Clinical aspects of Arteriovenous Fistula use in a haemodialysis population

Results based on retrospective and interventional studies

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Gothenburg 2021

Cover illustration: Anna Wärme 2020

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ISBN 978-91-8009-180-0 (PRINT)
ISBN 978-91-8009-181-7 (PDF)
http://hdl.handle.net/2077/68316

Printed in Borås, Sweden, 2021
Printed by Stema Specialtryck AB

Patience…

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ABSTRACT

When a patient suffers from end stage renal disease, the vascular access becomes the lifeline to perform regular haemodialysis (HD) treatment. The recommended first choice is the surgically created native Arteriovenous Fistula (AVF). The AVF is exposed for repeated needling when connecting the dialysis machine several times a week. The AVF patency is limited caused by stenosis, aneurysm, and infections. This requires additive interventions, in-hospital care, and sometimes abandonment of the AVF. The effect of access complications is uraemia progression, which jeopardizes patient survival. The overall aim of this thesis was to evaluate risk factors associated with AVF complications, and to analyse interventions that might prevent AVF dysfunction.

Far Infrared illumination (FIR) is an unrecognized method used by a few centres as an attempt to improve AVF flow. Study I was a prospective study that included 30 patients with a native AVF in the forearm with the patient as his/ her own control. The primary aim was to evaluate if one single treatment with FIR of the AVF changed AVF blood flow (BF) velocity, diameter, or inflammatory markers. FIR increased BF velocity of the AVF from 2.1 to 2.3 m/s ($p=0.02$). The diameter of the arterialized vein increased from 0.72 to 0.80 cm ($p=0.006$). The change in AVF blood characteristics correlated with plasma-urate ($p=0.004$) and serum-orosomucoid levels ($p=0.005$).

In Study II, the primary aim was to evaluate conditions that might lead to a dysfunctional AVF in a retrospective study of patients in regular HD treatment (33 Cases with AVF dysfunction, 33 Controls without) during a two-year follow-up. Cases had higher weekly doses of Erythropoiesis stimulating agent (ESA) than Controls both before (mean 8312 vs 4348 IU/w, $p=0.005$) and after (7656 vs 4477 IU/w, $p=0.018$) radiological AVF investigation/follow-up.

In Study III, the primary aim was to evaluate to what extent end-stage renal disease (ESRD) was related to a specific diagnosis, and how radiological intervention affected the AVF dysfunction. This was a retrospective study of 174 patients with clinically suspected dysfunction of the AVF. AVF venous stenoses were most frequent and were located mostly close to the anastomosis and less frequent at the puncture sites. Arterial stenosis was significantly more frequent among patients with diabetic nephropathy ($p<0.001$) and interstitial nephritis ($p<0.001$).

In Study IV, the primary aim was to determine risk factors that could explain the occurrence of AVF dysfunction. This was a retrospective analysis of 205 HD patients from two hospitals. The main finding was a higher weekly dose of ESA among Cases with AVF dysfunction versus Controls without dysfunction (median 8000 vs 5000 IU, $p<0.001$). In patients with DM, HbA1c was higher among Cases than Controls (50 vs 38 mmol/mol, $p<0.001$).

In conclusion, the AVF patency among HD patients is limited. Risk factors for AVF dysfunction are high doses of ESA and iron and for arterial lesions those with diabetic nephropathy and interstitial nephritis. FIR light may improve the maturation and patency of the AVF as prevention, and readiness for repeated radiological interventions helps to prolong AVF patency.

Keywords: Haemodialysis, AV Fistula, Far Infrared, Erythropoietin

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SAMMANFATTNING PÅ SVENSKA

Patienter med terminal njursvikt som behandlas med bloddialys (HD) är helt beroende av en fungerande anslutning- 'livlina'- till blodcirkulationen. Den bäst lämpade är ett kirurgiskt konstruerat blodkärl benämnd Arteriovenös Fistel-AVF. Fisteln utsätts för upprepade punktioner flera gånger i veckan, då dialysmaskinen ansluts till blodcirkulationen via ett speciellt slangsystem. Hållbarheten av en AVF är begränsad beroende på uppkomst av till exempel förträngning, försvagad kärlvägg eller infektion. Detta medför ytterligare ingrepp, sjukhusvård och ibland byte till annan typ av access. Följden av otillräcklig AVF funktion är fortskridande urinförgiftning, vilket äventyrar patientens överlevnad. Dock är möjligheten till icke-invasiva åtgärder för att förbygga komplikationer fortfarande begränsad. Syftet med denna avhandling är att utvärdera omfattning och typ av komplikationer som ger upphov till försämrad funktion samt utvärdera åtgärder för att förhindra AVF dysfunktion.

Studie I är prospektiv, där 30 patienter med en nativ AVF inkluderades. Syftet var att utvärdera effekten av en infraröd (FIR) behandling över AVF med avseende på blodflöde, kärldiameter och inflammationsmarkörer. Patienten var sin egen kontroll med analyser före och efter FIR behandling. AVF flödet mättes med ultraljud och blodprover analyserades. En FIR behandling ökade flödeshastigheten i fisteln från 2.1 till 2.3 m/s, ($p=0.02$). Diametern av den arterialiserade venen ökade från 0.72 till 0.80 cm, ($p=0.006$). Ett förbättrat blodflöde av FIR kunde kopplas till högre urinsyra i plasma, ($p=0.004$) och serum-orosomukoid nivå ($p=0.005$).

I studie II jämfördes retrospektiva data från 66 patienter fördelade på två grupper i regelbunden hemodialys under en tvåårsperiod. Syftet var att utvärdera vilka faktorer som kan leda till AVF komplikationer. HD patienter med AVF problem erhöll högre veckodoser (IU) av Erytropoes stimulerande läkemedel (ESA) än HD patienter utan AVF problem både före, (medel 8312 resp. 4348 IU, $p=0.005$) och efter intervention av AVF (7656 resp. 4477 IU, $p=0.018$).

Syftet med Studie III var att utvärdera hur bakomliggande diagnos och intervention påverkade AVF funktion. Retrospektiva data inklusive radiologiska undersökningar av AVF analyserades. Förträngning nära anastomosen i AVF var vanligaste problemet och därefter förträngning vid respektive punktionsställe. Arteriell stenos var vanligare ($p<0.001$) hos såväl patienter med DM och interstitiell nefrit. Perkutan angioplastik av AVF utfördes oftare hos patienter med diabetesnefropati.

I delarbete IV studerades retrospektiva data avseende HD patienter med respektive utan AVF problem. 205 patienter från två sjukhus inkluderades. En högre veckodos av ESA sågs hos de med AVF dysfunktion (median 8000 resp. 5000 IU, $p<0.001$). Dessa patienter erhöll också högre veckodoser av järn intravenöst före intervention (median 50 resp. 25 mg, $p=0.004$). Bland patienter med DM var HbA1c värdet högre hos fallen än kontrollerna (50 resp. 38 mmol/mol, $p<0.001$).

Sammanfattningsvis kan konstateras att hållbarheten av AVF hos HD patienter är begränsad beroende på både medicinska och kirurgiska faktorer. Förutom kirurgiska åtgärder finns ett behov av ytterligare icke-invasiva åtgärder, som exempelvis FIR ljus för att förbättra utmognad och hållbarheten av AVF. För att ytterligare förlänga hållbarheten kan strategier för anemi och diabetes förbättras.

LIST OF PAPERS

This thesis is based on the following studies that are referred to in the text by their Roman numerals.

I. Hadimeri U, Wärme A, Stegmayr B. A single treatment, using Far Infrared light improves blood flow conditions in arteriovenous fistula. Clin Hemorheol Microcirc. 2017;66(3):211-217. doi:10.3233/CH-170254.

II. Wärme A, Hadimeri U, Hadimeri H, Nasic S, Stegmayr B. High doses of erythropoietin stimulating agents may be a risk factor for AV-fistula stenosis. Clin Hemorheol Microcirc. 2019;71(1):53-57. doi:10.3233/CH-180381.

III. Hadimeri U, Wärme A, Nasic S, Fransson SG, Wigelius A, Stegmayr B. Angiography and phlebography in a hemodialysis population: A retrospective analysis of interventional results. Int J Artif Organs. 2019 Dec;42(12):675-683. doi:10.1177/0391398819863429.

IV. Wärme A, Hadimeri H, Nasic S, Stegmayr B. The association of erythropoietin-stimulating agents and increased risk for AV-fistula dysfunction in hemodialysis patients. A retrospective analysis. BMC Nephrology, 22 Article number 30:(2021). doi:10.1186/s12882-020-02209-6.

Figures 9,10,13,14,15,17,19,20,23 and 24 from our clinic with permission.

CONTENT

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme Inhibitor
ADPKD	Adult Dominant Polycystic Kidney Disease
ARB	Angiotensin II receptor Blocker
ASA	Acetyl Salicylic Acid
AVF	Arteriovenous Fistula
AVG	Arteriovenous Graft
APTT	Partial Thromboplastin Time
BMI	Body Mass Index
BF	Blood flow
BH	Buttonhole
BP	Blood Pressure
CCB	Calcium Channel Blockers
CAC	Coronary Artery Calcium
CDC	Central Dialysis Catheter
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRBI	Catheter-Related Bloodstream Infection
CRP	C reactive Protein
CRRT	Continuous Renal Replacement Therapy
CT	Computed Tomography
CVD	Cardiovascular Disease

DM	Diabetes Mellitus
DOPPS	Dialysis Outcomes and Practice Patterns Study
DUS	Doppler Ultrasound
eNOS	endothelial Nitric Oxide Synthase
EPO	Erythropoietin
ESA	Erythropoiesis Stimulating Agent
ESRD	End Stage Renal Disease
ESVS	European Society of Vascular Surgeons
FIR	Far Infrared light
FTM	Failure to Mature
G	Gauge
GFR	Glomerular Filtration Rate
GN	Glomerulonephritis
HD	Haemodialysis
HF	Haemofiltration
HHD	Home Haemodialysis
HIF	Hypoxia Inducible Factor
HO-1	Heme oxygenase
ICU	Intensive Care Unit
KDIGO	Kidney Disease: Improving Global Outcomes
LMWH	Low Molecular Weight Heparin
MRI	Magnetic Resonance Imaging

NH	Neointimal Hyperplasia
OR	Odds Ratio
ORM	Orosomucoid
PAD	Peripheral Artery Disease
PD	Peritoneal Dialysis
PICC	Peripherally Inserted Central Catheter
PTA	Percutaneous Transluminal Angioplasty
RBV	Relative Blood Volume
RC	Radio-cephalic
RCT	Randomized Controlled Trial
RRT	Renal Replacement Therapy
SNR	Swedish Renal Registry
TX	Transplantation
US	Ultrasound
USRDS	US Renal Data System
VCS	Vena Cava Superior
VA	Vascular Access

1 INTRODUCTION

Renal insufficiency can be acute or chronic. If the condition is severe with a remaining of 5-10% of normal function, the patient will need dialysis to survive. In acute instances, such dialysis is mainly performed by continuous renal replacement (CRRT) or intermittent haemodialysis (HD) technology using a double lumen CDC as access for blood. In the chronic situation, besides intermittent HD, peritoneal dialysis (PD) and transplantation (TX) are frequent alternatives, depending on age and local practise. In this Thesis, I will focus on chronic HD as the dialysis technique, and especially on the peripheral vascular access (VA) - lower arm arteriovenous fistula (AVF), which is recommended as the blood access for HD. Thereby the VA becomes the lifeline to perform regular HD. In Sweden, of the approximately ten thousand patients with ESRD, 30% receive intermittent chronic HD several times a week, whereas 60% are transplanted and 10% perform PD (Stendahl 2019).

1.1 ANATOMY AND PHYSIOLOGY

The kidneys are bean-shaped paired organs approximately 11 cm long and are situated in the abdominal cavity on each side of the vertebral column and partly covered by the lower ribs. Each kidney receives oxygenated blood via one artery from the abdominal aorta, which in turn is divided into several branches of smaller arteries that penetrate the kidney. The kidneys receive more than 1 L/min of blood with the person at rest. This constitutes approximately 20% of the total volume of blood circulation.

The distinct parts of the kidneys are the cortex and the medulla that consist of glomeruli as well as the different parts of the winding tubular system and collecting ducts. The system eventually leads the urine to the pelvic region of the kidney where the ureters transport the final urine to the bladder. Each kidney is comprised of approximately 1 million nephrons – denoted the 'functional unit' of the kidney. The nephron consists of small blood vessels that are subdivided from the greater vessels into a winding capillary network called glomerulus with specialized properties and cell functions (Figure1).

A B

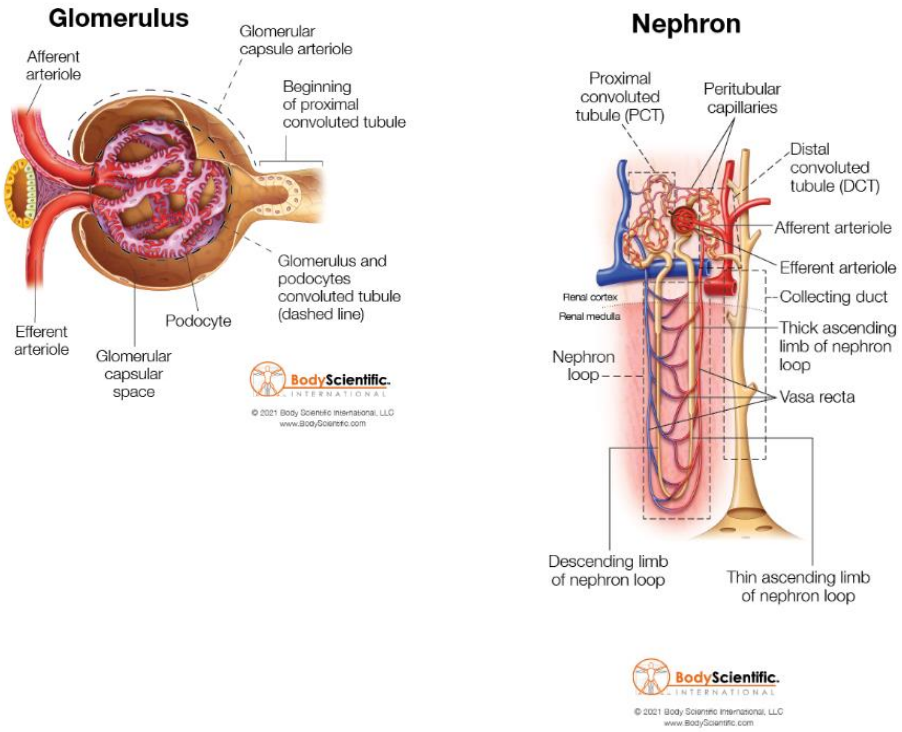


Figure 1. A, The glomerulus and its surrounding interstitial tissue and tubules and B, a nephron – the functional unit of the kidney. With kind permission from Body scientific.

The glomerulus is embedded in the Bowman capsule (a jar-like sac) that collects the primary urine as ultrafiltrate (180 L/day) from the blood circulation. Reabsorption of fluid, salts, and nutrients in the tubular part results in a final volume of urine of approximately 1.5 L/day. The kidneys are important for the homeostasis (inner milieu of the body) for optimal cell function by regulating the following: 1. electrolytes and body water; 2. acid and base balance related to respiration and metabolism; 3. excretion of metabolic waste products and toxins; and 4. endocrine functions such as **a)** the synthesis of erythropoietin (EPO) hormone for erythrocyte formation, **b)** renin and aldosterone to regulate blood pressure (BP), and **c)** conversion of inactive vitamin D into the biologically active form -1,25-dihydroxycholecalciferol- that regulates, for example, the concentration of calcium and phosphate, and promotes the healthy growth and remodelling of bone.

1.1.1 WHAT ARE THE PHYSIOLOGIC DEVIATIONS AND SYMPTOMS IN PATIENTS WITH KIDNEY DISEASE?

Consequences of impaired kidney function are diminished urine production, oedema, and reduced excretion of hydrogen ions leading to acidosis, urea accumulation, hyperkalaemia, anaemia, impaired D-vitamin synthesis, and hypertension. In addition, numerous other metabolites, called uremic toxins, are retained in the body (Vanholder, De Smet et al. 2003). Together, these will cause a progressive worsening into uremic symptoms, and finally death of the patient unless renal replacement therapy (RRT) is initiated. The uremic symptoms can vary considerably between patients ranging from lack of energy, loss of appetite, itching and headache and progressing to severe circulatory collapse with multiorgan failure necessitating ICU care for patient survival.

1.2 EPIDEMIOLOGY AND PREVALENCE

Worldwide, about 5 million people experience kidney failure. However, only a portion of all patients receives dialysis or a kidney transplant to remain alive (Jager, Kovesdy et al. 2019). Even if the availability of RRT is unlimited, the need for dialysis differs considerably between countries, for example, 16 per 10 000 patients in the USA and 4 per 10 000 patients in Sweden (Kimata, Tsuchiya et al. 2015, Stendahl 2019, USRDS 2020).

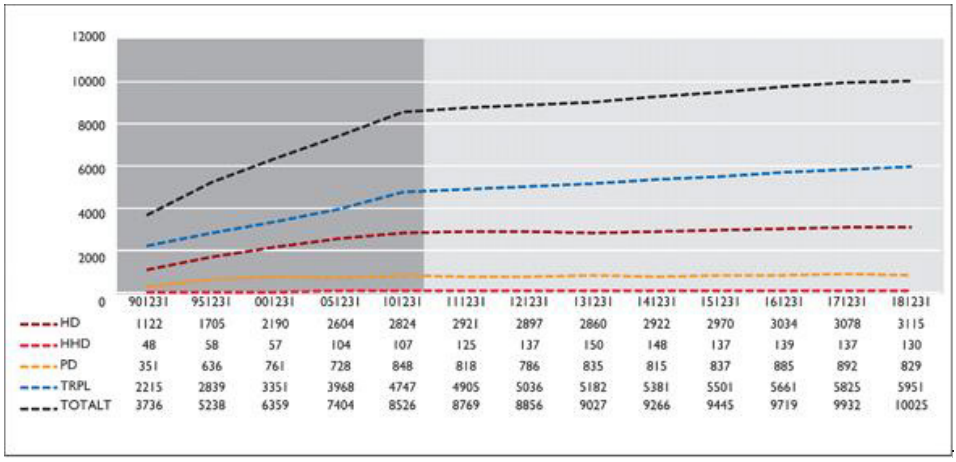


Figure 2. Distribution of patients with ESRD in Sweden over the years from 1990. The blue line represents those with a transplant kidney, red for HD, yellow for PD, and orange for home HD. The numbers can be related to a population of approximately 10 million to give an estimate of prevalence. With permission from SNR.

1.2.1 DISEASES LEADING TO RENAL FAILURE

In Sweden, the approximate prevalence of patients with diabetes mellitus is 0.5 million and hypertension 1.5 million. Fortunately, just a small proportion develop ESRD (Figure 2). Still, these are the most common diseases in Sweden that lead to kidney failure. Other less frequent diseases are glomerulonephritis (GN) of autoimmune origin, genetic, such as those with polycystic kidney disease (ADPKD) with successive enlargement of the kidneys and Alport disease (Figure 3). Others are those with inborn errors of protein function that contribute to chronic mineral disturbances. In addition, numerous patients suffer from urological and outflow obstructive diseases such as tumours engaging the kidney, prostate and urinary tract (Stendahl 2019).

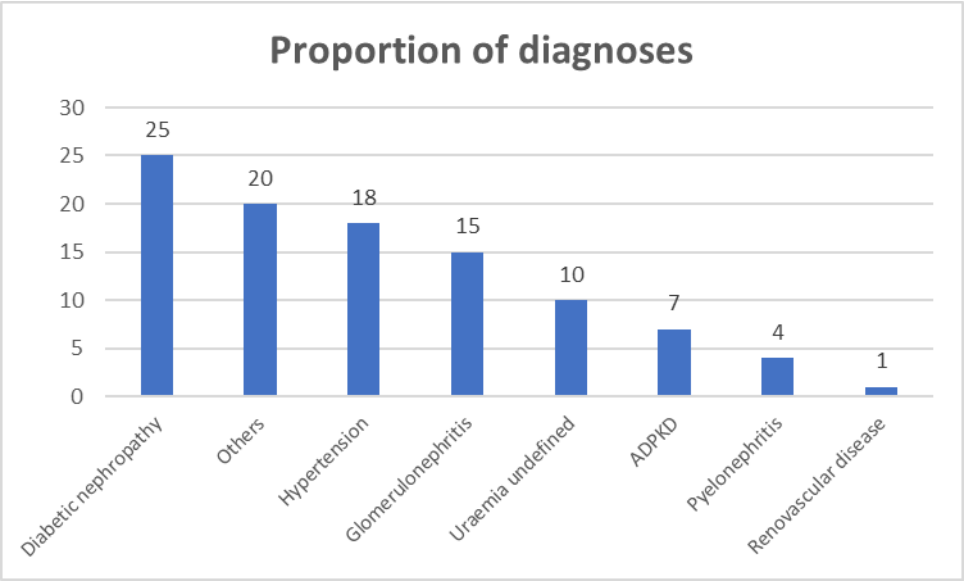


Figure 3. Proportion of diagnoses causing ESRD in HD in Sweden 2018. With permission from SNR.

1.2.2 CHRONIC KIDNEY DISEASE IS DIVIDED IN 5 STAGES DUE TO SEVERITY

One estimate of kidney function and the efficacy of the glomeruli to filtrate waste products (GFR, glomerular filtration rate) is the ability to clear waste products from the body (Clearance) with a normal value of 90-120 ml/min adjusted to a body surface area of 1.73 sqm. However, even at a normal GFR, kidney disease may be present with findings of proteinuria and/or haematuria that will be classified as G1 in accordance with Table 1. A less obvious finding

may be extreme hypertension that may cause severe subjective side effects and symptoms. In the early stages, this may only be visible by kidney biopsy or radiological investigations. Table 1 presents an overview of different grades of chronic kidney disease (CKD), mainly related to the clearance abilities of the kidneys.

Table 1. Grades (G) of kidney clearance function given as estimates of GFR, (ml/min and related to body surface area of 1.73 sqm).

Grade	Definition	Clearance
	Normal or high	90-120
G1	Normal or high* with proteinuria or haematuria	90-120
G2	Mild decrease	60-89
G3a	Mild -> moderate decrease	45-59
G3b	Moderate -> severe decrease	30-44
G4	Severe decrease	15-29
G5	Kidney failure	<15 without dialysis
G5D	Kidney failure	<15 with dialysis

*presence of proteinuria and/or haematuria as additional findings as markers for kidney dysfunction. Modified from KDIGO (2012).

