic conditions undergoing some improvement. This underscores the complexity of the VA, and the multitude of factors that influence it and the outcomes. Cellular response can be difficult to predict and directly relate to haemodynamic factors, and challenging to analyse and determine in vivo. Combining in vitro testing with CFD and complex flow disturbance to monitor both haemodynamic and cellular effects may therefore be a powerful tool in further unravelling the complexity of AV access. Such models are currently under development [109].

Haemodynamic conditions and clinical outcomes are not the only considerations in the choice of AV access. While certain modalities discussed may show statistically significant improved patency, decreased failure, or lower intervention rates, the cost of including such modalities is often not taken into account. As AV access and maintenance is often paid for by, e.g., governments or health insurers, a cost benefit is usually critical in the adaptation of such modalities. For example, endoAVFs may result in higher patency rates compared to radiocephalic AVFs, but these financial benefit could be mitigated by the increased cost of the more complex angioplasty or coiling procedures due to the deepness of the anastomosis. To properly assess efficacy of AV access modalities, cost analyses are of critical importance.

Current guidelines state that a minimum blood flow of 500 mL/min [110] is required to be considered suitable for cannulation and adequate haemodialysis, which is still orders of magnitude higher than physiological venous flow. The presence of a constant supraphysiological venous flow with an arterial pressure will inevitably result in non-physiological conditions in the venous system, which the vessel will try to normalise [7]. Apart from central venous catheters, which have their own significant drawbacks, no AV access solutions are currently available that mitigate this supraphysiological flow, which only needs to be present during the typical 12 hours of dialysis per week. Our research group is currently working on an implantable device that closes the AV access outside of dialysis sessions to normalise the flow, so that the supraphysiological conditions are only present during these 12 hours per week [111].

The modalities in this overview were selected based on the authors' expertise in peripheral AV access and a critical review of available literature. However, no formal systematic review was conducted, so some modalities or studies may have been unintentionally excluded,

introducing potential bias. Additionally, many of the included modalities are not widely used, and the supporting literature is often limited or lacks RCTs, so conclusions should be interpreted with caution.

Finally, pharmacological modalities, such as vasodilators or hypotensive medication, are at times administered to patients peri-operatively. As these can affect, e.g. the blood pressure, indirect effects on AV access haemodynamics can also be expected. Although they may result in improved clinical outcomes, due to their non-direct effect on haemodynamics, they lay outside the scope of this review.

4.5 Conclusion

In conclusion, while arteriovenous VA remains the preferred modality for haemodialysis, its inherent haemodynamic alterations continue to pose significant clinical challenges. Despite various attempts to optimize haemodynamics through alternative AV access modalities and advanced modelling techniques, the outcomes have seen only modest improvements over the traditional radiocephalic AVF. The complexity of AV access haemodynamics, influenced by multifactorial interactions between flow dynamics and cellular responses, underscores the difficulty in achieving consistent clinical benefits. The current standard of maintaining supraphysiological venous flow, while essential for dialysis, perpetuates non-physiological conditions in the venous system, with no viable alternatives to mitigate these effects yet available.

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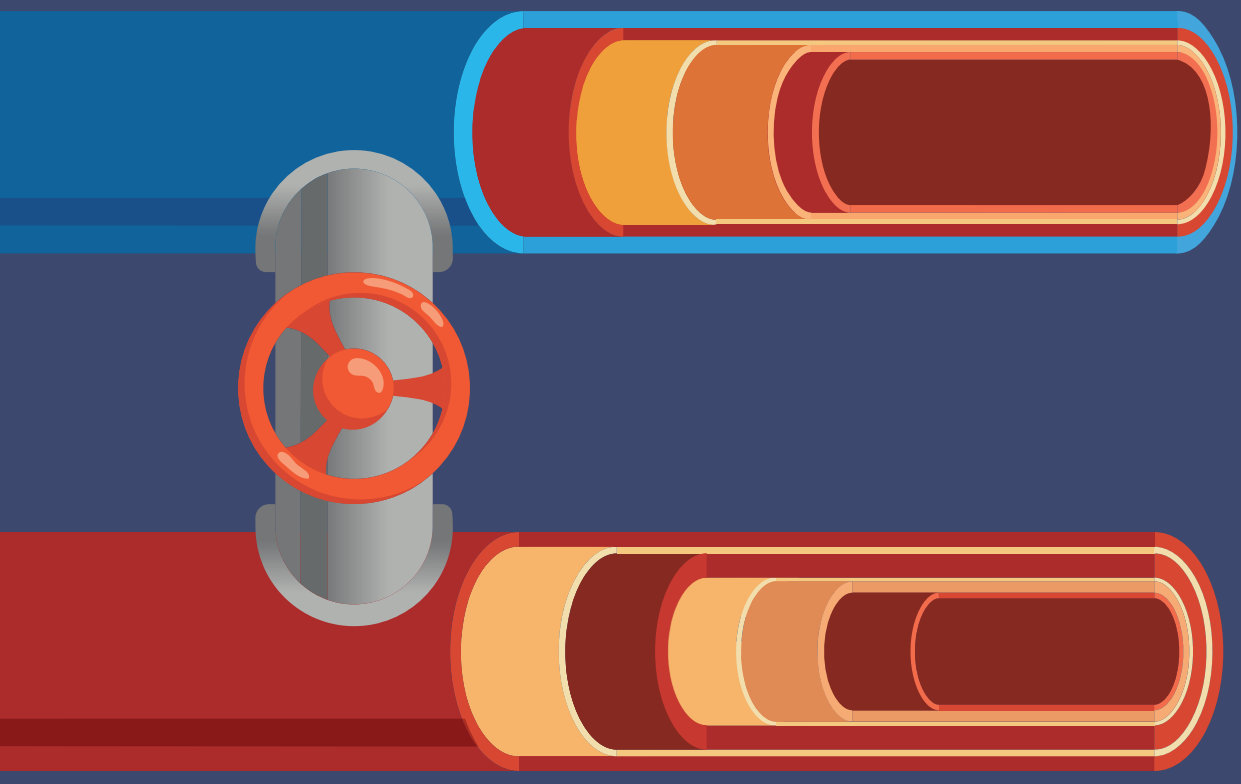

Intraoperative optimization of radiocephalic arteriovenous fistula surgery with contemporary techniques: a retrospective study

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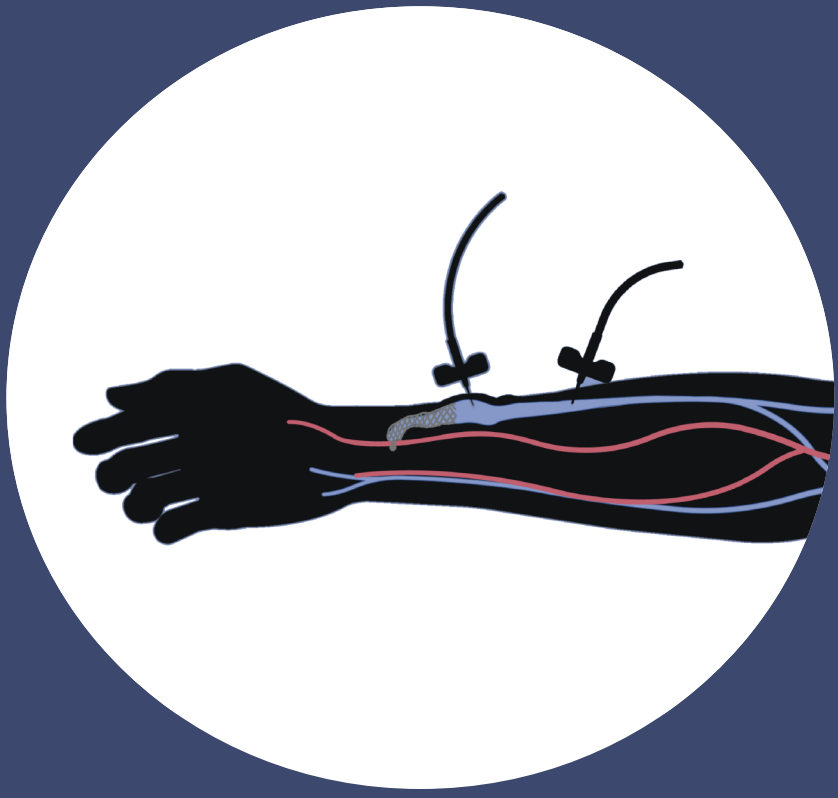

This chapter presents a clinical study evaluating optimisation of the arteriovenous fistula (AVF) procedure and geometry and improve haemodynamic conditions. While improved rates of AVF maturation were demonstrated, no measurable improvement in long-term patency was found compared to a historical control group. These findings reinforce the notion that correcting geometry alone may be insufficient to overcome the underlying issue of sustained supraphysiological flow, further motivating the development of flow-controlling solutions explored later in this dissertation.

Abstract

This retrospective study assesses the impact of a standardized intraoperative procedure on radiocephalic arteriovenous fistulas (RCAVFs) outcomes, combining Transit Time Flow Measurement, papaverine administration, and an external support device.

Consecutive RCAVF patients were included at The Hague Medical Center between November 2021 and October 2024. Intraoperative flow rates, maturation rates, and (assisted) patency rates at 6 and 12 weeks, and 6 months were compared to a contemporary control group from the same center. Maturation was defined as venous diameter ≥ 4mm, a flow ≥ 500 mL/min, and a palpable thrill. The number of interventions and per patient costs of interventions and procedures also recorded and compared.

The study compared 41 patients in the intervention group with 59 in a control group. The optimized procedure significantly improved intraoperative flow rates (210 ± 89 mL/min vs. 163 ± 85 mL/min, P = 0.008) and maturation rates at 6 weeks (77% vs. 43%, P = 0.002) and 12 weeks (91% vs. 59%, P = 0.003). Males showed higher overall maturation rates (66% vs. 38%, p = 0.03). However, no significant differences were found in primary or primary assisted patency at 6 months, nor in the average number of interventions per patient. The intervention group had significantly higher average costs per patient (€5242.06 vs. €4186.93, p=0.005).

The optimized RCAVF procedure enhances intraoperative flow and early maturation rates, with the most notable effects in the initial postoperative months. Further research is needed to determine the long-term benefits and cost-effectiveness.

5.1 Contemporary vascular access surgery modalities

Radiocephalic arteriovenous fistulas (RCAVFs) remain the vascular access of choice for dialysis patients [1], [2]. These RCAVFs provide durable autologous access with limited occurrence of excessively high flow [1], [2], hemodialysis-access induced ischemia [3], or aneurysm formation [4]. However, compared to more proximal AVFs, RCAVFs have lower maturation rates ranging from 56-77% in The Netherlands [5], [6], [7], [8], [9], [10], [11]. Globally RCAVF maturation rates have also remained poor [12], often necessitating interventions to achieve functionality [2], [13].

Several methods to improve maturation have been described in studies of variable size and quality. For example, the application of the vasodilator papaverine directly upon the anastomosis immediately after creation has been suggested to shorten maturation time with one week [14]. Secondly, monitoring intraoperative blood flow by Transit Time Flow Measurements (TTFM) may aid in predicting maturation [10]. AVFs with insufficient flow can be widened through angioplasty during index surgery [15] or surgically rectified, and followed more carefully. Recently, more evidence suggested that an external support device around the anastomosis site may aid maturation and prevent stenosis formation by optimizing the anastomotic angle and local hemodynamic conditions [16], [17]. As such methods may individually provide merit, integrating multiple modalities in a standardized RCAVF procedure could yield superior results. Although this may increase procedural costs of RCAVF placement, the combination of such modalities may also hold promise for ultimately reducing the overall costs of AVF care by reducing the need for costly interventions [2].

The presented study aims to retrospectively evaluate the effect of a standardized RCAVF procedure on AVF maturation and patency, including the intraoperative local application of papaverine and dilation of low-flow fistulas, and the utilization of an external support device. We assessed 6-month patency, and 6-month estimated AVF maintenance costs versus a historic RCAVF control group [10] from the same center in The Netherlands.

5.2 Methods

Subjects and study design.

Consecutive patients receiving an RCAVF with the optimization modalities between November 2021 and October 2024 were identified and included in the study. Patient demographics, medical history, antithrombotic therapy, type of anesthesia, and pre- and post-operative vessel diameters were collected. Data on interventions and functional status at 6 and 12 weeks, and 6 months were also collected. A previously published, historic control cohort from the same center [10] is used for statistical comparison. The research board of the Haaglanden Medical Centre approved this study.

Surgical procedure

Non-dominant arm RCAVFs were the preferred type of vascular access. Through ultrasound and doppler imaging, feasibility of placing such fistulae was assessed by measuring vessel diameters with and without a tourniquet. Patients were considered eligible for RCAVF surgery when the internal diameters of the cephalic vein and radial artery were at least 2 mm. Surgery was performed preferentially under local brachial plexus block. TTFM was used as predictive measure as described previously [10]. In the intraoperative optimization group AVFs with an intraoperative flow of less than 160 mL/min received arterial angioplasty of the juxta-anastomotic site (max 2 cm length in either direction) with an olive-shaped probe of up to 2mm and blood pressure was medicinally increased for the first several post-operative hours in the recovery ward. If flow rates did not exceed 160 mL/min, patients were invited for an additional clinical assessment 1 week post-surgery for close monitoring. Although TTFM was also used in the control group, no such procedures were performed upon measuring the flow. A VasQ (Laminate Technologies, Tel Aviv, Israel) implant was used as external support device. It consists of a nitinol braid and brace that structurally reinforces the juxta-anastomotic segment and produces a more laminar flow transition. The placement of an external vessel support device was standard [18], with the addition of the administration of 1 mL papaverine to the adventitia of the vein and artery after AVF creation [14]. All surgeries were performed in the Haaglanden Medical Centre in The Hague, The Netherlands.

Follow-up

Patients were generally discharged on the day of surgery, after which patients were followed for a period of 6 months. Maturation of the AVFs was determined through ultrasound performed by technicians or vascular surgeon in a vascular laboratory at 6 weeks. At 12 weeks, and 6 months functional status was assessed by the surgeon or a specialized dialysis nurse.

Definitions

AVF maturation 6 weeks postoperatively was considered as an adequate venous diameter (≥ 4mm over a length of at least 10 cm), a flow ≥ 500 mL/min, a palpable thrill and superficial enough to be punctured with two cannulae for hemodialysis [19].

Primary AVF patency was defined as intervention-free access survival. In assisted primary patency an intervention such as a percutaneous transluminal angioplasty (PTA) was necessary to maintain patency, but no full occlusion had occurred. Non-maturation, or maturation failure, is considered to be any AVF that is not mature at 6 weeks. Finally, acute failure was described as any vascular access failure that occurred within the first week after initial placement of the AVF.

Costs of interventions

The following interventional procedures relating to maturation and patency were considered: percutaneous transluminal angioplasty (PTA) of matured AVFs, PTA and/or coiling of

collaterals for assisted maturation, thrombectomy, central line placement and revision surgery. Furthermore, a distinction was made in the costs of RCAVF placement between the studied groups, based on the additional costs of the study group procedure. The costs for each type of procedure were based on the costs of materials used, personnel costs, and costs of hospital admission in our center. On average, the intraoperative optimization requires 5 minutes of additional surgical time compared to the RCAVF procedures in the historical cohort. The breakdown of procedural costs are outlined in Supplemental Table I (online). The total cost of procedures relating to AVF maintenance at 6 months was determined by multiplying the total number of interventional procedures in each group by the costs of each procedure. This value was then divided by the number of patients in the groups to estimate the average per patient costs. Only patients of which the full 6 months of data was available were included.

Statistical analysis

SPSS version 27.0.1.0 (IBM, Armonk, New York) was used for statistical analysis of the collected data. Unpaired sample t-tests were performed on the intraoperative blood flow, vein diameter and blood flow in the outflow vein. This was also done separately for males and females. Chi-Square tests were used to compare acute failures, interventions and AVF maturation rates between the two groups. A Kaplan-Meier and cox regression survival analysis was implemented to determine the hazard ratio for loss of (assisted) patency of the RCAVFs between the control and intervention groups. Mann-Whitney U test was performed to determine differences in per patient number of interventions, costs per type of intervention, and total costs.

5.3 Results

Study population

59 patients were included in the historical control group, and 41 underwent the optimized RCAVF surgery in the intervention group during the study period. This included every patient eligible for a RCAVF surgery, except for 2 that did not receive the optimized surgery due to nickel allergy (n=1), and patient preference (n=1). Table 5-1 shows the baseline characteristics of the patient populations. At 6 months post-surgery, 10 patients had incomplete follow-up data in the control group, and 3 in the intervention group. This was due to patients receiving a kidney transplant, transfers to a different center, and loss to follow-up. One patient developed distal emboli due to a proximal arterial stenosis not seen in pre-operative duplex ultrasound and was excluded from the post-operative analysis. One patient died from causes not related to the procedure.

Table 5-1: Baseline characteristics historic control vs current cohort including comorbidities and diameters

Patient characteristics	Control (n = 59)	Intraoperative Optimization (n = 41)	P
Age (mean, (SD))	63.5 (12.6)	58.9 (16.7)	0.07
BMI (mean, (SD))	28.7 (6.4)	28.3 (6.1)	0.38
Sex (% male)	66.1	85.4	
Smoking (%)	23.7	29.3	
Hypertension (%)	83.1	92.7	
Diabetes (%)	50.8	53.7	
Preexisting heart failure (%)	13.6	24.4	
Dialysis before surgery (%)	25.4	26.8	
Antithrombotic therapy before surgery (%)	54.2	53.7	
Anesthesia by brachial plexus (%)	83.1	95.1	
Preoperative venous diameters			
All patients (mm; mean, (SD))	2.45 (0.81)	2.44 (0.59)	0.47
Females (mm; mean, (SD))	2.11 (0.61)	2.64 (0.45)	**0.02**
Males (mm; mean, (SD))	2.63 (0.85)	2.41 (0.61)	0.10

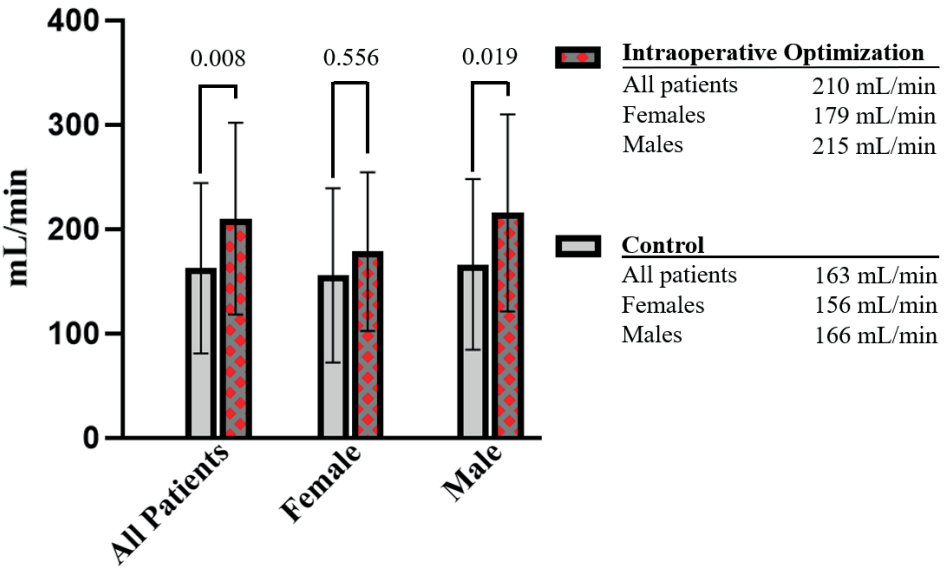

Figure 5-1: Intraoperative venous blood flow rates as measured by Transit Time Flow Measurement.

Procedure outcomes

All surgical procedures were technically successful, with the external support device (VasQ™, Laminate Medical, Tel Aviv, Israel) implanted, and papaverine and dilation of low-flow AVFs applied in the intervention group. Figure 5-1 displays the intraoperative venous flow, as measured by TTFM, in both groups, and split into male and female populations. Next to standard blood pressure augmentation during RCF surgery with flow measurements of <160 mL/min, intraoperative angioplasty was performed on one AVF in the intervention group with such low flow. Mean fistula flow was significantly higher in the intervention group compared to the control when including all patients (210 mL/min vs 163 mL/min, p=0.008). When examining per sex, only men had a significantly higher intraoperative flow rate in the intervention group (p=0.019 for males, p=0.556 for females).

