Tailoring hemodialysis vascular access : preoperative imaging techniques and computational modeling

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Tailoring Hemodialysis Vascular Access

- Preoperative imaging techniques and computational modeling -

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Tailoring Hemodialysis Vascular Access

-Preoperative imaging techniques and computational modeling-

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op gezag van de Rector Magnificus, Prof. mr. G.P.M.F. Mols
volgens het besluit van het college van Decanen,
in het openbaar te verdedigen
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"Doe al wat je doet niet half maar heel; niet het vele is goed maar het goede is veel"

- Simon Nuis -

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ABBREVIATIONS

AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BB-AVF	Brachiobasilic arteriovenous fistula
BC-AVF	Brachiocephalic arteriovenous fistula
BP	Blood pressure
bTFE	Balanced turbo field echo
CE-MRA	Contrast-enhanced magnetic resonance angiography
CKD	Chronic kidney disease
CO	Cardiac output
CoV	Coefficient of variation
CRP	C-reactive protein
CT	Computed tomography
CVC	Central venous catheter
DBI	Digital to brachial index
DSA	Digital subtraction angiography
DUS	Duplex ultrasonography
EBPG	European Best Practice Guidelines
e-CRF	Electronic case report form
EDV	End diastolic velocity
ESRD	End-stage renal disease
FBM	Fast-B-mode
GBCA	Gadolinium-based contrast agent
GFR	Glomerular filtration rate
HAIDI	Hemodialysis access induced distal ischemia
HD	Hemodialysis
ICC	Intraclass correlation coefficient
MIP	Maximum intensity projection
MMP	Matrix metalloproteinase
MPR	Multi-planar reformations
MRA	Magnetic resonance angiography
NCE-bTFE	Non contrast-enhanced balanced turbo field echo
NCE-MRA	Non contrast-enhanced magnetic resonance angiography
NIH	Neo-intimal hyperplasia
NO	Nitric oxide
NSF	Nephrogenic systemic fibrosis
NTx	Kidney transplantation
PAOD	Peripheral arterial occlusive disease
PD	Peritoneal dialysis
PSV	Peak systolic velocity
PTA	Percutaneous transluminal angioplasty
PTFE	Polytetrafluorethylene
PWV	Pulse wave velocity
RC-AVF	Radiocephalic arteriovenous fistula
RH	Reactive hyperemia
RI	Resistance index
RRT	Renal replacement therapy
VA	Vascular access
VMTK	Vascular Modeling Toolkit
WSS	Wall shear stress

CHAPTER

1

General introduction and outline of this thesis

END-STAGE RENAL DISEASE

Deterioration of renal function, characterized by a gradual decrease in glomerular filtration rate (GFR), has multiple etiologies and potentially results in renal failure. In patients in whom residual renal function is no longer sufficient to maintain homeostasis, renal replacement therapy (RRT) needs to be initiated in order to avoid the development of life threatening pathophysiological conditions associated with loss of renal function such as uremia, anemia, hyperkalemia, hypertension and edema¹.

Worldwide, the number of patients suffering from end-stage renal disease (ESRD) requiring RRT has grown substantially. At the end of 2009, 2.455.000 patients were estimated to depend on RRT, a number which is expected to increase to more than 7.124.000 by the year 2030². Preferably, these patients should undergo renal transplantation. However, shortage of donor organs requires alternative treatment modalities like peritoneal dialysis (PD) or hemodialysis (HD). The latter option is used in the majority of patients (69%)²⁻⁴.

VASCULAR ACCESS

Hemodialysis therapy requires access to the circulation to allow exchange of blood between the patient and the extracorporeal hemodialysis circuit. For efficient HD treatment, such a vascular access (VA) conduit should provide a flow of at least 600 ml/min and needs to be easily accessible for repetitive cannulation^{5,6}. In current clinical practice there are three options for the establishment of VA: the arteriovenous fistula (AVF), the arteriovenous graft (AVG), or placement of a central venous catheter (CVC). To identify the most suitable option for an individual patient, multiple factors should be taken into consideration, including time between VA creation and initiation of HD, as well as the condition of the patient's vasculature⁵. Nevertheless, guidelines advocate to avoid the use of graft material and CVC's as first choice options because of higher complication and mortality rates compared to native AVF's⁷⁻⁹.

Creation of an AVF comprises a surgical connection between an artery and a vein. In the vast majority of patients, AVF surgery is performed on the upper extremity vasculature, where, depending on the patient's vascular status, multiple fistula configurations can be employed. When located in the lower arm, a radiocephalic arteriovenous fistula (RC-AVF) is created by anastomosing the radial artery to the cephalic vein¹⁰. In case the lower arm vasculature is not suitable for AVF creation, secondary options can be exploited in the upper arm, including creation of a brachiocephalic arteriovenous fistula (BC-AVF) or brachio basilic arteriovenous fistula (BB-AVF) by anastomosing the brachial artery with either the cephalic vein or basilic vein at the level of the elbow¹¹⁻¹³.

By connecting the high-pressure arterial system with the low-pressure venous system, the

peripheral vascular bed is bypassed, resulting in the development of a low-resistance conduit that exposes the upper extremity vasculature to hemodynamic changes. Clinically, three different effects can be distinguished. *Local effects* are characterized by the increase of flow over the VA conduit due to a decrease in peripheral vascular resistance, and result in higher levels of wall shear stress (WSS) in the feeding artery as well as the draining vein. In response, endothelial cells in the arterial inflow vessel increase the production of nitric oxide (NO), which leads to arterial dilatation in an effort to restore WSS levels to baseline values¹⁴⁻¹⁶. Consequently, arterial dilatation results in a gradual flow increase^{17,18}. Another, more evident, local hemodynamic consequence is venous dilatation which occurs in response to increased pressure and flow in the draining vein^{18,19}. Ultimately, this process makes the fistula suitable for repetitive cannulation. *Peripheral effects* of VA creation comprise the dilatation of peripheral arterioles as well as the development of collateral inflow vessels in order to compensate for the decreased perfusion pressure distal to the anastomosis. The increase in cardiac output directly after fistula creation is considered a *systemic effect*: lower systemic vascular resistance provokes an increase in cardiac output in effort to maintain blood pressure²⁰. Altogether, in the short term these effects facilitate the process of adequate fistula maturation, and are mandatory to obtain a VA with sufficient diameter that allows for easy and repetitive cannulation, as well as a sufficient flow that enables adequate perfusion of the artificial kidney, and prevents the VA from thrombosis.

COMPLICATIONS AFTER CREATION OF ARTERIOVENOUS FISTULAS

Unfortunately, over the last couple of years AVF creation and its maintenance have become challenging due to changing demographic characteristics (e.g. age, gender) and increasing prevalence of cardiovascular comorbidities such as hypertension, diabetes mellitus, peripheral arterial disease and decreased cardiac function in the target population. These conditions negatively influence the quality of vessels utilized for AVF creation²¹, and increase the potential risk for postoperative complications.