1.2.3 TREATMENT OF CHRONIC KIDNEY DISEASE

1.2.3.1 MEDICATION

Medication as supplementation to counteract side effects of and prevent progression of renal insufficiency usually starts early, with a focus to prevent hypertension and metabolic disturbances such as in those with DM nephropathy (Fox, Matsushita et al.). When the patient reaches a GFR below 30-40 ml/min, additional prescriptions are usually given to compensate for endocrine disturbances such as lack of EPO and active vitamin D and secondary hyperparathyroidism besides correction for metabolic acidosis and oedema. This is based on diagnosis and individual prerequisites as well as evaluation of future transplant possibilities (KDIGO 2012). Additional important support to halter metabolic, physical, and mental disturbances is the advice given by dieticians and physiotherapists. In a study evaluated with muscle biopsies, an increase in muscular strength in patients with CKD was achieved after 12 weeks of regular exercise. Regular physical activity prevents anaemia, strengthens the skeleton, and preserves muscular mass, cardiac endurance and pulmonary capacity (Heiwe, Clyne et al. 2005). Thereby,

physical exercise is of great importance, and is recommended at all stages of kidney disease.

1.2.3.2 THE BEST OPTION IS A KIDNEY TRANSPLANT

During the progressive course of CKD, considerations must be made whether the patient is able to undergo a kidney transplant and if a donor is available, or if this is not an option. Although kidney TX is considered the most effective RRT (KDIGO 2012), not all patients can be offered such an alternative due to comorbidities or shortages of donor kidneys. Even if successful, TX ends up in a chronic rejection with approximately 50% of patients back in dialysis within 14 years and waiting for their second or even third graft (Coemans, Susal et al. 2018).

However, patients in most countries start up with dialysis even before TX, and preparations of those conditions are made. Since currently all HD patients need an access connecting the blood circuit with the dialysis system, the alternatives for the access placement must be prepared and discussed. The choice of dialysis will be based on local conditions and skills, but are also limited due to less suitable intraabdominal conditions for PD or problems with blood vessel access for HD after an earlier type of RRT and a progress of atherosclerosis and duration of the disease (Ho, Cho et al. 2016).

1.2.3.3 DIALYSIS

(From the Greek word "dissolution"; from διά, *dia*, "*through*", and λύσις, *lysis*,) dialysis treatment today can be provided by two mainly different techniques. One is by HD in a clinic or at home where the patient's blood is pumped through an extracorporeal hose system and purified through a semipermeable filter. This is by far currently the most common dialysis form worldwide in treating approximately 1.5 million patients (www.usrds.org), (USRDS 2020). Another technique is PD that uses a special dialysis solution intermittently infused and discarded into/out of the abdominal cavity. Blood purification is achieved via the peritoneum and its capillary circulation that act as a semipermeable filter.

1.2.3.4 HISTORY OF HAEMODIALYSIS

The first dialysis treatment on a human was performed in October 1924 by the German physician Georg Haas. Dialysis was performed for 15 minutes as an attempt to prevent a boy from dying of uraemia. Access to the blood vessels was gained using a glass cannula and Hirudin was used as anticoagulant to prevent clotting of the blood.

The first practical human dialysis machine was developed by W.J. Kolff and H. Berkin in 1943. This was a rotating drum driven by a sewing machine motor connected to a bicycle chain. Tubing systems were made of semipermeable sausage covers and the dialysate was prepared with various salts in an isotonic proportion.

In parallel, a dialysis system was developed by Nils Alwall in Sweden (Figure 4 and 6) who was one of the great Swedish pioneers in dialysis history. His research in the mid1940s focused on kidney physiology and the importance of the glomerulus. Experimental research was conducted in the hospital clinic and workshop on rabbits to imitate the ultrafiltration of the kidney function (separation of body water from waste products) through a semipermeable membrane. On September 3, 1946, Dr Alwall conducted the first HD treatment in Sweden. The vein and artery of a patient suffering from pulmonary disease were surgically exposed and two small cannulas were inserted in the wrist for connecting the vessels to the machine. Heparin was added to prevent blood clotting, and in the morning of the day after, the patient´s condition was improved with less oedema and less urea nitrogen. The treatment lasted for six days with diminished uremic symptoms and nausea.

Figure 4. Dr Alwall with the Dialyser unit. With kind permission from the "South Swedish Society for the History of Medicine".

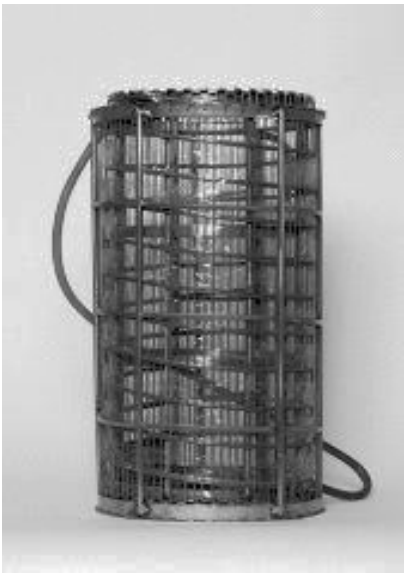


Figure 5. The inner cylinder of Dr Alwall´s first artificial kidney in 1946. With kind permission from the "South Swedish Society for the History of Medicine".

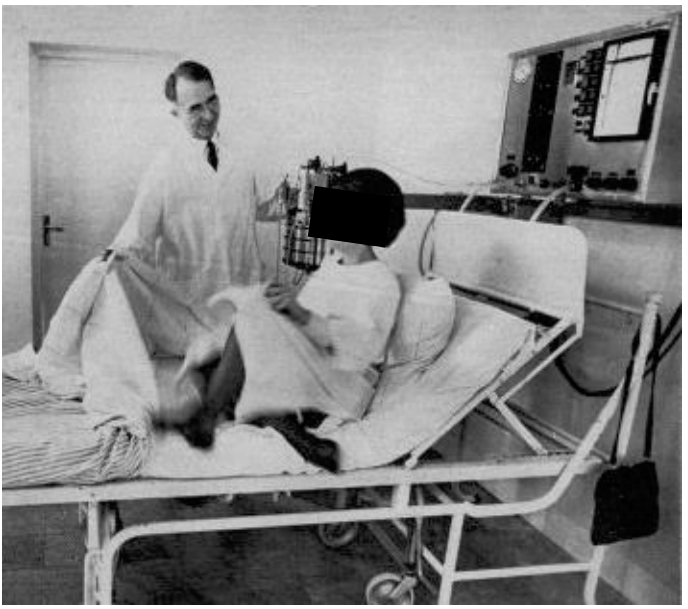


Figure 6. Dr Alwall preparing for dialysis treatment.
With kind permission from the "South Swedish Society for the History of Medicine".

The first HD machine that Dr Alwall developed was with plexiglass from a wrecked bomber plane and cellophane hoses. Later, a steel drum was developed where it enabled removal of excess of fluid from the patient (Figure 5). Thereby, the possibility of ultrafiltration (UF) was introduced using a negative pressure in the circuit (Persson 2015). Physicians working with these issues were confronted with the problem of VA since the vessels they used were only able to maintain function for a short period. Treatment of acute kidney injury was the only option at that time.

1.2.4 PHYSIOLOGIC PRINCIPLES APPLIED DURING DIALYSIS

1. Ultrafiltration is used to transport solubles over a semipermeable filter by the difference in hydrostatic or osmotic gradient. Small water molecules pass through the membrane by solvent drag.

2. Convection is forced fluid movement of BF and dialysate in different directions over the filter. This increases the rate of solute exchange between the blood and dialysate compartments.

3. Diffusion is the spontaneous movement of solutes from a region of higher concentration to that of a lower concentration. Osmosis is the movement of solutes over a semipermeable membrane where the size of the membrane pores also affects the possibility of the solutes to pass. If the molecule contains osmotic properties and is prevented by its size from passing through the membrane, water is partly drawn by an osmotic gradient to the molecule and the compartment where it is located. Transport is possible in both directions.

1.2.4.1 HAEMODIALYSIS TREATMENT TODAY

HD is offered in-centre clinics in a hospital or at home where the patient performs the dialysis. Most patients undergo treatment 12-15 hours/week. The geographic prerequisites can vary with longer distances in some parts of Sweden and may exceed more than 20 hours a week including travelling. The dialysis treatment affects the social, mental, and sexual lives, and the uremic symptoms among different patients vary considerably both before and after treatment. All current HD principles need a blood access for intermittent connection with the ECC. This can be either using an AVF, AVG or permanent CDC that mainly contains a double lumen and is placed in the vena jugularis externa or subclavian vein. The capacity of the AVF, AVG or CDC depends on the blood pump speed (Qb) of the ECC. The Qb varies between 180 ml/min and 450 ml/min depending on the type of HD principle and local preferences.

Intermittent haemodialysis treatment (*IHD)* is initiated when uremic symptoms and electrolyte disturbances increase the risk for morbidity and become life threatening (KDIGO 2012). The principle is based on the exchange of uremic waste products and electrolytes over a semipermeable filter and restoring electrolyte and body water balance. The filter is a plastic tube that contains thin semipermeable hollow fibres where the blood passes within the tubes and on the outside meets ultraclean water combined with adjusted salts-dialysate (Figure 7). During a regular HD session, the total amount of blood passing through the filter may exceed up to 75 litres, and the need for a patent blood access is essential. Since the HD session is 3-6 hours, the quantity of fluid removal from the body, i.e. ultrafiltration of 2-4 litres, may contribute to hypotensive events, which can be ameliorated by a change of sodium concentration and more frequent dialysis (Figure 8). Shorter HD sessions may seem pleasant for the patient from a practical point of view, but a short HD session is also tougher from a physiologic aspect and with subsequent risk for hypotensive events due to volume displacement between body compartments (Figure 9). This may impair AVF BF with a risk for intra-access thrombosis.

In a subgroup analysis of 1426 subjects from the HEMO study, Chang et al (Chang, Paik et al. 2011) showed a significant correlation of hypotension and the increased risk for AVF thrombosis. However, the results were based on a single HD session and lacked complete VA data. This classic HD technique with low flux dialysis membranes is usually performed with a blood pump speed of 180-400 ml/min depending on the global region (Hecking, Karaboyas et al. 2014).

Haemofiltration (HF) (Jackson and Litchfield) is based on convective mass flow by a positive hydrostatic pressure gradient where solutes together with water are driven through a filter into a waste. The demand to accomplish enough pressure infers the necessity to compensate with additive isotonic infusion in parallel to the patient, for the ultrafiltrate. Nowadays, this treatment modality is usually performed in the ICU department, most often via a temporary CDC. Since the BF speed is limited through the catheter, treatment is often provided during several hours in the ICU with a slower fluid removal. On the other hand, the risk for hypotensive episodes is less (Sharma and Waikar 2017). This dialysis technique with high-flux dialysis membranes is usually performed with a blood pump speed of 300-400 ml/min (Hecking, Karaboyas et al. 2014).

Figure 7. A dialyser tube divided to show the amount of fibres. With kind permission.

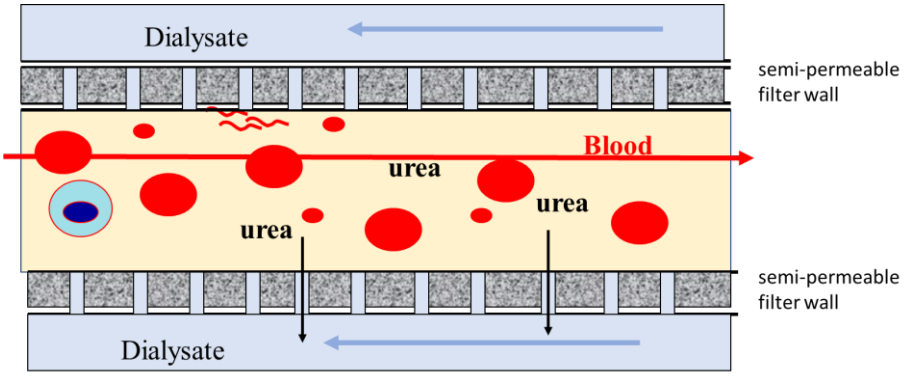


Figure 8. Principles of blood and dialysate exchange of the dialyser tube. With kind permission.

Haemodiafiltration (HDF) (Pecoits-Filho, Larkin et al.) is based on the advantages of both the IHD and HF techniques mentioned above where a higher pressure gradient is accomplished by adding infusion of extra fluid. Small solutes are removed by diffusion and large molecules more effectively by convection. However, there is no convincing evidence that the prognosis of patients is improved by such measures (Grooteman, van den Dorpel et al. 2012, Locatelli, Karaboyas et al. 2018). A high-flux membrane is used to increase efficacy of large molecule substances and convective therapy. This HDF

technique is usually performed with a blood pump speed of approximately 340 ml/min (Locatelli, Karaboyas et al. 2018).

Home haemodialysis treatment (HHD) is performed by the patient at home. The patient is educated to use a suitable machine where water distribution is assessed in accordance to municipality, and appropriate filters and equipment are designed for home use. The advantage of one being able to control and choose when to start, and how frequent and for how long the dialysis session will be is obvious. However, the cognitive and management demands are high on the patient´s ability to perform the treatment independently, unless assisted by a relative or staff. There is a potential risk for mis- and disconnection of hoses and needles where immediate assistance is required. Everyday short dialysis is appealing from the possibility for a more level homeostasis, lower BF rates and water balance (Twardowski 2004). Shorter daily dialysis treatment includes increased frequency of AVF cannulation, which may shorten the AVF patency. In a study by Suri, 332 patients with daily HD had significantly more AVF access repairs than conventional HD during one year, but the abandonment of AVF was similar (Suri, Larive et al. 2013). Results are conflicting since another prospective case control study including 77 patients compared dialysis thrice weekly vs six times a week where such complications were not established. The outcome variable was access procedures in that study (Achinger, Ikizler et al. 2013).

One cannot overlook the possibility of selection bias (younger patient, physically fit and less comorbidity) when choosing HHD. A multidisciplinary approach to optimize conditions was evaluated in 2004 where the patency of the AVF among HHD was not inferior to in-centre patients. Assisted survival from first use-of AV fistula was 90% at 1 year, and 66% at 5 years among 301 HHD patients (Lynn, Buttimore et al. 2004). This home HD technique is usually performed with a low-flux dialysis membrane with a blood pump speed of 180-300 ml/min (Parisotto, Schoder et al. 2014).

Figure 9. Haemodialysis machine.

1.2.5 PERITONEAL DIALYSIS

PD is recommended as the first choice before HD to save VA for the future and to facilitate the opportunity for home treatment and continuous dialysis around the clock if necessary (Chan, Blankestijn et al. 2019). PD is also recommended the first option in young patients when survival with ESRD is expected to be long, thereby saving the blood vessels for later use and cannulation. The access for PD is achieved by a permanent catheter that is surgically placed partly into the peritoneal cavity (Stegmayr, Sperker et al. 2015). The peritoneal membrane is used as a filter for the exchange of water-soluble waste products. Dialysis is achieved after a glucose solution with electrolytes is infused into the peritoneal cavity. After a dwell time of about 4-6 hours, the ultrafiltrate is tapped out through the catheter into a waste bag and thereafter replaced with fresh instilled clean dialysate (Figure 10). Residual renal function is preserved and a more level balance is accomplished regarding water and electrolyte levels (Rocco, Soucie et al. 2000). PD treatment is also a

vital option when the VA alternatives used for HD fail and new options are exhausted. PD can be performed with 1.5–2 litres of manual exchanges 4-5 times/24 hours daily, Continuous ambulatory peritoneal dialysis (CAPD) or using a machine that preferably performs automatic exchanges of approximately 500 ml of dialysis solution/20 minutes over night. The cycler programs vary in exchange volumes and fluid strengths.

Figure 10. PD machine and plastic bag with effluent.

1.3 VASCULAR ACCESS AND HAEMODIALYSIS

Vascular access history. Parallel with the development of the dialysis machine and supplementary medication, the possibility of gaining access to the blood vessels of the patient has been an area full of innovations.

During the beginning of the 1900s, different types of glass tubes were used for cannulation; however, these were rigid, frail and thrombogenic. During the middle of the 1940s, Nils Alwall used rabbits and constructed a short-cut connection using glass and a plastic hose between arteries and veins, also termed, 'AV-shunt'. However, this was difficult to keep open, and therefore a continuous need for heparin to prevent clotting had to be provided (Persson 2015).

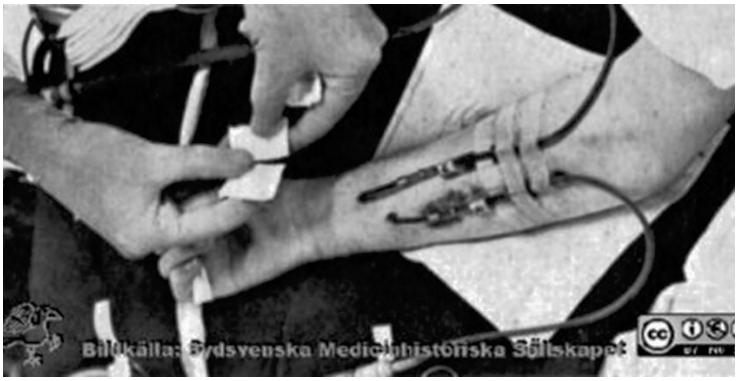


Figure 11. The Scribner shunt. With kind permission from the "South Swedish Society for the History of Medicine".

During the 1950s, progress was made when the Scribner shunt was developed (Bonello, Levin et al. 2004). This was made of Teflon and its reliability was improved over time. Now the patient could use the AV-shunt for several months, and patients with CKD could be offered treatment. Before this, only acute dialysis via a temporary access was possible. Belding Scribner, a medical doctor in Seattle, along with the engineer Wayne Quinton at the University of Washington further developed this idea. Teflon was now used as a new material that prevented clotting, and later, it was changed to flexible silicone (Figure 11). The next ground-breaking step in history was when the physicians Brescia, Cimino and Apell developed the AV-fistula in the mid- 1960s. By surgically ligation, they transposed a cephalic vein to the radial artery of the lower arm by a side-to-side technique. The practice of connecting blood vessels for easier cannulation was developed and applied for creating an access for repeated use. The results were based on 15 operations and was presented in 1966 (Brescia, Cimino et al. 1966). This approach enabled more long-term preservation of an access that was of vital importance for chronic HD patients. Initially, the vessels in the distal area near the wrist and thumb - so-called the "Snuff-box area", were used. By using the patient's own vessels, the risk of

infections decreased, and the use of this access as an alternative has been the recommended first choice ever since. Parallel with this option, the medical improvement resulted in the use of surgical techniques including the possibility to use plastic tubes inserted in the blood circulation. The alternative for the patients with limited blood vessel quality was an arteriovenous inter-positioned shunt made of different synthetic or biological grafts (AVG). The AVG has made it possible to sustain dialysis, especially for the elderly and diabetics with impaired vascular conditions in parallel to general cardiovascular diseases (CVD) that limit the expected time of survival (Olsha, Hijazi et al. 2015).

The third and least preferable access was inserting a permanent tunnelled CDC through either the external or internal jugular veins or through the subclavian vein down through the vena cava superior (VCS) with the tip in the upper part of the right atrium of the heart. The CDC was invented in the beginning of the 1970s and was an important supplement to the vascular option for the HD patient.

If the vascular conditions on the lower-arm are insufficient, upper-arm vessels are used for upper-arm AVF and AVG. The use of the upper-arm vessels has increased over the years in Europe and North America, while in Japan, lower-arm AVFs are used 95% of the time (Pisoni, Zepel et al. 2018). In the future, various new synthetic and biological grafts will enable further alternatives (Stegmayr, Willems et al. 2020). When the vascular options failed, the possibility of dialysis through the CDC became a life-saving alternative (Lok and Foley 2013, Olsha, Hijazi et al. 2015). Occasionally, even this location fails, and then insertion of a tunnelled permanent catheter may be performed in the femoral vein or even the lumbar vein (Gerasimovska, Kitanovska et al. 2016). However, the disadvantage of using the CDC for long-term treatment is the increased risk of local infections with the potential to disseminate via the bloodstream and even cause septic infections and endocarditis (Lok, Bhola et al. 2003, Lok and Foley 2013).

All three methods mentioned above have their pros and cons, yet in some way can be an alternative when the other is not suitable.

1.4 THE PRESENT THESIS FOCUSES ON THE LOWER-ARM AV FISTULA (AVF)

The AV-fistula (AVF) is in normal circumstances cannulated with two separate needles, each one connected with a hose to the extracorporeal circuit and pump-system on the dialysis machine. Via this bloodline system, the blood is pumped from the arterial needle placed in the AVF, through a dialysis filter (dialyser) of the dialysis machine and returned via the second needle to the venous circulation at the arm of the patient. Within the filter, uremic blood meets balanced salt and ultra clean water (dialysate), and there the exchange of waste products into the dialysate as well as removal of excess water (ultrafiltration) occurs. The AVF has limited function and patency because of anatomic, surgical, and medical factors. Different studies have shown one-year patency of 41-70% (Ethier, Mendelssohn et al. 2008, Kazemzadeh GH 2012), and the most common complications are stenosis, infection and dilatation-aneurysm of the vessel (Vascular Access Work 2006). Stenosis is one of the main reasons for impaired dialysis efficacy. Therefore, radiologic and/or interventional examination is common among these patients, which results in prolonged in hospital care and sometimes painful interventions (Leermakers, Bode et al. 2013, Lok and Foley 2013). The need for another access placement to proceed dialysis is often unavoidable (Thamer, Lee et al. 2018).

1.4.1 WHAT ABOUT ACCESS DATA IN SWEDEN?

The largest proportion of patients in HD in 2018 initiated treatment with a CDC (71%). This has remained unchanged during the recent years, and Sweden has not reached the international goal that at least 65% of patients should commence HD with a patent AVF (Stendahl 2019). The initial use of CDC when starting HD varied between different counties and within each county thereby reflecting prerequisites and availability (Figure 12). The prevalence of patients receiving treatment through an AVF is 70%, which indicates creation of an AVF after commencing HD. This can be explained by suboptimal time planning and/or allocation. The physician and planning staff knew more than 80% of patients within the prevalent pre-dialysis population. Therefore, the possibility of pre-HD preparation with a VA could be expected. The guideline for ESVS suggests creation of a permanent access 3-6 months before the planned initiation of HD (Schmidli, Widmer et al. 2018).

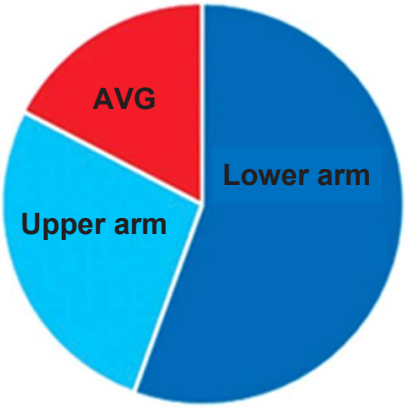


Figure 12. Proportion of the different newly AVF types (n=787), created in Sweden 2018. With kind permission from SNR.

1.4.2 THE GOLD STANDARD IS THE NATIVE AVF

The best and recommended first choice is created by the arterial and venous vessels in the lower arm. According to guidelines, the timely planning for such an AVF is essential, not only for maturation, but also if complications arise such as thrombosis, stenosis, or infection, which therefore can be corrected in advance of initiating HD.