Follow-up

The intervention group demonstrated significantly higher maturation rates compared to the control group at both 6 weeks (77.1% vs. 43.2%, p=0.002), and 12 weeks (90.6% vs. 58.8%, p=0.003). Additionally, males in the study showed a significantly higher 6-week maturation rate overall (65.5% vs. 38.1%, p=0.029), though no significant sex differences were observed within the specific study groups or at 12 weeks. The improved unassisted maturation in the optimalisation group resulted in a somewhat higher patency within the first three months. Over a 6-month period, there were no higher patency rates observed in the intervention group. Full details on pre-operative and post-operative measurements, as well as intervention and failure rates, are outlined in Table 5-2 and Supplemental Table II (online).

Interventions and cost of care

There was no significant difference in the average number of interventions per patient in the intervention group versus the control in the study period (0.38 vs. 0.61, p=0.23). The average per patient cost of interventions performed during the 6 months follow-up period and the total cost of care per patient as previously defined are found in Figure 5-3 (detailed cost breakdown in Supplemental Table III (online)). The average per patient costs in the intervention group was significantly higher than in the control group due to the higher costs of the index procedure as a consequence of external support placement (€5242.06 vs. €4186.93, p=0.005). Revision surgery consisted of proximalization of the AVF (n=9 in the control group and 2 in the intervention group).

Table 5-3: Venous diameters and postoperative maturation data at 6 and 12 weeks in the control and intraoperative optimization groups

	Preoperative Duplex		6 Weeks Postoperative Duplex			12 Weeks Postoperative Control		
	Control	Intraoperative Optimisation	Control	Intraoperative Optimalisation	P	Control	Intraoperative Optimalisation	P
Acute failure (%)			5.4	0.0	.137			
Interventions (%)			7.1	2.8	.367	7.3	9.7	.695
Venous diameter								
All patients (mm (SD))	2.45 (0.81)	2.44 (0.59)	4.1 (1.5)	4.4 (0.7)	.306			
Female patients (mm (SD))	2.11 (0.61)	2.64 (0.45)	4.2 (1.8)	3.7 (1.4)	.676			
Male patients (mm (SD))	2.63 (0.85)	2.41 (0.61)	4.1 (1.3)	4.5 (0.6)	.162			
Blood flow								
All patients (mL/min (SD))			699 (309)	764 (303)	.387			
Female patients (mL/min (SD))			590 (205)	723 (171)	.318			
Male patients (mL/min (SD))			754 (340)	769 (316)	.871			
AVF maturation								
All patients (%)			43.2	77.1	**.002**	58.8	90.6	**.003**
Female patients (%)			29.4	75.0	.091	50.0	75.0	.383
Male patients (%)			51.9	77.4	**.041**	63.6	92.9	**.010**

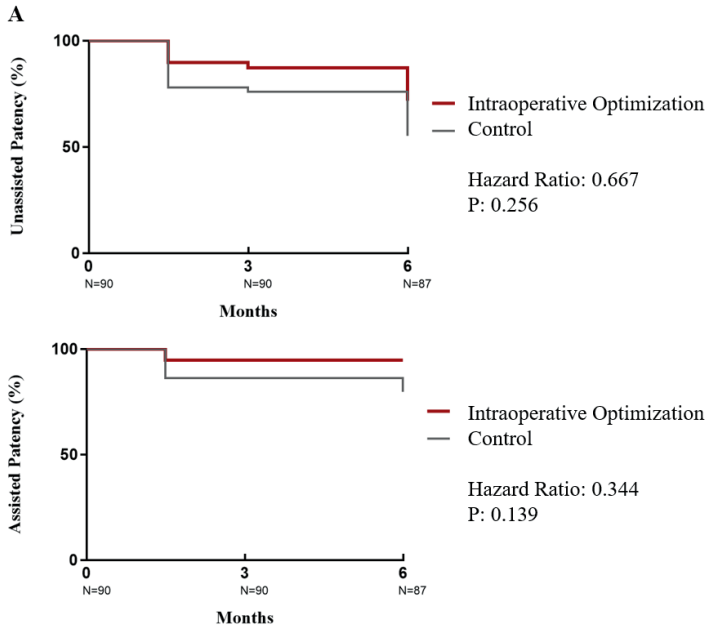

Figure 5-2: Kaplan-Meier curves of A) unassisted patency and B) assisted patency rates in the Intraoperative Optimization group versus the Control group.

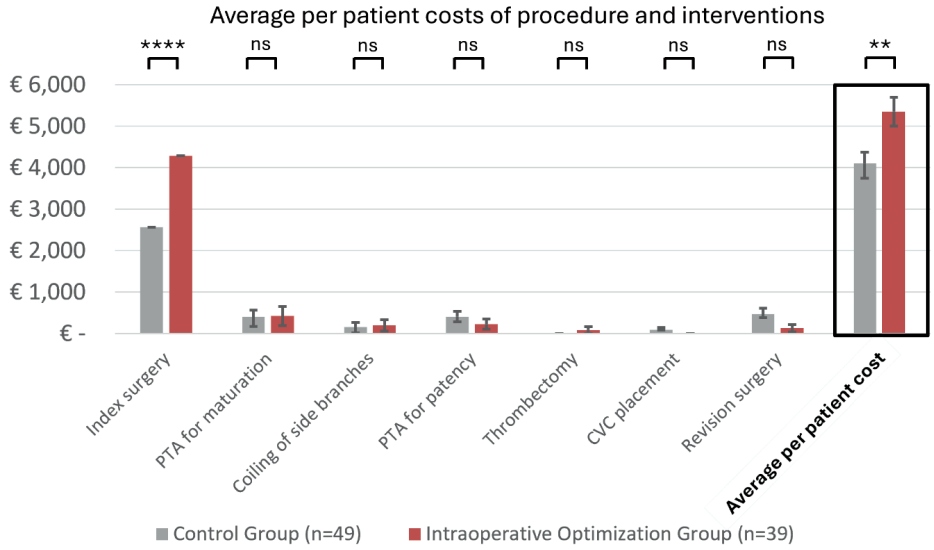

Figure 5-3: Intervention costs and standard errors of the means of different radiocephalic arteriovenous fistula (RCAVF) strategies at 6 months from placement. ns = not significant. PTA = percutaneous transluminal angioplasty. CVC = central venous catheter.

5.4 Discussion

The current study shows optimizing RCAVF using simple and readily available measures has a positive effect on maturation outcomes. The application of the procedural standardization with papaverine, prediction with TTFM and the external support device resulted in higher intra-operative blood flows and higher maturation rates as compared to the conventional surgical RCAVF technique. However, no significant effect on patency was found, nor a decrease in number of interventions. Average cost of care was higher in the group receiving the optimized RCAVF procedure.

Although pre-operative venous and arterial diameters did not differ, there was a substantial increase in maturation rates in the intraoperative optimization group. This was profound at both the early postoperative timepoints. This suggests that the intraoperative optimization results in better and faster maturation, which may be specifically beneficial for patients already on dialysis or patients that need to start HD soon after creation. Consequently, this could result in less CVC indwelling time and prevent new CVC placements. This needs to be confirmed in larger studies.

The difference in maturation rate between the groups is mainly provoked by a small and non-significant difference in venous diameters around the cut-off point of 4mm. It may be possible that higher flow rates in the intervention group at the time of creation led to more shear stress mediated venous distension. Additionally, the reduced early juxta-anastomotic stenosis as

has been observed in other studies with the external support device may have contributed to the improved maturation rates in our intervention group [16], [17], [20]. However, the device may not preclude stenoses that can also occur within the device outflow part, whereas the support mesh and any fibrotic tissue that forms around the implant likely stiffens the vessel, possibly complicating the angioplasty (Figure 5-4). Moreover, this device does not prevent stenosis further down the outflow other than a presumed limitation of turbulent and high-flow in the longer run possibly resulting in less shear stress and intimal hyperplasia [21].

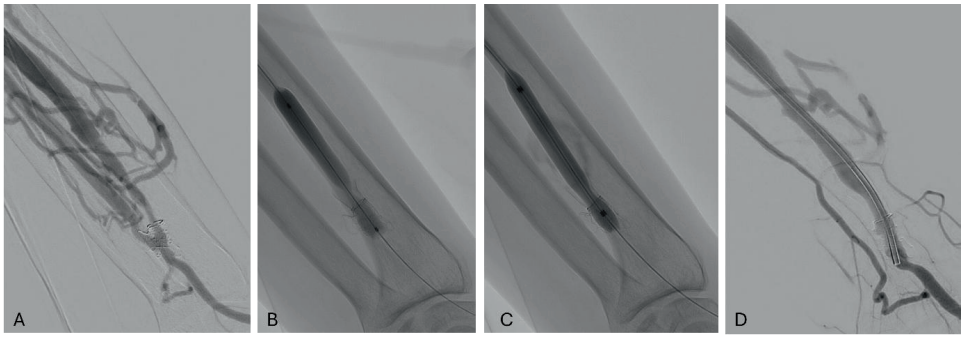

Figure 5-4: A) 6-month old radiocephalic fistula with a juxta-anastomotic stenosis originating within the outflow part of the external support device. B) Angioplasty with a 5 mm high-pressure balloon showing resistant stenoses, C) that was treated with a cutting balloon and repeated 5 mm high-pressure balloon, D) resulting in a clinically sufficient result.

Furthermore it must be noted that the intervention group included more male patients, a factor known to positively influence maturation [21], [22], [23], and supported by the presented data, This may have introduced a bias in the current cohort. However, although numbers were too low to reach statistical significance, the data suggests very similar trends in maturation in both men and women between groups, and the upper arm fistula and graft placement rate remained fairly constant in the study period as compared to previous periods. If patients had been selected for RCAVF based on larger cephalic vein diameters, these rates would have likely increased. In fact, these diameters were similar in the study cohort versus the historical controls and compared to other studies in the Netherlands [24]. Moreover, the rate of diabetic patients, which has been found to have a negative impact on maturation rate [25], [26], remained equally high over time (50-55%) in our center, and notably higher than the 40% in other Dutch cohorts reported in the past decade [7], [8], [24]. Together this may suggest that the effect of bias is limited.

The results in both groups were comparable with a general assessment of RCAVF maturation in the Netherlands [11]. Supplemental table IV (online) shows an overview of published RCAVF rates in the Netherlands since 2002. RCAVF maturation rates in the Netherlands seem to have decreased from 73% in 2002 [5] to 50-61% in more recent years [7], [8], [9], [10], [24]. This may be an effect of aging population and the rise of diabetic patients from an average of 16% in 2002 [5] to 51-59% in most recent cohorts in our region [9], [10]. However, the current study shows that even in this population it is possible to achieve high maturation rates.

Moreover, Dutch vascular access surgery is fragmented over many centers and therefore this study differs considerably with other studies with the external support device that report excellent RCAVF maturation of 89-100% [16], [17], [20]. These series are often non-randomized and originate from high volume centers with experienced and specialized vascular access surgeons. Although the prospective, pivotal trial of the external support device in the US demonstrated superior patency as compared to a historic control group, the study only included 15 RCAVFs (10% of the study population) [27]. Only one randomized pivotal study is available that was aimed to show safety and that was not powered to prove superiority [18].

The overall cost of care was higher in the Intraoperative Optimization group. Although there is a slight and non-significant reduction in interventions, and therefore related costs, this is negated by the increased costs of a more expensive index procedure in the intervention group when including the intraoperative optimization modalities. It is important to note that RCAVFs are generally the most cost-effective option initially [28]. However, costs rise significantly when complications such as stenoses develop or when more proximal fistulas are required as alternatives. This further emphasizes the importance of optimizing RCAVF procedures to avoid these costly complications.

Compared to average first-year AVF costs of care of ~15k USD found in an extensive US cohort [28], expenses found in the present study are considerably lower. It is important to notice that angioplasties in our center take place in an outpatient setting, coupled to the dialysis session, thus limiting admission costs. Although differences in prices and demographics between countries are not accounted for, this data does underscore that the cost analysis in this study likely underestimates the true financial burden, as it primarily focuses on interventions to promote maturation. An additional hurdle for cost-effectiveness of the external support device is the different sizes, requiring a larger amount of products to be taken in stock and at risk for expiration. This holds especially true for smaller volume centers that are common in the Netherlands. Lastly, hidden costs, such as failed punctures, missed dialysis sessions due to difficult-to-cannulate fistulas, and the need for further interventions, may not have been fully accounted for in the present cohort, emphasizing the need for improved further study into costs of care.

Every intervention-free day is valuable for a dialysis patient. However, in The Netherlands, a 6-week reimbursement limit for the specific diagnosis is placed by health insurers. For vascular access surgery, this limit is typically insufficient to include costly intra-operative measures such as endo-vascular devices or external support systems, which may hamper their introduction. Our data shows a significant increase in intraoperative flow and 6-week maturation rates. It should thus be clear that including a more expensive modality, such as the external support device, can add value for patients, but could also reduce overall costs for the payors, as intervention rates are reduced. Future randomized studies with longer-term results and robust cost-effectiveness analysis should steer decisions on the feasibility in our current health care system.

Finally, the presented study cannot differentiate between the effects of papaverine, intraoperative flow measurements, or the external support device. All measures taken together provide a clinical, but no financial benefit, considering the price of the external support device and the increased time of the procedure. Moreover, the same surgeon performed or oversaw surgeries in the intervention group, but only created roughly half RCAVFs in the control cohort. There has been a debate on AVF surgical expertise and volume, suggesting a high prior-volume of AVFs positively correlates with maturation rates [29], [30]. This may thus have introduced bias. To investigate the effect of the external support device, a randomized clinical trial is currently being designed at our and other institutions to fill the gap of level-1 evidence in which the same standardization of RCAVF procedure is anticipated, with the support device as only variable.

5.5 Conclusion

This study examined an optimized intraoperative RCAVF procedure that included the administration of papaverine, TTFM, and the placement of an external vessel support device. The effect of this procedure was studied on intraoperative flows, 6- and 12-week maturation rates, and 6-month primary and assisted patency. Compared to a historic control group from the same center, superior intraoperative flow rates, and 6- and 12-week maturation rates were found. No significant improvement in 6-month patency was observed. Due to the increased cost of the optimized procedure, costs of care increased. The optimized procedure may assist in achieving higher maturation rates, but long-term benefits so far seem limited based on this preliminary data. More randomized controlled trials are necessary to gain more insight into specific effects of each modality.

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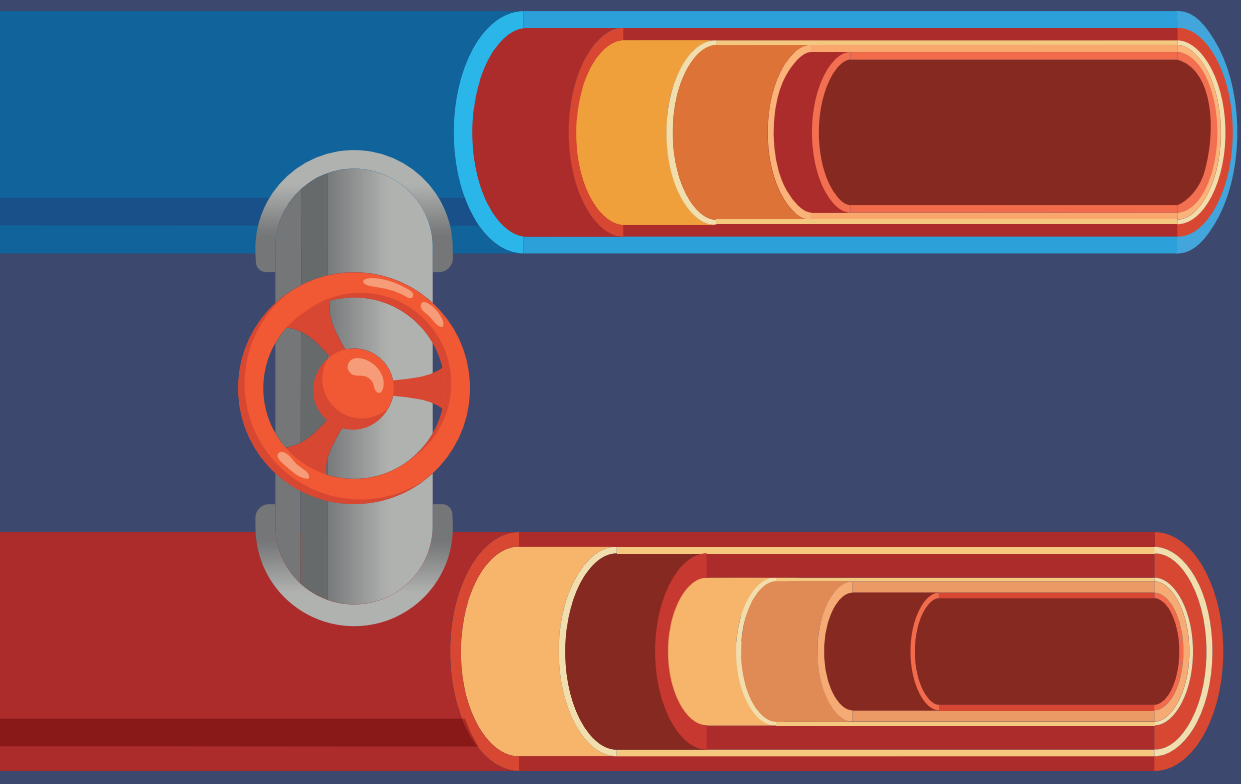

An implantable magnetic drive mechanism for non-invasive arteriovenous conduit blood flow control

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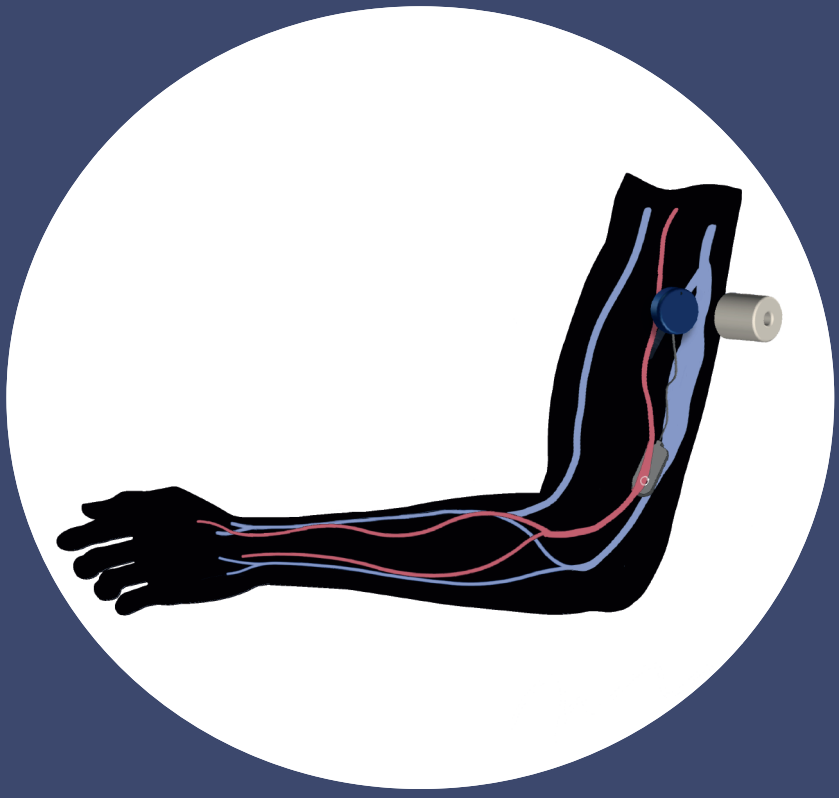

This chapter introduces the development of a novel implantable device, referred to as the Dynamic AVF, designed to non-invasively regulate blood flow through an arteriovenous fistula. The device aims to address the core physiological issue identified in earlier chapters: the deleterious effects of continuous supraphysiological flow on vascular integrity and access longevity. Benchtop experiments and cadaver studies were conducted to evaluate the mechanical feasibility and functionality of this concept, laying the foundation for in vivo validation in the following chapter.

Abstract

Hemodialysis patients usually receive an arteriovenous fistula (AVF) in the arm as vascular access conduit to allow dialysis 2–3 times a week. This AVF introduces the high flow necessary for dialysis, but over time the ever-present supraphysiological flow is the leading cause of complications. This study aims to develop an implantable device able to non-invasively remove the high flow outside dialysis sessions. The developed prototype features a magnetic ring allowing external coupling and torque transmission to non-invasively control an AVF valve. Mock-up devices were implanted into arm and sheep cadavers to test sizes and locations. The transmission torque, output force, and valve closure are measured for different representative skin thicknesses. The prototype was placed successfully into arm and sheep cadavers. In the prototype, a maximum output force of 78.9 ± 4.2 N, 46.7 ± 1.9 N, 25.6 ± 0.7 N, 13.5 ± 0.6 N and 6.3 ± 0.4 N could be achieved non-invasively through skin thicknesses of 1–5 mm respectively. The fistula was fully collapsible in every measurement through skin thickness up to the required 4 mm. The prototype satisfies the design requirements. It is fully implantable and allows closure and control of an AVF through non-invasive torque transmission. In vivo studies are pivotal in assessing functionality and understanding systemic effects.