In the preponderance of patients, VA complications are flow related and can be divided in either insufficient flow enhancement (e.g. early thrombosis, nonmaturation), excessive flow enhancement (e.g. steal syndrome, cardiac failure), or the development of stenoses within the VA conduit. It is believed that these complications result from inadequate vascular adaptation, poor vessel selection or poor surgical technique²². Early thrombosis and nonmaturation are more likely to occur in patients in whom marginal or diseased vessels have been utilized for AVF creation. Therefore, these conditions most frequently present after creation of a lower arm AVF²³. On the other hand, cardiac failure and steal syndrome are more common when upper arm vasculature is used for AVF creation, where vascular diameters are relatively large and allow for excessive flow

enhancement²⁴. Regardless of the location of the anastomosis, the majority of AVF's is subject to the development of stenoses in the VA conduit. While hemodynamic changes are mandatory for proper fistula maturation, continued exposure to locally elevated WSS levels appears to be responsible for ongoing vascular adaptation²⁵, potentially resulting in VA failure due to the development of stenoses or progression to high flow fistulas. In order to avoid the complications mentioned previously it is important to select the AVF configuration with the lowest probability of insufficient or excessive flow enhancement, as well as the configuration with the most favorable hemodynamic profile.

PREOPERATIVE ASSESSMENT

In current clinical practice, the most suitable VA configuration for the individual patient is decided upon preoperative vascular assessment in combination with the risk for postoperative complications and patency rates for each configuration. Previous studies have attributed significant predictive value to the vascular dimensions of the anastomosed artery and vein regarding the development of early failure and nonmaturation^{5,6,19,26,27}, thereby importantly influencing the strategy in VA creation.

Duplex ultrasonography (DUS) allows for objective depiction of adequate vessels for AVF creation that may not have been detected by physical examination. Generally, the most distal location where both artery and vein exceed a 2.0 mm threshold is chosen to create the surgical anastomosis⁶. By performing discrete diameter measurements over the intended arterial inflow and venous outflow trajectory, this location can easily be identified, and results in the creation of either a RC-AVF, a BC-AVF, or a BB-AVF. In case no suitable native vessels are identified during the examination, the surgeon can decide to explore other limbs, or reside to using prosthetic graft material. Although the clinical implementation of a routine preoperative DUS examination resulted in a significant reduction of postoperative failure rates²⁸, flow related complications persist²⁹.

In order to further reduce postoperative failure rates, alternative methods of preoperative vascular assessment have been widely investigated. For instance, mechanical characteristics of the upper extremity vasculature have been evaluated for their additional value in the preoperative work-up of patients^{27,30}; more compliant vessels are believed to result in better vascular remodeling, thereby allowing larger postoperative flow enhancement. However, regardless of the potential value, no objective quantification of upper extremity vascular stiffness has been introduced until now, which impedes the acquisition in the preoperative work-up of patients awaiting VA creation.

Furthermore, preoperative contrast-enhanced magnetic resonance angiography (MRA) examination of the upper extremity vasculature appeared to result in an improved depiction of the most suitable site for AVF creation by facilitating better local and global assessment of vasculature³¹, instead of vascular evaluation of discrete locations as is the

case with DUS. In addition, MRA enables interrogation of the central vessels, an area where DUS lacks diagnostic accuracy. Although preoperative vascular mapping with MRA is believed to be beneficial, its widespread clinical implementation has been hampered by the recent association between administration of certain types of gadolinium-based contrast agents (GBCA's) and the development of nephrogenic systemic fibrosis (NSF)³²⁻³⁴.

THE ARCH PROJECT

As discussed above, demographical factors (e.g. age, gender), comorbidities (e.g. hypertension, diabetes mellitus), anatomical factors (vascular diameter), mechanical factors (vascular compliance), and the presence of vascular pathology (stenoses, occlusions) have all been associated with AVF functioning and the development of complications⁶. Nevertheless, clinical decision-making is still generally based on the results of the preoperative DUS examination.

To further reduce AVF complications and improve long-term patency rates, computational modeling tools have increasingly become of interest³⁵⁻³⁷. By taking into account several patient-specific factors as well as their complex interaction, outcome after AVF surgery might be improved by predicting postoperative flow for multiple AVF configurations. As a result, the AVF configuration with the lowest probability of insufficient or excessive flow enhancement, as well as the configuration with the most favorable hemodynamic profile can be identified.

Within the 'patient-specific image-based computational modeling for improvement of short- and long-term outcome of vascular access in patients on hemodialysis therapy' (ARCH) project consortium (7th Framework European collaborative project), alternative preoperative imaging modalities and predictive computational models have been developed, calibrated and validated in both the experimental and clinical setting³⁸. From 2008 to 2012, industrial, technical, and clinical partners have been collaborating to provide the answers to the research questions addressed in this thesis.

GENERAL AIM OF THIS THESIS

The general aim of this thesis is to study the clinical feasibility of alternative preoperative imaging modalities in patients awaiting vascular access creation and to contribute to the development of predictive computational modeling tools.

SPECIFIC AIMS OF THIS THESIS

1. To provide an overview of current clinical evidence on the subject of vascular access for hemodialysis therapy.
2. To assess the feasibility of a novel non contrast-enhanced MRA technique for depiction of upper extremity vasculature prior to vascular access creation.
3. To describe the use of non contrast-enhanced MRA images in the preoperative assessment of upper extremity vasculature and to employ vascular segmentation techniques to obtain patient-specific vascular geometry.
4. To determine the reproducibility of brachial artery stiffness measurements.
5. To describe the development of a patient-specific pulse wave propagation model for simulation of upper extremity vascular access procedures.
6. To prospectively assess the potential of computational modeling for prediction of vascular access configuration and postoperative flow.

OUTLINE OF THIS THESIS

Over the last decades, tremendous progress has been achieved in the creation and maintenance of vascular access for chronic hemodialysis treatment. **Chapter 2** reviews current clinical practice for dealing with vascular access in the incident patient with end-stage renal disease. Furthermore, local, systemic and peripheral hemodynamic consequences of vascular access creation are discussed, together with their potential role in vascular access dysfunction. **Chapter 3** addresses the clinical study protocol that has been implemented to investigate the feasibility of alternative preoperative imaging modalities and the role of computational modeling. **Chapter 4** reports on the feasibility of a recently developed non contrast-enhanced MRA sequence for depiction of upper extremity vasculature prior to vascular access creation. The use of the obtained non contrast-enhanced images as well as the process of extracting arterial and venous geometry is described in **chapter 5**. **Chapter 6** assesses the reproducibility of brachial artery stiffness measurements by the non-invasive assessment of the local pulse wave velocity. **Chapter 7** explains the construction of a computational model that allows for simulation of outcome after upper extremity arteriovenous fistula creation. **Chapter 8** prospectively determines the performance of this computational model by predicting the most optimal vascular access configuration via simulating postoperative flow for multiple arteriovenous fistula configurations. **Chapter 9** provides a summarizing discussion in which the findings of this thesis are put in perspective and compared to previously performed studies. Also future directions for vascular access creation and management arising from this thesis are addressed.

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CHAPTER

2

Vascular access for hemodialysis therapies

A.S. Bode, J.H.M. Tordoir

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END-STAGE RENAL DISEASE

The kidneys play an important role in maintaining homeostasis inside the human body by their ability to remove metabolic waste products, electrolytes and water from the circulating blood. When the kidneys are no longer able to function at a level needed for daily life, end-stage renal disease (ESRD) occurs. In most patients, ESRD is the result of chronic kidney disease (CKD) and is characterized by a gradual decline in renal function until the capacity of the kidneys is decreased to 5-10% of their original function¹.