After surgically ligating the distal end of the cephalic vein on the forearm, the upper part of the vein is connected to a small hole created in the artery (anastomosis). This connection makes it possible for a portion of the arterial blood to bypass the distal capillaries and be shunted back directly through the venous side resulting in an artificial vascular fistula. After maturation, for 4-8 weeks, the AVF is ready to use (Schmidli, Widmer et al. 2018). Local physiologic conditions in the vascular wall induce dilatation of the vein, and the effect of shear stress modifies and transforms the endothelium of the inner vascular wall. Access to the HD circuit is possible by using two needles, most often 16 G (inner Ø 1.2 mm), placed in the AVF. The hose is connected to the arterial needle (‘arterial line’), i.e. the AVF section closest to the AVF anastomosis leading blood from the patient. The purified blood is returned to the patient via the second more proximal venous line. Blood pump speed varies between 180 and 400 ml/min, but in Sweden is usually set at 300 ml/min (Figure 13).

The AVF vascular segment has limited patency. A variation exists based study design, type of fistulas used, and patient population. Different studies show a one year-survival of 60-80% (Huijbregts, Bots et al. 2008), (Kazemzadeh GH 2012). Most often stenosis and/or thrombosis occurs and reoccurs, and the patient is subjected to several interventions during the dialysis career (Robinson, Akizawa et al. 2016).

Figure 13. AVF in use connected via two needles to the bloodline circuit.

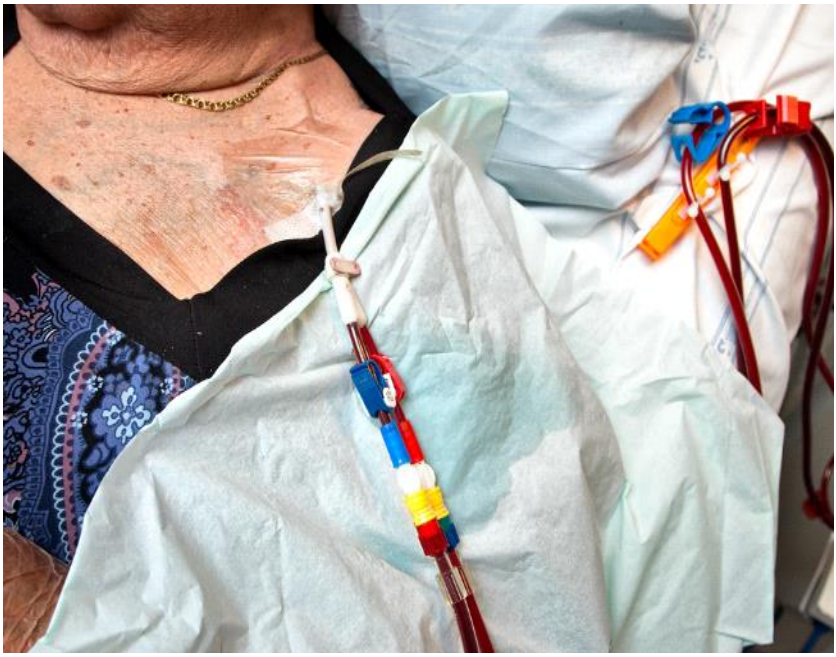


Figure 14. A tunnelled CDC via the left subclavian vein.

The subclavian vein as a VA conduit was introduced in 1961 by Stanley Shaldon. The basis for the 'Seldinger technique', introduced in 1953, was guidewires for indwelling catheters with ultrasound (US) and fluoroscopy for visual positioning guidance in the greater veins of the thoracic region (Seldinger 1953). Later, the use of silicon catheters was developed in the beginning of the 1970s when a coiled silastic tube with Dacron was created.

The CDC tube is divided into two chambers with dual lumen tips of different lengths with small holes on the side. The inflow and outflow of blood through the lumen is separated for less recirculation. The tip is placed in the junction of the superior cava vein and the right atrium of the heart (Figure 14). Principally, two different types are used today – the non-tunnelled (temporary) catheter (CDC) and the tunnelled catheter (TCDC). The temporary CDC is placed through the VCS with an easier technique, however, the risk for infections is higher compared to the subcutaneously guided TCDC (Lok and Mokrzycki 2011).

Advantages of the CDC are the possibility of immediate use in the acute situation and the less surgical manipulation required. Drawbacks are the higher incidence of infections (CRBI) due to foreign material and frailty of patients

that sometimes lead to exit site infection and in the worst scenario bacterial engagement of the cardiac valves leading to endocarditis (Lok and Mokrzycki 2011). Another drawback is the somewhat less dialysis efficacy related to the limited capacity to obtain a higher flow rate through the CDC. This also limits less blood pump speed, and thus the efficacy of dialysis. Besides intra-catheter thrombi and kinks, malposition in the superior cava vein increases the risk for vessel damage. This will lead to central stenosis of the proximal veins with impaired BF to the heart, and fewer future alternatives for peripheral AVF.

Arteriovenous Graft (AVG). The use of AVG began during the beginning of 1970 in parallel with the development of materials, i.e. Gore-Tex® and synthetic biocompatible material such as polytetrafluoroethylene (PTFE). PTFE has become the prosthetic graft of choice. This was another alternative, beside the CVC, to replace the failing autologous VA (Figure 15). It is usually placed as a loop or a straight graft connecting the artery and vein. The use of AVG usually allows a higher blood pump speed than the CDC and therefore allows shorter dialysis for urea reduction and is also considered an easier alternative for cannulation. The time from surgery to start using the AVG for dialysis is shorter, approximately two weeks, which therefore is an alternative to shorten the time for the patient with CDC (Schmidli, Widmer et al. 2018).

However, there are several drawbacks. One is the increased risk for infection caused by the tendency of skin bacteria such as staphylococci that create a biolayer around the AVG (Bachleda, Utikal et al. 2010). One study showed infections in 28.3% of AVGs versus 1.7% among AVFs. The most common agent was Staphylococcus that was detected in more than 85% of the cases where the infected grafts were removed completely (Bachleda, Kalinova et al. 2012). When the AVG is infected, the possibility to eradicate these pathogens is limited and treatment often ends up with explantation of the graft (Schmidli, Widmer et al. 2018). Another drawback is the increased risk for the elevated access flow to affect the cardiac function with high-output failure. The AVG patency is limited, usually 2-3 years, and is possibly explained by the worse condition among patients selected for this type of access. In contrast, the AVF in some patients may be patent for 5, 8 or even 10 years (Allon 2019).

Figure 15. AVG location testing before surgery.

Economy of the access

The cost for creating, maintaining, and the additional work up for interventions related to AVF failure is substantial among patients with ESRD. For instance, the annual outlay associated with VA is more than $1 billion in the US alone (Feldman, Kobrin et al. 1996, Lok and Foley 2013). This includes costs for surgical and radiological corrections to enable persistent treatment. The cost will further increase if complications such as infection, progressive heart failure, or access related problems occur. Data from Skaraborg hospital during three months in 2020 showed that 31% of the patients in regular HD spent a total of 124 days (mean 2.6 days) in the hospital related to VA interventions. In the frame of suffering for the patient and other restrictions in life, it is nevertheless a complex task for the physician to consider every aspect of the HD treatment such as prognostic variables based on morbidity, i.e. possibility of TX and expected survival. In addition, other variables are social factors such as family planning, occupational and psychological with coping strategies and stress related impairment.

1.4.3 PREPARING THE VASCULAR ACCESS

The placement of the AVF should be performed in good time, i.e. planning 3-6 months before dialysis initiation (Vascular Access Work 2006). The recommendation to start planning is when the GFR is below 30 ml/min. However, in practical terms, this is based on diagnosis and expected progress rate of the CKD. Nevertheless, the placement of AVF is preferably made

before the appearance of the symptoms of uraemia and the risk for severe complications.

The access team with nephrologist, access nurse, vascular surgeon and radiologist should plan for a suitable AVF during weekly clinical access rounds (Vascular Access Work 2006). The decision for the type of access is based on individual conditions such as dexterity, anatomy (location and size of vessels), earlier complications, earlier stenoses in the central vessels, dialysis mode, BF, progress of ESRD and diagnosis, alternative treatments, and expected survival time. Radiologic and US evaluations are compared and discussed. At our hospital, these meetings are recorded and re-evaluated regularly. Access complications, follow-up after surgery, reconstructive and other issues related to access planning for the patients are discussed in detail in accordance with guidelines (Vascular Access Work 2006).

The recommendations for placement of a native **AVF** are in the following order:

1. Radio-cephalic

2. Brachio-cephalic

3. Transposed brachio-basilic

For **AVG:**

1. Fore-arm loop

2. Upper-arm

3. Upper chest wall- 'necklace' before the

4. Lower extremity

…and permanent Central Vein Dialysis Catheter (CDC). However, CDC is suggested before the other options, when limited expected survival is foreseen (Olsha, Hijazi et al. 2015, Misskey, Faulds et al. 2018), or the alternatives above are not possible, related to the urgency.

Venipuncture. Patients with chronic renal insufficiency usually undergo frequent blood sampling before initiating dialysis treatment. It is therefore recommended to avoid punctures of vessels that may be involved in future VA such as PICC lines and venous puncture of the vessels in the non-dominant arm; instead preferably use veins not suitable for the creation of AVF. Some clinics use different bracelets, wristband and /or notations of the medical records to remind other caregivers about these routines, *"Save My Veins" and "Vein Preservation"* (www.bcrenalagency.ca), (Figure 16).

Figure 16. Wristband for vein preservation. With kind permission from 'Kidney for Life.org.'

1.4.3.1 ANATOMIC CONSIDERATIONS

The three essential components of a HD access are as follows (Ho, Cho et al. 2016):

Good inflow from the heart via an artery of reasonable size and location without negative impact on the end organ.

Good outflow from the vein and back to the heart.

Good conduit - A native vein or synthetic graft that is easily cannulated.

The following principles of surgical issues can be used:

- The native vein is chosen before an AV-graft due to a lower risk for infection (Lok and Mokrzycki 2011).

- Use of the most peripheral vein is suggested if size, quality, and location are satisfactory. This is based on the knowledge of limited patency of the AVF, where the possibility of the next VA should be considered. The most common is the radio-cephalic vein, moving proximal for the mid

arm cephalic followed by the antecubital vein, then the basilic vein and its anatomical alternatives.

- The rationale in choosing the non-dominant or less functional upper limb for AVF is based on the increased risk for bleeding during and after the dialysis session. This is of course an advantage during everyday activities such as personal hygiene, occupation and sports.

- Upper limb placement is also preferred due to hygiene, clothing and sometimes the social stress of having to expose the lower arm.

- The intention to avoid the use of a CDC should always be addressed when a new access is considered. Sometimes it is unavoidable, and in those circumstances, the option of where the next AV-fistula can be placed should be considered. The placement of a CDC on the side of AVF vascular return flow worsens prognosis of the AVF (Santoro, Benedetto et al. 2014).

- In some occasions, the most suitable AVF conflicts with the patient's wishes or preferences based on other than medical factors such as cosmetic, for example, a giant fistula on a small person or pain during cannulation.

A DUS investigation is performed to map preoperatively the vascular anatomy of the patient's arm. Sometimes both arms are investigated when in doubt of which one is most suitable. Caution should be emphasized on the different vessel characteristics such as BF, presence of venous branches and areas including atherosclerotic plaques or narrowing. Preoperative investigation also includes DUS to exclude thoracic central venous obstruction (TCVO), which may hamper the central venous return. Most studies recommend a minimum size of the artery of 2.5 mm in diameter and the vein preferably at least 3 mm (Schmidli, Widmer et al. 2018). However, there are studies showing that 2 mm also has the potential for patency. In a study by Hussain, there was an overall success of 82% for small calibre veins (Hussain and Farooqui 2020).

1.4.3.2 ARE THERE ANY RULES OF THUMB FOR AVF CREATION?

The following rules in many ways may be an easy checklist when discussing different parameters for successful AVF placement.

'**The rule of the 6, 'Keys to vascular access.'** (Vascular Access Work 2006)
1. 6 months ahead of dialysis initiation

2. 6 weeks to mature

3. 6 mm in diameter postoperatively

4. located less than 6 mm skin depth

5. straight part of the puncture area of 6 inches

The importance of a well-functioning access team cannot be underestimated. The team also provides patient education and instructions and the possibility for patient involvement to detect AVF murmur, optimize personal hygiene, perform exit site dressing, and report signs of AVF infection (Vascular Access Work 2006, Rushing 2010).

Surgery

Preoperative preparation includes painkillers and a suitable anaesthetic method. Regional anaesthesia is preferred before systemic or general sedation due to less risk, time and postoperative management (Jorgensen, Farres et al. 2020). If a complicated surgery is foreseen, the advantage of general anaesthesia is optional. Some surgeons encourage a temporary break in antihypertensive medication to avoid a too low BP with impaired BF and subsequent "Failure to Mature" (FTM) postoperatively (personal communication from vascular surgeon A. Lindhagen). The most common technique is to connect the venous end to the side of the artery, before using the side-to-side (STS) technique. Flow measurements of the AVF have shown more steal syndromes with the STS technique (Galic, Kvesic et al. 2008). A careful technique is vital, including an atraumatic technique during the surgical procedure combining avoidance of dryness and the use of loupe-glasses for optimal view. The suture technique is standardized, and a bloodless field is recommended by clamping the vessels nearby (Figure 17). Vascular spasm per operatively is prevented by using papaverine, thereby ameliorating ischemia and difficulties in handling the vessel. Studies show that the anastomotic area caused by ligation and surgical manipulation are prone to stenoses later.

Venous branches with the potential for both stenoses due to turbulent flow and shear stress could be ligated if hand ischemia due to impaired arterial BF flow is foreseen (Vaes, Wouda et al. 2015). The advantage of a correct angle of the vein to artery by end-to-side technique has to be considered (Konner 2002). An angle of less than 30 degrees resulted in less than 9% AVF failure (Rezapour, Sepehri et al. 2018), while an angle of > 46.5 degrees was associated with impaired AVF function (Yang, Li et al. 2020). Other options suggested are the suture technique; replacing the sutures with clips may improve AVF patency (Shenoy, Miller et al. 2003). Intraoperative measurement of the AVF BF is helpful; preferably, a flow of at least 200 ml/min is a predictor of improved patency (Lin, Chua et al. 2008, Stegmayr, Willems et al. 2020).

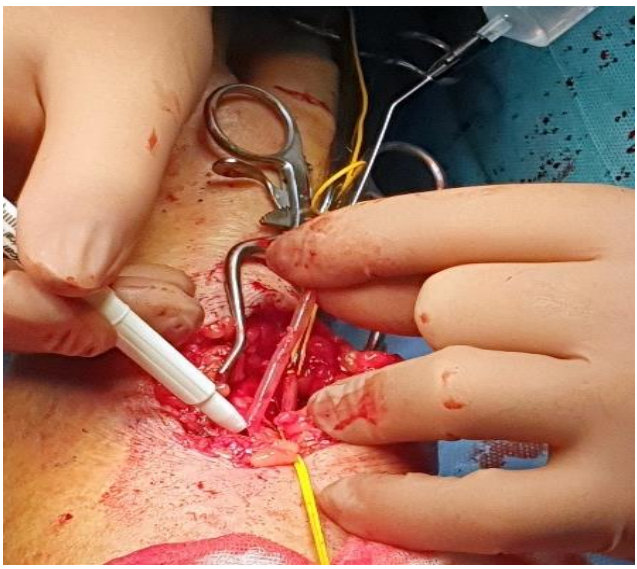


Figure 17. Cephalic vein is marked and tested before connection to the radial artery.

Immediately after surgery the patient is encouraged to be aware of warning signs of infection, bleeding, swelling and neurologic impairment. A program is provided with repeated wrist exercises by squeezing a ball and elbow movements. The patient is informed to avoid compression or exaggerated physical exercises during the first weeks (Vascular Access Work 2006, Rushing 2010).

The AVF thrill can be controlled with self-examination, and this is also taught to the patient at the dialysis unit. Any sign of suspected AVF such as bleeding, altered thrill or infection should be reported to the VA nurse or dialysis unit for evaluation. Repeated DUS monitoring where recurrent thrombosis, stenoses, localization and type of fistula are monitored, is recommended during the postoperative period, usually 4-8 weeks, depending on comorbidities. In a study evaluating AVF diameter and BF, vein diameter greater than 0.4 cm was associated with doubled dialysis adequacy (Robbin, Chamberlain et al. 2002). If a thrombosis occurs immediately postoperatively, it can be salvaged by thrombolysis or thrombectomy. However, this largely depends on the utility to surgeon, intensive care unit, thrombus location and possible contraindications that should be considered. Early planning of AVF creation also makes it possible to minimize acute situations with ERSD complications such as pulmonary oedema, cardiac arrhythmia, and pericarditis, and thereby avoiding the need for acute dialysis via a CDC.

Ready to use

A patent fistula is an AVF that is successfully cannulated with two needles for at least six HD sessions during a 30-day period. It should deliver at least 350 ml/min blood pump speed throughout the HD procedure to be finally considered adequate for HD, according to ESVS, (Schmidli, Widmer et al. 2018).

AVF handling

Together with the patient, the dialysis nurse has a unique possibility to regularly consider the optimal use of the AVF. Skin condition, dexterity, puncture technique, needle size, pain, location, regular monitoring of the AVF flow (Transonic®) and surveillance are recorded. Is the bloodstream hampered? Are there neurologic symptoms or peripheral ulcerations?

Puncture technique

Ever since dialysis was an option for patients with renal insufficiency, one of the major challenges has been the most optimal way of gaining access to the AVF by puncture technique. This is mainly the task of the access nurse but is also dependent on the interaction of the nephrologist, surgeon, and radiologist. The sizes of the needles are usually 15-17 G (Ø 1.4-1.0 mm) and are placed in the puncture area if possible 6-10 cm apart due to vessel type and option. These are called artery and venous needles (distal and proximal part of the fistula vein). After dialysis treatment, needles are removed and a light pressure with

sterile swabs is applied until bleeding stops. A subsequent trauma to the vessel wall activates the inflammation and coagulation cascade. Previous studies have addressed the different issues of cannulation techniques and associated access survival; hitherto there is a lack of compelling evidence in favour for a certain cannulation procedure (Figure 18). For example, one option is the use of soft needles to lessen the risk for penetrating the backside of the vessel wall; these have a blunt tip and flexible design (Nalesso, Garzotto et al. 2018). The use of edge up or downward during cannulation is discussed in a recent paper. By directing the edge upside down, the flap of the vessel will tighten against the vessel wall as a lid (Stegmayr, Willems et al. 2020).

Are there different AVF-cannulation techniques?

- The rope-ladder technique means a change of the needle placement site for each new dialysis, i.e., choosing another site at a defined distance along the AVF from the previous puncture sites. The rope ladder technique is possible if the cannulation segment is long and superficial; however, creating new holes for each treatment is painful for some patients.

- Area cannulation means puncturing of the same limited area, session after session. Some studies have shown the increased risk for aneurysm in the punctured area (Parisotto, Schoder et al. 2014).

- Using the buttonhole (BH) technique, HD needles are inserted through the same hole at the same angle and depth of penetration for each dialysis. The first punctures are performed with a sharp cannula to create a channel for reuse for the next dialysis. The scab from the previous insertion is removed with a thinner needle before the insertion with a blunt needle. This type of needle is used to minimize the cutting effect to the tissue. A drawback is the risk for infection when using an already traumatized channel where bacteria are prone to spread invasively. It is recommended that a ‘vascular map’ is designed for other users. This method seems advantageous for patients with the same nurse who knows the direction and depth during cannulation for every dialysis. Therefore, the use of the BH technique may be advantageous for patients in HHD (Atkar and MacRae 2013).

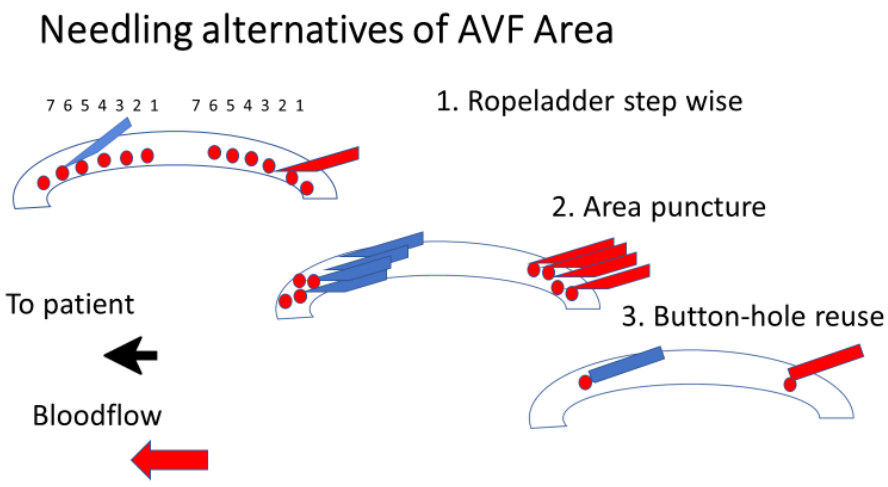


Figure 18. AVF needling alternatives. Picture by author.

Besides the operational routine, concerns of aseptic and hygienic routines are defined in a structural way. Caregivers and patients should pay attention to signs of infection such as fever, blistering, irritation, signs of disturbed circulation and change of the thrill and bruit of the AVF. The concept of 'look, feel and listen' are one of the recurrent strategies of regular monitoring in connection to the regular dialysis treatment (Vascular Access Work 2006).

What about the vascular endothelium?

Vascular smooth muscle cells (VSMC) are normally located in the tunica media of the vascular wall and are the most abundant cells together with fibroblasts. When the endothelium is damaged or dysfunctional, the VSMCs are activated and move to the intima layer of the vessel. The activation includes altered cell signalling with upregulation of growth factors, extracellular matrix, cholesterol crystals, lipids and inflammatory mediators subsequently affecting the vascular wall. Other cell types such as macrophages are recruited caused by the inflammatory reaction. These transform to foam cells, which are integrated to the vessel wall. This fibrous cap or 'plaque' may eventually rupture and induce platelet and leukocyte recruitment, with subsequent events including downregulation of endothelial Nitric Oxide Synthase (eNOS) and oxidative stress.

Neointimal hyperplasia (NH) is a special form of the vascular remodelling caused by VSMC associated with AVF use. The altered physiologic conditions of the venous conduit, from low to high pressure system, repeated trauma and turbulent BF lead to vascular wall thickening and impaired patency (Lee and Roy-Chaudhury 2009).

What are the special vessel characteristics associated with the AVF?

- Altered BF-the arterial blood with a higher pressure, bypassing the capillary network of the hand to the low-pressure venous system leads to vascular wall remodelling with increasing luminal diameter. A 5 to 10-fold increase of the BF is seen on the venous side when the artery is connected to the vein of the AVF (Pike, Shiu et al. 2019), also called wall shear stress (WSS).
- Excessive maturation with inward proliferation and decreasing of luminal diameter (Inston, Al Shakarchi et al. 2017).

Physiologic effects of Wall Shear Stress

WSS is a frictional force from blood that gives rise to changes of the cellular cytoskeleton of the vascular endothelial cells. The release of mediators affects the vessel tension and infers coagulation and inflammation. In straight vessels, the BF is laminar with a stable WSS and homeostasis. In vessel curves and branches, the flow is turbulent with subsequent oscillating flow and endothelial dysfunction (Inston, Al Shakarchi et al. 2017).