6.1 High flow as the core issue in peripheral vascular access

Most patients suffering from end-stage kidney disease turn to haemodialysis as renal-replacement therapy [1], [2], [3], [4]. For haemodialysis, blood is taken from the body, passed through an external dialysis machine that filters the blood of waste products, after which the 'clean' blood is returned to the body. It is estimated that around 3 million patients are undergoing haemodialysis globally [5].

For chronic haemodialysis, a high-flow and easily accessible vascular access site is necessary, as dialysis is usually performed in 3 sessions of 4 hours per week [6]. In most cases, the arm (Figure 6-1) is chosen as the most suitable vascular access site due to the superficiality of the vessels that facilitates frequent cannulation. However, flow through these vessels is to be increased from roughly 30 mL/min to the >600mL/min required for haemodialysis [7]. Since 1966 [8], this has been achieved by surgically placing an anastomosis between a major artery and vein in the arm, an arteriovenous fistula (AVF), as shown in Figure 6-1a. The difference in pressure between the artery and vein creates a low resistance pathway for blood that promotes an increased flow through these vessels. After placement, the vein expands over time to accommodate the increased flow through a series of complex mechanisms [9] before usage is possible, known as maturation. If the vein accommodates a flow of >600 mL/min and has a minimum diameter of 5 mm, the vascular access is considered patent [10]. AVFs can only be placed where major veins and arteries are in close proximity (Figure 6-1b). The preferred primary placement location is usually the wrist. When the vascular access fails here, more proximal locations can be used, where patency rate is higher, but vascular access-related complications are more frequent [7].

Unfortunately, primary patency of AVFs (i.e. mature and functional without intervention) at 1 year is estimated at only 60% [12], resulting in high reintervention rates due to the necessity of a vascular for haemodialysis, as well as high costs [13]. Moreover, there is a multitude of complications that can hinder functionality or is associated with the presence of the vascular access such as thrombosis, distal ischemia and aneurysms, most of which are linked to the constantly elevated and turbulent flow of blood through the anastomosis [14], [15]. Additionally, a well-functioning vascular access results in a higher burden for the heart, primarily due to the constantly elevated cardiac output, resulting in ventricular hypertrophy [16], [17].

A lot of research has been conducted on improving vascular access outcomes, but no large breakthroughs have taken place since the introduction of the AVF. Most recent innovations focus on optimizing local haemodynamics, but show limited benefits [18], [19]. The supraphysiological flow causing complications remains ever-present, whereas dialysis is only performed for a limited number of hours per week [6]. A vascular access in which the anastomosis can intermittently be opened and closed as shown in Figure 6-2, could remove the unfavourable high flow when not in use, while maintaining the functionality of the high-flow vascular access for dialysis. This could greatly improve patient outcomes.

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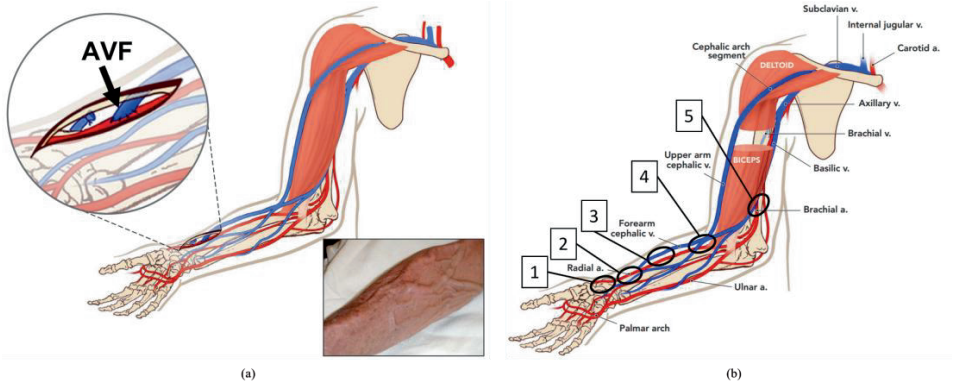

Figure 6-1: A graphic representation of a) an end-to-side arteriovenous fistula (AVF); and b) locations of AVF placement in the human arm. 1) In the snuffbox. 2) In the wrist. 3) In the forearm. 4) In the elbow fossa. 5) In the medial upper arm. Adapted from [11].

Working principle of the controllable AVF

Removing the high and turbulent anastomotic flow for the majority of the time is expected to result in a drastically reduced complication rate. However, it must remain possible to increase the flow sufficiently to allow successful dialysis. Simultaneously preventing infection and rejection risks, and additional damage to the anastomosis, e.g. in the form of traction on the sutures and vessels is crucial. Directly compressing the blood vessels is therefore not considered a feasible solution. A very short piece of synthetic graft, used for vascular access in certain cases, will form the anastomosis in a side-to-side fashion, shown in Figure 6-2, where fully compressing this graft will block flow and allow circulation to return to normal, while preventing the formation of thrombi (Figure 6-3) [20]. Alternatively, the anastomosis could remain in a minimal flow setting as to minimize risks resulting from high flow. Moreover, switching between a fully closed and fully open position and vice versa instantaneously may cause issues relating to changes in blood pressure, so a delay is required. Allowing different stages between fully open and fully closed positions can allow more accurate control and prevent flow greatly exceeding the necessary 600 mL/min.

The anastomosis is a crucial and fragile anatomical region. Directly applying mechanical force and energy to an implanted actuation device on this area is therefore considered an additional risk. As the outflow vein must remain accessible for frequent cannulation, the decision is made to disconnect the valve mechanism that manipulates the graft from the actuation mechanism, which can be placed at another location along the arm. An added benefit is that the actuation device location is not limited to potential AVF sites and can be placed at locations where more space is available, e.g. in anatomical fossae. The two components can be connected through a flexible transmission cable.

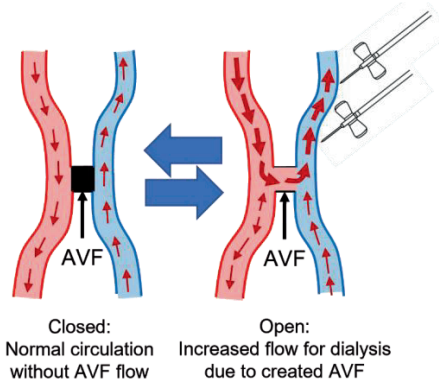

Figure 6-2: An illustration of how an adjustable Arteriovenous Fistula (AVF) could control the flow of blood for haemodialysis.

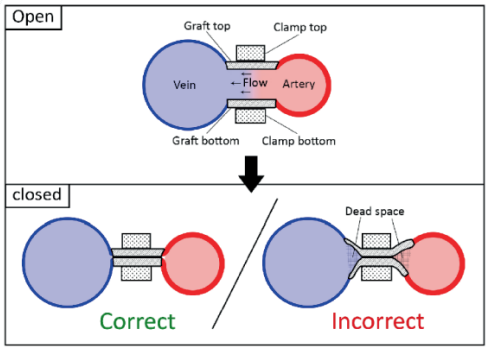

Figure 6-3: An illustration of how the AVF should be closed to minimize the risk of thrombus formation in the lumen of the graft outside of dialysis sessions.

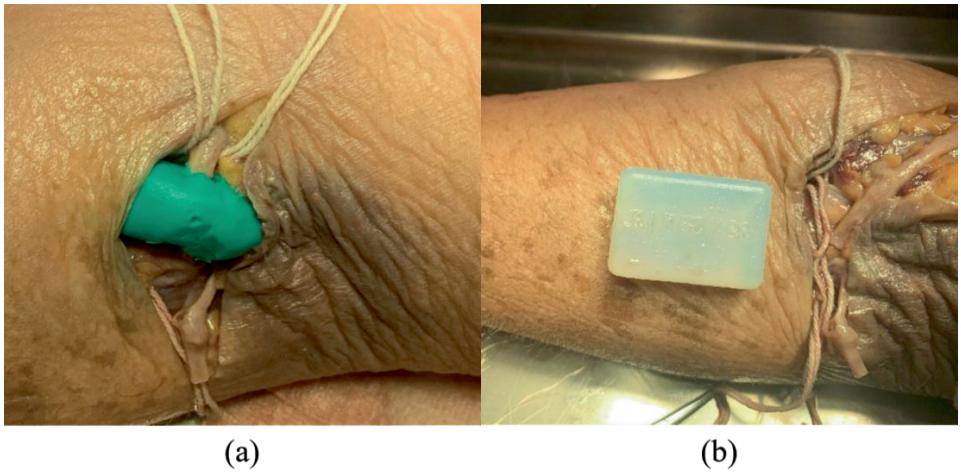

Figure 6-4: The incision made in the cubital fossa of a cadaveric arm. The cephalic vein and radial artery are exposed. a) shows the use of blocks of clay, and b) shows 3D-printed implant mock-ups utilized to determine the available design space and actuation method of the device to be developed.

Whereas primary vascular access placement is preferred in the wrist, target AVF locations are the elbow fossa in the posterior forearm, and the medial upper arm fossa between the biceps and triceps muscles. These locations are thought to provide more space for an implant, whereas the increased risks of an upper arm AVF relative to the wrist should mostly be mitigated with this concept.

Healthy systolic blood pressure values are already around 120 mmHg (16 kPa), but end-stage kidney disease patients often have the added burden of hypertension [21]. Manipulating the

anastomosis to control blood flow will thus require significant mechanical energy. Non-invasive methods of supplying energy to implantable medical devices are currently limited and output is generally low [22]–[24], whereas batteries require additional complexity for conversion to mechanical work. Conventional implanted energy supplies will likely make long-term usage of a dynamic AVF infeasible.

Contributions

This study provides a design synthesis of a fully implantable device that enables non-invasive transmission of mechanical energy to a valve that is able to control blood flow through an AVF. A unique aspect of this device is the energy transmission mechanism that enables repeated AVF closure over prolonged time. The resulting prototype is ready to be utilized in a large animal model in vivo study to provide insight into biological responses of actuation of mechanical components transcutaneously, as well as intermittently opening and closing an AVF [25]. First an overview of the design requirements is defined, after which the design synthesis and assessment methods of requirements are described, including benchtop experiments and in situ cadaver studies. Finally, results and future perspectives are discussed.

Design Requirements

The primary design requirements are as follows:

1. The device must be fully implantable subcutaneously to minimize risks of e.g. infection [26];
2. Energy transmission for actuation of the device is non-invasive, through a skin thickness up to 4.0 mm (SF2) [27];
3. The device manipulates the luminal area of a commercially available graft placed as a side-to-side anastomosis;
4. Anastomotic flow is in the range of 600-1000 mL/min for dialysis when the graft is opened [10];
5. Anastomotic flow is 0 mL/min when the graft is closed, at a pressure of 180 mmHg [28];
6. Resultant forces on the graft and vessels do not cause tearing of anastomotic sutures;
7. There is at least 1 intermediate stage between fully open and fully closed to control flow to a preferential value [7];
8. It takes at least 15 seconds to change the graft from fully open to fully closed [29];
9. Mechanical and biological lifetime of at least 10 years, or 1560 cycles
10. All materials in the device that are in direct contact with bodily fluids and tissues are used in other marketed implants and surgical instruments [30];
11. The device can be cleaned and sterilized according to ISO standards [31];

Additionally, a systematic placement, dimension and skin actuation study was conducted on a cadaveric arm, partially shown in Figure 6-4. Supplemental File 1 (online) elaborates this study. The valve dimensions were determined with blocks of clay moulded to different shapes and dimensions. The actuator dimensions and tactile energy transfer methods were assessed

by implanting various 3D-printed models, with the maximum dimensions being found as a 35 mm diameter disk with 10 mm thickness. The results indicate that the maximum dimensions of the valve are: width 10 mm, height 15 mm and length 30 mm. All actuation methods that rely on exerting pressure (e.g. by the fingers) on the skin were considered infeasible as a means of energy transfer. They remain very challenging due to the lack of grip, sliding tissue layers and possible fibrosis formation. Therefore a non-tactile energy transmission through the skin is preferred.

6.2 Dynamic AVF design synthesis and experimental method

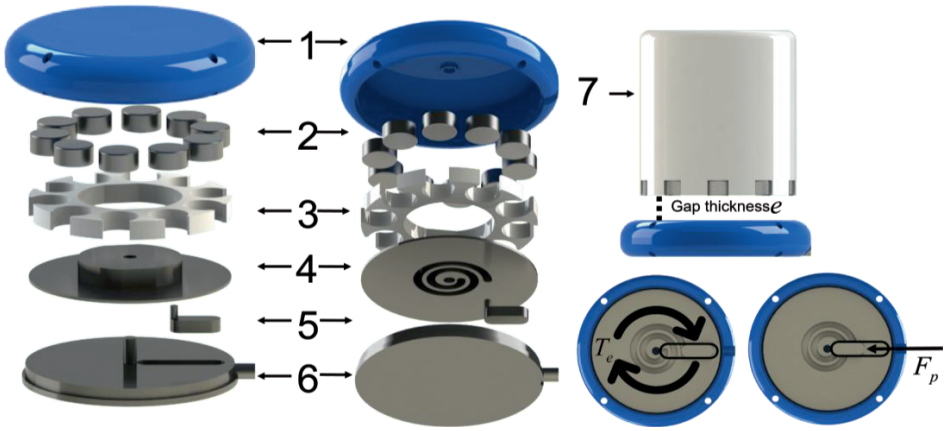

Figure 6-5: A 3D-model overview of the actuator component of the prototype and the working mechanism. 1) PEEK hood, 2) neodymium magnets, 3) 3D-printed magnet holder, 4) 316L Stainless Steel (SS) spiral, 5) 316L SS pin and follower, 6) 316L SS backplate and groove for the follower, and 7) external magnets used to apply torque $\boldsymbol{T_e}$ *to the actuator through an identical set of magnets. Upon rotating the external magnets, the actuator magnets rotate and guide the pin through the spiral in one linear degree of freedom through the groove in the back plate to generate output force* $\boldsymbol{F_p}$ *non-invasively through a gap thickness of* **e**. *Models were made in SolidWorks (Dassault Systèmes, Paris, France).*

Implantable actuator mechanism design

The detailed design of the actuator prototype is shown in Figure 6-5. It contains a ring of magnets with alternating pole orientation that can rotate around an axis. Permanent neodymium magnets are chosen due to the high field strength (H = 860-995 kA/m, Supermagnete, Webcraft GmbH, Gotmadingen, Germany) while being readily available. Dimensions are selected to maximize the volume of magnets in a ring configuration in the determined design space. An identical external magnet ring can be coupled to the implant through the skin. When coupled, rotation of the external magnets results in the same rotation of the magnetic wheel in the actuator, transmitting energy non-invasively. The magnets are coated in a very thin layer of silicone glue and placed in a 3D-printed (Dental resin, Form 2, Formlabs, Somerville, MA, USA) wheel, fastened to a CNC-milled 316L Stainless Steel (SS) plate with a spiral groove on the bottom. A SS follower is inserted into this spiral, and is limited

to 1 linear degree of freedom by a groove in the SS bottom plate. Through the spiral, rotating the wheel will result in linear displacement of the follower. The dimensional parameters of the actuator and detailed drawings can be found in Supplemental File 2 (online).

As velocities and accelerations should be small, output force can be determined through static equilibrium as shown in Figure 6-6a and Figure 6-6b:

$$\sum F_x = 0 : F_w = F_N \sin\theta + \mu_s F_N \cos\theta \tag{1}$$

$$\sum F_y = 0 : F_N \cos\theta = F_p + \mu_s F_N \sin\theta \,. \tag{2}$$

The pitch angle of the spiral thread θ is calculated as:

$$\theta = \tan^{-1}\left(\frac{\delta r}{\delta x}\right) = \tan^{-1}\left(\frac{p}{2\pi r(n)}\right), \tag{3}$$

where p is the pitch of the spiral, and $r(n)$ the radius of spiral at a specific point in the spiral, calculated as a function of p, the number of revolutions n and the maximum spiral radius

$$r_{\max} : \; r(n) = r_{\max} - p \cdot n \tag{4}$$

Solving for F_p yields:

$$F_p = \frac{F_w(\cos\theta - \mu_s \sin\theta)}{\sin\theta + \mu_s \cos\theta} \,. \tag{5}$$

Ignoring frictional losses, the transmission of input torque T_e to actuator output force F_p can be estimated as

$$F_p = \frac{T_e}{r}\frac{\cos\theta - \mu_s \sin\theta}{\sin\theta + \mu_s \cos\theta} \tag{6}$$

Following Figure 6-6c, when input torque is not applied, static equilibrium is determined by:

$$\sum F_x = 0 : F_N \sin\theta = \mu_s F_N \tag{7}$$

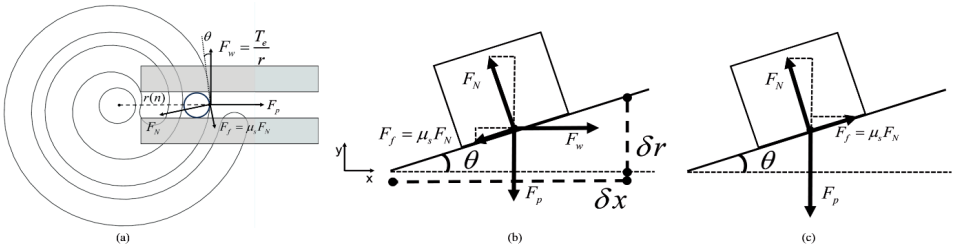

Figure 6-6: A free body diagram (FBD) of the pin that moves through the spiral when the spiral is rotated with input torque ***T_e****. The pin is constrained in 1 linear degree of freedom. a) The pin in the spiral b) The FBD of the pin when input torque is applied. c) The FBD of the pin when no input torque is applied.*

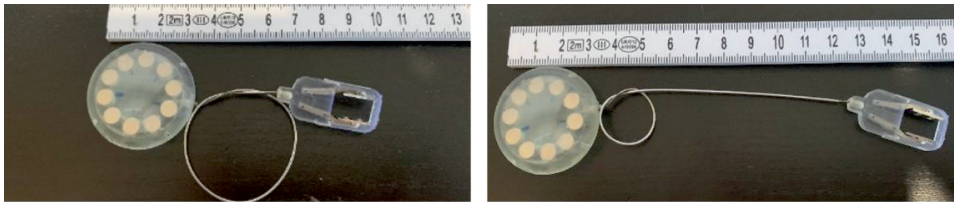

Figure 6-7: A 3D-printed mock-up of the device with the intended dimensions. If proven necessary, the distance between the valve and actuator component could be made variable by placing a loop with a knot in the transmission cable. a) Large loop with small distance between components. b) small loop with larger distance between components. This model was used in cadaver studies to verify fit and placement.

The spiral mechanism is thus stable and non-backdrivable, preventing opening of the valve due to blood pressure or external traction, when $\mu_s \geq \sin\theta$ is satisfied. This equates to $\theta \leq 14^\circ$ or a spiral radius of 1.4 mm in the presented configuration with an estimated friction coefficient of 0.25 [32].

A 1 mm thick lathed PEEK cover (a known biocompatible material [33]) with rounded edges and suturing holes is press-fitted over the top of the magnets. A 0.5 mm thick spacer is placed around the central rotation point of this cover to prevent contact friction between the magnets and the cover. Silicone glue is applied to seal the case.

Transmission Cable

The transmission cable is a 1 mm diameter flexible spiral grooved 316L SS Bowden cable, with a 0.5 mm 304 SS wire as core. The outer cable is welded to a small cylinder, in turn welded to the base plate of the actuator. The wire core is welded to the pin and follow of the actuator. A small threaded 316L SS cylinder is welded to the other end of the Bowden cable, and another, smaller threaded 316L SS cylinder welded to the wire core. The flexibility of the transmission cable allows a loop to be placed in the cable which enables a change in distance between the valve and actuator components and may decrease resultant forces on the graft and blood vessels, shown in Figure 6-7. However, this will result in a significant loss of mechanical efficiency [34] and is not expected to be necessary when placed along the humerus in the

upper arm or radius and ulna in the forearm in a human where the anatomy limits relative motion of surrounding tissues.