Over the last decades, ESRD has been more and more recognized as a global health problem with an increasing incidence and prevalence. Based on previous reports and current developments in global registries²⁻⁴, it is estimated that the total number of patients with ESRD increased from 1.479.000 in 2001 to 2.455.000 in 2009 (+66%). For these patients, the only treatment option consists of renal replacement therapy (RRT) by modalities such as hemodialysis (HD), peritoneal dialysis (PD) or renal transplantation (NTx). Despite the latter one being the treatment of choice, the number of available donor kidneys is not sufficient to treat all ESRD patients, and results in an average time of 4–5 years on a surgical waiting list. Therefore, alternative treatment modalities (HD + PD)

Figure 1: Development of the global end-stage renal disease patient population in need of renal replacement therapy over the years 2001, 2004 and 2009 regarding the 3 different treatment modalities^{2,3}. Based on the observed growth rates, the burden on renal replacement therapy will increase tremendously to a total of approximately 7.1 million by the year 2030 (*extrapolation of global registries based on current growth rates⁴)

have to be temporarily exploited before transplantation can take place. Moreover, the population analysis by Fresenius Medical Care reveals that the burden on these modalities will continue to increase: approximately 5.5 million patients will be depending on dialysis therapies by the year 2030 (Figure 1)⁴.

Dialysis therapies are based on removing waste products from the body by filtration of blood over a semi-permeable membrane. In HD, blood is extracted from the patient's circulation and purified in an artificial kidney where dialysate is flowing in opposite direction to blood. This counter-current flow maximizes the concentration gradient across the membrane to increase the efficiency of HD. The most important requirement to allow for efficient HD therapy is a reliable vascular access (VA) where blood can be extracted for purification and returned afterwards (Figure 2).

Figure 2: Schematic visualization of a hemodialysis circuit

HISTORY OF VASCULAR ACCESS

In 1924, Georg Haas performed the first HD treatment as an effort to sustain life and to relieve the features of uremia. Until 1929 he performed 11 treatments in uremic patients in whom he used glass cannulas for withdrawal and returning of blood⁵. His efforts were continued in 1943 by Willem Kolff who initiated the development of HD treatment as we know it today. He used a rotating drum kidney for extracorporeal purification of blood

Figure 3: Photograph of the rotating-drum kidney introduced by Willem Kolff in 1943. Blood runs around cellulose tubing which is wound around a drum made of wooden slats, dipping into the 'bath' of dialysate at the bottom of its turn. The movement of blood was powered by the rotation of the drum rather than a blood pump. (Origin of this picture not known)

(Figure 3), and required cannulation of the femoral or radial artery for extraction of blood, as well as cannulation of a large caliber vein for reinfusion. However, severe bleeding after the surgical cut down on the one hand and clotting of the extracorporeal circuit due to mismanagement in anticoagulation on the other hand resulted in a major limitation for HD treatment. In short: chronic HD therapy was hampered by the lack of a reliable access to the circulation.

The development of the Quinton/Scribner shunt in 1960 resulted in a major breakthrough. By connecting two Teflon cannulas (one in the radial artery and one in the adjacent cephalic vein) with a silicon rubber bypass tube, a low resistance high flow rate conduit was created that was suitable for repetitive cannulation (Figure 4)^{6,7}. Nevertheless, frequent infections and thrombosis initiated the search for better alternatives.

Only a few years later, Brescia, Cimino and Appel created an internal arteriovenous fistula (AVF) by subcutaneously connecting the radial artery to the adjacent cephalic vein⁸. Beside the fact that this approach resulted in less infectious and thrombotic complications, minimal postoperative problems were encountered: only two out of 15 operations failed. In the following years, several variations regarding fistula location and anastomotic

Figure 4: Quinton/Scribner shunt. (Origin of this picture not known)

technique were investigated and minor adjustments were implemented. For example, Gracz and co-workers investigated the possibility of creating a native AVF in the proximal forearm by connecting the perforating vein in the elbow to the brachial, radial or ulnar artery, which got wide-spread acceptance⁹. The only hurdle that still had to be taken was to come up with a solution for patients with no suitable peripheral veins for native AVF creation. A proposal from James May and Gilberto Flores-Izquierdo in 1969 resulted in the creation of a fistula in which a segment of the saphenous vein was implanted between the brachial artery and a proper vein in the elbow^{10,11}. Subsequent steps focused on the development of prosthetic graft material in order not to be dependent on native veins. Expanded polytetrafluorethylene (ePTFE) was introduced in vascular surgery in 1972 and was investigated by Baker and co-workers for its feasibility in VA creation¹². Until today, numerous publications have established the value of this prosthetic graft material and identified its pro's and con's in the dialysis population¹³.

Regardless of the use of native vessels or graft material, the development of stenoses within the VA conduit resulted in poor patency rates. In 1967, Charles Dotter performed a transluminal recanalization of an atherosclerotic obstruction and preluded the development of modern percutaneous transluminal angioplasty (PTA), which is able to deal with luminal narrowings within the VA conduit by endovascular dilatation by using a balloon¹⁴. Identification of these stenotic lesions became easy with the introduction of digital subtraction angiography (DSA) in 1979¹⁵. In DSA, images are acquired by exposing an area of interest to time-controlled x-rays while injecting a contrast medium into the blood vessels. The era of VA PTA started with a publication by Gordon et al.: "treatment of stenotic lesions in dialysis access fistulae and shunts by transluminal angioplasty"¹⁶.

Another important development in VA creation came from Shaldon in 1961. He introduced hand-made catheters for insertion in the femoral artery and vein by using the percutaneous Seldinger technique^{17,18}. In the following years, other vessels proved to be suitable as well: cannulation of the subclavian vein became the preferred method for temporary VA creation. The current opinion regarding central venous catheters (CVC) as a VA will be discussed further on.

OPTIONS FOR VASCULAR ACCESS

For a VA to be suitable for HD, certain criteria need to be met. Firstly, a high flow (usually in excess of 600 ml/min) needs to be provided to allow for efficient withdrawal of blood from the circulation as well as to prevent the VA from clotting. Secondly, the VA needs to be suitable for repetitive cannulation: a superficial cannulation trajectory with a sufficient length and diameter are mandatory to protect the patient from complications following miscannulation. Furthermore, the VA should have a good primary patency, have a low risk of complications and side effects, and leave opportunities for future procedures in the event of failure^{19,20}.

Although the ideal VA conduit does not exist, there are multiple options for access creation, each having specific advantages and disadvantages. Nowadays, decision-making in clinical practice takes place according to preoperative vascular imaging combined with knowledge regarding postoperative complications and patency rates for each configuration. Vascular imaging is performed to determine arterial and venous diameters and to assess their continuity within the upper extremity. Several observational studies have investigated the relation between minimal arterial and venous diameters and the risk of early failure and nonmaturation, thereby importantly influencing clinical strategy (Table 1)¹⁹⁻²³.