Laminar Flow (Q) in a tube is calculated with

Poiseuilles law: $Q= (\Delta v \times \pi \times r^4)/8 \times (\eta \times l)$,

where:

Q=Flow, Δv=pressure difference (v2-v1), π=3.14, r=radius of vessel, η=blood viscosity, l=length of vessel.

Shear Stress induces eNOS with concomitant synthesis of NO, which diffuses to the smooth muscle layer inducing vascular dilatation. With a dysfunctional endothelium, the balance between dilating and constricting mediators is altered in favour of constricting function (Cahill and Redmond 2016).

The altered BF conditions (both volumetric and directional) affect channels via extra and intracellular signalling as well as having a downregulating effect on

heme oxygenase-1 (HO-1) that may contribute to NH. The effect on this signalling pathway is not fully understood (Inston, Al Shakarchi et al. 2017, Pike, Shiu et al. 2019).

HO-1 is an intracellular enzyme that catalyses the cleavage of heme to ferrous iron, CO and biliverdin. HO-1 seems to be induced by oxidative stress, and the released CO affects vascular tone and induces nitric oxide synthase (NOS) with subsequent widening of the vessel (Araujo, Zhang et al. 2012). When the BF is oscillating and turbulent, the upregulation of HO-1 is supressed with subsequent narrowing of the vessel. Experimental studies showed an increase of the amount of HO-1 with treatment of human umbilical venous endothelial cells (HUVECs) with FIR radiation. The increase in HO-1 protein remained significant after 2 hours (Lin, Liu et al. 2008). Another study by Hsu showed inhibition of VEGF (Vascular Endothelial Growth Factor) induced proliferation by FIR compared to the non-treatment group that only received heat. This indicates the non-thermal molecular response of the vascular endothelium and possible limitation of vascular proliferation (Hsu, Chen et al. 2012). However, the studies with FIR were performed on small populations, endothelial cells, and mice models (Lin, Chung et al. 2013).

The uraemic milieu combined with repeated vessel trauma, medication, and the non-physiological connection between vein and artery provides the basis for local molecular events of the vascular endothelium where stenosis and thrombosis are the end products of these events. Several signalling pathways leading to disruption, hyperplasia, and a stenotic formation of the vessel wall have been investigated through the years to find potential strategies to minimize complications.

There are potential sites along the AVF wherein the irregular BF causes downregulation of the HO-1, which in turn leads to less protection against atherogenesis. These are the cannulation sites along the puncture area, the anastomosis between artery and vein and near the venous branches reflected by measurements and outcome of the interventions with percutaneous transluminal angioplasty (PTA) (Lee and Roy-Chaudhury 2009, Inston, Al Shakarchi et al. 2017).

1.4.4 PREVENTION AND MEDICAL PROPHYLAXIS OF AVF STENOSES AND THROMBOSES

Different kinds of prophylactic medication have been evaluated to reduce the risk of stenosis and thrombosis development of the VA.

1. A Cochrane review investigated fifteen randomized controlled trials (RCT) and concluded that no beneficial effect was gained when using antiplatelets, fish oil, Vitamin K-antagonists, or sulfinpyrazone. The study comprised 2230 patients and the primary outcome was AVF patency (Tanner and da Silva 2016).
2. A study evaluating combinations of Omega 3 fatty acids (fish oil) and aspirin showed a lower incidence of interventions during three months of fish oil treatment, as well as aspirin, but there were no effects on patency or time to abandonment (Viecelli, Polkinghorne et al. 2019).
3. The use of statins was evaluated in an observational study from register data of >9000 pairs of users/non-users, where the risk for angioplasty and reconstruction on AVF (used as composite endpoints) was reduced by 18 % in those who were prescribed statins (Chang, Chang et al. 2016).
4. In a prospective study, the use of a recombinant pancreatic elastase (vonapanitase) to decrease vascular wall remodelling after AVF creation showed promising results in favour of maintaining patency of the native AVF in a placebo trial after three years (Peden, O'Connor et al. 2017).
5. Antihypertensive drugs (ACE, ARB and CCB) were retrospectively evaluated among more than 42000 patients, and it was shown that these drugs were associated with prolonged AVF primary patency. However, if this was a causal relationship was not fully established based on reporting bias (Chen, Chien et al. 2016).
6. During recent years, studies have shown prolonged AVF patency and increased access flow with FIR (Lin, Chang et al. 2007, Vatansever and Hamblin 2012, Lin, Yang et al. 2013). In a prospective case-control study that included 145 patients during one year, cases receiving FIR showed a significantly longer patency and fewer incidents of AVF malfunction (Lin, Chang et al. 2007).

1.4.5 COMMON COMPLICATIONS ASSOCIATED WITH THE USE OF THE AVF

In one of our patients with a newly created AVF, the absence of thrill over the AVF was discovered postoperatively by the nurse before the patient was discharged from the hospital. The surgeon was immediately contacted and took the patient for surgery. The wound was reopened where a thrombus was localized intravenously and treated with thrombectomy and subsequent LMWH medication. The AVF BF was restored completely and the AVF could be used for several months after.

Failure to Mature (FTM) is a complication of the AVF before the first successful cannulation for HD treatment, mostly caused by thrombosis. The prevalence varies in studies between 15 and 60% (Lok 2019). This condition entails additive interventions, in hospital care days, and on occasions 'bridging' with a CDC. Several factors during the maturation of the AVF are associated with this condition. Predictors are older age, suffering from coronary artery and/or peripheral vascular disease, and ethnicity. Several score systems for these factors have been used through the years to foresee this condition (Lok, Allon et al. 2006).

A prospective study favouring postoperative hand exercises with a handball showed a beneficial effect for AVF diameter and improved BF (Fontsere, Mestres et al. 2016). However, not all patients can comply with the exercises, wherein muscle electrostimulation could be an alternative (Martinez, Esteve et al. 2017). Postoperative BF measurement with DUS is an established method for follow-up with the intention to assess diameter and to avoid a too early initiation of cannulation; also, it helps to find side branches as potential sites for development of stenosis and steal syndrome (Banerjee 2009). Several of these variables are also predictors for late fistula failure, apart from the cannulation consequences.

Stenosis The most common complication during AVF use is stenosis and/or thrombosis (Vascular Access Work 2006). The mechanisms and origin of the stenosis are multifactorial and caused by upstream; trauma of the vessel, medication, uraemia and downstream factors; endothelial remodelling and impaired vasodilatation, due to altered local conditions, (Lee and Roy-Chaudhury 2009). The subsequent narrowing of the AVF lumen is mainly through scarring, calcification and thromboses (Smith, Gohil et al. 2012). A one-year follow-up study showed that 28% of 150 patients could not use their AVF due to insufficiency (Kimball, Barz et al. 2011). DM was also shown to contribute to increased AVF problems. The mechanisms leading to impairment

of glucose metabolism and prevalence of arteriosclerosis are not fully elucidated among diabetics. Early dysfunction after PTA correlated to diabetes as well as a shorter patency after first time creation (Aktas, Bozkurt et al. 2015).

Regular monitoring of the AVF is performed during dialysis to detect early signs of dysfunction. Changes in BF and function indicate possible stenosis or other complications that require radiologic or surgical intervention. The effect of the intervention is different among certain patient populations and some have relapses early after the procedure, especially diabetics and women. The reasons for this are not yet fully understood.

1.4.5.1 OTHER COMPLICATIONS

Repeated trauma - cannulation

The AVF is exposed to repeated puncture often at least thrice a week. The injury releases a local cascade of procoagulant and reparative growth factors that will lead to scarring, thickening, and narrowing of the vessel, eventually leading to stenosis, turbulence of BF and thrombosis.

Aneurysm

One of our patients suffered at home from acute rupture and bleeding from his AVF. Luckily, his wife was home and assisted him with an urgent call to our dialysis unit and AVF compression at the same time. When he arrived at the emergency room, our vascular surgeon could close the ulceration immediately by stitching. The follow dialysis treatment was performed via a single needle technique through a newly created hole. His description from this acute event included the comprehensive cleaning of the kitchen and change of wallpapers.

The differentiation between a so-called false and real aneurysm is based on how the three layers of the vessel wall are engaged. Aneurysms may develop over time spontaneously, but are mostly caused by weakness in the vessel wall due to repeated cannulation or a nearby stenosis with turbulent BF (Huber, Carter et al. 2003).

The aneurysm is often associated with scarring, thrombus, infection and stenosis, which requires a multidisciplinary evaluation (Inston, Mistry et al. 2017). In complicated cases, there is a risk for spontaneous rupture from the exit site and thrombosis. The subsequent bleeding may exceed several litres, which is potentially life threatening. The aneurysm can be surgically treated

with open surgery, and endovascular stent graft if necessary (Hedin, Engstrom et al. 2015).

Infection

Local exit site infection is usually of gram-positive origin such as Staphylococcus spp. mostly Staph aureus, (SA) and coagulase negative (CoNS) in more than 50% of such cases (Schmidli, Widmer et al. 2018). These infections may lead to generalized septicaemia and endocarditis. Infections are the most common cause of morbidity among patients on HD. Several causes such as repeated puncture, impaired immunologic response, ulcers, diabetes and foreign bodies (joint-prostheses, catheters and pacemakers) are co-factors that lead to an increased susceptibility for infections (Li and Chow 2011). Procedural factors such as hygiene routines, wet dressings and isolation are attended for regular update within staff and patients to minimize the risk spread of bacteria. (Vandecasteele, Boelaert et al. 2009).

Dialysis associated steal syndrome (DASS)

The altered BF conditions of the blood circulation in combination with generalized vessel disease such as diabetes and peripheral artery disease (PAD) may lead to limb ischemia distal of the artery usually starting in the fingers of the hand (Ho, Cho et al. 2016).

DASS can be classified in four stages according to the ESVS (Schmidli, Widmer et al.).

stage 1: slight coldness, numbness, pale skin, no pain

stage 2: loss of sensation, pain during HD or exercise

stage 3: rest pain

stage 4: tissue loss affecting the distal parts of the limb, usually the digits of the hand

Limb ischemia is rare among patients with radio-cephalic AVF (less than 1%), but is more common when using arteria brachialis (5-10%), (Scheltinga, van Hoek et al. 2009, Schmidli, Widmer et al. 2018). When this proximal connection is created, BF conditions are altered with shunting from the arterial to the venous side in the upper arm (Figure 19). This arteriovenous short cut with a higher share of arterial total blood volume will impair distal BF. Keep

in mind that selection of a more proximal placement is based on impaired distal vascular conditions. Therefore, this placement may compromise an already vulnerable vascular bed of the lower arm, especially among diabetics and women. In a study on eight patients performing reconstruction of the brachio-cephalic AVF with a mean follow-up period of 43.5 months, there were no recurrent steal syndromes (Matoussevitch, Konner et al. 2014). A digital brachial index (DBI) could be an additive measurement to discriminate the possible flow dysfunction, although the absolute threshold to predict such condition is not established. The diagnosis is based on clinical and additional BF measurement and the goal is to improve circulation and, if possible, preserve the AVF.

There are several ways of treating the steal syndrome based on different causes and locations:

- Ligation of outflow veins, endovascular, interventional, banding and narrowing
- Revision Using Distal Inflow, (RUDI)
- Distal Revascularisation Interval Ligation, (DRIL)
- Proximalisation of the Arterial Inflow, (PAI)

Figure 19. Arterial insufficiency in left hand due to steal syndrome.

1.4.6 HAEMOSTASIS

The inside of the blood vessel, the endothelium, is built of one layer with tightly connected cells forming a layer with continuous contact with the blood. When the endothelium is disrupted, the blood and endothelial cells act together

forming a blood clot. This is regulated by several systems activated in concert to limit the trauma; otherwise, the blood will literally pour out of the body.

The primary system activates platelets in blood and smooth muscle cells in the middle layer of the vessel wall by two steps.

- Vasoconstriction by local myogenic constriction of the smooth muscle cells in the vessel wall caused by tissue stretch.

- When collagen from the middle layer of the vessel wall is exposed and chemically interacts with receptors of the platelets, the platelets are activated with subsequent secretion of granules stimulating release of proteins such as fibrinogen and von Willebrand factor. These proteins contribute to the 'stickiness' of the blood and the recruitment of additional platelets building up a local blood clot.

The secondary system is similarly activated and is divided into the **intrinsic** and **extrinsic** pathway leading to formation of a fibrin clot.

The **intrinsic** way is activated by using more converting steps, via proteins exposed by trauma. It is somewhat slower of the two, but more effective, using even more converting steps. Heparin is a drug used to modulate this system.

The **extrinsic** way is the spark activated by a tissue factor (Factor III) from traumatized cells and is faster than the intrinsic way. Warfarin (a vitamin K-antagonist) is a drug used to modulate this system to inhibit the coagulation. These two systems are activated in several steps. The ability of a multiple and stepwise activation of the intrinsic and extrinsic way is built on two important principles. One is the concept of the stepwise activation of inactive proteins in the blood. The other is when one protein is activated; a subsequent protein amplification occurs to strengthen the effect.

Fibrinolysis system

To counteract the coagulation system and not become a walking clot (and in this thesis occlude the vessels), there is also a negative feedback system where thrombin acts as the target player that at the same time activates plasminogen into plasmin. Plasmin is a proteolytic protein that breaks down the clot, thereby forming degradation products that are subsequently transported to the liver and kidneys to be wasted with the urine and faeces.

What about anticoagulation of the haemodialysis patient?

Hirudin was initially used during the first experiments performed on blood circulating outside the body**.** This substance is secreted via the teeth of leeches when they suck the blood from their host. Initially, this substance was extracted from hundreds of leech-heads, and ground in a blend of water and sand for subsequent filtration. Some years later, Jay Mclean, a medical student, discovered heparin in the human body (Mueller and Scheidt 1994). One of the major hurdles in HD treatment is to overcome the effect of the coagulation system; or 'keeping the blood not too fluent and yet not too sticky by haemostasis'. The coagulation disorder among uremic patients was described in the 1870s by Bright (Mortberg, Lundwall et al. 2019). Due to platelet dysfunction, bleeding - such as nose bleeding, prolonged haemorrhage and petechiae among others, have been reported in 40-50% of patients (Lutz, Menke et al. 2014). The platelets of uraemic patients contain higher levels of nitric oxide and prostacyclin that inhibit aggregation. Both pro- and anticoagulant factors are affected by the uraemic state, drugs, diagnosis, and the extracorporeal circuit, which limits the possibility for optimal haemostasis. High concentrations of activators in the blood returning to the AVF is initiated by the blood membrane contact during HD, which may favour clotting of the AVF area (Svensson, Friberger et al. 1996).

The patient with continuous anticoagulation of other reasons- Double trouble?

Disorders such as pulmonary embolism (PE), arrythmia and cardiac failure require continuous prophylactic anticoagulant treatment in addition to the LMWH administered during HD. The balance between the pro and anti-coagulant mediators are delicate, which therefore entails consideration when preparing for AVF surgery. An example is the risk for prolonged bleeding peri- and postoperatively regarding increased risk for thrombus in a coronary stent (McBeth, Weinberg et al. 2016).

Besides this, the patient is bedridden during treatment at least 3 hours, which therefore increases the risk for thrombosis due to inactivity. When dialysis treatment is performed, heparin is used to prevent clotting of the extracorporeal circuit. The effect of unfractioned Heparin can be reversed but has a shorter halftime and continuous intravenous bolus doses are required. Low Molecular Weight Heparin (LMWH) can be accumulated since it is excreted by the kidneys with a longer half-time, better bioavailability, and a more predictable dose-response (Hirsh and Levine 1992). Both substances regulate the coagulative action of thrombin. However, LWMH leads to increased risk for

bleeding during cannulation of the AVF, which is why the dose is adjusted accordingly. The uremic state itself also includes decreased ability of platelets to aggregate with a prolonged bleeding time via eNOS; however, this is counteracted by increased levels of von Willebrand factor. During on-going bleeding or in conjunction with surgical interventions heparin free solutions are chosen. In conclusion the clinical challenge is to optimize condition both bleeding and thrombus risk simultaneously.

1.4.7 HOW IS AVF FUNCTION CLINICALLY EVALUATED?

1. Monitoring

Inspection: Local skin blistering, redness, or wounds in the AVF area should be considered as a potential risk for infection and even bacteraemia. Hands with swelling, abnormal coloration or dermatitis should prompt immediate further investigation to clarify the reason. Patient reporting sensory changes due to suspected nerve conditions with numbness, tingling or loss of sensibility or muscular weakness indicates nerve engagement and requires evaluation.

When raising the AVF arm, the venous BF back (return pressure estimated by height in cm above right atrium level) to the heart is controlled by visually confirming the collapse of the vein. If not, there may be a stenosis of the outflow vein. (Figures 20 A and B)

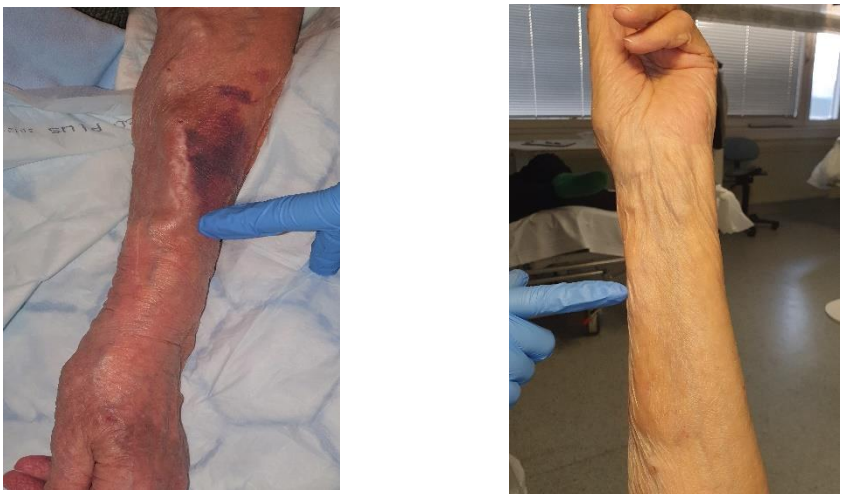


Figure 20. Collapsing vein, A; before and B; after arm elevation.

The upper chest area and neck are also part of the vascular supply and return from the upper extremity is therefore affected by physiologic abnormalities such as a central stenosis (look for collaterals!). A stenosis in that area can be the side effects of a previously located catheter in the specific central vein or lymph oedema related to space occupying masses in the axilla, thrombosis, or earlier trauma, for example, a collarbone fracture or surgery.

Adequate distal arterial flow through the radial and ulnar arteries and the presence of a sufficient anastomosis in the hand can be controlled by the '**Allen´s test**'. This is an easy way to check arterial BF to the hand. The radial and ulnar arteries are the major contributors of the blood supply to the hand. Compression of each one separately confirms the circulation by visually evaluating the skin colour change after repeated fist clenching.

Palpation: Is there a temperature difference between the arms? Hands? What is the skin condition? Hard? Subcutaneous nodule? Dry? General dermatitis - Wet? Sweat- anxiety? Pulses of both radial and ulnar arteries can be easily examined, and if uncertain, a Doppler check-up is recommended.

Auscultation: A Thrill and bruit can be examined with a stethoscope over the AVF and analysed and identified to monitor potential changes over time. The different sounds identified are helpful indicators for clinical guidance to assess possible changes of BF in the AVF. In the hands of an experienced nurse, the sensitivity and specificity of the methods are not negligible. To look, feel, listen, and record changes over time, one can follow the quality and potential complications over time with relative accuracy (Ho, Cho et al. 2016).

2. Surveillance with mechanic device

Regular surveillance of AVF BF is used to predict, monitor, and improve AVF patency, for example, a reduced intra-access flow from a stenosis or increased venous pressure by a venous outflow stenosis. What is the best modality? Is it reliable? Drawbacks? Side effects?

The association of access flow and pressure is calculated by:

Flow = Pressure gradient (ΔP)/Resistance (R). Where ΔP is the gradient between the fistula artery and central vein, and R is the resistance in the access.

Different dilution techniques (modified from Koirala Anvari 2016)

There are several ways to evaluate the AVF BF that are built on differences of glucose and sodium concentration, haematocrit, temperature and conductivity that can be used during the HD treatment such as 'Glucose pump test (GPT)', 'Dialysate temperature (TD) test', 'Transcutaneous Access Flow Monitor (TFAM)' on the skin by measuring the haematocrit, and 'On line Dialysate Conductivity (ODC)', using sodium chloride (Koirala, Anvari et al. 2016). The Transonic® technique is based on using a bolus dose of sodium injected into the extra- corporeal bloodline. This dilution alters the haemoconcentration and the ability of the blood to reproduce the sonar signal to a small sound sensor attached to the bloodlines (Figure 21). The change is computed by a software-program, 'Krivitski-method', and gives an accurate estimate of BF in the AVF (Krivitski 1995).

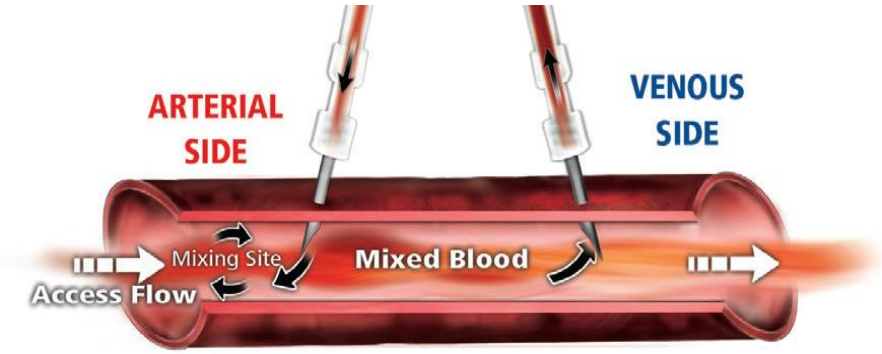


Figure 21. Haemodynamics of access flow measurement with lines reversed by the Krivitski Method. Line reversal creates an artificial recirculation loop with a mixing site at the arterial side of the access. With kind permission from Transonic®.

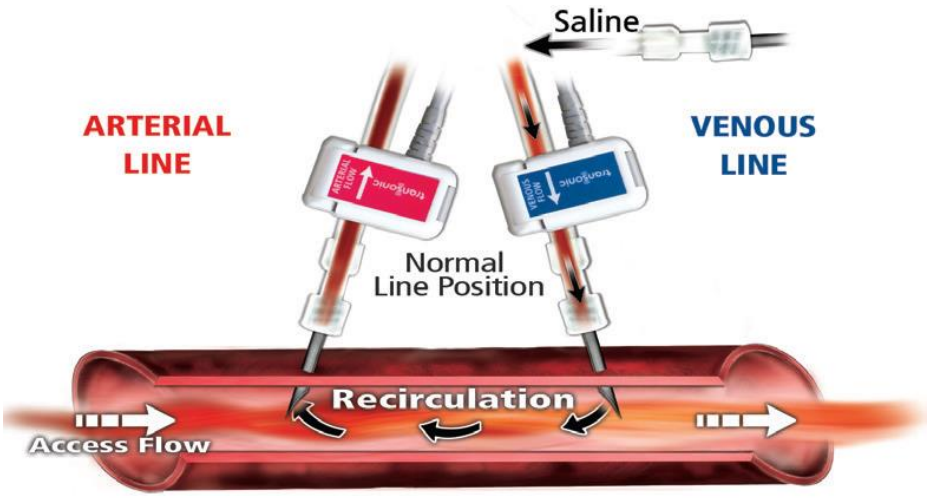


Figure 22. Recirculation measurement. Saline is introduced into the venous sensor with the dialysis lines in a normal position. Access recirculation (backflow) through the VA into the arterial needle is measured. With kind permission from Transonic®.