Valve design

Figure 6-8 displays the design of the valve mechanism that is screwed onto the threaded end of the Bowden cable. The outer cable is screwed onto the frame of the valve, and the wire core into a cylinder that is guided linearly through the frame. This is a H7/G6 fitting in which the tolerances are smaller than the diameter of a red blood cell [35], thus should prevent tissue formation inside the casing as no supply of blood is possible. The cylinder is fastened to a linkage functioning as mechanical pinch valve. It supplies force symmetrically to minimize graft displacement, and thus traction on sutures and vessels. Due to the geometry of the graft, the highest compression force is required close to the fully collapsed state. The linkage has a favorable transmission ratio that can achieve this, whereas displacement of external components has been minimized to prevent excessive interaction with adjacent tissues. The exterior parts of the links feature compliant joints which are thought to be more resistant to effects of fibrosis than pinhole joints, but still enable parallel compression and uniform force distribution over the closed graft. Side plates are welded to the frame function both to fasten the axes around which the links pivot and to create a housing for the linkage. A silicone block is placed between the 2 main pivot points to maintain rotatability while preventing fluid from seeping into the linkage. The compliant joints allow the compressor plates to self-balance into a parallel position to prevent dead space forming when fully closing the graft. A 6 mm internal diameter Acuseal vascular graft (GORE Medical, Flagstaff, AZ, USA) was chosen as prosthetic graft, with the same width as the compressor plates. The graft comprises an elastomer layer between 2 sheets of expanded polytetrafluorethylene (ePTFE). The elastomer layer allows creation of a seal similar to the usage of rubber O-rings. The graft is sutured to the two compressor plates that are welded to the linkage. All components of the valve are titanium and produced with wire electrical discharge machining, except for the cylinder that was processed in a lathe.

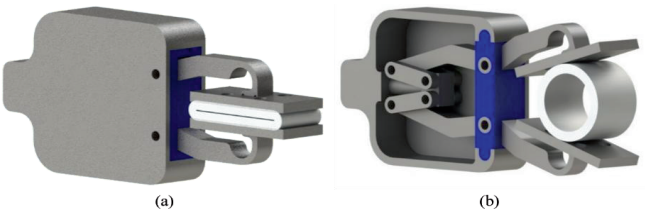

Figure 6-8: The 3D-model of the valve mechanism with the graft placed between the compressors. On the left it is shown without one of the side plates to expose the internal linkage, where the graft is in the fully open position with a relatively low transmission ratio in the linkage. On the right the side place is shown, and the graft is fully closed. The design of the linkage creates a favorably high transmission ratio in this position to fully close the graft. Models were made in SolidWorks (Dassault Systèmes, Paris, France).

Development of test setup for benchtop mechanical characterization

The device is mechanically characterized in a benchtop force measurement setup. A schematic overview is shown in Figure 6-9. The setup contains fixation for the prototype, and a mount for the magnetic coupling, identical to the magnetic ring in the actuator, of which the distance to the prototype can be varied. Silicone sheets of thickness 1.0 mm can be stacked and placed between the magnetic pairs to mimic different thicknesses of skin [36]. The rotation axis of the magnetic coupling is fixed to the mount through a set of ball bearings to minimize friction and restrain motion to 1 rotational degree of freedom.

The input torque supplied to the prototype device is measured through a laser cut polymethyl methacrylate (PMMA) spiral with deformable arms as described in [37] and shown in Figure 6-9: a magnet is glued to one of the arms so that the deformation of the spiral from applied torque results in a change in magnetic field on a fixed Hall sensor (OH49E, Ouzhuo, Nanking, China). The sensor is calibrated by applying torque to the exterior of the disk, with the rotational axis connected to a force transducer (QSH02003, FUTEK, Irvine, CA, USA) through a known moment arm. The signal is amplified by a CPJ Strain Gauge Conditioner (Scaime, Juvigny, France) and read in LabVIEW through a NI MyDAQ (National Instruments, Austin, TX, USA). The Hall sensor value is measured through an Arduino NANO (Arduino, Monza, Italy) and read in Arduino software. All data is processed in MATLAB (MathWorks, Natick, MA, USA). A second order polynomial is fit to the calibration data due to the higher order dependency of magnets, Hall sensor distance and Hall sensor values ($R > 0.99$). The calibration data with curve fit and the sensor characteristics can be found in Supplemental File 3 (online).

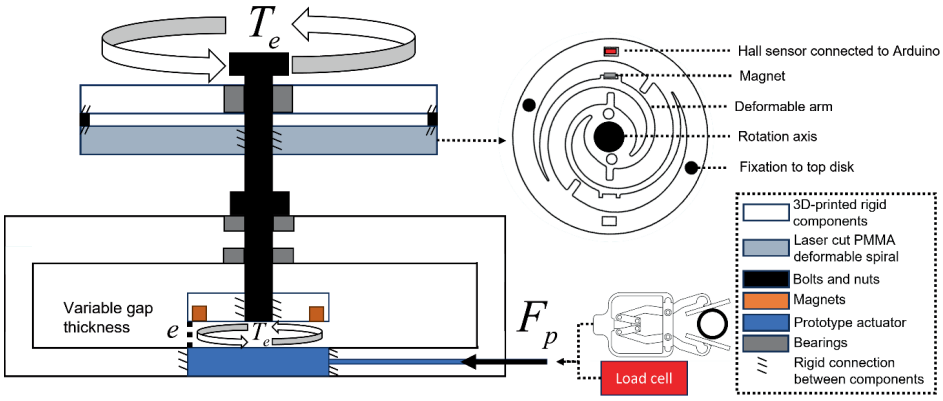

Figure 6-9: A schematic cross-sectional overview of the benchtop test setup to measure input torque T_e *and output force* F_p *in the prototype device through different gap thicknesses* **e**. *Torque is measured through a spiral with deformable arms, a magnet and Hall sensor, and force is measured through a load cell.*

Experimental validation

Dimensions and implantation

A 3D-printed (Dental Resin, Form 2, Formlabs, Somerville, MA, USA) mock-up of the device with the intended dimensions (Figure 6-7) is placed into a single cadaveric human arm (embalmed in formaldehyde) to verify the implantation method and dimensions of the device ex vivo. The authors state that every effort was made to follow all local and international ethical guidelines and laws that pertain to the use of human cadaveric donors in anatomical research. The mock-up includes a 10 cm long transmission cable with a loop to represent the largest dimensions that may be expected. The mock-up of the valve is first sutured to the graft with a suture through each of the suturing holes on the compressor components. An incision is made on the distal and medial side of the cadaver arm. The brachial artery and basilic vein are mobilized to allow placement of a 1 cm piece of vascular graft to be anastomosed. Small incisions are made in both the vein and artery, and the graft is anastomosed between the vessels. Other than the length of graft, this process is identical to standard placement of arteriovenous grafts [7]. A subdermal pocket is created proximally to the anastomosis, and the actuator is sutured to the cutis through the suturing holes in the PEEK hood. The cable loop is placed parallel to the skin. The wound is then sutured closed. This same mock-up is placed in the neck of a thawed fresh frozen sheep cadaver, where the anastomosis is placed between the carotid artery and external jugular vein, to assess translation of the current prototype to a large animal model for future in vivo assessment.

Maximum torque transmission

To determine the maximum torque transmission that can be supplied to the implant, the setup shown in Figure 6-9 is used. The actuator is exchanged with a magnetic ring identical to that of the setup, covered with a 1.5 mm layer of plastic to compensate for the actuator cover. This ring can rotate freely and is fixed to a load cell through a known moment arm. With 1-5 layers of 1 mm thick silicone to mimic skin, the upper magnetic disk is rotated manually until magnetic decoupling (i.e. slipping) from the lower magnetic disk occurs 20 times. The lower magnetic disk is fastened to a load cell (QSH02003, FUTEK, Irvine, CA, USA) with a known moment arm to determine to the torque supplied, and the signal is amplified (CPJ Strain Gauge Conditioner, Scaime, Juvigny, France) and read. The peak data is retrieved and processed in MATLAB.

Maximum force

The device prototype is placed in the test setup with the valve component detached from the transmission cable. A prototype without cable loop is utilized and the cable remains fixed in the same position in the following experiments. The distal end of the wire core of the transmission cable is fastened to a load cell (QSH02003, FUTEK, Irvine, CA, USA) to measure the maximum output force until decoupling of the magnets occurs. As the actuator spiral contains 2 full rotations, force is measured in 1 full rotation intervals at 0, 1 and 2 rotations, with 1-5 layers of 1 mm thick sheets. Each measurement is performed 5 times. The sensor

signal is amplified (CPJ Strain Gauge Conditioner, Scaime, Juvigny, France) and read in LabVIEW through a NI MyDAQ (National Instruments, Austin, TX, USA). The measurements are evaluated against numerical simulations that integrate the measured maximum torque and (6) in MATLAB.

Actuation torque

With the device prototype fastened in the setup (Figure 6-9), input torque to actuate the device is measured 1) without the valve fastened, 2) with the valve with no graft placed, 3) with the valve and unpressurised graft, and 4) with the valve pressure pulses of 180/120mmHg, generated by intermittently decreasing the volume of a closed vessel system. Pressure is measured with a PU5405 pressure gauge (ifm GmbH, Essen, Germany) in LabVIEW through a NI MyDAQ (National Instruments, Austin, TX, USA).

A minimal distance of <0.5 mm between the external magnets and the silicone was kept at all times to prevent contact friction between these surfaces. Measurements are performed by manually rotating the disk for 2 full rotations in intervals of 1/8 rotation. For each instance, the measurement is performed 5 times from open to closed for skin 1-5 mm in 1 mm intervals. In measurements 3) and 4), pressure in the graft is increased to >360 mmHg upon closure. A laser triangulation sensor (optoNCDT 1120, Micro-Epsilon GmbH, Ortenburg, Germany) measures displacement of the distal end of the valve compressor to determine displacement of the valve and verify no leakage occurs resulting from pressure and pulses. A photo is included in Supplemental File 3 (online). The sensor values are processed in MATLAB and torque is estimated by means of the fitted calibration data.

6.3 In vitro and ex vivo validation of a Dynamic AVF

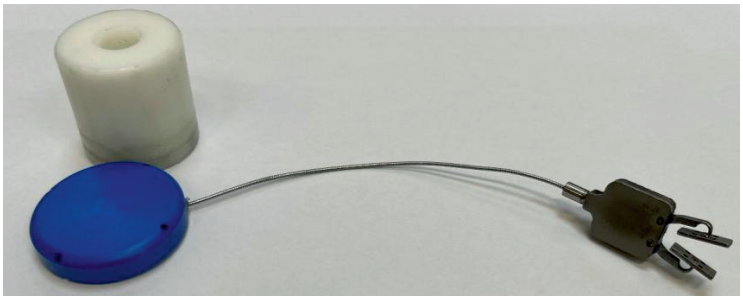

Figure 6-10: The manufactured prototype of the implant device used in the experimental setup, and the external magnets that can be utilized to actuate the prototype.

The fabricated prototype is shown in Figure 6-10.

Ex vivo cadaver studies

Shown in Figure 6-11, placement of the device at the target locations was possible in both cadavers and tension in the skin resulting from the implants appeared negligible. The actuator

unit could easily be identified and external magnetic coupling was possible. Coupling and rotation, and movement of the arm and neck caused no apparent damage to the anastomotic sutures.

Maximum torque transmission

Figure 6-12 displays the mean ± standard deviation (SD) that could be transmitted between the 2 sets of magnetic rings. Maximum torque transmission between the sets of magnets were: 0.18 ± 0.009 Nm at 1 mm thickness silicone; 0.10 ± 0.006 Nm at 2 mm; 0.057 ± 0.002 Nm at 3 mm; 0.038 ± 0.002 Nm at 4 mm; and 0.021 ± 0.001 Nm at 5 mm.

Maximum force

Figure 6-13 shows the maximum forces estimated and mean ± SD measured force values at different skin thicknesses and positions in the spiral.

Actuation torque

Figure 6-14 displays the measured input torque supplied to the device in the 4 configurations with skin thicknesses 1-5 mm. Up to a skin thickness of 4 mm, the graft could be fully collapsed to block fluid with pressure pulses of 180 mmHg (Figure 6-15a), but this was not possible with a skin thickness of 5 mm. When the external magnets were replaced by a larger set (d=6 mm, h=6 mm), full graft collapse could be achieved. Figure 6-15b shows the relative displacement of the distal end of the valve compressor in closed position when pressure pulses are applied. Displacement remains below 0.01mm with pressure exceeding 360 mmHg.

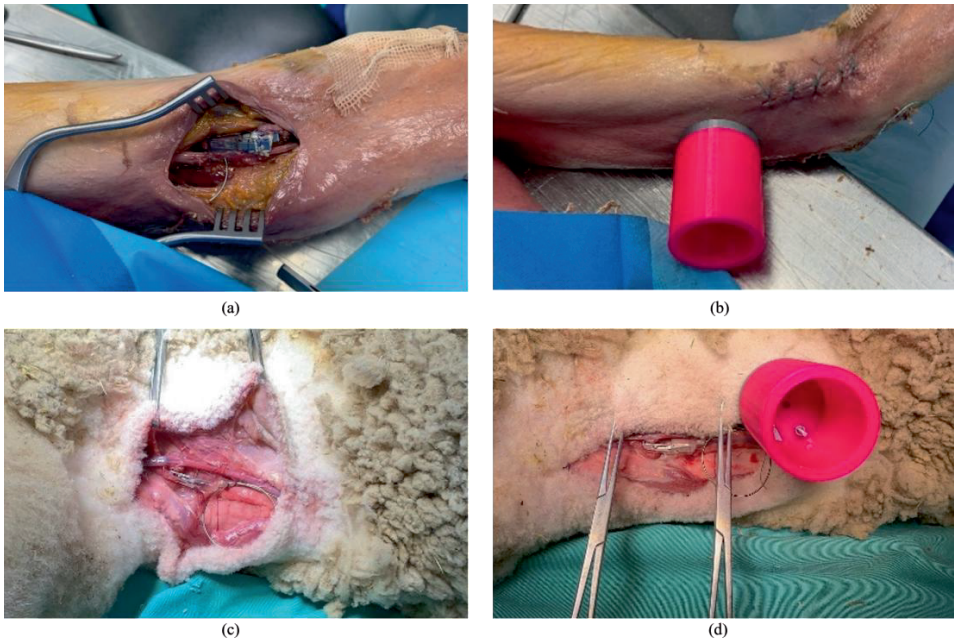

Figure 6-11: The cadaver arm (top) and sheep (bottom) with the mock-up of the device implanted. a) The surgical incision created on the medial side of the upper arm between the biceps and triceps, with the valve anastomosed between the brachial artery and basilic vein in the distal upper arm and the actuator in a subdermal pocket proximal to the shoulder. b) The closed incision and magnets easily coupled through the skin. c) The surgical incision on the anterolateral side of the neck of the sheep, with the valve anastomosed between the carotid artery and external jugular vein cranially and the actuator in a subdermal pocket proximal to the chest. d) The skin be placed over the implant, showing coupling with the external magnets is still possible.

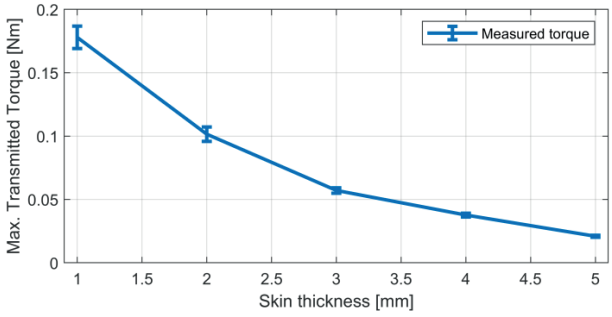

Figure 6-12: The average ± standard deviation of the maximum torque transmitted between the sets of magnetic rings through 1-5 mm thickness of silicone skin model.

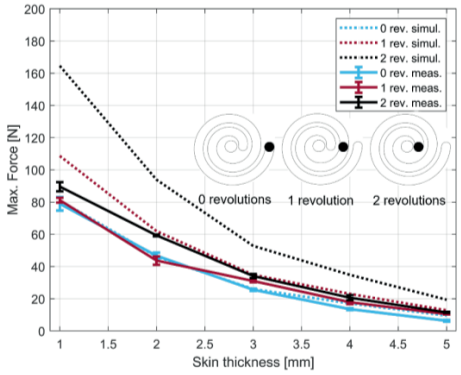

Figure 6-13: The simulated and measured average ± standard deviation of the maximum force generated on the transmission cable by the actuator components at various position in the spiral and through 1-5 mm thickness of silicone skin model.

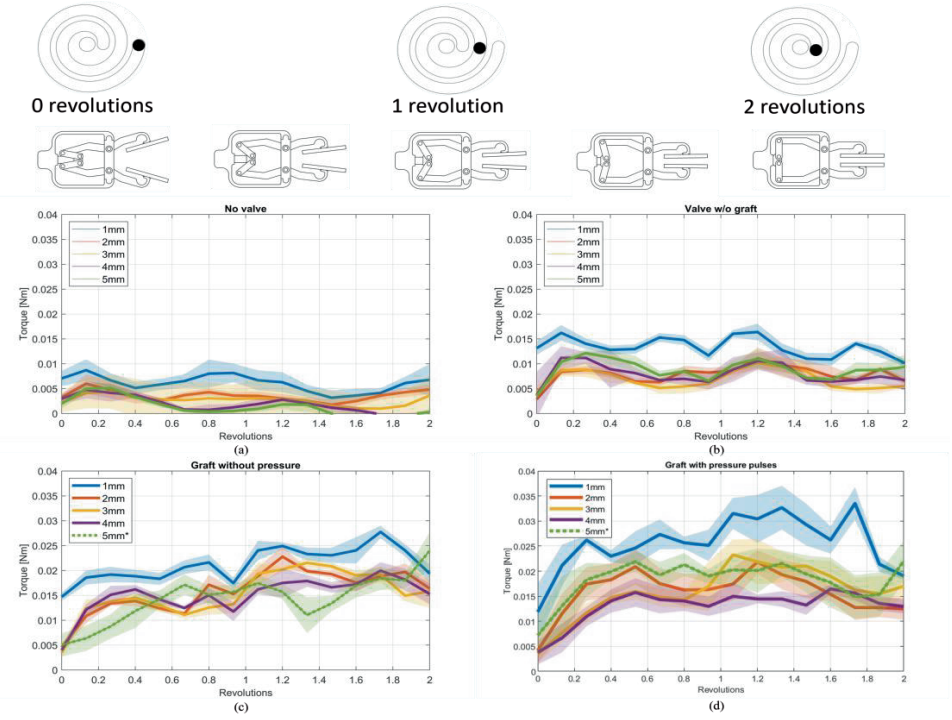

*Figure 6-14: Torque measurements. Top: the position of the valve at pin positions in the actuator spiral. Bottom: the measured input torque required to fully actuate the device with silicone skin model thickness 1-5 mm in: a) the actuator without the valve component connected; b) the actuator with the valve connected; c) the actuator and valve with an unpressurised graft placed between the compressors; and d) the actuator and valve with graft pressurized to 180 mmHg. *indicates a different external magnet configuration was used than in the other measurements.*

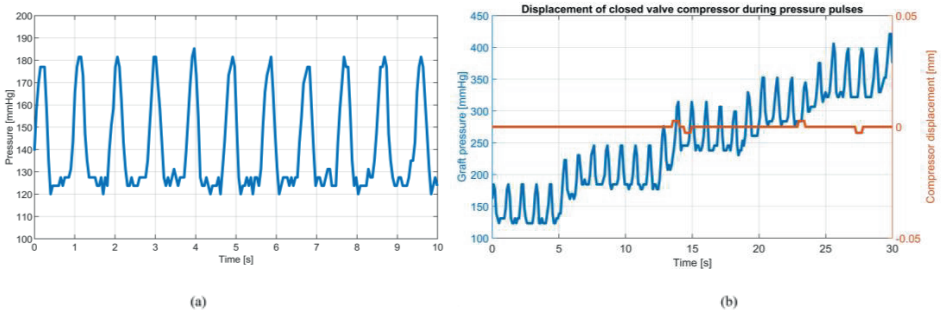

Figure 6-15: a) Measurement of the pressure profile applied to the synthetic graft at 63 beats per minute in the torque measurement of the prototype device in Figure 6-14d. b) Measurement of the pressure profile applied to the synthetic graft at 63 beats per minute and the resulting displacement of the distal end of the compressor of the closed valve.