Table 1: Minimal vascular diameters for successful creation of a radiocephalic fistula

Study	Radial artery diameter (mm)	Cephalic vein diameter (mm)
Wong et al. ²¹	1.6	1.6
Silva et al. ²²	2.0	2.5
Malovrh ²³	1.5	1.6
K/DOQI Guideline ¹⁹	2.0	2.5
European Guideline ²⁰	2.0	2.0

Regarding postoperative VA patency, the following definitions are applied²⁴:

Primary patency

Primary patency (intervention-free access survival) is defined as the interval from time of access placement to any intervention designed to maintain or reestablish patency.

Assisted primary patency

Assisted primary patency (thrombosis-free access survival) is defined as the interval from time of access placement to access thrombosis, including intervening manipulations (surgical or endovascular interventions) designed to *maintain* the functionality of a patent access.

Secondary patency

Secondary patency (access survival until abandonment) is defined as the interval from time of access placement to access abandonment, including intervening manipulations (surgical or endovascular interventions) designed to *reestablish* the functionality of thrombosed access.

According to the NKF-K/DOQI guidelines¹⁹, a direct surgical connection between an artery and a vein as distal as possible in the upper extremity on the non-dominant side is the preferred configuration. In case distal vascular diameters are not suitable for creation of an AVF, more proximal vessels are utilized (Figure 5). When proximal vascular diameters are still not suitable, or in case native vessels are no longer available, one may consider the use of prosthetic graft material to create an access conduit. When HD therapy needs to be initiated before either an AVF or AVG is created, a CVC can be used as a temporary VA. However, CVC use should be minimized because of increased risk of sepsis, increased mortality, and development of central venous stenosis, which compromises future VA procedures in the ipsilateral upper limb²⁵. Unfortunately, many patients require a CVC either to start dialysis or as a bridge between AVF failure and the creation of a new VA.

Primary vascular access

A distal radiocephalic arteriovenous fistula (RC-AVF) is considered the best option for primary VA creation. Although creation of a RC-AVF may be compromised by insufficient vascular diameters, postoperative flow enhancement and dilatation of the venous cannulation trajectory are usually sufficient to meet the demands for dialysis prescription. Furthermore, it leaves more proximal sites for future procedures in the event of failure.

After a longitudinal or transverse incision near the wrist, the cephalic vein and radial artery are dissected from their surrounding tissue. Next, the cephalic vein is mobilized towards the radial artery where the anastomosis is created (Figure 6). Following successful creation of a RC-AVF it may function for years with a minimum of complications, revisions and

Figure 5: Upper extremity locations for native AVF creation. 1) Arteriovenous fistula at the anatomic snuffbox between the radial artery and the cephalic vein. 2) Arteriovenous fistula at the level of the wrist between the radial artery and the cephalic vein. 3) Location for proximalization of an arteriovenous anastomosis after failure at wrist level. 4) Arteriovenous fistula at the level of the elbow between the brachial artery and the cephalic vein / medial cubital vein. 5) Arteriovenous fistula at the level of the elbow between the brachial artery and the basilic vein.

Figure 6: Surgical creation of a radiocephalic fistula A) at the level of the wrist, and B) at the level of the anatomic snuffbox.

interventions. On the long term, RC-AVF's have a low incidence of thrombosis (0.2 events per patient per year) and infection (2%) compared to more proximal AVF's and the use of grafts²⁰. However, relatively high numbers of early thrombosis and nonmaturation are important disadvantages of this fistula configuration. Observational studies report early failure rates varying from 5% to 46% and secondary patency rates from 42% to 83% after one year of follow-up^{22,26-34} (Table 2). Older studies incorporated in the meta-analysis performed by Rooijens et al³², identified lower primary failure rates, which might be explained by the increase in comorbidities in the ESRD patient population nowadays. When a wrist RC-AVF has failed or is impossible to create, a more proximally located anastomosis (from the mid-forearm to the elbow between the radial artery and cephalic vein) may be employed before residing to secondary native VA procedures.

Table 2: Failure rates and secondary patency rates of radiocephalic fistulas

Study	Number of AVF's	Early failure (%)	1-year patency (%)
Silva et al. ²²	108	26	83
Golledge et al. ²⁶	107	18	69
Wolowczyk et al. ²⁷	208	20	65
Gibson et al. ²⁸	130	23	56
Allon et al. ²⁹	139	46	42
Dixon et al. ³⁰	205	30	53
Ravani et al. ³¹	197	5	71
Rooijens et al. ³²	86	41	52
Biuckians et al. ³³	80	37	63
Huijbregts et al. ³⁴	649	30	70

Forearm cephalic and basilic vein transposition and elevation

Forearm vein transposition or elevation results in more possibilities to create a forearm VA. In obese patients it might be necessary to elevate the cephalic vein in order to create a superficial cannulation trajectory. When the cephalic vein is not suitable due to its size or previous events of thrombophlebitis, the basilic vein can be transposed from the ulnar side to the radial side through a straight subcutaneous tunnel from the elbow to the radial artery. Alternatively, the basilic vein can also be anastomosed to the ulnar artery, though an additional volar transposition might be necessary to facilitate needling and to improve patient comfort during HD.

Secondary vascular access

Although the RC-AVF is preferred over any other type of fistula, initial VA creation more and more comprises the vessels in the upper arm, especially in the dialysis population with associated comorbidities such as diabetes mellitus, coronary artery disease, and peripheral arterial occlusive disease³⁵.

Elbow and upper arm cephalic vein arteriovenous fistulas

When forearm fistulas are no longer considered to be an option, more proximal vessels can be utilized for creation of a native AVF. The large caliber brachial artery and the cephalic vein can be anastomosed in the elbow, either directly or by involvement of the perforating vein from the median cubital vein (Figure 7). By ligating the basilic vein proximal to the anastomosis, venous return is directed through the cephalic vein. Brachiocephalic fistulas (BC-AVF's) usually have a high primary function rate and a good 1 year patency³⁶⁻⁴⁰ (Table 3). The most important disadvantages of BC-AVF's are the higher incidences of distal ischemia and high-output cardiac failure due to the relatively large flow enhancement, which will be discussed further on.

Figure 7: Surgical creation of a brachiocephalic fistula. **A)** vascular anatomy prior to vascular access creation, **B)** Creation of a Gracz fistula by anastomosing the perforating vein of the cubital medial vein to the brachial artery, and **C)** Creation of a brachiocephalic fistula by anastomosing the cephalic vein directly to the brachial artery.

Table 3: Failure rates and secondary patency rates of brachiocephalic fistulas

Study	Number of AVF's	Early failure (%)	1-year patency (%)
Murphy et al. ³⁶	208	16	75
Zeebregts et al. ³⁷	100	11	79
Lok et al. ³⁸	186	9	78
Woo et al. ³⁹	71	12	66
Koksoy et al. ³⁸	50	8	87

Upper arm basilic vein arteriovenous fistulas

In case the cephalic vein cannot be used for AVF creation, the more deeply located basilic vein can be utilized. Due to its deep and medial position in the upper arm, a superficialization and transposition procedure has to be performed in order to allow for repetitive cannulation (Figure 8). Patency rates after one year are reported between 47% to 89%, with primary failure rates of 2% to 23%^{36,40-44} (Table 4). Compared to BC-AVF's, brachio basilic AVF's (BB-AVF's) are more likely to mature, although they are more susceptible to late thrombosis⁴⁰. Moreover, creation of a BB-AVF is preferred over lower limb VA or the use of prosthetic graft material because of lower infection and thrombosis rates, as well as superior primary and secondary patency rates⁴⁵.