Recirculation infers that the purified blood from the dialyser returned via the venous needle to the AVF, once again re-enters the HD machine via the arterial needle (Figure 22). Therefore, the total amount of blood for purification is reduced during the session leading to impaired dialysis efficacy. The recirculation indicates a possible stenosis or improper placement of needles.

Static and dynamic venous pressure are other methods used during dialysis treatment to monitor the pressure change in different parts of the bloodline. An outflow obstruction increases the pressure of the venous line due to higher resistance. Diminished arterial inflow or 'suction' of the arterial line may predict inflow stenosis. Repeated readings give a trend analysis. It is recommended to apply the static venous pressure for trend, thereby eliminating the influence of needle size, pump speed and machine type (Koirala, Anvari et al. 2016).

Radiologic modalities used for diagnosis

The most common modalities for evaluating the blood vessels and AVF function are DUS, digital subtraction angiography (DSA), computed tomography (CT) (Locatelli, Aljama et al.), and magnetic resonance imaging (MRI), and phlebography. Each modality is chosen with their specific advantage based on patient conditions, availability, cost, and the specific question at hand. Some centres also use carbon dioxide (CO_2) as contrast

medium. This is advantageous for those patients with contraindication for iodine use. The depicting quality is high, and the CO_2 is diffused via the lung as the breath. Drawbacks with the use of CO_2 are nausea and the risk for neurotoxicity (Ho, Cho et al. 2016).

There are several advantages of using US. It is easily accessible in clinical use, non-interventional, relatively cheap, and there is no need for contrast agents. Drawbacks are limited possibility to examine obese patients and central veins. When AVF intervention is indicated, the use of angiography (DSA) clarifies and guides interventions of dilatation and stenting of the vessels. MRI has excellent resolution, but it is costly, time consuming and some patients, such as those with cardiac implantable devices and claustrophobia, are not suitable for this. CT has high resolution and can clarify lumen conditions up to the central vessels. However, exposing the patient for radiation is also one of the drawbacks to consider. Often the results from the different examinations are evaluated in the context of an integrated approach with the results from clinical regular surveillance. Phlebography is a method that visualizes the venous part of circulation and is used to diagnose thrombus of the veins. It has high sensitivity and specificity but is time consuming and exposes the patient for radiation.

Preoperative considerations

There is a variety of approaches to treat the failing AVF. These are based on utilities, surgical skill, interventional options, patient conditions and service structure. Dysfunction or total occlusion momentarily lead to extra blood sampling, immediate investigations in collaboration with interventionists and vascular surgeons, in-hospital treatment, and sometimes the need for another access and/or surgical reconstruction. The time frame is therefore of vital importance since the patient relies on dialysis for their survival. However, there is still controversy concerning the timing of such interventions and the cost benefit outcome. When should an intervention be performed without worsening of the AVF? Is it a stenosis that eventually cannot be treated? Instead, a new trauma is inflicted on the vascular wall.

Treatment of the failing haemodialysis access

PTA is currently the main modality of treating the failing AVF (Aktas, Bozkurt et al. 2015, Schmidli, Widmer et al. 2018).Thereby the need for surgical reconstruction has decreased with the advantages of less trauma and the possibility of immediate use of the AVF after the intervention. However, there are a few drawbacks. The pressure used for inflating the balloon can sometimes

fracture or damage the vascular wall, which inflicts additive trauma to the endothelium and leads to a new future stenosis. A cutting balloon may induce secondary fibrosis in the scarred areas that will be more resistant to dilatation in the future. Venous branches visualized during the procedure may be the culprit lesion that leads to subsequent surgical procedure.

What should be considered when planning for a PTA?

The choice of method is based on various factors.

1. Patient diagnosis or contraindications such as contrast dose impairing residual kidney function, or allergy?

2. Next possible AVF alternative, if the previous one fails?

3. Earlier AVF placement? Does the anatomy differ? Possible catheter placement?

4. Location of stenosis? Several?

5. Cannulation sites during HD?

6. Duplex colour Doppler (DUS) perioperatively gives additive information.

7. Placement of needles in relation to stenosis?

8. Duplex colour Doppler (DUS) perioperatively gives additive information.

9. Size of catheter, Drug Eluting Balloon (DEB), Drug Eluting Stent (DES)?

10. Stenoses that are 50 or 70% of lumen - increased risk of fracture or rupture of vessel?

11. Positioning of needle tip. Retrograde? Antegrade? Regarding stenosis?

Where is the stenosis usually located in the AVF?

Knowledge of the physiological reactions associated with BF, vascular injury and anatomic predisposition is the basis for assessing the risk areas and subsequent intervention.

The following factors should be addressed:

1. Is the feeding artery affected by PAD with sclerotic plaques that will impair inlet BF?

2. Is there a stenosis of the anastomosis between the artery and vein due to the surgical trauma during AVF creation?

3. The first 15 mm after the arterial junction into the AVF is affected by shear stress when the high BP and flow from of the artery enters the low-pressure system (venous side). At this site, vascular remodelling of the endothelium of the thinner vein occurs.

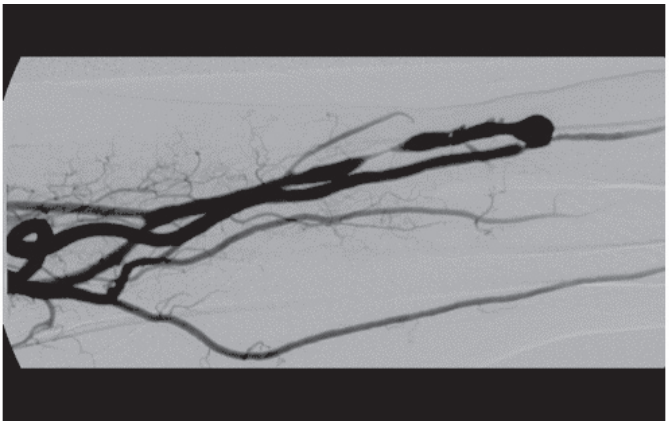
4. Are the cannulation sites damaged? Are there side branches where turbulent flow give rise to stenosis? Should this be ligated if the loss of blood-flow in the AVF is due to higher flow into these branches?

5. Is there an outflow central stenosis of the thoracic vein due to earlier CVCs?

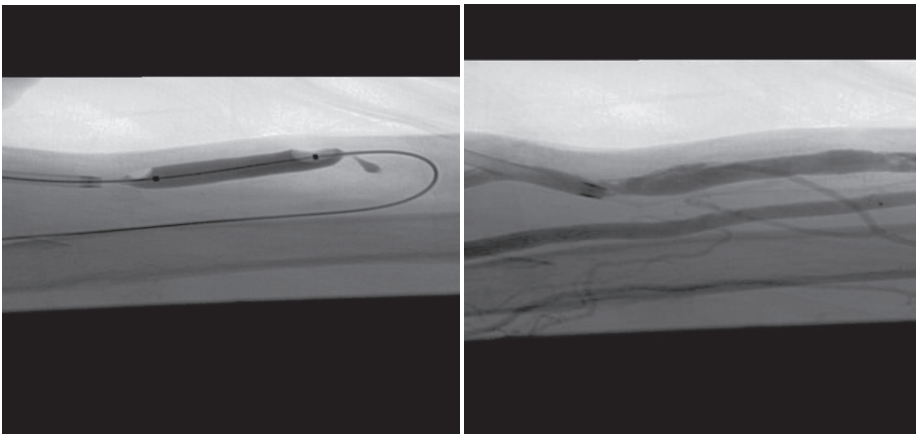
6. Are there residual stenoses from earlier PTA?

1.4.8 HOW IS THE PTA USUALLY PERFORMED?

PTA is the most used method of treating AVF stenosis. The patient is prepared with tranquilizers and painkillers that include local anaesthesia in the puncture area. A duplex colour ultrasound (DUS) is used for guidance of the appropriate cannula insertion. By needle puncture of the radial or femoral artery, a guide wire is inserted through the needle. After removing the needle, an introducer catheter is threaded along the wire. After the wire is removed, a catheter containing contrast medium is inserted and injected, to visualize the vessel anatomy. Thereafter, the infusion catheter is replaced by a catheter with a thin inflatable balloon thread over a guidewire, and then placed in the stenosis. By inflating the balloon (containing saline) to a high pressure, usually more than 10 ATM, the stenosis is dilated. If successful, the BF is restored and is controlled by repeated angiogram and the catheter is removed (Figure 23). In certain cases, the introducer is left in place for immediate dialysis if required. When the stenosis is rigid and hard to dilate, a cutting balloon (CB) is used, combining angioplasty and microsurgery. When inflated, the balloon with special micro-blades incise the intima to permit the dilatation of the vessel. If the vessel wall is not dilated enough a metal stent is placed. This stent can sometimes be covered with a drug (Paclitaxel®) for local limitation of the subsequent inflammatory reaction.



A



B *C*

Figure 23. AVF visualized by x-ray to show A) stenoses at the lower arm level, B) balloon inserted and dilated, C) restored lumen size and flow after dilatation before extraction of introducer.

Thrombolysis

A thrombus in the AVF circuit is usually associated with an already existent stenosis, repeated cannulation, or built up from venous side branches. In more unusual cases, hypotension can be the cause. In acute situations, the thrombus can be dissolved by an intravenously injected solution such as Actilyse®. Thereby, tissue plasminogen activator (tPA) after binding to fibrin, activates

plasminogen into the active plasmin. The function of plasmin is to dissolve the thrombus. A successful thrombolysis should include investigation of vascular conditions and if present eliminate stenoses or aneurysms. Without such measure, long-term patency of the AVF is short and recurrence of thrombosis still requires correction of the underlying cause. Recent studies comparing open surgery versus endovascular treatment have not shown any benefit with either method; this indicates the complexity of the intervention. Thrombectomy plus simple reconstruction of the anastomosis of the vein to the artery proximally showed a better 1-year secondary patency rate of 70-90% compared with 44-89% for endovascular therapy (Tordoir, Bode et al. 2009).

The recommended AVF flow of **GRAFTS AND FISTULAS** suggested by **KDOQI GUIDELINES** (Vascular Access Work 2006):

- Intra-access flow measurements such as Transonic® US dilution is the preferred method for A-V graft and fistula surveillance.
- Low-flow Thresholds: Grafts < 600 ml/min; Fistulas 400-500 ml/min.
- When access flow is less than 1 L/min and has decreased by more than 25% over four months, the patient should be referred for further evaluation.

Is there an upper limit for AVF flow? Yes!

The upper arm fistula created by using the arteria brachialis located proximal of the elbow needs special considerations. The vascular BF is usually higher than that of the lower arm, and sometimes comprises the cardiac function with consequent cardiac output failure and pulmonary hypertension. The increased blood-volume of several litres per minute impairs the cardiac dynamics over time. Symptoms can be diffuse with shortness of breath, coughing or local pain over the AVF, sometimes with insidious onset leading to significant strain on the cardiac effort. A BF > 2 L/min has been shown to impair cardiac performance, High Output Heart Failure (HOHF). In a case control study that included 100 chronic HD patients, patients with AVF flow > 2 L/min (24% of the patients) showed significant dilatation of left heart ventricular dimensions and volumes (Saleh, El Kilany et al. 2018). The absolute limit has been debated and others suggest a maximum of 1-1.5 L/min of the AVF (or access flow >20% of cardiac output) before surgical intervention is implicated (Wijnen, Keuter et al. 2005). One must keep in mind that the size of the patient and thus the relative increase of cardiac output should be considered (Stegmayr, Willems et al. 2020). A longitudinal observation of NT-pro-BNP may help to guide a progressive cardiac burden (Warja, Laveborn et al. 2020).

Treatment includes surgical restriction or banding of the significant AVF vessels. However, the decision is also based on other causes for cardiac failure in this population such as diabetes and other CVD that may be present.

1.4.9 ANAEMIA IN THE HAEMODIALYSIS PATIENT

Anaemia is a common complication of kidney disease and is usually more pronounced among HD patients. The condition contributes to symptoms such as fatigue, loss of exercise tolerance, cognitive disturbances, and cardiac failure that sometimes requires hospitalization (Drueke, Locatelli et al. 2006). The most common reasons for anaemia are impaired EPO production due to loss of viable renal mass, frequent blood sampling, and blood loss via the extracorporeal circuit of the dialysis machine. In addition, insufficient up-take of iron by the gut (1-2 g/year), bleeding from cannulation, and local or systemic inflammation caused by contact with a noncompatible (nonbiologic) device and the uremic state itself are other factors (KDIGO 2012).

Erythropoietin and the kidney

EPO is a glycoprotein synthesized by interstitial fibroblasts near the capillaries adjacent to proximal tubuli cells in the kidney. Under hypoxic conditions, EPO production is increased and is carried with the bloodstream to the bone marrow. Hypoxia Inducible Factor (HIF) is bound to the EPO hormone. When oxygen is low, the complex is activated and stimulates erythroblasts to erythrocyte formation. This feedback-loop can be regulated by inhibiting the endogenous breakdown of HIF (Provenzano, Besarab et al. 2016, Semenza and Prabhakar 2018).

Patients with ESRD receive erythropoiesis-stimulating agents (ESA) to compensate for the anaemia related to blood loss and endocrine impairment from renal insufficiency. ESA stimulates erythrocyte production in the bone marrow. However, high doses of ESA are associated with increased risks for stenosis in the AVF among dialysis patients (Koulouridis, Alfayez et al. 2013, Jeong, Ko et al. 2017). Other studies have shown that ESA contributes to local endothelial hypertrophy via the local effects of TGF-β and PAI and subsequent development of AVF stenosis (Ikegaya, Yamamoto et al. 2000).

Anaemia among CKD patient should be treated

The rationale to treat anaemia in the HD patient is based on several components. Firstly, the possible reasons for its cause, other than renal, should be treated, ruled out, or at least reconsidered. However, initiation of treatment can be of an urgent nature (blood transfusion) and often includes several other

disease related considerations such as infection, and active bleeding (KDIGO 2012). However, caution is recommended with a blood transfusion if a recent metal stent has been placed in the coronary arteries since this increases the risk for stent thrombosis (Gutierrez 2009) or risk for immunisation (Leffell, Kim et al. 2014). Secondly, haemoglobin targets are suggested to remain from 100 g/L to 115 g/L, and values reaching over 130 g/L should be avoided due to increased risk for stroke, CVD and death (Drueke, Locatelli et al. 2006, Singh, Szczech et al. 2006). Treating anaemia related to ESRD is often based on a combination of ESA with a supplement of intravenous iron.

There are several types of ESA on the market with different properties concerning glycosylation, half-time, receptor affinity and conversion properties. Lower ESA doses by 25% are needed when administered subcutaneously than intravenously, which ameliorates side effects such as hypertension and possible AVF failure (Wright, Wright et al. 2015, Jeong, Ko et al. 2017).

Haematocrit is the proportion of erythrocytes in the blood

The treatment of anaemia, especially among HD patients, includes evaluation of the ultrafiltration (removal of plasma water) during dialysis. The relative increase of erythrocytes in blood during HD is related to volume removal and this affects the haemoglobin concentration, haematocrit (HCT). HCT is quite stable within a healthy person. However, among patients with ESRD, the proportion varies considerably based on blood viscosity and the mechanical trauma by the blood pump in the extracorporeal circuit (Javid Mahmoudzadeh Akherat, Cassel et al. 2017). Therefore, when assessing haemoglobin values, one should consider the patient's volume status and laboratory tests. These should be performed under standardized conditions to avoid misinterpretation before any adjustment of ESA dosage is required. Modern dialysis machines offer this function in real time using RBV (relative blood volume) or 'crit-line' where a value below 90% indicates a reduction of water content in plasma and a relatively higher ratio of erythrocytes. The haemoconcentration of blood post-dialysis and the risk for increased clotting of the AVF versus benefits for the patients with kidney failure and Sickness Impact Profile (SIP) were previously discussed (Besarab, Bolton et al. 1998, Moreno, Sanz-Guajardo et al. 2000, Han, Guedes et al. 2020).

Side effects of treatment with ESA

The optimal haemoglobin target when using ESA has raised concern over the last decade since several multi-centre studies (TREAT, DRIVE, CHOIR, and CREATE) presented negative outcomes for patients when reaching haemoglobin values over 120 g/L (Strippoli, Navaneethan et al. 2006).

Also, other studies have indicated that ESA doses above 8000 U/Week contribute to loss of AVF patency and AVF stenosis (Koulouridis, Alfayez et al. 2013, Perez-Garcia, Varas et al. 2018). EPO receptors are also identified within the vascular endothelium and affect the proliferation and subsequent development of stenosis in the AV fistula (Ikegaya, Yamamoto et al. 2000). Another effect of EPO stimulation on endothelial cells is Endothelin secretion (ET-1) which increase vascular tone with subsequent hypertension (Stegmayr and Plum Wirell 2001).

1.4.10 DIABETES AND AVF COMPLICATIONS

The prevalence of diabetics among patients with ESRD is 25% in Sweden and is even higher in the US and Australia (Stendahl 2019, 2020) Both ESRD and DM amplifies the risk for CVD. Altered metabolic conditions such as increased blood-pressure, dyslipidaemia and impaired coagulation function lead to further damage of the vascular endothelium (Fox, Matsushita et al. 2012). The mechanisms are complex and engage both intima and media of the vessel, with progression of vascular stiffness, narrowing and sclerosis. The dyslipidaemia among diabetics leads to LDL adhering to proteoglycans of the vascular wall and modification by oxidation or glycosylation. Reactive substances are released in several steps, which in turn activate monocytes that transforms into macrophages. The macrophages stimulate and upregulate the local inflammatory reactions on the vascular endothelium leading to further damage. A meta-analysis of the association between diabetic patients and AVF failure demonstrated an increased rate of AVF failure compared with non-diabetic patients, with pooled OR of 1.68, $p<0.001$, (Yan, Ye et al. 2018). Several studies of patients with ESRD and DM show accumulation of advanced glycation end products (AGE) with subsequent upregulation of VGEF, which in turn stimulates angiogenesis and neo-revascularization. It is reasonable to assume this will affect the AVF among these patients, although confirming studies are still lacking (Vanholder, Argiles et al. 2001, Yuan, Guo et al. 2013).

1.4.11 MINERAL BONE DISORDER AND VASCULAR CALCIFICATION IN THE HAEMODIALYSIS PATIENT

The endocrine regulation of calcium/parathyroid and vitamin D homeostasis is impaired among HD patients and contribute to calcification and ageing of vascular endothelium (Ketteler, Block et al. 2018). The optimal levels of calcium, phosphate and PTH are difficult to achieve for several patients, despite dietary modifications, dialysis regime and medication. This contributes to vascular calcification, subsequent rigidity, and turbulent BF of the vessel, thereby amplifying the risk for AVF complications. However, the results of research regarding this disturbance have been a topic of debate. In a study evaluating 602 patients on HD, other processes such as anatomy and vein mechanics, instead of mineral metabolites, were suggested to be further evaluated (Santoro, Pellicano et al. 2016, Kubiak, Zelnick et al. 2019). One method of evaluating the vascular calcification is to measure the coronary calcification by CT scan of the aorta, estimated with the CAC score (MESA Calculator https://www.mesa-nhlbi.org/Calcium/input.aspx). Patients with very high risk are those with diabetes, smoking history, hypertension, high cholesterol, and > 65 years of age. Another tool is the pulse wave velocity measurement where the propagation of the pulse wave through the blood circulation is affected by vascular tension. The velocity of the pulse wave is positively correlated to the arterial wall rigidity and BP. In a cohort study by Temmar et al of 150 patients regarding aortic calcifications, there was a gradual but significant rise in later CKD stages (Temmar, Liabeuf et al. 2010). In a prospective study of pre-existing arterial calcification of the radial artery before surgery, the blood volume of the inflow artery, recorded at 6 weeks postoperatively, was significantly higher in a non-calcification group versus a calcification group, although there was no difference in maturation time (Kim, Jung et al. 2019). However, the use of these modalities to predict AVF patency before creation remains to be fully elucidated.

1.4.12 ADULT POLYCYSTIC KIDNEY DISEASE (ADPKD)

Patients with this genetic disease have an increased risk for extra-renal manifestations with cardiac valvular defects and intracranial aneurysms (Ecder and Schrier 2009). Other possible locations of vascular involvement is the AVF with increased fistula diameter. In a previous study by Hadimeri et al, there was a significantly larger AVF diameter in patients with ADPKD compared to controls. An explanation could be weakness of the vessel wall due to impaired collagen support (Hadimeri, Hadimeri et al. 2000). Patients with

ADPKD are usually younger when they initiate dialysis treatment, and therefore the expected time in HD is longer. In a study from Taiwan including 2228 patients (Lee, Chen et al. 2020), those with ADPKD had better performance of the AVF/AVG than non-ADPKD during the first 180 days after AVF creation but was worse the following year possibly due to vascular dilatation (Lee, Chen et al. 2020).

Optimal planning and use of the AVF may include extra monitoring, concerning the cannulation technique and risk for developing high-output flow fistulas among these patients to prevent risks for aneurysm formation or cardiac failure related to valvular abnormalities (Hadimeri, Caidahl et al. 2009).

1.4.13 FAR INFRARED LIGHT (FIR)

FIR is part of the electro-magnetic radiation spectrum from the sun. Radiation in the form of heat is emitted when a molecule de-excites from a higher to a lower quantum level. This non-ionizing, invisible radiation is divided into three bands – near, middle, and far that comprise different wavelengths. The energy is emitted in the form of direct light conversion and stimulates the thermoreceptors of the skin in penetrating the skin approximately 3-4 cm. This light stimulates tissues and is used as treatment for different medical conditions such as muscle pain and ulcers due to impaired arterial circulation (Firapy®). Different lamps in several sizes that deliver pure FIR radiation have become widely used sources to generate therapeutic effects within the radiation spectrum from 3-25 μm (Figure 24). In Taiwan, it is used in several HD units where most of the current research originates. The FIR light is regularly used to reduce the risk for AVF complications, but its physiological effect is not fully understood.

The effects on inflammation have been studied on DNA, fibroblast cell cultures, animal models and vascular endothelium (Toyokawa, Matsui et al. 2003, Yu, Chiu et al. 2006, Lin, Chung et al. 2013). Previous studies have reported improved one-year AVF patency on HD patients (Lin, Chang et al. 2007, Lai, Fang et al. 2013). Patients receiving FIR regularly for one year had lower incidences of AVF complications compared to those who did not receive FIR (12.5 vs 30.1%, $p<0.01$). Another study by Choi et al. showed improved pain relief during cannulation (Choi, Cho et al. 2016). HO-1 is involved in HD-induced inflammatory stress and was reduced in patients treated with FIR therapy. Thus, the induction of HO-1 by FIR may promote the patency of AVFs by preventing many of the causative factors that lead to AVF stenosis. The benefit of FIR on HO-1 against ischemia and reperfusion injury was

detected in a rat- model that showed less apoptotic activity in rat testis after FIR (Tu, Chen et al. 2013). However, the results from these studies are mainly from a single centre, and there are no dose-finding studies on human yet.