6.4 Discussion

A prototype has been developed and produced to satisfy the design requirements. This list of requirements was amended following a cadaver study that provided preliminary information on maximum dimensions and energy transmission methods. The presented device is fully implantable and allows non-invasive closure and control of a synthetic graft. The device is non-backdrivable and the graft can remain stable in every position between fully open and fully closed. Motion of the device and its components have been minimized to prevent effects of fibrosis tissue formation, pain and interaction with fragile tissues such as nerves. From an anatomical point of view, there are no adjacent nerves in the antecubital fossa in the forearm (the target implantation site). In the upper arm, the device can be safely implanted between the brachial artery and the basilic or cephalic vein without interference with the median nerve, which typically presents more dorsally. After placement, migration of the components as well as the encapsulation of the materials should be monitored over time.

Due the large number of uncertainties and unknowns remaining, the focus of the prototype is to provide more data and supplement the requirements list in upcoming in vivo studies [25], for example relating to fibrous tissue formation and biological responses to the energy transmission and manipulating the AVF. Currently, the device dimensions and choice of transmission are based on a study of a single cadaveric arm. As almost all dimensions tested could be implanted, the maximum dimensions may be larger than tested in this study. Although subjective, this study suggested tactile energy transmission was not feasible. However, the effect of the embalming cannot be neglected as this could have reduced the frictional coefficient of the skin. Moreover, fibrous tissue forms around foreign material upon implanting, which will more rigidly encapsulate the implant in the surroundings and may affect the feasibility of external tactile manipulation. The dimensional requirements and placement method were verified by implanting a mock-up of the device into a second cadaveric arm, but anatomical variations have not been taken into account. Even though the

force and pressure applied to the skin are considerably lower than the generated force, it is crucial to acknowledge that pain and pressure ulcers (decubitus) are risks of the transmission method. It is worth mentioning that the force application duration is much shorter than typically known to cause decubitus [38]. The actuator is fixed with sutures and edges are rounded as preventative measures. A thin, low friction skin pad may also be added to reduce shear forces and stresses on the skin during actuation. These phenomena may be further assessed in future studies. The mechanical tests included silicone rubber sheets to mimic skin as the magnetic properties are similar [36]. The exponential curve of the measured torque values seen in Figure 6-12 may be considered representative of the higher-order dependence of magnetic attraction versus distance. This data was used to estimate the maximum force that could be supplied by the actuator in (1) and (6). These equations predict that the actuator can supply a higher force when the pin and follower approach the center of the spiral where the moment arm is at its smallest. Figure 6-13 shows the measurements with a similar pattern as the simulation, but the overestimation in the calculations is larger when the spiral radius is smaller. In part, this may be explained by the presence of friction in the benchtop model. In reality force in the cable is generated through a stick-slip motion between the pin and the spiral: torque is applied to overcome static friction as in Figure 6-6b, and the pin rests in the position in Figure 6-6c until sufficient torque is applied to overcome friction again. In the experimental setup, each slip pulls the pin further inwards, which results in a slight elongation of the cable and an increase in force on the load cell. Hereafter the pin returns to the static position of Figure 6-6c. When the radius of the spiral is larger, the pitch angle θ is smaller following (1). The pin therefore faces a steeper gradient closer to the rotation axis: for the same tangential displacement to slip and stick, δx, the radial displacement δr is larger. In other words, the radial component of the frictional force F_f increases with decreasing r, meaning greater force is necessary to overcome static friction and advance the pin inwards through the spiral. This phenomenon has not been accounted for in the calculations and results in an overestimation of the actual force that can be realized close to the rotational axis of the spiral. The coefficient of friction between the spiral and the following pin has a large impact on the force transmission and the efficiency. In the current model this has been estimated from literature as a constant value of in 316L SS to 316L SS [32]. However, this is more complex in reality and depends largely on the surface finish, lubrication, and forces [32]. In future models this coefficient may be determined experimentally in this configuration.

Figure 6-14a and b show the torque necessary to overcome the internal resistance of the actuator and the actuator with valve when unloaded. Unsurprisingly this resistance is higher with the valve as the valve adds additional resistance due to the moving components. Following Figure 6-14c and d, placing the graft adds more resistance, and applying pressure to the graft further increases the necessary actuation torque. The patterns appear similar in all measurements with the graft placed, and can be related to the transmission of forces to the graft by the valve; the torque pattern is an integration of the resistance of the graft, and internal resistance and the transmission ratio of the device. The internal resistance is in part a result of manufacturing imperfections.

The design requirement was to fully collapse a graft at 180 mmHg through a skin thickness of 4 mm, which included a safety factor of 2. A pulsatile pressure of 180/120mmHg in a used to simulate in vivo working conditions. A closed system was used in which pressure is equal in all directions throughout the system. The pressure was representative of arterial pulses in the context of the design requirement, where primarily the pressure tangential to the graft surface is of interest. The pressure pulses did not result in leakages through the closed valve. However, the variation in input torque was larger with the pulsatile flow (Figure 6-14d), which may be explained by the pressure variations. Future evaluation may include fluidic flow at such pressures as an improved representation. However, Figure 6-15b shows that there was no displacement of the compressor of the closed valve even with pressure pulses exceeding 360 mmHg, suggesting no leakage is possible well within the requirement and safety factor, and the device is non-backdrivable.

In the test setup it was found that collapse was feasible up to a thickness of 4 mm, and no longer possible with a thicker skin. When utilizing larger magnets to actuate the prototype it was possible to collapse the graft with a skin thickness of 5 mm, demonstrating that some design freedom remains in the external component to further optimize energy transmission. Additionally, the configuration of magnets was chosen to be maximized for the determined design space. In the experiments torque transmission and force generation was found to exceed the requirements. Therefore, future iterations should feature a bottom-up approach to optimize the magnetic transmission. In situ cadaver studies showed that placement of the device was possible in both a human arm and sheep neck. A larger incision and an adjusted surgical protocol for the anastomotic surgery were necessary. This will likely have adverse effects when used in patients and will need to be studied separately to address benefit-risk ratio of the implant. The resultant forces on the anastomosis and sutures were only assessed in the cadaver studies shown in Figure 6-11. Even though excessively moving the cadavers did not show any apparent damage to the sutures, this model did not include actuation of the valve component. However, the linkage has been designed in a symmetric configuration to minimize lateral displacement, and therefore traction on the anastomotic sutures. Although the cable forces necessary to actuate the valve and close the graft are significant, the outer sheath of the Bowden cable compensates for these forces [39] to minimize traction on the anastomosis. This should be formally assessed in future studies.

For in vivo applications the device will require assembling in a clean environment. As the actuator contains magnets and tight-fitting components of different materials, gamma or other low temperature sterilization will be feasible methods of sterilization because the high temperatures of other methods could result in demagnetization of fracture of components. Although it has not yet been assessed, it is expected that meeting relevant standards should be possible. However, this requires validation, and the optimal dose to achieve sterilization standards may be found experimentally.

Due to the inclusion of magnets in the actuation device, certain procedures such as magnetic resonance imaging will not be possible. The clinical implications of this drawback are

expected to be limited, and outweighed by the potential benefits of removing anastomotic flow, but requires formal assessment.

Lifetime was set as a requirement for the device, but this has not yet been evaluated as it is likely affected greatly by in vivo factors, e.g. toxicity, foreign body response and everyday use. Increasing tissue layer thickness between the implant and external magnets, e.g. due to fibrosis, remains a risk factor for the transmission. To advance development of the device, in vivo studies are imperative to assess biocompatibility and better understand systemic response to intermittently closing an AVF, but also to study functionality of moving mechanical components and magnetic energy transfer.

While the device is eventually to be used in humans, the necessity of animal studies and anatomical and biological differences with the animal model cannot be ignored. The current prototype has been designed to take these into account, for example by allowing skin to be thicker through stronger external magnets, but also with a loop in the transmission cable when a different implant location must be used. These studies may therefore be conducted with minimal changes and safety and mechanical performance data should be translatable to human use. Goats are to be used as AVF models due to similarities in size, thrombogenicity, vascular response and skin thickness, while being even more prone to stenosis formation [40]. If used, placement will occur in the neck as shown in Figure 6-11c and d due to the proximity, diameters and superficiality of vein and artery.

A novel method for non-invasively transferring large amounts of energy to a medical implant and generating a high force has been demonstrated, which is an advantage when compared to existing energy transfer methods that are limited to low energy outputs [21]-[23]. While the current study focuses on the use of this method for AVF closure through a mechanical pinch valve, the actuation device could find application in other use cases, or inspire the development of novel implantable devices that require high energy transmission and forces.

6.5 Conclusion

A fully implantable magnetic actuator-effector device has been presented, which enables non-invasive transfer of energy through the skin and can be used to actuate a mechanical valve system or potentially other types of end-effectors. Through this actuator, a valve component that manipulates an AVF for dialysis can be non-invasively controlled. The focus of the device was to be utilized in large animal model in vivo experiments to assess biological responses to intermittently closing the AVF, magnetic actuation, and moving mechanical components. The maximum dimensions and actuation method for non-invasive energy transfer were determined through a study on a single cadaveric arm. The developed prototype features a ring of magnets that can be controlled by an identical ring of magnets from outside the body. Rotation of these magnets can generate the high force required to fully close a short piece of synthetic graft as AVF. Benchtop and in situ experiments showed that the device

meets the design requirements, and should be suitable for use in upcoming in vivo animal studies.

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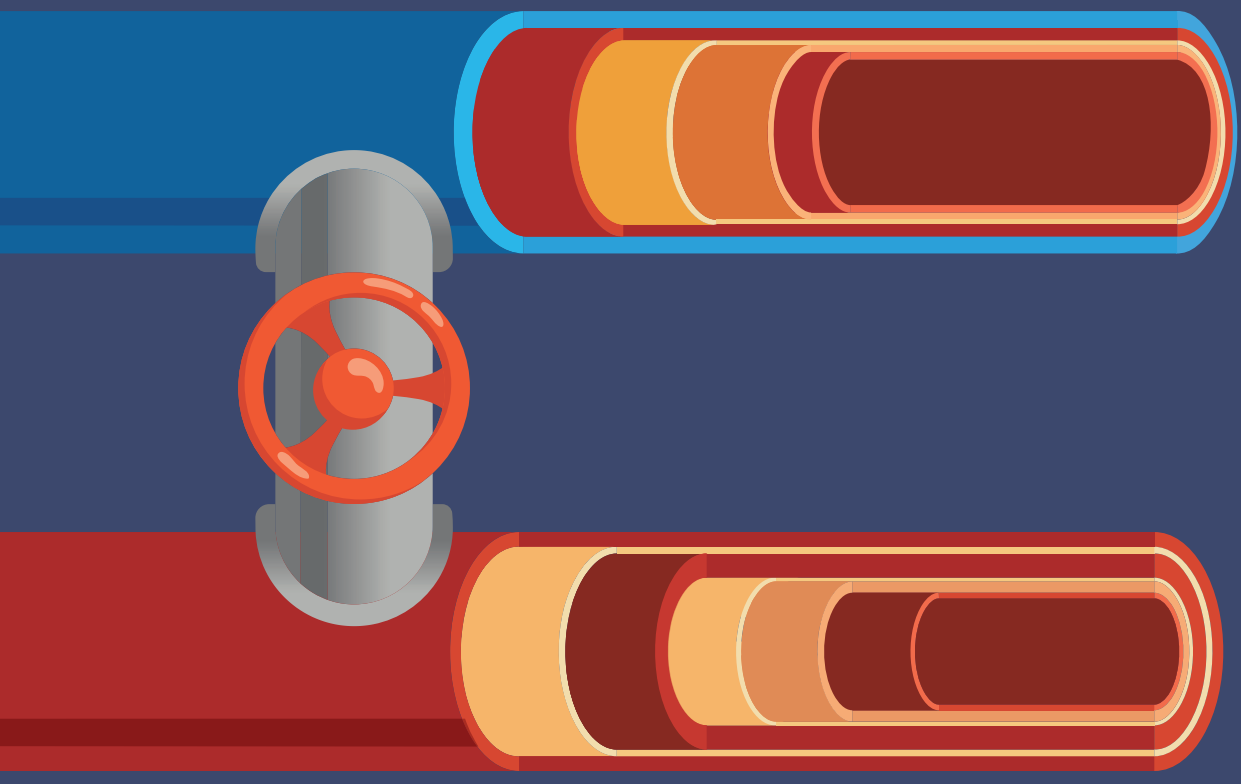

Evidence-based in vivo development of an implantable arteriovenous conduit blood flow control device

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Unpublished (to be submitted after completion of controlled in vivo study)

Building upon the feasibility studies presented in Chapter 6, this chapter details the in vivo evaluation and iterative design refinement of the Dynamic AVF in an animal model. These studies aimed to assess the device feasibility, safety, and (long-term) functionality under physiological conditions. The findings provide critical insights into the technical challenges, biological responses, and practical considerations necessary for further development and eventual clinical translation of the device.

Abstract

Dialysis access complications significantly compromise the quality of life and health outcomes for patients undergoing haemodialysis, underscoring the critical need for enhanced treatment modalities. Arteriovenous fistulas (AVFs) are the preferred access method; however, they often face challenges related to maturation and patency rates, necessitating multiple surgical interventions and posing risks such as high-output heart failure. This chapter presents preclinical development efforts for a dynamic arteriovenous fistula (DAVF) device designed to regulate blood flow and mitigate these complications.

A question-based development framework was employed to systematically address key concerns related to the DAVF's safety and efficacy while optimizing evaluation processes. Preclinical studies utilized a goat model to test the functionality and safety of the DAVF through iterative design improvements, which were implemented across three iterations in five animals. Key questions focused on the device's implantability, acute functionality, and long-term performance.

The device demonstrated initial successful flow control and implantability; however, long-term functionality was hindered by mechanical failures and complications arising from foreign body response. Acute functionality was achieved, with flow rates exceeding 500 mL/min; yet issues such as post-operative seroma and tissue buildup around the implant necessitated further refinement of the device's design.

Long-term effects could of the implant could not yet be studied. Improved connections and foreign body response management were found to be crucial developments to further improve functionality. Future studies are proposed to assess long-term performance and potential clinical outcomes using a more suitable animal model, such as sheep, to enhance translatability to human applications. Securing adequate funding for continued development remains paramount to advancing the DAVF toward clinical evaluation.

7.1 Preclinical Development of a Dynamic AVF

Dialysis access complications significantly impact the quality of life and overall health outcomes for patients on haemodialysis, highlighting the urgent need for improved treatment modalities [1]. Arteriovenous Fistulas (AVFs) are the preferred modality, which create a permanently supraphysiological flow. After a maturation period in which the vein remodels to accommodate a sufficiently high flow, efficient dialysis is enabled. However, maturation and patency rates remain poor, with patients requiring an average of 1.5 surgical interventions per year [2], [3]. Additionally, the high flow conduit has been linked to high-output heart failure [4]. The altered flow conditions are considered the primary culprit [5].

Previously, an implantable device designed to control the flow through an arteriovenous fistula (AVF) was introduced. This device can open and close the arteriovenous connection, thereby eliminating supraphysiological flow through the AVF outside of dialysis sessions which could improve clinical outcomes [6]. Benchtop and ex vivo studies have shown feasibility, suggesting that this device could offer meaningful benefits to patients. Clinical investigations are required to demonstrate its safety and efficacy before it can be approved for market use. Securing ethical approvals, establishing a comprehensive clinical development strategy, and providing evidence of safety, performance, and risk management are necessary steps to be completed prior to commencing clinical trials.

Preclinical testing in animal models can address uncertainties regarding the device's safety and performance in the lead up to the clinical phase in an earlier stage. Risks can be managed and signals of efficacy may be established. However, such studies are typically costly. Due to the large amount of uncertainty that remains in this transitional phase from academia to an industrial product, resources for such studies are often limited. This creates a paradox: de-risking the device through animal studies is necessary to attract funding, yet funding agencies typically prefer to invest in upscaling rather than development. This underscores the need for meticulous planning and innovative development strategies to bring the device into the clinical setting.

To tackle these challenges, the integration of a question-based development framework [7] is explored to optimise the clinical and preclinical evaluation processes of the novel vascular access device. This structured approach enables the systematic identification and resolution of critical questions surrounding safety, efficacy, and technical performance. The aim is to establish the in vivo feasibility and functionality of the dynamic arteriovenous fistula (DAVF) device [6] by strategically prioritizing preclinical evidence generation and assessing greater risks early in the development process.

The focus is on maximizing data collection and de-risking the device using a limited number of animals. This will inform the design of an updated device ready for large-scale animal testing and, eventually, formal verification and clinical validation for market approval.

Establishing initial functionality and safety is paramount, as no further studies can be conducted without a functional and safe implant.

This chapter presents a proof-of-concept verification method for the DAVF device's working principles in a relevant in vivo environment. By investigating the initial in vivo effects on functionality and safety, we aim to optimize the device design for studying disease outcomes in a larger, controlled animal cohort. This larger study is later to be submitted to a scientific journal. Although formal safety evaluations, such as biocompatibility and cytotoxicity tests, are necessary development steps prior to commencing clinical studies, they are considered out of scope for this chapter.

7.2 Question-based preclinical development of Dynamic AVF

Does the device reach the site of action?	Does the device achieve its intended effects?	Does the device have beneficial effects on the disease outcome?	What is the target population?	Are there off-target effects?
• **Can the device be implanted at the target location?** • **Can the device be non-invasively operated by a user in the relevant environment?**	• **Is flow of blood through the device enabled/blocked?** • **Does the device remain functional for its intended lifetime?**	• **Is stenosis/neointimal hyperplasia in the outflow vein reduced?** • **Is cardiac burden reduced?**	• Who should the device be used on? • What are additional risk factors (e.g. BMI, age, gender)?	• **What are the off-target effects?** • **Does the device cause unintended tissue damage, such as vessel rupture?** • **Is thrombus risk increased?** • **Is infection risk increased?** • Does the device cause decubitus? • Is motion impaired in patients?

Figure 7-1: Overview of general (top) and specific (bottom) questions to be answered regarding the Dynamic Arteriovenous Fistula (DAVF) device, following the Question-Based Development framework [4]. Questions in bold are considered to require investigation prior to commencing clinical trials with the device.

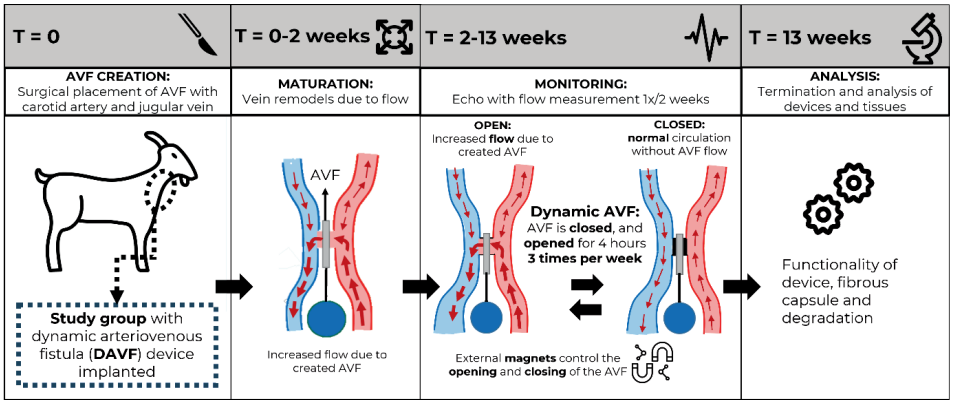


Figure 7-2: General overview of the study setup performed on an Arteriovenous Fistula (AVF) created with the Dynamic AVF (DAVF) implant.

All animal studies were performed in compliance with Dutch government guidelines, the Directive 2010/63/EU of the European Parliament, and was approved by the Institutional Committees for Animal Welfare at Leiden University Medical Centre and Utrecht University (permit number AVD1160020197505, protocol number 7505-3-1).

Figure 7-1 shows the most important clinical unknowns to be answered with the DAVF prior to market introduction [4]. Those in bold are considered to require assessment in an animal model before starting clinical assessment. Figure 7-2 shows an overview of the study setup. Dutch Milk Goats (age ~18 months, weight 60-75kg) are chosen as animal model due to the similarity is size and weight, blood pressure, vessel sizes and vascular response [5], [6]. Animals were healthy and female, due to availability and ease in housing.

The focus in these initial animal studies is placed on the following questions:

- "Does the device reach and function in the site of action?"
    - Can the device be implanted at the target location?
    - Can the device be non-invasively operated by a user in the relevant environment?
- "Does the device achieve its intended effects?"
    - Is flow of blood through the device enabled/blocked?
    - Does the device remain functional for its intended lifetime (minimum 1 year, target of 5 years)?

These questions are further subdivided into parts in 3 sets of animal studies. Between each study, findings and outcomes are carefully studied, and necessary changes to the device are incorporated. First the general study procedure is described.