Figure 8: Native brachio basilic arteriovenous fistula. **A)** The basilic vein is completely mobilized from underneath the fascia in continuity with a section of the medial cubital vein through a longitudinal incision. **B)** Subsequently, the vein is transposed into a subcutaneous tunnel on the anterior surface of the arm and anastomosed to the brachial artery in an end-to-side fashion.

Table 4: Failure rates and secondary patency rates of brachio basilic fistulas

Study	Number of AVF's	Early failure (%)	1-year patency (%)
Murphy et al. ³⁶	74	3	75
Segal et al. ⁴¹	99	23	64
Wolford et al. ⁴²	100	20	47
Harper et al. ⁴⁴	168	23	66
Keuter et al. ⁴³	52	2	89
Koksoy et al. ⁴⁰	50	4	86

Tertiary vascular access

Prosthetic vascular access

When native AVF creation in the upper extremity is not feasible anymore, implantation of prosthetic graft material should be considered the next option. The most frequently used grafts are prosthetic ones made of either polyurethane (Vectra) or polytetrafluoroethylene (PTFE), and can be implanted on several locations in the upper extremity in either a straight or looped configuration (Figure 9). Short-term functional patency is usually good. However, the development of neo-intimal hyperplasia (NIH) with subsequent stenosis increases the risk of thrombotic occlusions. Primary patency rates vary from 60% to 80% after 1 year of follow-up and 30% to 40% after 2 years. Secondary patency rates are between 70% to 90% after 1 year and 50% to 70% after 2 years⁴⁶⁻⁴⁹. These patency rates can only be obtained with a strict follow-up protocol to diagnose and treat flow decrease at an early stage.

Figure 9: Prosthetic graft configurations in the upper extremity. **A)** Straight forearm arteriovenous graft from the radial artery at the wrist to the antecubital fossa in the elbow, **B)** Looped forearm arteriovenous graft from the brachial or radial artery to the antecubital fossa in the elbow, **C)** Straight upper arm arteriovenous graft from the brachial or radial artery to the axillary vein, **D)** Looped upper arm arteriovenous graft from the axillary artery to the axillary vein.

Measures to improve AVG patency rates have been widely investigated. Improvement of the compliance mismatch between prosthetic graft and both artery and vein was not proven to delay the development of stenotic obstructions⁵⁰. Also, pharmacological treatment with dipyridamole and Aspirin showed a significant but modest effect in reducing the risk of stenosis and improved the duration of primary unassisted patency of newly created AVG's⁵¹. Given the available evidence, anti-coagulant agents should be used routinely in patients with AVG's but not in patients with AVF's⁵².

Exotic vascular access

In difficult cases, VA surgery can also focus on the thorax or lower extremity (Figure 10). Probably the only indication for AVF creation in the lower extremity is bilateral central venous obstruction. These obstructions compromise the venous return to the heart and often result in venous hypertension and edema in case an upper extremity fistula is present. The VA conduit in the lower extremity can either be a straight or a looped traject. Initially, the saphenous vein or superficial femoral vein are exploited to create the fistula and allows for good patency rates⁵³. Preoperatively, the ankle/brachial index should be measured to rule out the possibility of peripheral arterial occlusive disease (PAOD) which could lead to a further decrease in arterial inflow after VA creation. Postoperatively, a strict follow-up protocol is advocated to monitor for distal hypo-perfusion and infection, in particular when prosthetic graft material is used to create the VA.

Figure 10: Prosthetic graft configurations for the thorax and lower extremity. **A)** Necklace graft from the subclavian artery on one side to the subclavian vein on the other side, **B)** Straight graft from the axillary artery to the femoral vein, and **C)** Straight and looped prosthetic graft configuration in the lower extremity. Please note that saphenous and superficial femoral vein transposition are the primary options for thigh AV fistulas.

A meta-analysis reporting on the outcome of lower extremity AVF's distinguishes three different configurations: the AVG in the groin, the AVG in the proximal part of the leg and the femoral vein transposition. Mean primary patency rates after 12 months were 48%, 43% and 83%, respectively. Mean secondary patency rates after 12 months were 69%, 67% and 93% respectively. Abandonment of the VA occurred more frequently when prosthetic graft was used compared to femoral vein transposition (18% vs. 1.6%; $P < 0.05$). Ischemic complaints manifested more frequently in native fistulas when compared to AVG's (21% vs. 7.1%; $P < 0.05$)⁵³.

Central venous catheters

Temporary CVC's are useful to gain immediate access to the circulation and facilitate HD treatment on short notice. However, the use of this type of VA has some important disadvantages: a shorter usability compared to AVF's, a significant risk of infection and the development of central venous stenosis^{25,54}. Therefore, placement of a CVC should only be performed in patients with acute renal failure who need immediate dialysis therapy, or in patients with chronic renal failure in whom a permanent VA by means of a fistula or graft is not a viable option, or has not matured yet. Also, patients with limited life expectancy, severe distal ischemia or cardiac failure may be better off using a CVC. Another indication for temporary dialysis by means of a CVC is in patients with a renal transplantation in the near future. In clinical practice, two types of catheters are used: non-tunneled catheters with a limited use and high morbidity; and tunneled catheters, which can be used for several months or even years (Figure 11).

Figure 11: Central venous catheters: **A)** Non-tunneled central venous catheter, and **B)** Tunneled central venous catheter

PREOPERATIVE WORK-UP

Patients diagnosed with ESRD should be instructed to abstain from venipunctures in the upper extremity (except the dorsum of the hand) in order to prevent formation of scar tissue: fibrotic changes in the venous wall hamper postoperative dilatation. When patients approach

the initiation of dialysis therapy, referral to a VA surgeon is mandatory. Following preoperative examinations, the surgical procedure is performed after which a period of maturation has to be taken into account before repetitive cannulation can take place. Here, the possibilities of preoperative work-up are discussed.

Medical history and physical examination

A thorough medical history allows the surgeon to identify patients with an increased risk for postoperative complications at an early stage. Studies have shown that the chance of successful creation and utilization of a VA is decreased in women, negroid patients, as well as in patients with diabetes, peripheral arterial occlusive disease and multiple attempts for VA creation in the past^{55,56}. When medical history is combined with physical examination, a first impression regarding the quality of vessels can be obtained. For the veins, diameters and distension are estimated after application of a tourniquet. Also, the length of the future cannulation segment and its corresponding depth are recorded. Subsequently, the quality of arterial pulsations is examined by palpation. Additionally, blood pressure measurements on both arms are performed to rule out significant arterial inflow stenoses. Finally, inspection of the neck should take place to identify collateral veins and skin lesions due to previous indwelling CVC's: previous CVC's might hamper successful creation of an AVF due to central venous stenosis.

Besides that interpretation of physical examination depends on the experience of the physician, less straightforward results may be obtained in obese patients due to a deeper location of the vessels⁵⁷. When solely depending on the results of physical examination, proximal vessels and prosthetic material might be used despite sufficient quality of vessels in the distal forearm. Therefore, objective imaging of arterial and venous structures in the upper extremity is recommended.