Figure 24. FIR treatment of AVF.

During recent years, the ESVS has added the possibility of using FIR light for AVF improvement to their Guideline:

Medical treatments for promoting AV fistula maturation

'We suggest that any decision to apply Far infrared therapy in adults with end-stage kidney disease during the first three months after arteriovenous fistula creation must balance a possible reduction in thrombosis against uncertain effects on maturation and bleeding' (Evidence grade 2C) (Gallieni, Hollenbeck et al. 2019) (Schmidli, Widmer et al.).

Medical treatments for maintaining long-term arteriovenous access patency Arteriovenous fistulas

'We suggest far infrared therapy may be considered for improving long-term arteriovenous fistula patency in adults with end-stage kidney disease' (2C) (Schmidli, Widmer et al. 2018).

1.4.14 WHAT CLINICAL ASPECTS OF AVF SHOULD BE DEVELOPED FOR BETTER PREVENTION AND THERAPY?

This first part of the thesis shows a remaining problem with AVF function, being a vital key for adequate dialysis. Questions evoke of the prevalence of AVF stenosis and the possible mechanisms of its development. Also, of importance is whether there are any non-invasive methods for improving AVF function. Several questions remain unanswered concerning the prevention of AVF complications.

- Are there missed risk factors that should be considered in the prevention of AVF failure?
- May our prescriptions of/ or lack of drugs be associated with AVF complication?
- Is the dialysis extent a reason for problems?
- How much benefit or harm is made by radiological interventions? Should such interventions be performed earlier or later during the AVF follow up?
- Are there any favourable effects or other problems associated with radiological or surgical interventions?
- FIR is a non-interventional method. However, it is rarely used what may be based on scepticism. Can we achieve more physiological results that motivate a more active or reluctant approach to FIR?
- Which type of patients should be especially monitored?
- What are the physiological, laboratory, and technical aspects and effects of the treatment that may contribute to stenoses?
- Is there any use of non-interventional methods?

2 AIM

The overall Aim of this thesis was to evaluate the clinical factors that may contribute to AVF dysfunction, as well as possible treatment strategies to improve AVF performance among HD patients.

The specific aims of each study were:

Study I

To investigate whether a single FIR treatment could alter blood flow velocity, AVF diameter or inflammatory markers.

Study II

To clarify in a case-control study if any medical and/or laboratory factors associated to AVF stenosis can be altered.

Study III

To clarify the reasons and beneficial effects and duration of AVF patency after radiological interventions.

Study IV

To investigate if there are further risk factors that are associated with dysfunctional AVFs.

2.1 ETHICAL ASPECTS

Study I

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden (Ethical committee number 424-13, approved July 24, 2013).

Study II-IV

The Ethics committee in Gothenburg approved the study, (EPN, DNR, 402-14), and informed consent was waived since the study subjects were de-identified and no intervention to the patients was induced by the study (retrospective data only). Included additions were approved by the Ethics committee in Gothenburg, Sweden, (2014-08-22, T-037-15, 2015-01-09).

3 PATIENTS AND METHODS

Anna Wärme´s (AW) participation to the studies.

Study I

AW, in collaboration with Ursula Hadimeri (UH), designed the study protocol, applied for ethical approval, recruited patients, collected, recorded, and analysed data, and wrote the manuscript draft. The content was discussed continuously from a clinical and radiological point of view. Continuous monitoring of FIR treatment and calibration of the emitter were done in collaboration with the Medical Technician and the company in Taiwan. Results were presented by AW and UH as a poster in Amsterdam at the ERA-EDTA congress in May 2014.

Study II

AW contributed to study design, analysis and recording of medical, laboratory and radiological data from 66 patients of the dialysis unit of Skaraborg hospital. AW presented a pilot study at the Nordic Society of Nephrology (NSN), Stavanger in Aug 2015, at the NSN in Malmö in September 2017, and at the Swedish Congress of Nephrology Spring meeting in Umeå 2016. AW analysed data and revised the manuscript with co-authors.

Study III

AW assisted in retrieving data from 174 patients that performed 522 radiologic interventions from Skaraborg and Umeå in collaboration with co-authors. Demographic, radiologic, and clinical data were recorded. AW discussed radiologic findings, outcome and influenced the manuscript from a clinical view.

Study IV

AW recorded retrospective medical and radiologic data from 205 patients in Skaraborg and Umeå in collaboration with co-authors. AW analysed the data, performed basic statistic calculations, drafted, and revised versions of the manuscript all the way to final submission. AW presented a poster at the NSN in Åbo, Finland in Aug 2019, as well as an oral presentation for attending virtual meeting, ERA-EDTA in Milan in June 2020.

AW participated in writing applications for Ethical Approval as well as proposals for funding for Studies I-IV. All applications were granted by The Local Research and Development Council Skaraborg.

Overall, the patients were recruited from the HD units of Skaraborg Hospital, Västra Götalands Region (VGR) and from The Northern Sweden University Hospital, NUS, Umeå in studies III and IV. The regional ethics review board of Gothenburg approved all studies in this thesis (see page 58). All patients were >18 years of age.

3.1 PATIENTS

Study I

Thirty patients suffering from CKD 4 and 5 who attended Skaraborg hospital with a native AVF were included. All had a patent native AVF in the forearm. Of these, 14 were on regular chronic HD. Two patients were treated with PD, whereas 14 had an AVF that was not in use or they were not yet on regular HD. All patients in the HD and outpatient clinic with a lower arm AVF, and in line with the inclusion criteria, were consecutively asked and informed to participate in the study. Inclusion criteria were all patients above 18 years of age who were able to receive informed consent (Table 2). Exclusion criteria were ongoing antibiotic treatment, AVG and/or suspected infection (Figure 25). Twelve patients suffered from DM. The mean age was 60 years with uraemic status (transplant, dialysis or not yet start of dialysis). The study was performed during 2013. The patient was his/her own control and the study was designed as prospective.

Table 2. Demography of patients included in study I.

Variables	Patients n=30
Male/female	17/13
Age, years, mean (SD)	59.9 (14.2)
Diabetes, (yes/no)	12/18
BMI, (kg/m^2), mean (SD)	27.6 (5.5)
Statin treatment, (yes/no)	12/18
Anticoagulation treatment, (yes/no)	8/22
ESA treatment, (yes/no)	20/10
Uric acid lowering drug, (yes/no)	3/27
Duration of AVF, months, mean (SD)	59.9 (42.3)
Haemoglobin, g/L, latest, mean (SD)	119 (15.5)

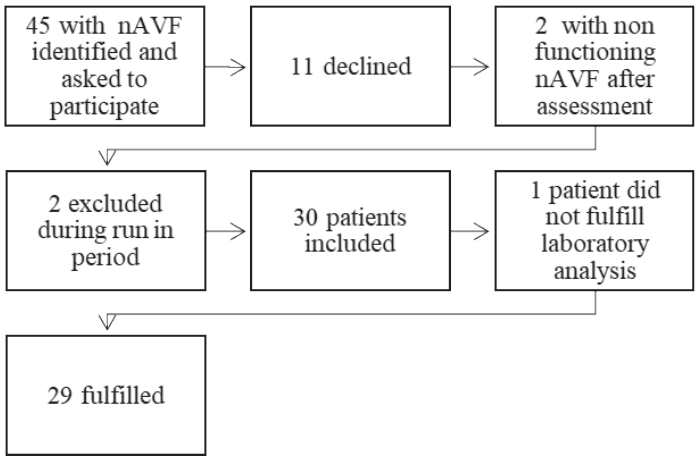


Figure 25. Patients eligible for FIR study (Study I).

Study II

Retrospective data from 66 patients in regular HD from Skaraborg were divided into two groups – Cases and Controls. Cases consisted of 33 patients who had performed at least one radiological investigation due to suspected AVF malfunction. The control group included 33 patients with a patent AVF without the need for radiologic investigation. The patients were matched according to age (+/- 10 years) and diagnosis (Table 3). The follow-up period was two years. Data within one month before and after radiological investigation were analysed. For the control group without intervention, repeated analyses each year were performed. Patients with AVG were excluded.

Table 3. Demography of patients included in study II.

	Controls n=33 (%)	Cases n=33 (%)
Age, years, mean	68.1	68.4
Male/Female	24/9 (73)	19/14 (58)
Vintage of HD, (months)	43.9	43.1
BMI, (kg/m^2), (mean)	27.7	27.1
Smoker/non-smoker, yes/no	18/15 (54)	17/16 (52)
Diabetes, yes/no	9/24 (27)	8/25 (24)
Hypertension, yes/no	13/20 (39)	11/22 (33)
Glomerulonephritis, yes/no	7/26 (21)	5/28 (15)
ADPKD†, yes/no	2/31 (6)	2/31 (6)
Other diagnoses	10/23 (30)	6/27 (18)

Demographic data. Mean values and ratios of variables in the two groups.
No significant difference existed between Cases and Controls in any variables. The percentage of Yes responses are given. †: ADPKD – Adult polycystic kidney disease.

Study III

Retrospective data were used from 174 patients who had performed radiologic AVF investigations and endovascular treatment during 2006-2014 in Umeå and Skaraborg. Patients with AVG and upper arm access were excluded. All 522 radiological investigations were performed due to suspected AVF impairment. The examinations were re-evaluated, and demographic data are presented below (Table 4).

Table 4. Demographic data of patients that performed radiological investigation due to suspected malfunction of the AVF.

	Total n=174 (%)
Age, years mean, (SD)	65 (14)
Men/Women	105/69
Tobacco users, yes/no	49/125 (28)
Diagnoses:	
Glomerulonephritis	28 (16)
Diabetic nephropathy	47 (27)
Interstitial nephritis	24 (14)
Hereditary diseases	18 (10)
Nephrosclerosis/ hypertensive disease	38 (22)
Others	19 (11)

Study IV

A retrospective analysis of 205 patients in a Case: Control design were analysed. Patients were from Skaraborg and Umeå. Laboratory and dialysis treatments among 153 patients with suspected AVF malfunction were compared to 52 patients with a patent AVF. Ninety percent of the Cases had a radio-cephalic (RC) fistula with a dominance for end-to-side anastomosis (Table 5). Four hundred and seventy-three investigations based on clinical suspicion of AVF dysfunction were recorded, but not all patients showed a significant stenosis. The follow-up period was nine years.

The radiological and laboratory data from Cases included referral for investigation based on suspicion of a dysfunctional AVF. Cases were compared with patients without any dysfunction during at least two years (Controls). Cases had performed repeated investigations, and each episode was recorded as an independent episode and compared with repeated data from the Controls. Repeated data from Controls (one-year apart) were used as an independent episode allowed the which use of the data at least twice.

Table 5. Study population at baseline presented as proportion, mean (SD) or median (quartiles) - comparison of data between Cases and Controls.

Variable	Cases n=153	Controls n=52	p-value
Age, years mean (SD)	65.9 (13.5)	65.7 (16.5)	0.565
BMI, (kg/m^2), mean (SD)	26.5 (4.9)	27.8 (6.1)	0.370
Haemodialysis vintage, mean, months	10.3 (33.9)	74.8 (45.1)	**<0.001**
StKt/V, median (quartiles)	2.0 (1.4-2.4)	2.2 (2.0-2.4)	0.099
Female, n (%)	60 (39)	13 (25)	0.064
Diagnosis:			
Glomerulonephritis	25 (16%)	12 (28%)	0.28
Diabetes Mellitus	42 (28%)	10 (23%)	0.24
Tubulointerstitial nephritis	24 (16%)	3 (7%)	0.07
Polycystic kidney disease	15 (10%)	3 (7%)	0.38
Nephrosclerosis/Hypertension	35 (23%)	11 (26%)	0.80
Other	11 (7%)	4 (9%)	0.90

3.2 METHODS

3.2.1 CLINICAL MANAGEMENT

Study I

To assess BF conditions of the AVF, DUS examination of the AVF was performed before and after a single FIR treatment. The Acuson Sequoia 512 DUS with colour Doppler 6 L3 (Mountain View, CA, USA) was used. Measurements were repeated over three different points over the AVF and the mean value was recorded. FIR was performed using a wide spectrum Far-Infrared Therapy Unit (model TY 102N, WS Far Infrared Medical Technology Co., Ltd., Taipei County 231 Taiwan). Before the first DUS investigation, systolic and diastolic BP and heart rate were measured with a manometer (MAXNIBP, CAS 740-1, CAS Medical systems Inc., Branford, CT, USA). Body temperature was measured with an ear thermometer (Genius 2, Covidien Inc., Boulder, USA).

The FIR emitter was placed 25 cm (measured with ruler) over the AVF and light treatment was performed for 40 minutes. Treatment was terminated at least one hour before scheduled end of dialysis by using timer. (Figure 22).

Study II

Patients with a native AVF in regular HD were included. AVF BF conditions were measured with an US dilution system (HD03, Transonic®, Systems Inc., Ithaca, NY, US).

A measurement was performed during HD by using an US sensor clamped to the arterial and venous bloodline, respectively. BF through the line was reversed by changing the bloodline at the needle sites. A fixed bolus dose of isotonic sodium chloride was injected in the bloodline to mix with the incoming arterial blood in the AVF. Thereafter, a new measurement of the mixed blood was recorded on the other sensor attached to the venous line. The difference of the concentration measurements was calculated and stored in the software program.

The Radiologic register in Skaraborg was used to achieve data from radiological investigations performed on the patients of the Case group. Results were used from DUS, Phlebographies, Angiographies, Percutaneous Angioplasty, and surgical interventions.

Study III

Concerning clinical suspicion of AVF impairment, radiologic investigations between 2006 and 2014 from the radiologic registers in Skaraborg and Umeå were re-evaluated by a specialist (UH). Location, size, and frequency of stenosis, as well as aneurysm and thrombosis were recorded. Patients with AVG were excluded.

Study IV

The association of AVF dysfunction and dialysis treatment, on-going medication, laboratory, and demographic data were compared between two groups. Retrospective data between 2006 and 2014 in Skaraborg and Umeå from 153 Cases and 52 Controls were included.

3.2.2 AVF BLOOD FLOW

Study I

DUS measurements were performed over the AVF with the patient in a supine position. The focus was the wrist and the area including the AVF up to the veins at the distal part of the upper arm. Three measure sites were identified and marked – the first over the feeding artery, the second over the fistula area, and the third point over the arterialized vein (distal part of the AVF localized towards the heart; here denominated the vein). Thereafter, the transducer was placed over the AVF where the typical flow curve, audible thrill, and the

feature of the vessel anastomosis (artery, fistula, and vein with measurable flow) could be localized. This was repeated to ascertain the relevant point to optimize data sampling. Diameter and flow measurements of the vessel were performed twice if data were congruent (three times otherwise) over each of the three sites and recorded. The mean blood flow at each point was given in m/s.

Studies II-IV

AVF BF was measured with the Transonic® system (see Study II).

3.2.3 RADIOLOGIC AVF INVESTIGATIONS

Phlebography or venogram was used for examination of the venous limb of the AVF. Two needles were placed in the AVF and a contrast agent was injected continuously to visualize a thrombus or obstruction impairing AVF flow. However, the anastomosis area and the arterial side could not be examined due to the high BF from incoming arterial blood; therefore, a tourniquet was placed around the upper segment. Another drawback was the need for iodine contrast that could hamper residual renal function. The needles can be left in place for subsequent dialysis and the investigation usually takes 30-60 min.

3.2.4 PERCUTANEOUS TRANSLUMINAL ANGIOGRAPHY

An invasive investigation in real time where iodine contrast and sometimes x-ray examination are used concomitantly. A catheter is placed either in the AVF area or via the inguinal vein where a contrast medium is injected to visualize a possible occlusion from a thrombus or stenosis. This method depicts both arterial and venous vessels using either a femoral or brachial approach depending on skills and utilities. Angioplasty during the same procedure is performed with an inflatable balloon to dilate the vessel and restore AVF BF. Different blends of balloons and/or cutting balloons were used accordingly, and on a few occasions, a stent was needed. This intervention usually takes 60-120 min. Thrombolysis is used to dissolve a prevalent thrombus of the VA. Tissue plasminogen activator (Alteplase®, Boehringer Ingelheim, Germany) activates plasminogen to plasmin that dissolves the thrombus. This is infused intra-venously and treatment is performed in the hospital with continuous monitoring of the patient since adverse events such as bleeding can occur.

3.2.5 LABORATORY ANALYSES

Laboratory blood analyses of the studies were performed at the Department of Clinical Chemistry at Skaraborg Hospital and Umeå (SWEDAC and Umeå University Hospital Laboratory, according to SS-EN, ISO 15189).

Study I

Selected biomarkers such as p-urate, s-proteins (including, albumin, antitrypsin, ORM, haptoglobin, IgG, IgA, IgM), haemoglobin and LDL-cholesterol were obtained via samples from the non-fistula arm.

Study II and IV

Blood values for albumin, calcium, HbA1c, CRP, haemoglobin, ferritin, platelets, phosphate and PTH were used twice; before and after radiological investigation among the Cases within two months. Dialysis efficacy was measured with stKt/V.

Study III

No laboratory values were included in this study.

Table 6. The laboratory values investigated were as follows:

	Reference value
Haemoglobin	100-120 g/L
Platelets	165-387 x10^9/L
Albumin	36-45 g/L
Calcium	2.10-2.50 mmol/L
Phosphate	0.60-1.5 mmol/L
Ferritin	7-120 µg/L
Parathyroid hormone	1.5-7.6 ρmol/L
CRP* (C-reactive protein)	<5 mg/L
HbA1c	31-46 mmol/mol (IFCC)
Fibrinogen	2-4 g/L
Cholesterol	3.9-7.8 mmol/L

**data <5 mg/L are given as 4.99 mg/L*

Since we lacked information about the weight for several patients, a rough estimate was calculated as follows:

- ESA responsiveness/resistance (ESA/Hb) was calculated using the ESA doses (U/week) divided by the haemoglobin value (g/L). This was a modified estimate of ESA resistance based on the EPO Resistance Index by Santos et al (Santos, Hortegal et al. 2018).
- the iron administration in mg/w was related to the haemoglobin level (Iron/Hb).

3.2.6 ON-GOING MEDICATION

Study I

Current medication with anticoagulants, statins, antihypertensives, uric acid lowering drugs and weekly dose of ESA were recorded.

Study II and IV

Different blends of ESA, intravenous iron and low molecular weight heparin (Innohep®), vitamin-K antagonist, statins, alfa-receptor blocker, beta-receptor blocker, angiotensin-receptor blocker (ARB), angiotensin converting enzyme inhibitor (ACE), acetylsalicylic acid (ASA) and diuretics were recorded.

3.2.7 DIALYSIS REGIMEN

Study I

In this study, there was a mixture of patients with and without maintenance dialysis. For those patients with HD and PD, the uraemic treatment was based on clinical practice guidelines (Vascular Access Work 2006) concerning target values for dialysis efficacy.

Studies II-IV

Patients in maintenance HD from Umeå and Skaraborg were included. The patients underwent dialysis treatment according to clinical practice guidelines. Patients with and without residual urine output were observed. The most common treatment frequency was 4 hours thrice a week.

3.2.8 RADIOLOGIC INVESTIGATIONS

Studies III-IV

Referrals for radiological investigation due to clinical suspicion of dysfunction were based on a combination of monitoring, surveillance, and trend analysis of AVF BF. To find a potential culprit lesion a pre-emptive DUS was performed in 307 cases (Table 7).

Table 7. Different clinical findings in referrals for intervention.

Clinical finding	Total n=473 (%)
High venous pressure and/or recirculation	67 (15)
Poor access flow	167 (35)
Local swelling of AVF area	19 (4)
Prolonged bleeding after de-cannulation or cannulation problems	71 (15)
Preoperative investigation due to access problems	43 (9)
Others [a]	106 (22)

[a] *'Others' are a blend of worsened dialysis, pain and artery suction*

3.2.9 STATISTICS

Studies I-IV

Analyses were mainly processed with Excel and with SPSS 19, 22 and 25 (IBM Software, SPSS Inc. Chicago, Illinois, USA). Categorical data for cross-tabulation and frequencies were analysed with Fisher´s and Chi-2 test. Group statistics were determined with the Student´s t-test if normally distributed, or the Mann Whitney´s test if skewed distribution. The Wilcoxon Signed rank test was used for paired statistics with the patient as his/her own control. To evaluate correlations, the Pearson´s test (r) was used for parametric distribution, and the Spearman´s rank correlation test (r_o) used if the data did not meet the assumption about normality. All tests were two tailed with significance level of $p < 0.05$. Descriptive data are presented as means (±SD), or median with ranges.

Study II

Measurements between Cases and Controls were used in a Case: Control mode (1:2 mode) to increase the statistical power for differences among groups. Gender was not included as a matching parameter, with the further intention to explore this outcome in the analysis.

Study III

The ANOVA (Analysis of Variance) was performed to compare diagnoses and numbers of venous stenoses. The Kaplan-Meier survival curve was used for comparing AVF survival related to various diagnoses.

Study IV

The variables that differed between Cases and Controls, using univariate comparisons, were included in a multiple logistic regression analysis (Table 8). A stepwise logistic regression model was then performed with group (Case=1; Control=0) as the outcome. Variables from the univariate analysis with a p-value <0.1 were included in the first step. These were gender, prescription of ESA, PTH, standard Kt/V (stKt/V), iron administration/week, low molecular weight heparin (LMWH), and alfa receptor-blockers (Odds ratio (OR) and 95% CI).

Table 8. Logistic regression model with group as the outcome variable.

	Univariate		**Multivariate model**			
			Step I [1]		**Final model [2]**	
Variable	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
ESA, U/W[3]	1.11 (1.06-1.17)	<0.001	1.15 (1.07-1.23)	<0.001	1.15 (1.07-1.23)	<0.001
LMWH, U/W[3]	1.04 (0.99-1.08)	0.054	1.06 (1.003-1.11)	0.049	1.06 (1.01-1.11)	0.013
Female	2.35 (1.47-3.76)	<0.001	1.91 (0.96-3.80)	0.063	2.26 (1.19-4.27)	0.012
Doxazocin	3.07 (1.58-5.95)	0.001	2.74 (1.04-7.24)	0.042	3.99 (1.57-10.13)	0.004

[1]Variables from the univariate analysis with p-value <0.1 included in step I. [2]Backward Stepwise model (Wald). [3]OR calculated for a change of a thousand units. HbA1c included several missing data (around 50%) and is therefore not included in the multivariate model.

4 RESULTS

Study I

A single treatment with FIR resulted in a significant increase in BF velocity over the fistula from a mean of 2.1 m/s (SD±1.0) to 2.3 m/s (±1.0), (p=0.02), (Figure 26). The venous diameter increased significantly from 0.72 (±0.2) cm to 0.80 (±0.2) cm (p=0.006). The increase in fistula BF velocity after FIR correlated positively with baseline p-urate (r_o=0.52, p=0.004) and the increase in venous diameter correlated with the baseline s-ORM levels (r_o=0.51, p=0.005) (Figures 27-28). There was no significant difference in BP before and after treatment. There were no complications recorded within 30 days after FIR exposure.