Placement procedure

Animals were anaesthetised with domosedan (0.4mg/kg, intramuscular), propofol (10mg/kg/h, intravenous) and sufentanil (2-3ug/kg/h). The graft was sutured to the DAVF valve through the suturing holes with 6-0 Prolene suture (Ethicon, New Brunswick, NJ, USA). A midline incision was made in the neck and unilateral jugular vein and carotid artery were identified and mobilised. Animals received heparin until activated coagulation time (ACT) measured at least 250s. Vascular clamps or vessel loops were placed distally and proximally around the target artery, and arteriotomy was performed. The blood vessel was flushed with heparin, and the DAVF graft was sutured to the hole created using a continuous/parachuting suture. The same procedure was performed on the target vein to establish the arteriovenous conduit in a side-to-side fashion. Vessel clamps or loops were released to verify flow. Perivascular flow probes (PS Series 4 and 6mm, Transonic, Ithaca, NY, USA) were placed around the proximal and distal artery to measure flow values with the connected measurement system (TS420, Transonic, Ithaca, NY, USA) to determine AVF flow, and verify that the conduit could be fully opened and closed by the device. The actuator was then sutured into a caudal subdermal pocket so placement was as described in previous cadaver studies [2]. Hereafter functionality was again established by arterial flow measurement, after which the incision was closed. Buprenofine (35ug/h) analgesia was supplied through a plaster

underneath the tail. A removable foam brace was placed around the neck of the animals for the first 2 post-operative weeks to allow to surgical wound to heal and limit movement of the neck.

Monitoring and ultrasound analysis

Animals were kept in standard housing and received standard feed. The first 2 weeks after implantation, the DAVF was left in an open position to enable maturation. This period is shortened from the typical 6 weeks maturation period maintained in humans due to the vessels in the neck of the animals being larger than in the human arm. The DAVF was closed and opened 3 times per week by fixating the animal, locating the implant and connecting the magnetic activator component non-invasively. Two full rotations enabled full opening or closing. Thrill assessment (i.e. assessing the presence of turbulence in the outflow vein as a vibration of the vessel when placing fingers onto the skin above the vessel) was performed to confirm the fistula and DAVF were functional. After the maturation period of 2 weeks, the DAVF was placed in a closed position, and opened thrice per week to emulate a dialysis patient.

Once per 2 weeks an ultrasound with Doppler imaging (Philips CV50, Amsterdam, The Netherlands) was performed on the juxta-anastomotic region to assess AVF and DAVF function, and flow in the proximal and distal artery in both open and closed states. To simulate a realistic dialysis scenario, animals were fixated by animal caretakers, and not anaesthetised. Volumetric flow [L/min] was determined with the average blood flow velocity [m/s] and diameter of the vessel [m].

Termination

After 13 weeks of study [7] the animals were anaesthetised with the placement regime. The carotid artery and jugular vein around the AVF were dissected free approximately 5cm proximal and distal to the anastomosis. Flow measurement with perivascular probes was repeated. The connective tissue around the DAVF implant was also removed so that the DAVF could be removed with the fibrous capsule intact. The blood vessels were then ligated so as to explant the anastomosis with the DAVF device still connected. Animals were terminated by administering a lethal dose of potassium intravenously. Devices were dissected and disassembled to assess function with a strong focus on understanding of the resulting changes in component-tissue interaction due to foreign body response.

Animal study iterations

Iteration 1

The first set of animal studies focused primarily on the establishment of in vivo implantability, acute functionality, feasibility of non-invasive actuation and foreign body response to the implant. It was not known what the effect of foreign body would be on mechanical components that are intermittently moved, so the valve linkage remained bare to assess this unknown. Material was 316L stainless steel. A 6mm inner diameter GORE AcuSeal graft

(GORE Medical, Flagstaff, AZ, USA) was used. The baseline device used in the first in vivo study is shown in Table 7-1. The risk of vessel rupture due to the device was not properly understood, so a stress-relief loop in the transmission cable was included [2].

Iterations 2 and 3

Findings from the initial animal studies with the baseline device were incorporated into updated designs. The following studies focused on assessing:

- Effect of foreign body response on valve
- Long-term flow control
- Long-term functionality of valve
- Long-term functionality of implanted device
- Durability and wear

7.3 Dynamic AVF can function in large animal model

Three devices versions were used in a total of 5 animals over a period of 2 years. Table 7-2 shows the differences in devices used. Table 7-2 displays a general overview of learnings, findings and failure modes of each device version and animal.

Implantation was successful in all animals included. Acute flow values in open and closed states are shown in Figure 7-3a. In animal #5 the device was open and closed several times during the surgery to demonstrate flow can repeatedly be restored. Figure 7-3b shows these flow vales.

None of the devices were functional for the full 13 weeks of study. Versions 2.1 and 3 were fully functional for 2 weeks after placement as determined through thrill assessment. One echo was performed successfully on a fully functional device in animal #4 with device version 2.1. Results are shown in Figure 7-4. In open position, a noisy signal is present in the proximal artery that is indicative of a functional, high-flow, low-resistance AVF (Figure 7-1a). Upon closing the DAVF, a normal arterial signal returns that suggests the AVF is closed and circulation is again normalised (Figure7-4bFigure 7-2).

Primary design changes

Version 1 of the device featured a bare stainless steel linkage. After surgical placement it almost immediately lost the functionality to control venous flow, despite magnetic coupling and some rotational actuation being possible. After termination at 13 weeks, it was found that a large amount of scar tissue forming in and around the moving components (Figure 7-5a) had rendered the valve mechanism entirely non-functional. The transmission cable and actuator were found to be intact after dissecting the device. The Version 2 prototype therefore featured a casing around most of the linkage to limit such effects.

A transmission cable with a loop was placed in Versions 1 and 2 of the implant to allow the valve and actuator component to move with respect to each other [6]. The intent was to minimise the resulting traction forces on the anastomosis caused by movement of the neck

in the animals. In the 13-week study period, no vessel rupture or bleeding had been established, but a thick fibrous capsule had formed around the cable loop. Functionality of the loop itself was lost, but the loop itself reduced the efficiency of the drive train due to the increase in friction in the transmission. As such, the decision was made to include a straight cable in a slightly updated Version 2.1. In one animal, Version 2 was exchanged with Version 2.1 halfway the study period. The remainder of the study showed no signs of excessive traction or bleeding complications. However, the connections of the cable were found to be under increased stresses and the cable dislocated from the actuator close to the termination date. Version 3 featured a thicker but straight cable with more robust connections to the valve and actuator.

Key learnings on DAVF

The following are considered the key learnings of the animal studies with the DAVF implant:

+ The DAVF can be implanted between a major vein and artery in the neck in an in vivo goat model with standard surgical techniques;
+ In an acute setting, the DAVF can control the AVF flow to the desired values;
+ After recovery from surgery, locating and non-invasive coupling with magnets to the implant is possible and intuitive;
+ No blood vessel rupture occurred with a cable loop or with a straight cable throughout the study period;
+ The magnetic actuator remains in the correct location and identifiable throughout the study period;
+ The magnetic actuator remains functional throughout the study period and after explantation;
- Foreign body response causes tissue buildup around implanted parts that prevent moving of uncovered components (Figure 7-5a). Detrimental effects were found to start after about a week;
+ Functionality of valves could be restored after removing external fibrous capsule and internal mechanisms were fully intact (Figure 7-5b);
- Post-operative seroma can cause a temporary inability to couple magnets by increasing the tissue layer in the magnetic coupling; and
- High forces, stresses and strains on the transmission cable and connection points occurred during the follow-up period that resulted in dislocation of the transmission cable from the actuator mechanism, and fracture of the inner wire.

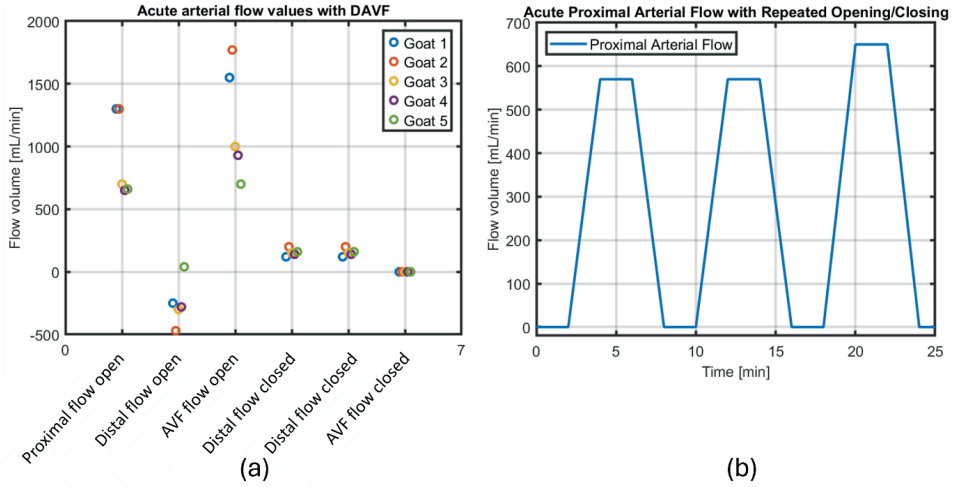


Figure 7-1: Arterial volumetric flow rates as measured with arterial flow probes. Flow probes were placed around the proximal (caudal) and distal (cranial) carotid artery. Recordings were done with the Dynamic Arteriovenous Fistula (DAVF) in both open and closed position. Arteriovenous Fistula (AVF) flow was calculated as proximal flow minus distal flow. a) (Average) flow rates in all goats tested. b) Representation of flow after repeatedly restoring physiological flow by opening and closing the DAVF several times.

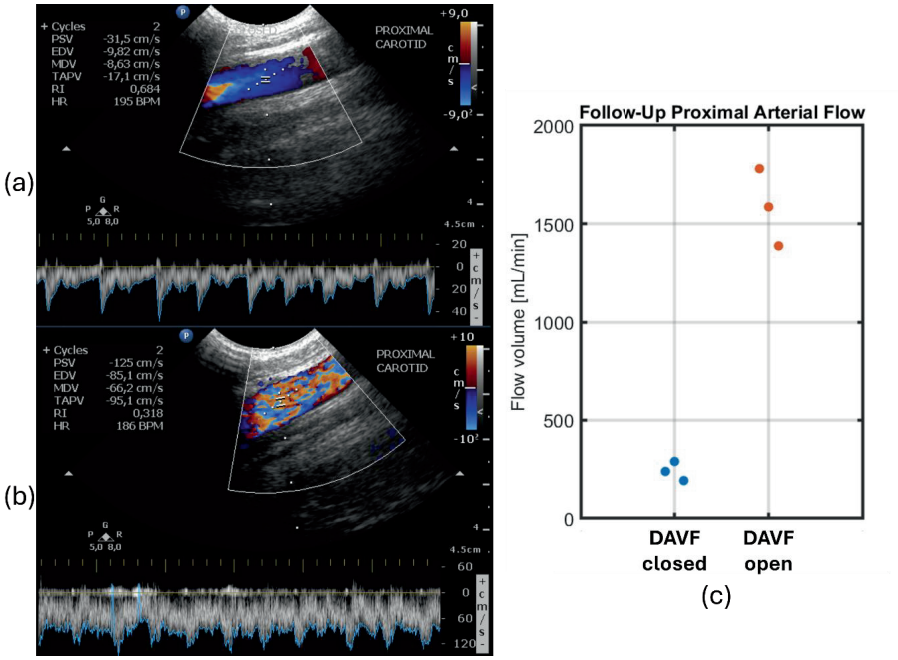


Figure 7-2: Blood flow measurements in the carotid artery as measured with Doppler Ultrasound 1 week after device placement. a) Ultrasound image of the proximal arterial flow ~5cm from the Arteriovenous Fistula (AVF) with the Dynamic AVF (DAVF) in closed position, and b) in open position. c) The estimated volumetric flow rates of the 3 measurements performed in both positions.

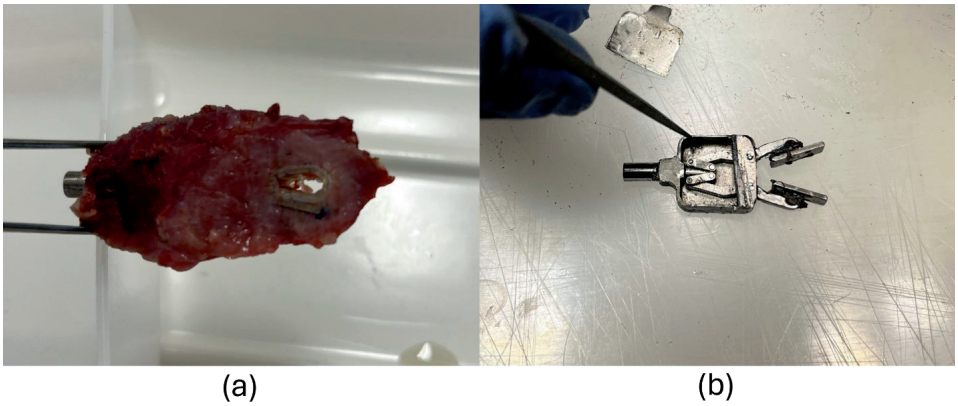


Figure 7-3: Explanted DAVF valve decoupled from the transmission cable. a) Large amount of fibrosis tissue found around the entire valve, and it can no longer fully collapse the graft. In b) this fibrous capsule is removed and functionality is restored. Upon cutting open the valve casing, it can be seen that the interior is clean and not affected by fluid or tissue ingress, suggesting the casing and seal function adequately in protecting shielded components.

Table 7-1: Overview of the different prototypes developed and tested during the development of the dynamic arteriovenous fistula (AVF) implant. Pictures of the prototypes are shown, together with a summary of the changes of each prototype with respect to the previous prototype.

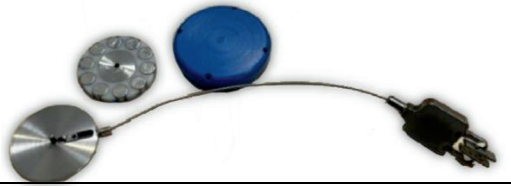
Device version		Changes with **respect to** previous version
1		- **Baseline device** - No casing placed around linkage with pinhole joints to determine feasibility of maintaining movability of components when exposed to foreign body response. - Strain-relief loop in transmission cable. - 6mm Goretex Acuseal graft (GORE Medical, Flagstaff, AZ, USA) was used. - Transmission cable welded to actuator and fixed to valve through threaded connection.
2		- Valve material switched from 316L stainless steel to Grade 5 Titanium. - Pinhole joint at compressor replaced by compliant joint. - Casing placed around remainder of linkage with silicone seal around main pivot points as described in [6]. - Complete inside is sealed (Figure 7-3).
2.1		- Cable loop removed and straight cable used.
3		- D=5mm thin-walled PTFE graft GORE Medical, Flagstaff, AZ, USA used - Straight cable. - Thicker cable with threaded fastening on both inner and out wire on both ends. - Magnets fully coated in ultraviolet-cured stereolithography (3D-printable) resin.

Table 7-2: Summary of findings, learnings and failure modes of each dynamic arteriovenous fistula (DAVF) implanted and explanted in each tested animal.

Device Version	Goat number	Findings and learnings	Failure mode(s)
1	#1 & #2	- Implantation feasible and graft can adequately be controlled through skin in an acute setting. - Before/after post-operative swelling coupling of magnets is easy and does not appear to cause discomfort. - Rotation of magnets possible to some extent before decoupling occurs when required torque becomes too high. - Rotation of magnets results in some effect on valve and graft, but cannot be fully closed. - Rupture of AVF and/or sutures does not occur during implantation (t=13wks). - Significant outward remodelling of jugular vein because graft could not be closed properly. - After explantation, magnetic actuator can still convert magnetic torque to force and linear displacement on transmission cable through skin model. - No device-related side-effects noted other than post-operative swelling.	- Insufficient magnetic torque transmission due to post-operative swelling and scar tissue around actuator to fully collapse graft. - Scar tissue in valve component resulted in excessive resistance to movement.
2	#3 & #4	- Silicone seal and G6 fitting prevents scar tissue and blood from entering into casing. - Preventing scar tissue from forming around moving components maintains functionality to some extent but does not fully resolve non-functionality. - Externalising the actuator increases the amount of torque than can be transmitted and restores some of the functionality but does not fully resolve issues. - Confirmed suboptimality of externally placing actuator through dislocation of actuator from cable.	- Insufficient magnetic torque transmission due to post-operative swelling and scar tissue around actuator to fully collapse graft. - Inefficiency, hysteresis and longitudinal elasticity of transmission cable when placed in a loop. - Dislocation of transmission cable on side of actuator both before (goat #4) and after (goat #3) externalising actuator at point of welding. - Dislocation of valve from graft (goat #4).
2.1	#4	- Previous device malfunctioned and transmission cable dislocated so implant was replaced by a new device with a straight cable. - Clean device with externally placed actuator and straight cable can fully control and collapse graft in alive and awake animal in the weeks following re-implantation. - Using a straight cable as opposed to one with a loop does not (immediately) rupture anastomosis. However, scar tissue had had the time to form around the graft and anastomosis which likely provided additional structural rigidity and helped prevent this from occurring. - Graft can be closed for 2 days and reopened to increase flow sufficiently.	- Dislocation of transmission cable on side of actuator at point of welding.
3	#5	- Implantation easier with straight cable - Directly placing a device with a straight and thicker cable does not cause rupture of graft/anastomosis - Significantly lower force requirement with smaller, thin-walled graft (5mm diameter) which facilitates control with lower magnetic torque input - Absence of silicone around graft does not prevent full closure and expulsion of blood from graft lumen. - Fastening thin-walled graft to valve more challenging. - Fully encapsulating implanted magnets with cured resin prevents oxidation. - Increased thickness of cable with improved fastening no longer failure point in cable. - Post-operative swelling no longer (temporarily) disables device functionality due to reduced force requirement on graft and increased transmission efficiency of cable.	- Dislocation of valve from graft due to high motoric activity of animal. - Fracture of inner wire in transmission cable at location of kink close to actuator. - Scar tissue forming around moving components of valve (that were outside the casing) prevent the graft from being reopened. - Elasticity of PTFE reduced

7.4 Discussion

This study aimed to establish a proof-of-concept of the DAVF working principles in a relevant in vivo environment, and optimise the device design by investigating initial in vivo effects on the functionality and safety. Through 3 iterations of the design, tested in a total of 5 animals, acute functionality and potential for longer-term functionality was demonstrated. Long-term functionality appeared to be primarily hindered by mechanical malfunction.

Acute functionality of the devices demonstrated both implantability of the device and the ability to control the blood flow to intended values in an animal. Flows exceeding the 500 mL/min required for dialysis [11] were immediately achieved, with typical turbulent flow patterns indicated by the thrill in the blood vessels. After fully closing the device, circulation appeared normalised with physiological flow values returning in the carotid artery and venous thrill disappearing. Notably, the device design allowed for stable control of flow at any value between fully open and fully closed. This feature enables titration of AVF flow to an ideal value, maximising dialysis efficiency while minimising negative consequences of high flow and turbulence, such as excessive inward and outward remodelling and cardiac burden. These effects are particularly prominent in upper arm AVFs, the target location for the device, as flow values are typically higher [1]. However, the higher flow also improves maturation rates. Thus, the benefits of upper arm AVFs may be maintained while mitigating their potential drawbacks by allowing flow control. Further, long-term evaluation is required to confirm these findings.

The animal studies showed no adverse effects of the implant other than post-operative swelling around the implant and surgical incision. The actuator could always be easily identified and magnetic coupling was always possible except for some instances when surgery-related seroma was present. Animals showed minimal resistance to actuation, suggesting it caused little pain. With device versions 2.1 and 3, it was temporarily possible to control flow to desired values non-invasively during the follow-up period. Establishing that flow can be controlled through ultrasound in the follow-up period even only a single time holds tremendous value in demonstrating proof-of-concept. This shows that it is possible and feasible to create an implant that can control flow, and opens the door to continued development. This next phase should focus firstly on maintaining consistent flow control over extended periods, which proved challenging due to several factors. Primary issues were 1) post-operative swelling (seroma) around the implant site, 2) foreign body response causing fibrous tissue formation around the device and components, and 3) excessive forces and stresses occurring on the connections between components in the device. In such an animal model, these effects are inevitable as they are dictated by biological response to tissue injury foreign material, and animal behaviour is unpredictable. To manage these risks, alternative approaches are necessary, with mechanical solutions often being the easiest to implement. To tackle the root causes of the failures and malfunctions, mechanical improvements to the design in future iterations should include:

1. A method of reducing effect of foreign body response to ensure functionality is maintained even after prolonged periods of implantations
2. An improved connection of the graft to the valve that prevents dislocation of the graft from the valve
3. An improved transmission cable and connection that remains functional in transferring work from the actuator to the valve, and is sufficiently flexible to allow placement and prevent excessive forces on the graft and anastomotic sutures.