Duplex ultrasonography

Due to its non-invasive character, clinical availability and low costs, duplex ultrasonography (DUS) is an important diagnostic imaging modality. Several studies have shown that routine preoperative DUS examination is responsible for a change in surgical approach: Allon et al. registered an increase in native fistula creation in patients in whom an additional DUS examination was performed, compared to patients who were only subjected to a physical examination (64% vs. 34%)²⁹. The same study showed that the patient population with successful HD on an AVF could be doubled (16% vs. 34%) when a preoperative DUS examination was performed. Silva et al. reported an increase in the construction of AVF's (from 14% to 63%), a reduction of the use of prosthetic graft material (from 62% to 30%), and a reduction of primary catheter use (from 24% to 7%) when preoperative mapping of arteries and veins with DUS was performed²². However, regardless of its positive influence, there is still no consensus on the parameters of the examination and how the results should be interpreted.

According to the European Best Practice Guidelines (EBPG)²⁰, the complete upper extremity vascular tree should be visualized; from the subclavian artery to the arteries in the wrist, and from the distal cephalic and basilic vein to the subclavian vein. Over these vessels, diameter, course, continuity, side branches and possible stenotic segments need to be identified. During the examination it is important to apply a venous congestion pressure to induce dilation of the veins, which results in reliable and reproducible measurements⁵⁸. Examples of arterial and venous DUS acquisitions are visualized in figure 12.

Arterial and venous diameter measurements determine the most suitable location for AVF creation²¹⁻²³. Guidelines from the Vascular Access Society advocate AVF creation at the most distal site where both artery and vein have a diameter >2.0 mm. American guidelines are more conservative with a venous diameter $>2,5$ mm (Table 1).

Although routine DUS examination has resulted in increase in native AVF creation, it has an important limitation: central vessels cannot be visualized adequately due to their location behind the clavicle. As a result, pre-existing central venous stenoses and arterial

Figure 12: Preoperative duplex ultrasound examination. **A)** Axial venous diameter measurements are performed on multiple locations over the cephalic and basilic vein together with **B)** longitudinal diameter and flow measurements over the radial, ulnar, brachial and subclavian artery. Furthermore, the detection of pre-existing stenoses **C)** may influence clinical decision-making.

inflow stenoses are difficult to identify. For sufficient depiction of these vessels, other imaging techniques have to be employed, particularly in patients with an increased risk for central venous stenoses (multiple CVC's in the past) or when a difference in blood pressure between both arms has been registered.

Digital subtraction angiography

Additional preoperative imaging can be performed by means of digital subtraction angiography (DSA). Depending on the position of an intravenous catheter, arterial and venous structures can be visualized separately by injecting a contrast agent during x-ray examination. Although the acquired images are two-dimensional, detailed information regarding the *complete* arterial and venous vascular tree can be obtained. Moreover, stenoses, occlusions, side branches and collateral pathways can be identified easily (Figure 13). Nonetheless, DSA has a very important limitation which prevents routine

Figure 13: Examples of digital subtraction angiography where A) no pathology is detected in the central venous system, B) a significant central venous obstruction is depicted due to multiple previous indwelling CVC's (note: CVC in place during examination), C) two stenoses are detected in the cephalic vein which may compromise postoperative functioning, and D) an occluded cephalic vein with multiple venous side branches is visualized.

implementation in clinical practice: administration of a contrast agent. Most commonly, nephrotoxic iodinated contrast agents are used which potentially result in temporary or permanent loss of residual renal function. This occurs in approximately 20% of the predialysis patients in whom a DSA is performed⁵⁹. Therefore, careful selection of patients is required given that residual renal function is strongly correlated to overall patient survival⁶⁰. In an attempt to overcome this limitation, alternative contrast agents have been investigated: both gadolinium and CO₂ proved to be useful^{59,61,62}. However, also the utilization of these contrast agents is not free of risk, e.g. CO₂ requires a large dose administration for diagnostic images, thereby increasing the risk for pulmonary, cardiac and cerebral embolisms.

Magnetic resonance angiography

Another possibility to obtain structural and functional data of the upper extremity is by magnetic resonance angiography (MRA), which allows the radiologist to visualize both central and peripheral vessels. Prior to the introduction of MR contrast agents, non contrast-enhanced MRA (NCE-MRA) techniques were the only option but suffered from many artifacts, limited fields of view and long acquisition times. With the introduction of gadolinium-based contrast agents (GBCA's) these limitations were solved, and contrast-enhanced MRA (CE-MRA) became the standard of reference for diagnostic vessel imaging.

Figure 14: Typical example of a CE-MRA examination of the upper extremity where all arterial (A) and venous (B) stations are depicted. (With courtesy of Planken et al.¹³³)

Also in VA surgery, this method proved to be of additional value: a prospective study by Planken et al. showed that MRA examination prior to VA creation potentially results in a 30% decrease of nonmaturing fistulas because of improved depiction of the most suitable site for VA creation⁶³. Figure 14 shows a typical example of upper extremity CE-MRA.

However, several years after the introduction of GBCA's, a relation seemed to exist between the administration of linear GBCA's in patients with ESRD and the development of nephrogenic systemic fibrosis (NSF)⁶⁴. Although this condition only occurs in a very small percentage of the examined population, GBCA exposure in the ESRD population needs to be restricted. For that reason, the MRI community has shown interest in alternative MRA sequences and contrast agents: novel non contrast-enhanced techniques are the focus of current research to abstain from contrast administration in the future, and more stable (macrocyclic) GBCA's have been introduced for which no unconfounded cases of NSF have been reported until now.

Given the associated risks, angiographic techniques should not be used as a first choice for preoperative imaging. However, in patients who are at risk for central vascular pathology or in whom DUS is inconclusive, they are justifiable when appropriate precautions have been taken into account: decent prehydration, use of the lowest possible dose of contrast, and postprocedural HD in case a CVC is already in use.

USING THE ARTERIOVENOUS FISTULA

To facilitate HD, a VA should be easily accessible and suitable for long-term use with minimal risk of complications. It is reasonable to assume that complications caused by cannulation, such as hematoma, infection, and aneurysm formation, lead to morbidity, hospitalization, access revision, and an increased use of CVC's.

Pre-cannulation assessment

No consensus has been reached on when the VA is suitable for first time cannulation. Exploration of the DOPPS-database revealed that 42-62% of the newly created AVG's is cannulated within 2-4 weeks after surgery, while 36-98% of the native AVF's is cannulated within 2 months⁶⁵. Only fistulas with a sufficient flow (>500 ml/min) and diameter (>4.0 mm) are suitable for a first cannulation attempt^{66,67}. These parameters should therefore be investigated by a routine DUS evaluation 6 weeks after surgery.

Needling

For repetitive fistula cannulation 3 different techniques have been described: the rope ladder technique, the area technique, and the button-hole technique (Figure 15). The rope ladder technique uses the entire length of the cannulation segment for puncturing: every dialysis session, two new puncture sites, approximately 5 centimeters apart, are

Figure 15: Cannulation techniques. **A)** Rope-ladder technique, **B)** Area technique, and **C)** Button-hole technique

chosen. As a result, gradual remodeling of the entire cannulation segment will occur. However, in the majority of patients, often the same area of the fistula or graft is cannulated for reasons of comfort and ease (area technique). This may lead to aneurysmatic dilatations of the puncture areas with subsequent stenoses in adjacent regions. The button-hole technique centers around cannulating the AVF at exactly the same location, at exactly the same angle for every dialysis session. The first 8-12 times the fistula is cannulated, a sharp needle is used to create a trajectory which is kept open by inserting a plug after the dialysis session. After formation of the canals, dull needles can be used for cannulation after removing the crust.