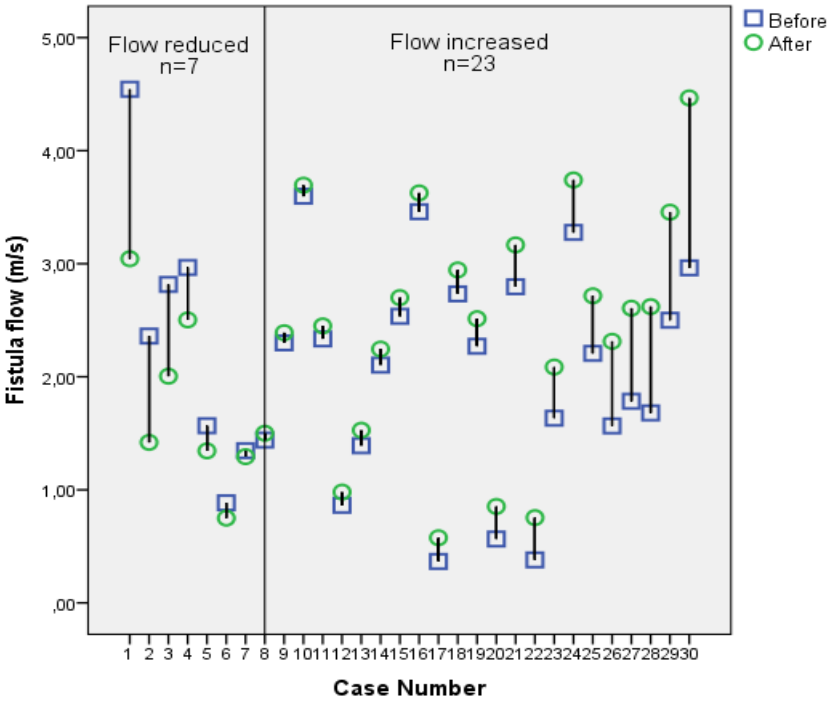


Figure 26. Distribution of AVF BF change before and after FIR in 30 patients.

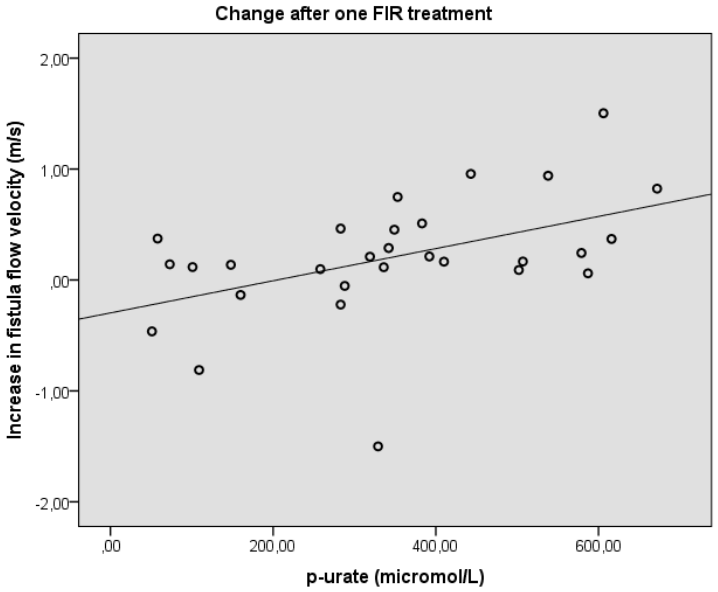


Figure 27. The correlation of AVF flow change and baseline p-urate by using Spearman rank test, (r_o=0.52, p=0.004).

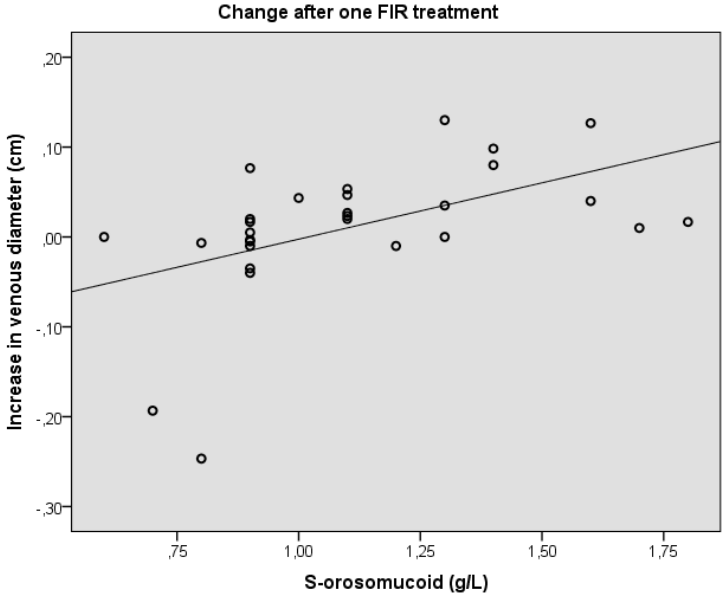


Figure 28. The increase in venous diameter correlated with the baseline s-orosomucoid levels (r_o=0.51, p=0.005).

Study II

Cases had higher weekly doses of ESA than Controls both before, mean 8312 (±7119) U/w versus 4348 (±3790) U/w, p=0.005, and after 7656 (±6795) U/w versus 4477 (±3895) U/w radiological investigation, (p=0.018). The haemoglobin levels were similar before radiological investigation but were lower after invasive radiological investigation in Cases versus Controls at the follow-up measurement (mean 110 g/L (±9.9) versus 117 g/L (±12), p=0.007). The s-phosphate was higher in Cases versus Controls before (1.8 mmol/L (±0.7) versus 1.5 mmol/L (±0.4), p=0.010), but not after radiological investigation.

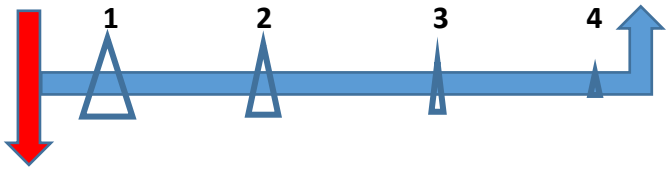
In a smaller pilot study, there was a significant difference between genders (Table 9 below). Thus, there was a reason to test this hypothesis continuously.

Table 9. Female gender was significantly more associated with AVF malfunction than male. Fisher's test was used to compare frequencies among cases (n=13 and controls, n=10), p=0.033.

	AVF	AVF	
	Intervention	No intervention	Total
Women	8	1	9
Men	5	9	14
Total	13	10	23

Study III

There was no significant difference in the number of investigations related to diagnosis (p = 0.524). Of the 174 patients investigated, there were 89% forearm AVFs with radio-cephalic (RC) mainly located in the non-dominant arm. The median number of examinations were 2 (range 1–20) for each patient. In 65 patients, only one examination was performed. The patency of the AVF from creation to the first PTA (all stenoses) was longest for patients with GN compared to other groups. The time interval for all patients to the first PTA was at a median of 9.5 months (mean = 25 ± 36 months). The time in months from the previous PTA (all stenoses) to the next PTA was significantly shorter for those with diabetic nephropathy than those with GN (mean = 7 months (± 9), versus 13 (±19), p = 0.007), and interstitial nephritis (IN), (mean 12 (±12), p = 0.016). Overall, there were 57 occlusions and all except one was dilated. Of these, more than 80% were successful (Figure 29).



Stenosis area	1	2	3	4
Distance, mm	5	28	70	160
% of stenoses (n=422)	56	31	11	2

Figure 29. In total 689 stenoses were detected. Of these, 422 venous stenoses had a reduced lumen of a diameter of ≥ 50% where the distance from anastomosis was possible to measure (in millimetres). The number of stenosis varied between the patients with most having only one stenosis, whereas a few had four or more stenoses. The median distances to the stenosis areas are given above.

Study IV

A radio-cephalic (RC) fistula was present in 90% of the Cases; the remaining 10% had a mid-arm placement. All Controls had a radio-cephalic (RC) fistula. In both groups, there was a dominance for end-to-side anastomosis. DUS was performed as a pre-emptive examination in 307 of the investigations.

Median weekly doses of ESA were higher in Cases than in Controls (8000 vs 5000 IU, $p<0.001$). There was no significant difference in mean values of calcium and phosphate between Cases and Controls. For more specific results, see (Table 10). At least one significant stenosis (>50% of the lumen) was detected in 348 examinations. Of these, a subsequent PTA was performed on 248 occasions (71%). The most common radiologic outcome and interventions are presented in Table 11. Multiple regression analyses revealed significant associations with AVF dysfunction and female gender, prescription of doxazocin, doses of ESA and LMWH among the Cases. There was no difference between the groups regarding haemoglobin, CRP, or ferritin.

Table 10. Comparison (mean and SD) for Controls and for Cases. Data collected before vs after intervention (Cases) and for Controls (after 1 year free of AVF problems) and repeated within 8 weeks later for both groups. Also included are parametric and non-parametric comparisons between Controls first data and Cases before intervention.

Variable	Controls				Cases				Controls vs Cases	
	First data	Data <8w later	n	p-value	Before intervention	After intervention	n	p-value	Parametric p-value	Non-parametric p-value
Calcium, mmol/L	2.34 (0.41)	2.35 (0.41)	117	0.674	2.35 (0.17)	2.35 (0.17)	417	0.736	0.729	0.737
Phosphate, mmol/L	1.60 (0.43)	1.57 (0.41)	117	0.548	1.65 (0.45)	1.66 (0.49)	413	0.873	0.193	0.214
Calcium x phosphate product	3.7 (1.0)	3.7 (1.0)	117	0.197	3.9 (1.1)	3.9 (1.2)	433	0.158	0.197	0.261
Platelets, ($x10^9$)	246 (88)	250 (95)	117	0.340	237 (76)	241 (82)	379	0.253	0.253	0.396
Haemoglobin, g/L	114 (12)	114 (12)	118	0.531	114.7 (11.9)	112.9 (12.3)	427	**0.001**	0.261	0.23
PTH, pmol/L	33 (27)	34 (25)	100	0.740	27 (25)	34 (106)	349	0.253	**0.022**	**0.009**
Cholesterol mmol/L	3.89 (0.79)	3.78 (0.83)	10	0.547	4.2 (1.5)	3.8 (0.9)	30	0.169	0.231	0.524
HbA1c*, mmol/mol	49 (20)	54 (20)	17	**0.039**	58 (17)	58 (16)	101	0.448	**0.033**	**0.037**
Ferritin, µg/L	449 (244)	510 (489)	104	0.133	467 (255)	486 (251)	313	0.095	0.701	0.871
Drug prescriptions:										
ESA, U/W	4667 (3654)	4673 (3701)	78	0.975	7063 (387)	6982 (382)	333	0.153	**<0.001**	**<0.001**
Iron, mg/W	43 (65)	34 (35)	72	0.211	59 (60)	55 (44)	234	0.257	0.073	**0.004**
LMWH, U/W	11949 (5062)	12270 (5581)	74	0.282	14225 (8022)	14537 (8174)	227	0.183	0.064	**0.028**
HD conditions:										
Recirculation, %	0.7 (4.5)	0.2 (1.7)	61	0.385	4.7 (11)	0.7 (3.7)	130	**<0.001**	**<0.001**	**<0.001**
Access flow, ml /min	1105 (494)	1090 (497)	61	0.622	631 (446)	866 (512)	158	**<0.001**	**<0.001**	**<0.001**
HD, hours/w	12.2 (2.7)	12.0 (2.3)	78	0.196	12.1 (2.4)	12.3 (2.4)	320	**0.009**	0.348	0.61
StKt/V	2.16 (0.53)	2.17 (0.58)	72	0.831	1.88 (0.59)	1.90 (0.59)	257	0.237	**<0.001**	**<0.001**

*HbA1c results are given only for blood samples taken from patients with DM. PTH-Parathyroid hormone, ESA-Erythropoietin stimulating Agent, LMWH- Low Molecular Weight Heparin, HD-haemodialysis. Bold p-values indicate statistically significant values.

Table 11. Common findings of radiological investigations (n=473) of Cases and the measures taken.

Radiological findings:	**Total (%)**
Significant stenosis	348 (74)
No abnormality detected	40 (8)
Other findings [a]	85 (18)
Measures taken:	
No direct radiological measure [b]	140 (30)
Additional radiological investigation	32 (7)
PTA-dilatation ± stent	248 (52)
Others [c]	53 (11)

a) Collaterals, aneurysm, spasm, non-significant stenosis. b) Of these, 27 were referred for surgical intervention, and the remaining 99 for subsequent PTA, thrombolysis, coil or thrombectomy. PTA - Percutaneous Transluminal Angioplasty. c) Others are a blend of Cutting Balloon Angioplasty (CBA), interrupted procedure and nitroglycerine treatment.

5 DISCUSSION

The overall aim of this thesis was to evaluate the clinical factors that may contribute to AVF dysfunction, and to clarify possible interventional treatment strategies to improve AVF performance among HD patients.

Study I

The key finding was an increase of AVF flow already after one FIR treatment.

This direct effect on the venous diameter was not clarified in any other studies. However, Lin et al showed increased AVF flow and patency of the AVF in a prolonged study (Lin, Chang et al. 2007). The authors showed that patients who received repeated FIR therapy for one year during HD had better AVF function.

Since FIR light penetrates skin approximately 3-4 cm, the improvement we found may be explained by the stimulation of thermoreceptors as confirmed by the warm sensation some patients experienced. In addition, metabolic and local vasodilatation may be contributors. The latter seemed valid since the present study showed a significantly better outflow diameter even at approximately 20 minutes after ending FIR.

Aside from the effect on newly created AVFs, FIR also seems to be beneficial for long-term secondary patency after angioplasty (Lai, Fang et al.). In an animal model, Yu et al (Yu, Chiu et al.) verified an increase in skin microcirculation that persisted for up to one hour after FIR treatment. This suggests a non-thermic biologic effect; however, this needs further evaluation.

It is well known that urate is involved in pro-inflammatory effects associated with increased risk for CVD as well as a marker for uraemia (Jin, Yang et al. 2012). Our study showed a larger increase of AVF BF after FIR when baseline p-urate was higher. Therefore, patients with higher uric acid levels may further benefit from FIR treatment.

Another finding of the present study was the positive correlation of ORM and the increase, by FIR, of the venous diameter of the AVF. ORM is an acute phase reactant that increases during inflammation (Luo, Lei et al. 2015). However, its regulation and importance has not been fully elucidated. Some reports have shown a poorer outcome for patients with cardiac failure, diabetes and increased ORM levels. Whether this is a cause, or a consequence is still unclear. Future studies may clarify if patients with such conditions may benefit

even further from FIR. An increase of wound healing speed during FIR was shown in a study by Toyokawa et al. These authors noted that with FIR there was a greater production of fibroblasts that expressed TGF-β1 in wounds. This was suggested as a possible mechanism for the promotive effect of FIR irradiation on wound healing (Toyokawa, Matsui et al. 2003). Other studies have shown that FIR contributes to the upregulation of HO-1. HO-1 is involved in the dilatation of blood vessels together with eNOS to increase BF (Lin, Liu et al. 2008, Lin, Chung et al. 2013).

Neointimal hyperplasia is a consequence of shear stress due to complex molecular events that engage the vascular wall, including activation of TGF-β1. The endothelial response, turbulent BF and repeated puncture are the driving mechanisms for the thickening and altered blood conditions that lead to stenosis of the AVF.

The local inflammatory activity of the vascular endothelium caused by BF and several local molecular mechanisms may therefore be improved by FIR treatment. Still, results are conflicting and there are no dose finding studies concerning optimal FIR dose.

The present study supports immediate effects of the use of FIR, both to improve AVF maturation and flow conditions, and to counteract local inflammation.

Study II

The key finding was the significantly higher ESA dosing among patients with a dysfunctional AVF.

The present Case-Control study confirmed our previous pilot study from 2015 (Wärme, Hadimeri et al. 2015) where the main finding was the use of higher ESA doses in patients with AVF dysfunction (Figure 30). This was valid although there was no difference in variables such as haemoglobin or CRP levels when comparing Cases to Controls. This was also shown by others in later studies (Jeong, Ko et al. 2017).

Therefore, the high doses of ESA in Cases indicate reduced responsiveness to ESA within the patient. This lack of response did not seem to be related to inflammation (since CRP did not differ between groups), indicating that Cases held a partial resistance to ESA. The reduced responsiveness does not seem to be strongly related to low grade inflammation in the frame of the present study.

Previous studies (Ikegaya, Yamamoto et al. 2000) hypothesized that increased ESA binding to EPO receptors may contribute to the development of AVF stenosis with intimal hyperplasia and extracellular matrix accumulation. Since ESA is currently the first choice in treating anaemia among HD patients, the question arises if ESA may contribute to local hypertrophic effects on the vascular endothelium. This should motivate clinician to consider prescribing lower doses of ESA in patients at risk (see Study IV).

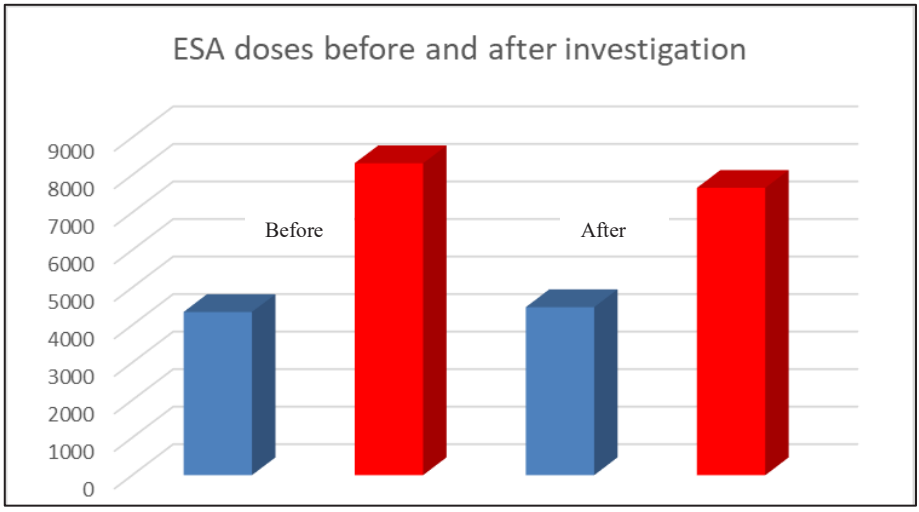


Figure 30. Mean ESA doses (U/week) among Controls (blue) and Cases (red) before (4348 vs 8312, p=0.005) and after investigation (4477 vs 7656, p=0.018).

Study III

The key finding is that AVF dysfunction is complex and occurs for several reasons.

Stenosis, which is most common, develops along the entire AVF segment and it seems that different locations associate with distinct properties. The most common locations are the first part of the vein, cannulation area and side branches, and the arterial segment before the anastomosis, albeit to a lesser extent. The pathogenesis of stenosis development seems to differ between these distinct parts (Stegmayr, Willems et al. 2020). The findings in this study strengthens the hypothesis that the origin of the stenosis in the puncture area is mainly associated with the repeated trauma and not the diagnosis *per se*.

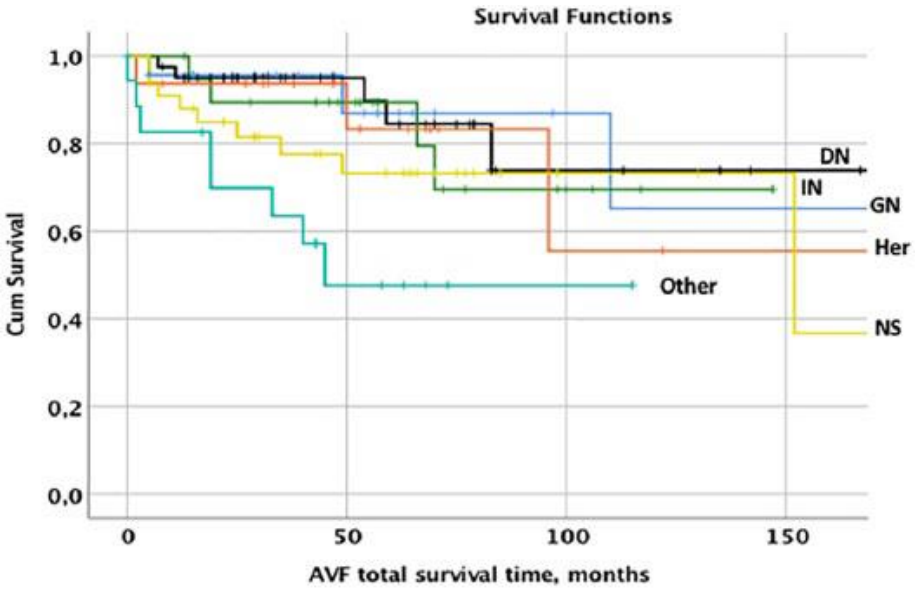


Figure 31. Distribution of cumulative survival of AVF related to the various diagnoses glomerulonephritis (GN), diabetic nephropathy (DN), interstitial nephritis (IN), hereditary diseases (Her), nephrosclerosis (NS), and other diagnoses (Other).

The diagnosis did not affect the frequency of venous stenoses or the degree. Another interesting finding that there was no difference in time from AVF placement to the first investigation between different diagnoses also strengthens this. Patients in this study with diabetes performed like those with other diagnoses regarding venous stenosis (Figure 31), but experienced more frequent interventions due to a multiplied risk for CVD (Fox, Matsushita et al. 2012). One possible explanation could be stiffness of the vessel that lead to cannulation problems with repeated trauma and subsequent scarring and narrowing of the vessel. Another explanation is the general condition with atherosclerotic disease and comorbidities and increased levels of AGE (Arsov, Graaff et al. 2014, Jeong, Kwon et al. 2019). The present study strengthens that the AVF dysfunction in patients with DM mainly have arterial stenosis, which was more frequent in patients suffering from DM thus indicating the higher prevalence of peripheral arterial disease.

Patients may suffer from numerous arterial and venous stenoses of the vascular conduit. In this study, the remaining degree of the stenosis correlated positively with the initial size of the stenosis. Therefore, it seems important to intervene before the stenosis becomes extensive. The access team should be alert and include multidisciplinary specialists such as surgeons and radiologists.

Study IV

The key finding of this study was that ESA dosing was higher among Cases despite shorter vintages in dialysis both before and after radiological investigation.

As shown in our previous Case-Control study (Study II), ESA doses in this larger observational study were almost double compared with controls. The mean value of vintage in months (less than a year) may reflect a poorer general condition of the patient immediately before initiation of regular HD. Another explanation may be an interruption of the AVF maturation process by early stenosis/thrombosis; however, FTM occasions were not analysed in this study.

Data from this study suggest that metabolic mechanisms, other than optimal calcium-phosphate product and PTH, affect AVF function. AVF malfunction with diminished BF may explain increased clotting events, which therefore require higher LMWH dosing.