Although the transmission cable is a seemingly simple component, the accuracy in transmission, high axial forces, and stresses in the connections that result from movement of the animal make it considerably more complex. Using off-the-shelf components for this purpose posed challenges. Although use of custom-made parts was explored, costs quickly became excessive, deeming it less feasible for use in a setting where funding was limited. The transmission cables used were salvaged from other medical devices, which performed adequately temporarily, but ultimately failed. Optimisation of a custom-made transmission cable assembly and connections in an upcoming design could solve many of the issues faced.

Additionally, changing the animal model may be promising in reducing risks. Although goats are good models for studying vascular physiology in AVFs [8], [9], their anatomy and behaviour introduces issues that may not be present during in patients. The long and flexible neck of a goat is a far less rigid implantation location than, e.g., along the humerus in the human arm. The forces and stresses on the joints during clinical application are likely overestimated in the goat model, which introduces design changes that may not be relevant in the target environment. This is further amplified by the unpredictable behaviour of goats, which can lead to sudden movements and impacts that are not typical in human patients. Such erratic behaviour can cause additional stress on the implant and surrounding tissues, potentially leading to complications or device failures that would not occur in a more controlled clinical setting. To avoid including safety features that are only necessary in pre-clinical studies, switching the in vivo model to an animal with a shorter neck and more predictable behaviour may complement the design changes proposed. However, maintaining adequate translatability in vascular response from the animal model to the patients is crucial to make any claims regarding safety and performance.

Whereas the initial results of the mechanical implant in controlling flow through the arteriovenous fistula are promising, the effect on disease outcomes remains unclear. The short-term success in flow regulation does not necessarily translate to improved long-term clinical outcomes for dialysis patients. Factors such as the cardiac burden and the prevention of stenosis or thrombosis, as well as any currently unknown device-related adverse effects need to be thoroughly investigated. Long-term studies are essential to assess the sustained efficacy and safety of the implant. These studies should include comprehensive monitoring of patients over several years to evaluate the device's durability, the stability of flow control, and any potential adverse effects that may emerge over time. Additionally, comparative analyses with current standard-of-care treatments will provide crucial insights into the relative benefits and risks of this novel approach. Only through rigorous long-term evaluation

can the true clinical value of the DAVF be determined in improving disease outcomes for dialysis patients.

Finally, preclinical trials in animal models present significant challenges when evaluating academic medical devices. Factors, such as the choice of animal species, experimental conditions, and complex device-biological interactions influence study design and outcomes. These trials are inherently unpredictable due to biological variability and unforeseen complications. Many unknowns persist, including the long-term physiological effects and the translatability of findings to human applications. Incorporating the question-based development framework [7] emphasized systematic identification and assessment of uncertainties throughout the development process. The presented approach was to first map key clinical issues and risks and then implant a device very early on in the development. This included clear questions to which the prototypes were tailored. By structuring testing around key safety and efficacy questions, this approach did not aim to build a fully functional device, but rather to address uncertainties as early as possible. Thereby it provided structure for future development steps and evidence to base design choices on.

Future work

The next phase of device development should focus assessing the performance and safety of the DAVF in a long-term study. After incorporating the design changes proposed, a study is to be performed that examines not only the functionality of the device in controlling the AVF flow throughout the study period, but also evaluates the effect of disease outcomes by including a control group. Figure 7-0-4 shows the proposed study setup. An emphasis is placed on determining cardiac burden of the DAVF versus a traditional AVF, rather than incurrence of adverse events or neointimal hyperplasia. It features the measurement of cardiac burden through pressure-volume loops, pulmonary artery catheter, left-ventricular wall thickness measurement, and NT-proBNP measurement, a known cardiac stress biomarker [12]. The venous outflow is studied through histopathology for vascular smooth muscle cells and intimal hyperplasia. Finally, the animal model should be changed to sheep. Primary benefits of this model include the shorter neck and calmer nature which should result in lower forces and stresses on the device connections. Vascular response to AVFs in sheep is thought to model that of humans adequately [9], [13]. It is intended to submit this study to a scientific journal for publishing.

Given the substantial resources required for these efforts, the financial burden is considerable. While academic funding plays a crucial role, it is often insufficient to fully support these costs. Securing alternative funding sources, such as industry partnerships or venture capital, will be essential to propel the device toward clinical use.

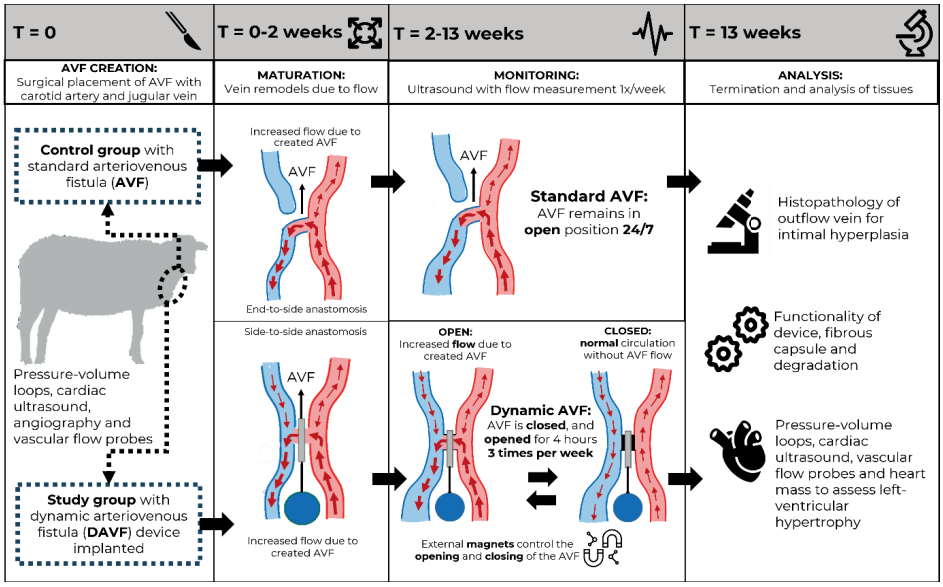


Figure 7-0-4: Proposed setup for a pre-clinical, controlled in vivo study that assess performance of the device in both functionality and disease outcomes. This study is to performed on sheep, and assesses the effect on the venous outflow and the cardiac burden.

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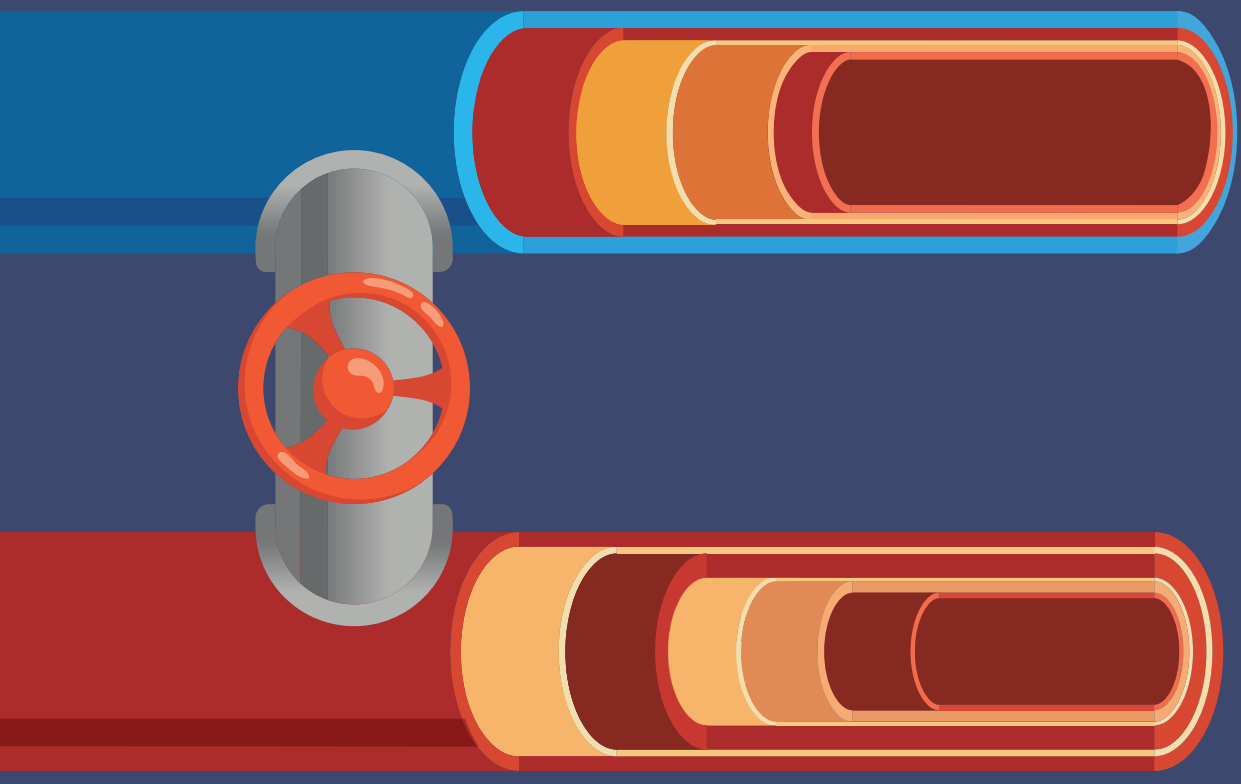

General discussion and conclusions

8.1 Synopsis

This dissertation aimed to develop and evaluate a novel medical device for improved vascular access for haemodialysis. It started by examining the regulatory landscape of medical devices in the European Union in **Chapter 2,** and proposed a framework for the development thereof. **Chapter 0** examined an unapproved use case of central venous catheters (CVCs), in which contrast media was injected directly into the catheter. In an in vitro setting this was found to be safe in incidental use which can mitigate the need for additional procedures. Hereafter the haemodynamic conditions in peripheral (arteriovenous) vascular access was studied in a literature review in **Chapter 4**. Although many modalities exist that aim to improve vascular access outcomes by modifying local haemodynamics, none consistently show better patency. The permanent arteriovenous connection and high blood flow is thought to be the primary culprit. **Chapter 5** described a clinical study with such a modality, an external vessel support device, which also found that patency did not improve compared a historic control group. To tackle the primary cause of vascular access complications, the permanently supraphysiological flow, **Chapter 6** described the design of an implantable device that can non-invasively open and close the arteriovenous connection. Benchtop and cadaver studies showed feasibility of this device**. Chapter 7** focused on the in vivo development and iterative improvement of this device. Although some issues remain in the design of the device, these animal studies demonstrated that the implant, named the Dynamic Arteriovenous Fistula, holds promise for tackling the core issue in vascular access for dialysis. However, future studies are necessary to establish long-term functionality and effects on disease outcomes.

Please refer to the respective chapters for the in-depth discussions on each topic.

8.2 Strategies to improve vascular access

For patients with end-stage kidney disease (ESKD), vascular access is crucial for haemodialysis, with peripheral arteriovenous access being the preferred method [1], [2]. However, this approach has significant limitations, including increased cardiovascular risks like heart failure [3], [4], [5], [6] and long-term vascular injury leading to poor patency rates [7]. These issues place a heavy burden on patients both physically and psychologically [8], [9], [10]. Despite these challenges, the basic design of peripheral vascular access has remained largely unchanged since its introduction in 1966, still relying on a permanent arteriovenous connection for high-flow access.

Drawbacks of current standards of care

Although the arteriovenous fistula (AVF) continues to be the most used VA [11], its inherent drawbacks highlight the critical need for novel strategies aimed at optimizing vascular access in the haemodialysis population. As described in Chapter 4, and further highlighted in Chapter 5, none of the currently used methods substantially reduce complications related to the altered haemodynamic conditions in the long term or improve patency. Arguably, some minor

improvements have been made with the introduction of new types of grafts, which, for example, can allow earlier cannulation. However, these often introduce other issues, such as higher infection rates [1].

Insufficiently discussed in this dissertation are the cosmetic concerns associated with peripheral VA for haemodialysis. These significantly impact patients' psychological well-being and quality of life [12]. The physical alterations resulting from VA creation, such as prominent scarring, skin discoloration, and vascular bulging, can lead to body image disturbances and emotional distress. Patients often perceive their VA as a visible marker of illness, leading to feelings of self-consciousness and efforts to conceal the access site [12]. These concerns affect VA decision making [13]. They were also found to influence daily activities, clothing choices, and social interactions [14].

One significant advancement in haemodialysis vascular access is the central venous catheter (CVC), which eliminates the need for permanent high-flow conditions and does not require vessel maturation. This allows patients with poor vascular conditions to undergo haemodialysis when it might otherwise be impossible [1]. However, CVCs are not universally superior to peripheral methods, as the choice of vascular access must be tailored to each patient. CVCs come with their own set of issues, such as thrombosis due to stagnant blood flow when not in use and infections from the permanent transcutaneous connection [1]. However, this permanent transcutaneous connection may also be used for other procedures to mitigate the need for some interventions, as described in Chapter 0. As such, only looking at outcomes directly related to the VA may provide an incomplete picture.

Potential ways forward

Despite the potential benefits of CVCs, 75% of US haemodialysis patients receive their treatment via peripheral, arteriovenous VA [11]. As described in Chapter 4, it is apparent that to significantly improve longevity of the VA and reduce complications rates related to the VA, directly addressing the permanent high flow is necessary. As simply introducing changes to the haemodynamic profile around the VA has shown little benefit, the solution may thus lie in reducing the supraphysiological flow rates when not in use and bringing the circulation to a more normalised state. The lower incidence of VA complications, such as stenosis, heart failure and haemodialysis access-induced distal ischemia, in distal AVFs [15] supports the idea that lower flow rates are paired with lower complication rates. The trade-off to this decision is that maturation failure is more common with low VA flow, as this causes less wall shear stress-induced outward remodelling [16], [17], [18]. The implantable arteriovenous conduit blood flow control device, introduced in Chapter 6, was designed to control arteriovenous flow through the conduit to normalise the circulation when the VA is not in use. When placed in the upper arm, it may allow high flow that promotes maturation, patency and efficient haemodialysis [19], while minimising complications by returning the circulation to a normal physiological state when not dialysing. Theoretically it can thus harvest the benefits of both low-flow distal AVFs and high-flow proximal VA at the same time. Figure 8-1 summarises the theoretic advantages and disadvantages of this device. However, this

technology is still new. A risk-based approach, described in Chapters 2 and 7, was implemented in the development that aimed to address the largest risks as early as possible. Although initial benchtop and in vivo data demonstrates feasibility of this device, so far only initial in vivo data exists and long-term functionality of this device has yet to be shown. Any such improvements on clinical outcomes remain to be evaluated in clinical trials whereas unknown and unforeseen risks may arise such as infection due to the implantation of foreign material, or thrombosis when not fully mitigating dead volume in the arteriovenous connection or at the venous or arterial interfaces. It therefore cannot yet be claimed that removing arteriovenous flow outside dialysis sessions will result in improved VA. Finally, the last inherent drawback is that cannulation of the vascular access is still required with the DAVF, which may even be further complicated by the presence of rigid materials and magnets around the VA site.

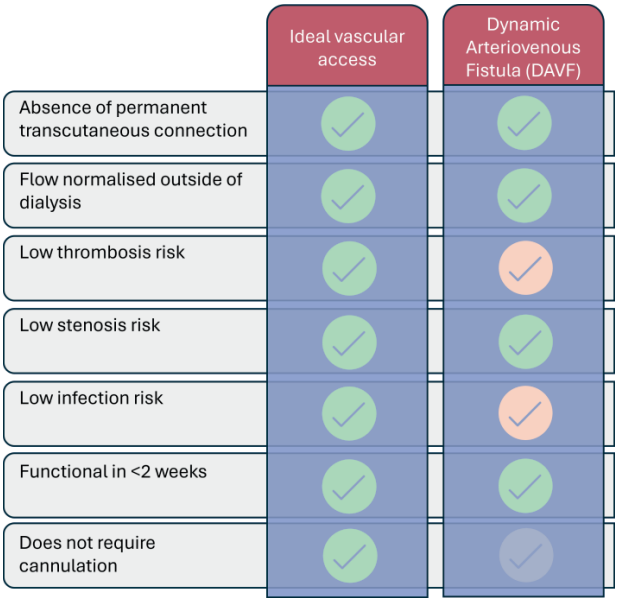

Figure 8-1: pros and cons of the Dynamic Arteriovenous Fistula versus an ideal vascular access. Thrombosis and infection risk are expected to be dependent on device design and remain to be evaluated in animal and clinical studies.

8.3 Critical factors in developing medical devices

Due to the mechanical and fluid dynamic nature of VA, the aim of this dissertation was to develop medical device strategies to improve clinical VA outcomes. Such strategies typically require insight from all relevant stakeholders, which include clinicians, surgeons, nurses, engineers, material experts, regulators, and of course patients. Although finding alignment between each expertise was found to require time and a lot of open-mindedness to gather

knowledge from outside the respective fields, innovations are thought to improve overall with such an approach as they inevitably should adhere to the specified requirements set by each stakeholder. For example, a technically sound device that is difficult to use, or is unpleasant or undesirable for patients is unlikely to maximise clinical benefits, improve care or reduce costs as adoption of the device will be hindered.

Interdisciplinarity of development teams

Improving alignment between stakeholders may be supported in several ways. First, strengthening basic interdisciplinary understanding is essential. In particular, medical education in the Netherlands currently pays limited attention to medical technology and innovation, representing a missed opportunity to prepare future clinicians for their role in device development. However, this is currently being recognised and improving [20]. Second, structured stakeholder involvement throughout the entire device life cycle, from early ideation to clinical implementation, can help ensure that clinical needs, regulatory constraints, and user requirements are addressed in parallel [21]. Third, fostering openness to innovation is critical. Technical feasibility, clinical usability, regulatory compliance, and manufacturability often pull in different directions. Navigating these competing demands requires open-mindedness, transparent communication, and a commitment from all team members to understand perspectives outside their domain of expertise. This includes not only a willingness to adopt new approaches but also increased exposure to innovation processes within training and practice. Increasingly, grant schemes and innovation programs designed to bring together multidisciplinary teams from the outset, such as the Delft Health Initiative grant under which the presented work was conducted, incentivises early collaboration between clinicians, engineers, and other stakeholders. Establishing such integrated teams at the beginning of the development process may significantly enhance efficiency, alignment, and the likelihood of successful translation. Together, these strategies may facilitate the development of more effective, acceptable, and sustainable solutions in VA and beyond.

Regulatory hurdles

Another central challenge highlighted in this research is the demanding regulatory environment in the European Union [22]. While essential for patient safety, these regulations require extensive documentation, prolonged approval timelines, and considerable financial investment. For early-stage innovations such as the Dynamic AVF implant, this means a high burden of proof even before human trials can begin. This reality contributes to the so-called “valley of death,” where many promising ideas fail to progress beyond preclinical development due to lack of resources, regulatory hurdles, or both. The enormous focus on safety by the Medical Device Regulations (MDR) is likely in place to benefit patients by mitigating risks and avoiding device failures prior to market introduction, but this may have unintentional secondary consequences. If many necessary clinical innovations do not reach the market due to excessive funding requirements resulting from overly stringent regulations, patients will ultimately suffer. Pathways exist in which orphan devices can receive conditional

approval where no other treatments are available and benefits may outweigh risks (MDR Annex VII) [22], but these are not often used [23]. There is therefore no simple answer on how to balance regulatory requirements and accelerating device development to maximise patient benefits.

Academia versus industry

A scientific approach has been taken to develop medical device strategies to improve clinical VA outcomes. The academic environment offers a unique advantage in this context, providing the flexibility to explore novel therapies and concepts with minimal commercial pressure. This relative independence allows for a more objective evaluation of technologies, facilitating the early development of devices from a clinical need rather than market forces. As a result, many medical devices originate within universities, where interdisciplinary teams can experiment and iterate without the immediate constraints of profitability. At the same time, this may create challenges in the valorisation of such technology as innovation is less likely to reach the clinical setting if there is little chance of profit and major changes are required to enable regulatory approval. Academics may thus benefit from greater exposure to the principles of industrialisation and implementation. A shift in mindset, supported by education on regulatory strategy, manufacturing processes, and commercialisation, could enhance the position of academic inventors and improve the rollout and real-world impact of their innovations.