Which technique should be used in a particular VA is still matter of debate. Studies emphasize that AVG's should be cannulated by the rope-ladder technique in order to prevent the graft from disintegration with subsequent aneurysm formation⁶⁸. In AVF's, more and more evidence exists that button-hole cannulation is a valuable alternative technique that is associated with reduced complication rates: less hematomas, less aneurysms, and less pain during cannulation. On the other hand, significantly more attempts are necessary for successful cannulation. Also higher infection rates have been observed in the patients

cannulated with the button-hole technique⁶⁹. Particularly in patients with a short cannulation segment, the button-hole technique is preferred over other techniques.

Monitoring for complications

In order to detect VA dysfunction at an early stage, a well structured monitoring program needs to be implemented on the dialysis ward. Monitoring should consist of a full physical examination of the VA prior to every dialysis session: inspection, palpation, auscultation. Also volume flow, recirculation, and static and dynamic arterial and venous pressure measurements can be performed during the dialysis session. Observed changes over time should be documented and further investigated by means of vascular imaging techniques like DUS, DSA or MRA. In case vascular pathology is visualized, preemptive correction of the lesion may result in prolonged fistula survival.

HEMODYNAMIC ASPECTS OF ARTERIOVENOUS FISTULAS

Physiological setting

Both heart and vascular tree are responsible for efficient transport of blood through the body and are controlled by the nervous system. This neural innervation is dedicated to maintain optimal hemodynamic parameters by acting on cardiac output, circulating volume, peripheral vascular resistance, and blood viscosity. Within the arterial vascular tree two separate forces can be distinguished which influence local hemodynamics: one acting perpendicularly on the arterial wall which influences all layers of the artery, and one acting parallel on the arterial wall (Figure 16). The latter one, wall shear stress (WSS), represents the effect of friction of blood flow on the endothelium and is quantified by Pascal (Pa) or dynes per square centimeter.

Figure 16: Schematic visualization of forces acting on the arterial wall: axial pressure (blood pressure) influences all layers over the arterial wall and acts perpendicular in all directions. Wall shear stress acts longitudinal over the inside of the arterial wall and is caused by friction of blood with the endothelial cells. As a result, blood velocity near the vascular wall is lower when compared to the center of the vessel.

Vascular access creation

In order to be suitable for HD, flow over the AVF needs to be at least 600 ml/min^{19,20}. For this, the feeding artery needs to dilate. Based on Pouseuille's law, where volume flow (Q) is proportional to the product of the pressure gradient (ΔP) and vessel radius (r) to the fourth power, divided by the viscosity (η) of blood, the brachial artery lumen would need to dilate by nearly 80% to achieve the required flow increase⁷⁰. Clinical studies have revealed smaller increases (40-50%)^{71,72} but identified other factors influencing postoperative flow enhancement: an increase in end diastolic velocity (EDV) and the contribution of retrograde flow on total fistula flow. Therefore, the surgical connection of an artery with a vein results in a changed hemodynamic profile. Clinically, three different effects can be distinguished: local, peripheral, and systemic.

Local effects

Local effects are directly provoked by the bypass of the peripheral arterioles: the sudden decrease in peripheral vascular resistance results in an increased blood flow over the VA conduit. The endothelial cells of the feeding artery are subjected to increased WSS (Figure 17), and respond by increasing the production of nitric oxide (NO)⁷³. Initially, NO facilitates relaxation of the smooth muscle cells but on the long term, also matrix metalloproteinases (MMP's) are activated which break down the fibrous tissue supporting the media layer of the artery⁷⁴. The NO mediated arterial dilatation is initiated in order to attempt restoring WSS levels to physiological values^{75,76}. The gradual increase in arterial diameter results in a gradual flow increase to a maximum value within 4-12 weeks after AVF creation^{21,77-79}. Postoperative venous dilatation ultimately determines fistula suitability. Venous dilatation occurs rapidly after fistula creation and continues for several weeks. Wong et al. presented a venous diameter increase of 51% one day after surgery, which further increased to 123% after twelve weeks²¹. These findings were confirmed by Corpataux et al. who found that the venous lumen increased by 86% at 1 week and 179% at 12 weeks⁷⁹. Besides an increase in venous diameter, the vessel wall will also thicken as a result of elevated pressures and micro trauma following repetitive cannulation. Another local hemodynamic consequence of AVF surgery is turbulence. At the arteriovenous anastomosis, flow is directed from the arterial system into the venous system over a pressure gradient. The magnitude of this pressure gradient depends on total vascular resistance of the AVF itself, and is determined by the location and size of the anastomosis. As discussed above, flow velocity and volume flow increase and become turbulent, which can be felt at the site of the anastomosis as a thrill (Figure 17). In case of a venous outflow stenosis / obstruction, this thrill can become pulsatile.

Systemic effects

Chronic kidney disease is often accompanied by a gradual decrease in cardiac function. At initiation of dialysis therapy, almost 75% of the patients is diagnosed with left

Figure 17: Computational fluid dynamic analysis of flow over the arteriovenous anastomosis; panel A represents the distribution of the velocity profile of blood. By further post processing, the obtained velocity profile can be used for creation and analysis of flow profiles (panel B [note the presence of turbulence at the heel of the anastomosis]). In panel C, wall shear stress (WSS) over the anastomosis is displayed; high levels of WSS are present at the 'outer curvature', while low levels of WSS are acquired just proximally of the anastomosis in the outflow vein; a typical location for the development of stenotic lesions. (Adapted with permission from A. Ramuzzi, L. Antiga, L. Botti)

ventricular hypertrophy, left ventricular dilatation or systolic dysfunction^{80,81}, and is considered to be the consequence of adaptive remodeling in response to pre-existing pressure- or volume overload⁸². Directly upon fistula creation cardiac output increases due to a reduction in peripheral vascular resistance, increased sympathetic nervous system activity and an increase in stroke volume and heart rate. The lower systemic vascular resistance induces an increase in cardiac output in effort to maintain blood pressure. Iwashima et al.⁸³ published a significant increase in left ventricular end-diastolic diameter (+4%) and cardiac output (+15%) 14 days after surgery.

Peripheral effects

Depending on the size and location of the anastomosis, peripheral perfusion decreases; blood is flowing through the VA conduit, rather than continuing to the distal extremity. Moreover, the anastomotic pressure drop may induce a retrograde flow in the artery distally of the anastomosis. This retrograde flow from the distal artery occurs in about 75% of all forearm fistulas and accounts for approximately 25% of the blood flow into the venous limb of the fistula⁸⁴. Nonetheless, blood supply to the distal extremity may remain adequate because of peripheral dilatation of the arterioles and the development / adaptation of collateral inflow vessels.