As shown in Study II, there was no difference in haemoglobin, ferritin or CRP levels between Cases and Controls regardless of higher doses of both intravenous iron and ESA. Another finding was the absence of inflammatory activity, which contributes to functional iron deficiency.

The use of ESA among Cases, regarding diagnosis at baseline differed significantly using Analysis of variance (ANOVA), (Figure 32). Patients with glomerulonephritis (GN) and nephrosclerosis (NS) received the highest weekly dose of ESA.

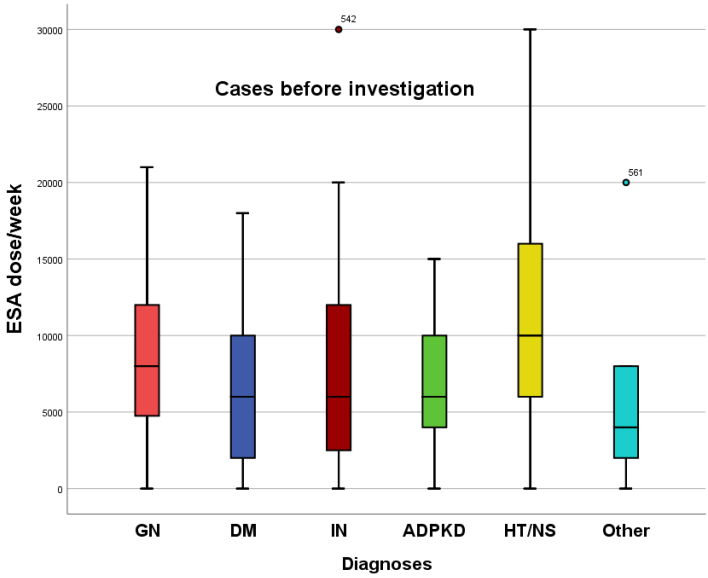


Figure 32. There was a significant difference in ESA doses between some diagnoses among cases(n=153). By using one-way ANOVA, we could see that ESA doses were significantly higher among patients with nephrosclerosis compared to DM (mean 10500 U/w vs 6100), p=0.040.

Using multiple regression analyses, the remaining risk factors for AVF dysfunction were prescriptions of higher doses of ESA and LMWH as well as female gender and the use of alfa-receptor blockers.

Increased morbidity and shortened life expectancy was shown for HD patients administered ESA doses above 8000 units/w by Perez -Garcia et al, (Perez-Garcia, Varas et al. 2018).This was a retrospective study using a propensity score matching for more or less than 8000 U/week. The administration of intravenous ESA might enhance ESA-receptors in the stenotic fistulae caused by NH. The induction of extracellular matrix accumulation contributes to intimal thickening of the vessel wall (Ikegaya, Yamamoto et al. 2000).

A previous observational study that included 1239 patients suggested that intravenous iron doses above 800 mg within 6 months contribute to endothelial damage. An increased superoxide production by mononuclear cells as well as enhanced adhesion of these cells to vascular endothelium may increase oxidative stress and atherogenesis (Kuo, Hung et al. 2012).

The association of plasma fibrinogen and ESA/Hb could be one of the contributors to thromboembolic events (Corwin 2007, Pfeffer, Burdmann et al. 2009, Nishio, Chhatkuli et al. 2013). Inflammation is another cause of elevated fibrinogen levels, however this was not the case in the present study since CRP levels were almost normal and were similar between Cases and Controls.

Instead, the thromboembolic tendency, estimated by visual clotting of the dialyser, encouraged the dialysis staff to increase the dosage of LMWH, which may explain these higher doses among Cases.

Another interesting finding is the more common use of alfa receptor blockers among Cases. The explanation may be an elevated BP caused by higher doses of ESA, i.e. ESA contributes to a rise in BP which motivates the clinician to intensify antihypertensive treatment (Stegmayr and Plum Wirell 2001). However, levels of BP were not analysed in this study.

5.1 LIMITATIONS OF THE STUDIES

Study I was not blinded and included a limited number of patients. Also, there was a mixture of treatment modalities for patients with renal insufficiency and dialysis vintage. The FIR treatment was evaluated after one single treatment. However, the patient was his/her own control and repeated measurements of AVF BF was performed by one experienced radiologist (UH).

Study II was retrospective with small differences of results, such as CRP, PTH and haemoglobin, between Cases and Controls. The Case-Control design with diagnoses, age and size of study population was an attempt to neutralize external factors as much as possible. By not randomizing the groups according to gender, an attempt was made to evaluate differences in clinical and laboratory outcomes.

Study III was retrospective with an extended observation time, 9 years, during which changes of treatment options and guidelines had developed. The material also consisted of patients without significant AVF stenoses since referral was based on clinical suspicion of AVF dysfunction. Another limitation is that a possible proximal venous stenosis was diagnosed later with additional investigations. However, the inclusion period of several years made it possible to evaluate AVF patency and the impact of repeated investigations and different diagnoses.

In Study IV, the repeated use of measurements of Cases and Controls may be a limitation. However, we considered each episode as independent among controls. Paired statistics were used with each patient as his/her control in both groups as well as between groups (before vs after for each episode). Therefore, the results on both the group and individual level are presented with parametric and non-parametric methods. Age, gender, and diagnosis were considered similar in both groups. For some patients, retrospective HD data were missing from the years 2006-2008.

6 CONCLUSIONS

In Study I, we showed that a single FIR treatment significantly increased AVF BF velocity and vein diameter, thus indicating significant efficacy for improving AVF flow. Therefore, FIR can be recommended for the short-term, and based on previous studies, also for long-term follow-up strategies to facilitate postoperative maturation and patency of poorly matured AVFs. FIR treatment can be used to mitigate further the local inflammatory response associated with AVF intervention.

In Studies II and IV, we found that patients with AVF dysfunction received higher weekly ESA doses. The necessity of higher doses was discussed. There was no difference between Cases and Controls in haemoglobin, CRP, or calcium, thus indicating a possible local effect of ESA on the receptors of the vascular endothelium.

Study III showed that venous AVF stenoses were more common than arterial stenoses, and most stenoses were located within 5 mm from the anastomosis. A considerable number of stenoses were also present at the puncture areas. The latter indicates that cannulation techniques may need to be improved. Arterial stenosis is more common among men and patients with DM and nephrosclerosis, thus indicating that more general vascular disease is of importance.

Study IV confirmed the association between higher ESA doses and AVF dysfunction. In addition, after multiple regression analyses, the remaining risk factors for AVF dysfunction were female gender, higher doses of ESA and LMWH and more frequent use of alfa-receptor blockers. We suggest that these factors be continuously evaluated when assessing AVF function. Variables such as calcium and phosphate were not significant risk factors.

For those with DM, an inverse correlation between stKt/V and HbA1c indicates that less dialysis dose was associated with a worse metabolic control.

In conclusion, besides female gender, factors associated with AVF venous stenosis are higher doses of ESA, and intravenous iron, but not the calcium-phosphate metabolism. Arterial stenosis was associated with DM and nephrosclerosis. Repeated and timely radiological interventions are helpful to maintain AVF patency. Other preventive measures may be to accept lower Hb levels using a somewhat lower ESA dose and allowing lower iron stores. FIR may be a preventive measure to support AVF flow and patency, which may also limit the inflammatory response.

Still, questions remain for the numerous patients that will have an AVF that fails before HD is ended.

To be continued…

7 FUTURE PERSPECTIVES

Treating Anaemia

Recent studies have shown positive results with drugs acting on the intracellular transcriptional complex of HIF as an alternative to ESA for anaemia treatment.

Microsurgery

Fistulas can be created via an endovascular technique, instead of open surgery, with less trauma and minimized manipulation of vessels; this is also possible to perform in the outpatient clinic (Hull, Jennings et al. 2018).

Several biological or biogenic vascular grafts

From decellularized arteries or tissue, engineering could help to solve this important problem for HD patients. Biologic cytoskeletons made of harvested fibroblasts in cell culture may be used to create new blood vessels such as autologous collagenous tubes (Stegmayr, Willems et al. 2020). New biocompatible devices designed to reduce flow disturbances of the AVF anastomosis may be a metal sheath used for vessel external support that is wrapped around the artery at the anastomosis (Peden, O'Connor et al.), and an external mesh braid that determines vascular diameter without contact with blood (Karydis, Bevis et al. 2020).

Surgical technique

How should sutures be placed through the vessel? Are there weak spots? And what about blood/foreign body contact? The advantage of including all three vascular layers is to achieve a stronger adaption to minimize leakage, and easier to perform. Is it possible halfway through the vessel in certain cases? to avoid endothelial damage and change of BF of the anastomosis? Should we use continuous or interrupted sutures? (Aitken, Jeans et al. 2015).

Dialysis filters and different priming solutions

may be improved by new types of coating and be compatible with less coagulant activity. For example, heparin coated dialysers or heparin/albumin as priming solutions have been shown to increase blood compatibility to lessen the risk for coagulation during dialysis (Skagerlind and Stegmayr 2017).

Cannulation technique

What about the use of soft needles in different materials? Bevel up or down? The argument that a small flap from the vascular wall during cannulation interferes with the bloodstream with subsequent turbulent flow increasing vascular shear stress has been studied (Stegmayr, Willems et al. 2020).

Advanced Glycation End (AGE) products

The accumulation of AGE is amplified among ESRD patients, especially in those with advanced CVD and DM with an OR of more than 3 (Meerwaldt, Hartog et al. 2005). The use of glucose free dialysate and specialized dialysis filters have shown a reduction of AGE, thus indicating less exposure on the vascular tissue; but this remains to be evaluated in further studies (Graaff, Arsov et al. 2014, Ramsauer, Graaff et al. 2019).

FIR-therapy

Randomized Controlled Trials suggest that the regular use of FIR therapy in HD patients with AVFs can improve AVF function. However, more randomised controlled multi-centre, clinical and blinded trials are required. Today, there is a lack of evidence and experience in people of other ethnicities besides Asian (Chen, Chien et al. 2016).

High flow AVF

Many patients in HD have cardiac disease. BF > 2L/min within the AVF is unfavourable. Can we find robust predictors and methods to avoid additional cardiac strain on these patients in the future?

ACKNOWLEDGEMENTS

Henrik Hadimeri, **Associate Professor** in Nephrology, my main supervisor, and colleague, who made it possible for me to enter the journey of research. For providing research facilities and for pushing and encouraging me during my clinical work as well as in the gym.

Bernd Stegmayr, **Professor** and my co-supervisor and great source of wisdom. For endless support and patience during our ZOOM meetings and our mini conferences together with our fellows in different lodges in Scandinavia. Everyone should have a Bernd in their life!

Ursula Hadimeri, **MD**, **PhD**, my colleague, and co-worker during the first years of our efforts with registers, late trains, submissions, and non-functional internet weekends with apples in the garden. For great knowledge in radiology, anatomy and what you can extract from an angiography picture and how to manage all the pictures and stacks in the SECTRA archives.

Salmir Nasic, Salmir the "Magician". For support with statistical advice and great patience when discussing what methods goes with what. My talent for this subject has always been my 'Achilles heel', but You provided hope for me in this area.

Malin Skagerlind, Research nurse, PhD, who helped us with the inclusion of patients and excel files of patients from Umeå, and at the same time You also Dissertated. Impressive!

Albert Crenshaw, for professional and swift language check of our papers and this thesis. Helpful, considerate, and meticulous. What else is there to wish for?

Bernd Ramsauer, for help and useful advice, especially with help to introduce me to the SNR Database, with all its possibilities and what one can and cannot do.

Björn Peters and **Henri Afghahi**, fellows, colleagues, friends, and schedule wizards. For always helping me out when time was lacking.

Pawel Nitkowski and **Maher Hamoud**, our vascular surgeons in Skövde for interesting discussions, teaching surgical matters and endless support.

Thomas Tamras, assistant physician, for collecting data concerning AVF interventions in our clinic during summer 2020.

Valentin Hadimeri, for collecting data in Excel files, moped excursions and shooting pool in the library.

Barbara Usener, **UNILABS,** for valuable advice concerning laboratory tests.

Ann Wigelius, Diagnostic Radiology, Department of Radiation Sciences, Umeå University Hospital, for additive insights concerning vascular access.

All other colleagues and friends at the Department of Nephrology, **SkaS**, for collaboration and for all support during the work of this thesis. **Especially** for all practical help and for pleasant cooperation during the work with the FIR-study.

My colleagues and friends at **FoU**, **(Research & Development Centre), SkaS.** For helping me out in practical and formal matters concerning research work.

Peter Johansson, Caroline Olofsson and **Martin Waldenvik, Bild o Media and IT, SkaS,** for valuable advice and help during the writing process, graphical style, posters, presentations, and cover illustration for the thesis.

…and especially, **Anna-Lena Emanuelsson-Loft** for fonts, subheadings wingdings and other very important details. **Åsa Nilsson**, research nurse, **FoU** for important stuff in protocols.

Colleagues and **staff** of the **Dialysis** unit, **DIAVERUM in Falköping.**

Karin Terstappen, **PhD**, for valuable advice concerning study design.

Finally, to **Evelina** my wife and my **Family** for endless support and providing me with input from real life, such as work in horse stables and gardening.

Ulla-Britt, my mother, who taught me where the sun is-over the clouds!!

To my two wonderful horses, **Shevil** and **Sarina** for adding silver lining on my days. To my cats, **Cocos, Citrus** and **Sigvard**-for always being there with endless affection and early Sheba mornings in the kitchen.

To **George Michael, Elton John, 10 CC, Van Halen, Nazareth, Alice Cooper, Sham 69, Britney Spears, Lady Gaga** and **Backstreet Boys** for the music.

To my friends at **Securitas**, for watching over me, at late evenings in my office.

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APPENDIX

Mapping inför AV-fistel
Vänster arm

Behöver mappas operationsdagen **Ja**
Undersökning utförd med värme **Ja**
Undersökning utförd med stas **Ja**
Puls **Tydlig**

Vener överarm

V. Subclavia andningsvariation **Ja**
V. Cephalica prox. Ø = **4,0** mm
V. Cephalica dist. Ø = **4,4** mm

Artärer överarm

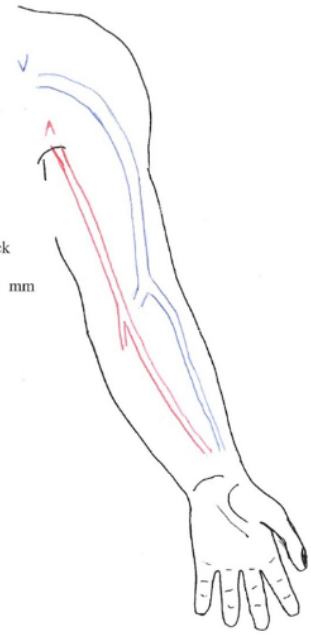
A. Brachialis **124** cm/s Ø = **5,5** mm
A. Brachialis flödesvolym **170** ml/min

Artärer underarm

A. Ulnaris prox. **104** cm/s Ø = **5,0** mm
Nivå på förgreningen Radialis-Ulnaris **3** cm dist. armveck
A. Radialis mid. **143** cm/s Ø = **3,2** mm
A. Radialis **5** cm ovan handleden **105** cm/s Ø = **2,4** mm

Vener underarm

V. Cephalica prox. Ø = **2,2** mm
V. Cephalica mid. Ø = **2,0** mm
V. Cephalica **5** cm ovan handleden Ø = **1,3** mm
Går ner på djupet **2** cm dist. armvecket.



BMA-anteckning:
Vener:
V Cephalica på underarmen är smal och fin. På överarmen är V Cephilaca vid och fin.
Artärer:
Alla artärer ser bra ut men någon vägginlagring.

Kärlkirurg är vidtalad i samband med undersökning.

Doktor-anteckning:

Figure 33. Preoperative mapping of blood vessels in the AVF arm.

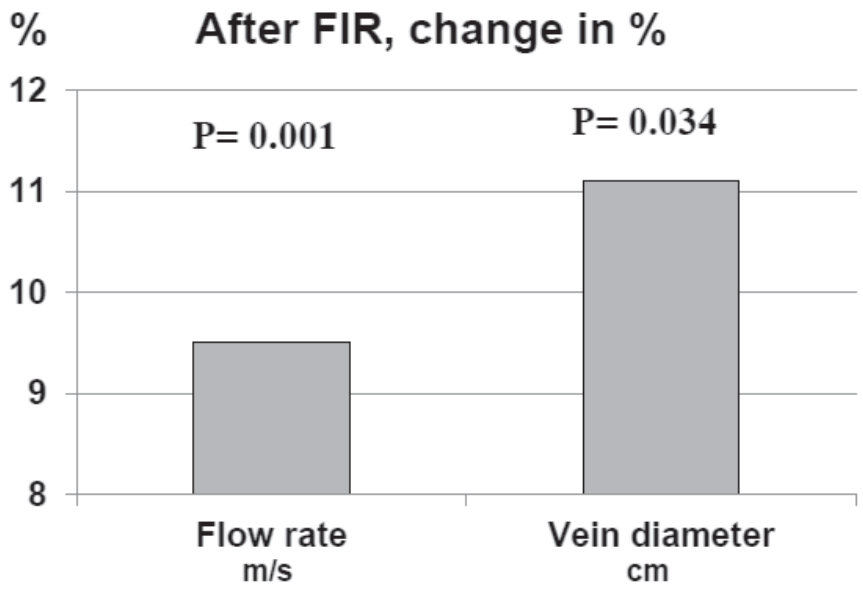


Figure 34. From study I. Change in AVF flow and vein diameter.

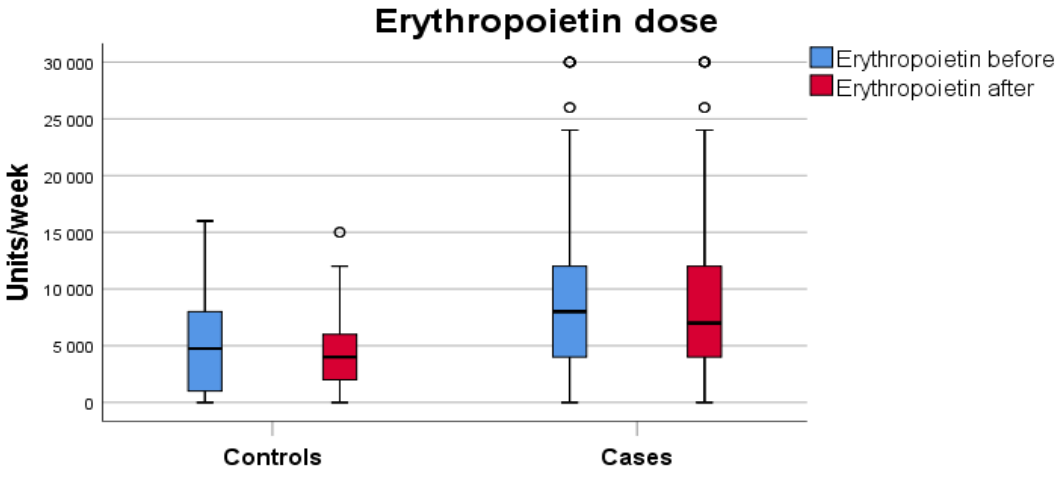


Figure 35. From study IV. Median weekly dose of ESA before and after intervention. There was a significant difference in doses between cases and controls, p<0.001.

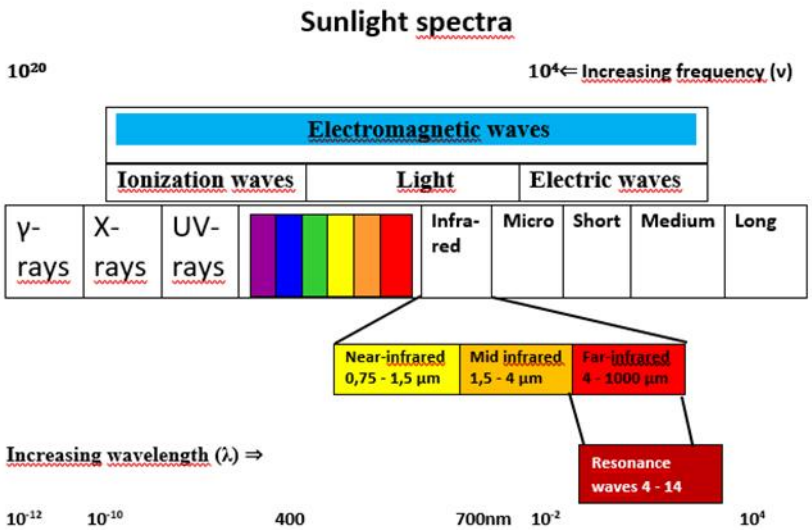
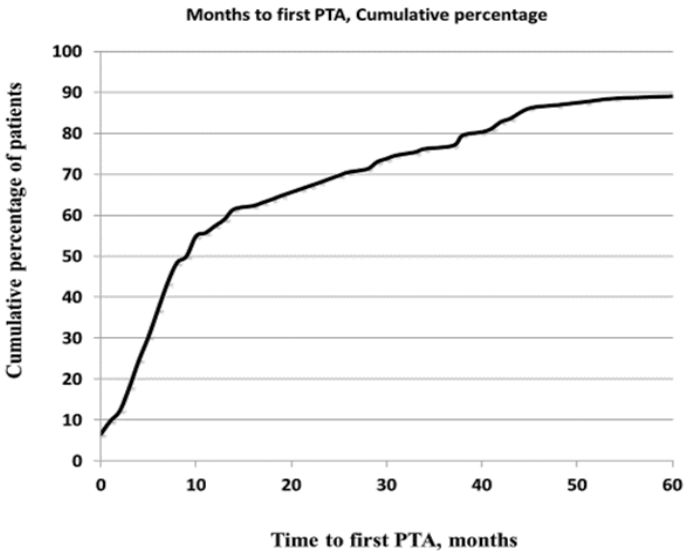
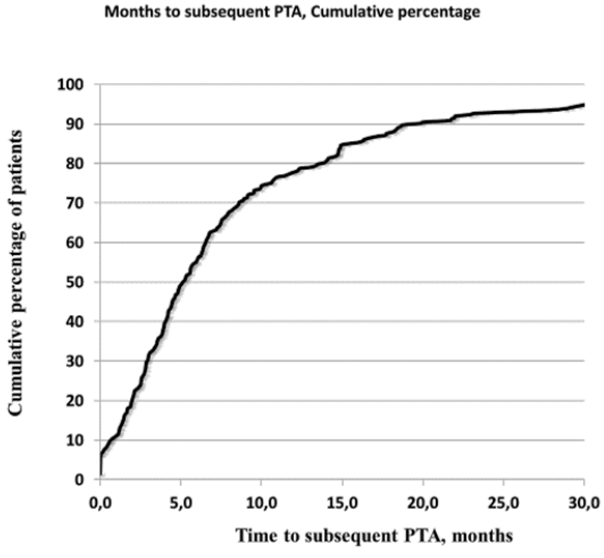


Figure 36. The sunlight spectrum modified by kind permission from Firapy®





Figures 37 and 38. From study III. Cumulative percentage of patients from surgical creation and to the subsequent PTA in months.