Moreover, academia is often driven by the demand for scientific output and high-impact publications, which can sometimes overshadow translational goals [24], [25]. This raises fundamental questions about the role of academia in society and its responsibilities in the innovation pipeline. Should universities take a more proactive role in advancing technologies toward clinical and commercial application, or should this remain the responsibility of the market? Bridging this gap may require more structured pathways that support the transition of academic innovations into industry and clinical practice. An active stance from academia that provides freedom for researchers to support and participate in start-ups could benefit valorisation. At Delft University of Technology, valorisation is one of the three pillars of the “knowledge triangle”, where the importance of research results in innovation is recognised.

Ultimately, this research illustrates that improving vascular access outcomes through device innovation is not simply a matter of invention. It requires navigating a complex ecosystem of scientific, clinical, regulatory, and logistical factors. Acknowledging and addressing these critical factors from the outset, through open collaboration, adequate funding strategies, and a shared commitment to patient-centred design, is key to successfully advancing devices like the Dynamic AVF toward clinical impact.

8.4 Limitations and future directions

Further development of the Dynamic AVF

Although the research presented in this dissertation suggests a device such as the Dynamic AVF may be a solution to many of the complications presented by the peripheral VA, no such claims can yet be made. Clinical studies are not only necessary under the MDR to achieve market approval, but they are also critical in establishing performance and severity of known risks, as well as identifying currently unknown risks. A question-based approach as proposed may be of benefit in prioritising the highest risks early on.

Before clinical studies can be undertaken, a well-controlled animal study is required to demonstrate primary safety and long-term device functionality [26], alongside biosafety assessments such as cytotoxicity testing [27]. Although translatability of outcomes in an animal model to the clinical setting can be questioned, funding agencies will typically require a signal that improved outcomes may be achieved prior to allocating large amounts of funding to such a project. Importantly, these studies demand that devices be manufactured in a controlled and standardised manner, with full traceability of components and processes [27], [28]. This, in turn, often results collaboration with a certified medical device manufacturer and adherence to stringent quality management systems.

The financial requirements for this stage of development are substantial, and the academic setting alone is not equipped to meet the regulatory, technical, and operational demands of taking a high-risk implantable device such as the Dynamic AVF through to clinical translation. To address this gap and advance the device toward market approval, a start-up company has been established to continue development, secure funding, and initiate the necessary regulatory and clinical pathways: XS Innovations. However, academia must remain involved as centres will be necessary to perform clinical studies, and results will ideally be independently published in peer-reviewed journals. This may then serve as an example of how academia and industry can work together to bring clinical innovation to patients through scientifically grounded and patient-centred development.

Dialysis cannulas

Addressing flow-related complications in the VA itself received a lot of a attention both in this dissertation and in literature. However, cannulation of the VA may also be considered a primary issue for haemodialysis patients. The large, 15G (1.65mm outer diameter) cannulation needles used have remained relatively unchanged. They are associated with considerable pain and the formation of aneurysms, leading to both functional deterioration and adverse cosmetic outcomes [29]. These sizes are needed to reach efficient blood flows over the haemodialysis circuit. The discrepancy in AVF and needle size, however, results in frequent miscannulations [30] which are stressful events for dialysis nurses. Moreover, miscannulations result in bleeding complications, extended dialysis ward stays and missed dialysis sessions [31]. These effect are exacerbated by the widespread adoption of maturation criteria that accept 4mm diameter veins, compared to the previously used 6mm [2], [32].

Finally, miscannulations damage the AVF wall resulting in blood vessel narrowing that leads to dysfunction requiring painful interventions [33]. A smaller cannulation needle could significantly improve patient comfort and increase successful first-time punctures, reducing damage and discomfort from miscannulations. However, the dialysis machine's required blood flow necessitates large lumen [34], [35], which means the needle size must be increased before connection. A new type of cannula or needle could be developed that allows a small insertion diameter while enabling a sufficiently large lumen for sufficiently high blood flow to and from the dialysis machine.

The interdisciplinary team that developed the Dynamic AVF (Chapters 6 and 7) contains a large number of the skillsets necessary to develop such and innovation and bring it from bench to bedside. Following the extensive collaboration between clinicians in an academic hospital and engineers in a technical university, funding has been secured to develop a new and cost-effective dialysis cannula that can increase the lumen from a small insertion diameter to one that enables flow rates that are adequate for centre haemodialysis.

Home haemodialysis

Whereas this dissertation primarily focused on improving VA for in-centre haemodialysis, the insights and technologies developed may also contribute to facilitating home haemodialysis, an area of growing clinical and societal interest. In home haemodialysis, patients typically dialyse during the night which allows more time to filter blood as they are not bound to hospital visits [36], but it requires patients to self-cannulate. Home haemodialysis offers several potential benefits over conventional in-centre therapy, including improved patient autonomy, better quality of life, and in some cases, superior clinical outcomes due to more frequent and flexible treatment schedules [36]. Reducing the number of hospital visits, which is in part being made possible by the increased availability of monitoring systems, also contributes to cost savings in healthcare systems [37], [38]. However, it requires a lot of autonomy from patients. Adoption of home haemodialysis thus remains low in countries such as the Netherlands [39], in large part due to concerns around patient safety, complexity of self-cannulation, and the fragility of the VA.

These concerns may in part be combated by a device like the Dynamic AVF. Removing the high VA flow prior to removal of the cannulas would greatly reduce the risk of bleeding complications, which have a beneficial effect of the ability of patients to self-cannulate. This will require patients to be sufficiently autonomous to control their implant themselves which may be established through proper design and usability studies that include patients themselves. However, if this can be achieved, the Dynamic AVF may make home haemodialysis more attractive for patients than it is today.

In parallel, the development of a novel cannula with a smaller insertion diameter, as outlined in the previous section, could directly address one of the major barriers to patient uptake of home haemodialysis: fear of self-cannulation. The current standard 15G needles are associated with significant discomfort and a steep learning curve, discouraging patients from initiating or continuing home therapy [37]. A redesigned needle system that allows easy

insertion with minimal pain, yet expands to accommodate the high flow rates required for haemodialysis, could significantly reduce the psychological and physical burden associated with cannulation. This, in turn, may increase patient willingness to consider and maintain home-based therapy.

8.5 Concluding remarks

ESKD patients remain dependent on haemodialysis due to a lack of alternative treatments and insufficient donor kidneys. VA is their lifeline. Therefore, these patients continue to be burdened by high complication rates and frequent interventions to maintain patency of their VA. There is a lot of room for improvement, which medical devices could potentially fill. A device was developed that can open the high-flow conduit only during dialysis sessions. Based on the current understanding of VA, this strategy holds promise. However, it is subject to a lot of development risk and long lead-times before it can meaningfully benefit any patient. Interdisciplinary teams with expertise in every relevant aspect of medical device development is of paramount importance to ensure all requirements from all users are considered and met. Advancing vascular access for haemodialysis thus requires sustained interdisciplinary collaboration, where clinically grounded innovation is systematically developed, validated, and translated into practice to deliver tangible benefits for patients with ESKD.

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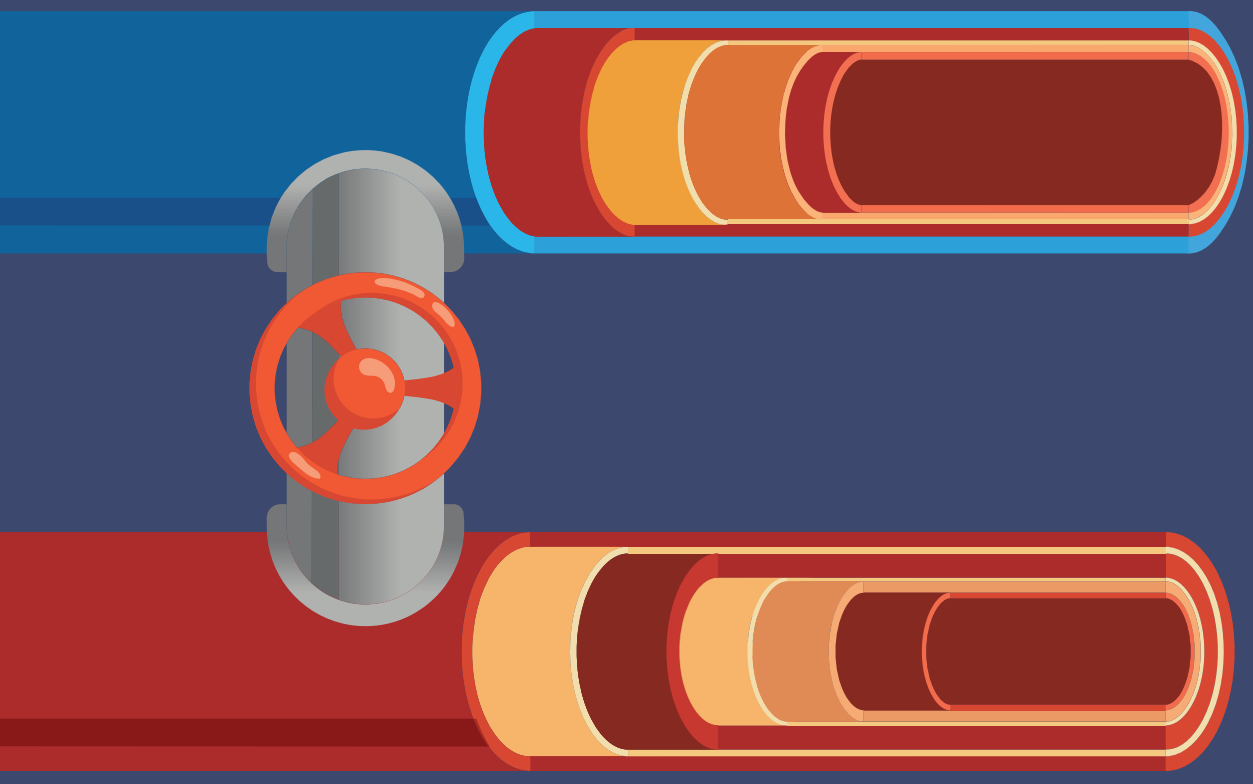

Acknowledgments

Curriculum Vitae Nicholas Andrew White

Acknowledgments

Rotterdam, 15 October 2025

In a few weeks, my work will be in print, and in two months, I will be defending my PhD. As I near the completion of my dissertation, I find myself reflecting on the past five years.

It was October 2020, and I was in the middle of my MSc thesis. I distinctly remember telling everybody around me that I had zero interest in pursuing a PhD. “Why waste 4 years of my life on a niche topic, stuck in a lab and burdened with stress 24/7?” Until then I had not even considered a real option. Then I got the question from my supervisors, Joris and Tim, if I wanted to continue my MSc research in a PhD. This caught me somewhat by surprise, but I knew I enjoyed the topic. After some fierce internal debate, fuelled by some positive stories of other PhD candidates, I ended up deciding to just give it a go.

Looking back, this was perhaps one of the best decisions of my life. Despite the occasional, and somewhat inevitable, stress, I have thoroughly enjoyed establishing myself as a researcher. However, I feel even more thankful for the opportunities it has given me to develop in a myriad of skills I could not have anywhere else. Most of all though, I am grateful to all the people I have had the pleasure of meeting and working with along the way. In my opinion, these contributed most to this experience.

First and foremost, I would like to thank my promotors, Tim, Joris and Jenny. It has now been 6 years since I first connected with you, and the end of my PhD marks just another milestone in our collaborative effort. **Tim**, your design philosophy and enthusiasm will resonate with me for the rest of my career. The countless brainstorming sessions, your experience in medical device design, and the constant source of new ideas have helped me greatly in achieving this milestone. **Joris**, your inexhaustible enthusiasm for improving patient outcomes and quality of life remains an inspiration to me. Despite having a background in mechanical engineering, with your guidance I feel like I have almost become a nephrologist by association. Both of you, thank you for encouraging me to start this project in the first place, and thank you for your excellent mentorship along the way. **Jenny**, although you remained slightly more in the background throughout this period, you always managed to provide me with valuable input at the right times. Not only on the content of my PhD, but also in your general concern for my wellbeing. Your career is a source of inspiration for me.

To the members of my doctoral committee, **prof.dr.ir. F.J.H. Gijsen, prof.dr. J.F. Hamming, dr.ir. A.I.P.M. Smits, and dr. C.Y. Wong**, thank you for taking the time to review my dissertation, provide feedback, and for being a part of this promotion ceremony.

Koen, though you are not part of my formal promotion committee, your involvement and commitment have been invaluable. To me you have been a continuous source of support, and it fascinates how you remain calm when things inevitably do not go as planned. I very much look forward to extending our collaboration in the coming years. **Adam**, your strong opinions and insights have often proven to be remarkably correct, even when they may have frustrated me. Your feedback and input have been not only valuable but also enjoyable.

Early in my PhD I was lucky enough to start developing prototypes. This allowed refine the design and device from the outset. This would not have been possible without the help of the LUMC workshop, specifically **Joric and Huybert**, for which I am very thankful.

Additionally, I have spent many hours at the GDL in Utrecht conducting studies. Thank you to **Evelyn, Joyce, Marlijn and all the caretakers** for always being fun to work with and helpful, patient and responsive when unexpected issues occur. Of course I also cannot forget lab animals that were included in research presented in this dissertation, without which developing an implant would not be possible.

At the LUMC I also had the privilege of collaborating with colleagues dedicated to improving vascular access for haemodialysis. **Eduard, Gelisa and Margreet**, your expertise in the surgical, practical, physiological and clinical aspects of vascular access were very valuable to me. You have taught me a lot and are a pleasure to work with.

Having started this PhD during the COVID pandemic, the first months were unfortunately quiet at the universities – and at times even lonely. Luckily, lockdowns eased and people found their way back to the labs. Having experienced a period without colleagues made me appreciate even more the value of having people around to discuss ideas and complain about things over many cups of coffee and other types of drinks. Thank you to everyone in the MISIT lab: **Arjo, Daniel, Jan-Willem, Kim, Koen, John, Lorenzo, Marit, Nick, Robin, Roos and Sara**, and thank you to everyone else in the **BMechE department**. Our Rotsjes Friday meetings with **Made, Novella, Sabine, Suzanne and Zhuotao** were always fun and useful, and something to look forward to. And also thank you **Bernard, Loïs, Roel, Rosalie, Wouter** and anyone else in the **Nephrology department** I may be forgetting for making me feel at home.

Towards the end of my PhD, I was fortunate enough to found a start-up company to further develop the Dynamic AVF. Although it has been quite overwhelming at times, I also appreciate the plethora of learning experiences it provided me with. Paramount to this are of course those tirelessly putting in the effort to bring this project forward: **Alexandra, Esther, Maaike, Ruairi and Toon**, I am very happy to have you on board and still learn lots from you daily. I also want to express my gratitude to our investors–**FIRST Fund, Medtech TTT, UNIIQ, Delft Enterprises, Libertatis Ergo Holding, Graduate Entrepreneur Fund and NWO**–for their financial support and faith in the Dynamic AVF.

In these acknowledgments I can of course not forget my family and friends, who have supported me throughout and provided me with the necessary fun and distraction. **Jackie and Renzo**, thank you for remaining such good friends through all the phases of life we have now passed. **Derek**, thank you for all the numerous evenings cooking together and sharing good wine and conversations. Your passion never ceases to amaze me. **Sjoerd**, I am glad to have you as such a stable and reliable friend despite me successfully fending off all your attempts to recruit me in the navy. **Frank, Joost, Lars, Lars, Sam, Thomas and Thomas**, having known you so long it is inevitable to eventually see less of each other. However, when we do get together, I am happy that it always immediately feels like the old times. **Alexander, Bas, Bob, Freddy, Laurens, Maurits, Max, Michiel, Paul, Philip, Pim, Quinten and Simon**, thank you for the many fun moments we have experienced throughout the years. Coming together as a group is always something I look forward to and enjoy. **Marie-José, Georges, Pauline, Aymeric, Emilie, Baptiste, et aussi Julie et Pol**, merci pour tous les bons moments passés ensemble. Je me sens chanceux d'être accueilli dans votre famille. **Pat, Jackie, Phong, Michael, Anthony, Sally, Richard, Elaine and Patrick**, thank you for your kindness and encouragement over the years. Your support has been a reminder that family is always there, even from a distance. **Pedram**, I am glad that you have also become a part of the family. Your enthusiasm and optimism are always uplifting. **Emma and Dorus**, thank you for always being

there to be a listening ear or just to have fun. I am happy to have by my side during my defence and play a part in the special occasion. I feel lucky to have you. **Mum and Dad,** thank you for your unwavering support throughout my academic journey. Your belief in my potential and concern for me has felt like I have never been in it alone. Thank you for always being there for me. I would not be the person I am today without you. And finally, **Clémence**, having met you right at the start of my PhD, it has always felt like I did it together with you. Thank you for always being there for me, for sharing both highs and lows, celebrating milestones-both big and small–and for your endless support.

Curriculum Vitae
Nicholas Andrew White

14-10-1996	Born in Voorschoten, The Netherlands

Work Experience

Sep 2025 – present	Researcher at **LUMC**, Leiden
Jul 2024 – present	Co-Founder & Lead Engineer at **XS Innovations**, Leiden
May 2021 – Jun 2025	PhD Candidate at **TU Delft**, Delft and **LUMC**, Leiden
Sep 2022 – Jul 2024	Chair at **Young Medical Delta**, Delft

Education

Sep 2018 – Feb 2021	**MSc Mechanical Engineering**, Biomechanical Design track at TU Delft, Delft (cum laude)
Aug 2017 – Jan 2018	**Minor Exchange Program Biomechanical Engineerin**g at KTH Royal Institute of Technology, Stockholm
Sep 2014 – Jun 2017	**BSc Mechanical Engineering** at TU Delft, Delft
Sep 2008 – May 2014	**VWO Gymnasium** at Stedelijk Gymnasium, Leiden

Conferences (speaker)

Vascular Access Society Conference, Padova, Italy (2025)

Int. Society for Applied Cardiovascular Biology Conference, Vienna, Austria (2024)

Int. Society for Medical Innovation and Technology Conference, Cáceres, Spain (2024)

Int. Society for Medical Innovation and Technology Conference, Lukang, Taiwan (2023)

European Society for Artificial Organs Conference, Bergamo, Italy (2023)

Vascular Access Society Conference, Porto, Portugal (2023)

Dutch Biomedical Engineering Conference, Egmond aan Zee, The Netherlands (2023)

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Awards

Winner NWO Venture Challenge (Fall 2023 edition)

Young Investigator Award (Society for Medical Innovation and Technology Conference, 2023)

Best Oral Communication (Vascular Access Society Conference, 2023)

Grants and funding

Kolff+ Creativity Grant, Dutch Kidney Foundation (EUR 120k, innovative dialysis needle)

Convertible loans: UNIIQ, FIRST, Thematic Technology Transfer (EUR 1.1M, XS Innovations)

Thematic Technology Transfer MedTech (EUR 20k, DAVF)

Dutch Research Council (NWO) Take-Off 2 (EUR 250k loan, XS Innovations)

Winner Dutch Research Council (NWO) Venture Challenge (EUR 25k, DAVF)

Dutch Research Council (NWO) Take-Off 1 (EUR 40k, DAVF)

Scientific Output

White, N. A., Oude Vrielink, T. J., van der Bogt, K. E., Cohen, A. F., Rotmans, J. I., & Horeman, T. (2023). Question-based development of high-risk medical devices: A proposal for a structured design and review process. *British Journal of Clinical Pharmacology*, *89*(7), 2144-2159.

White, N. A., van der Kroft, S. L., van der Bogt, K. E., Oude Vrielink, T. J., Camenzuli, C., Calleja-Agius, J., Sánchez-Margallo, J.A., Sánchez-Margallo, F.M., van de Stadt, H.J.F., Dankelman, J., Rotmans, J.I., & Horeman, T. (2024). An implantable magnetic drive mechanism for non-invasive arteriovenous conduit blood flow control. *IEEE Transactions on Biomedical Engineering*. *71*(8), 2379-2390.

Xiao, Z., Postma, R. J., van Zonneveld, A. J., van den Berg, B. M., Sol, W. M., **White, N. A**., ... & Rotmans, J. I. (2024). A bypass flow model to study endothelial cell mechanotransduction across diverse flow environments. Materials Today Bio, 27, 101121.

White, N. A.[‡], Xiao, Z.[‡], de Winter, E. P., Li, M., De Vries, M. R., van der Bogt, K. E., & Rotmans, J. I. (2024). Hemodynamic considerations in arteriovenous vascular access modalities for hemodialysis. *The Journal of cardiovascular surgery*. 2025 Feb;66(1):3-16

White, N. A., van der Molen, A. J., Limpens, R. W., Maas, J. J., van der Bogt, K. E., Horeman, T., & Rotmans, J. I. (2024). In vitro safety of power injection of contrast media through central venous hemodialysis catheters. *The Journal of Vascular Access*, 11297298251333014.

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