VASCULAR ACCESS COMPLICATIONS AND THEIR TREATMENT

Prior studies have revealed that patient variables influence the choice and outcome of VA creation. Lin et al. identified age as an important factor for postoperative flow enhancement. In elderly patients, 18.9% of the newly created fistulas failed to mature while in younger patients this was only 13.6%⁸⁵. Moreover, high age in combination with diabetes mellitus resulted in even higher failure rates (28.6%). The influence of gender is controversial in the literature. A study from Caplin et al. showed comparable preoperative diameters of arteries and veins in both male and female patients which resulted in the successful creation of an AVF in 72% of the female and 77% of the male patients. On the other hand, multiple studies suggest higher rates of nonmaturation and primary failure in the female population, with subsequently a higher percentage of AVG's and more endovascular and surgical revisions^{28,86-90}. The meta-analysis of Rooijens et al.³² illustrated comparable maturation and patency rates for RC-AVF's in male and female patients. Other determinants involved in decision-making were peripheral arterial occlusive disease, race and obesity⁵⁵. Elevated homocysteine levels do not induce VA failure⁹¹, while elevated lipoprotein levels in negroide dialysis patients are believed to be a risk factor for fistula complications⁹². A retrospective study revealed C-reactive protein (CRP) as an independent predictor for VA thrombosis⁹³.

Nonmaturation of arteriovenous fistulas

Although no well-established criteria have been defined for maturation, fistulas are considered mature when they can be routinely cannulated with two large-bore needles and deliver an adequate blood flow for the total duration of dialysis (typically 350-450 ml/min). Depending on the fistula configuration, a mature forearm AVF will have a blood flow of 600-1200 ml/min while an upper arm AVF will have a flow between 600-2000 ml/min. Therefore, nonmaturation of native fistulas is characterized by either insufficient flow enhancement, insufficient venous dilatation or by cannulation difficulties due to a deep location of the cannulation segment, which is the consequence of either poor selection of vessels, poor technique, or postoperative hemodynamic instability.

Physical examination combined with DUS or DSA should identify the underlying cause. In the majority of cases, nonmaturation is caused by vascular abnormalities in the juxta-anastomotic region (Figure 18). Using angiography, Beathard et al. identified venous stenoses and accessory veins in 78% of the nonmaturing fistulas. 43% of these cases showed abnormalities around the anastomosis⁹⁴. Another study described that 61% of

Figure 18: Nonmaturing fistula with a clear stenotic segment in the juxta-anastomotic region. After diagnostic DSA, a balloon is inflated in order to dilate the narrowed vessel segment. Post-procedural angio-graphy reveals no residual stenosis.

the stenoses in nonmaturing fistulas is present in the juxta-anastomotic region while 39% of the stenoses were located in the venous outflow⁹⁵. Proximal arterial inflow stenoses were identified in 25% of the nonmaturing fistulas when the complete upper extremity vascular tree was imaged⁹⁶. Therefore, in nonmaturing fistulas, the complete arterial inflow and venous outflow should be evaluated for identification of arterial inflow stenosis, venous outflow stenosis, or accessory veins which hamper a proper fistula maturation. Treatment of nonmaturing fistulas comprises percutaneous transluminal angioplasty (PTA) of stenoses, thrombectomy, thrombosuction, thrombolysis, ligation or embolisation of accessory veins, main stream banding, and superficialisation of the outflow vein in case the depth of the cannulation segment results in cannulation difficulties. A systematic review by Voormolen et al. revealed an 86% success rate after surgical or endovascular intervention in nonmaturing fistulas with primary and secondary patency rates of 51% and 76%, resp⁹⁷. When interventional procedures do not result in successful maturation, surgical revision of the anastomosis can be performed using local anesthesia. When the involved vessels are too severely diseased for AVF creation, more proximal vessels can be utilized before residing to graft material.

Stenosis and thrombosis

Fistula stenosis and thrombosis

Endothelial and smooth muscle injury (hemodynamic stress, surgical injury, dialysis needles, PTA) result in the migration of smooth muscle cells and myofibroblasts from the media to the intima, where they proliferate and form the lesions of venous neointimal hyperplasia (NIH), which narrows the vessel lumen⁹⁸. These lesions can be indentified in the complete venous outflow tract but are more common in certain areas, particularly around the arteriovenous anastomosis.

Depending on the anastomotic configuration, distribution of WSS differs over the various locations: some sites are exposed to high and others to low WSS (Figure 17). High levels of WSS are associated with appropriate vascular dilatation and a relative lack of NIH. Most likely this is the result of endothelial quiescence, high levels of NO and low levels of inflammatory cytokines. On the other hand, low or oscillatory WSS tends to be involved in limited vascular dilatation and an increase in NIH: endothelial deactivation, low levels of NO and increased inflammatory mediators predispose to the development of vascular stenoses (Figure 19)⁹⁸. While hemodynamic shear stress is the most important factor for stenotic AVF failure, other factors like surgical injury, and repetitive cannulation also play a role. Also, the treatment of AVF stenosis, PTA, can result in significant endothelial and smooth muscle cell injury and potentially result in an exacerbation of the re-stenotic lesion⁹⁹. Reduction of the vessel lumen by more than 50% together with a reduction of access flow (AVF < 500 ml/min; AVG < 600 ml/min or >25% decrease with a total flow < 1000 ml/min) require vascular imaging and pre-emptive treatment in order to avoid VA failure¹⁹. Other conditions suspicious for the presence of stenosis are cannulation difficulties, upper

extremity edema, prolonged bleeding time, or ischemic complaints. In RC-AVF's, 55-75% of the stenotic lesions occurs around the anastomosis, while 25% is localized in the venous outflow tract. In patients with BC-AVF's stenotic lesions are also often localized where the cephalic vein enters the subclavian vein (cephalic arch), while BB-AVF stenosis frequently occurs where the basilic vein enters the brachial vein^{100,101}.

Figure 19: Schematic visualization of the processes involved in the development of stenoses which are influenced by wall shear stress. (Taken with permission from European Vascular Course, Maastricht, 2010)

Endovascular treatment by percutaneous transluminal angioplasty (PTA) is the first option for arterial and venous stenoses and provides good salvage rates^{102,103}. During this procedure, a balloon is inflated over the stenosis, resulting in luminal widening. Some stenoses may not be sufficiently dilated using conventional balloons, however, cutting balloons or ultra-high pressure balloons may give better results¹⁰⁴. In case of frequent re-stenosis surgical revision may be performed by proximalisation of the anastomosis or by inserting a patch or graft interposition.

AVF thrombosis has an incidence of approximately 0.2 events per patient/year²⁰. When present, thrombectomy, thrombosuction or thrombolysis should be performed as soon as possible (<24 hours) in order to prevent thrombus adhesion to the vessel wall. Timely correction might result in the avoidance of CVC's. Early detection of VA dysfunction with subsequent vascular imaging and prophylactic treatment reduces the actual number of complications and results in higher patency rates. Therefore, dedicated DUS examination should be performed regularly in order to detect structural and functional abnormalities in the in- and outflow trajectory of the VA.

Graft stenosis and thrombosis

Patients in whom prosthetic graft material is used for VA creation are also at risk for graft dysfunction and graft thrombosis: on average 0.8 thrombotic complications are observed per patient per year^{20,105}. Hence, graft monitoring by flow measurements or DUS is recommended; with preemptive endovascular treatment, graft thrombosis may be reduced. Stenosis in AVG's are particularly common near the venous anastomosis and are caused by turbulence and compliance mismatch. Also, in the cannulation segment, excessive ingrowth of fibrous tissue through the puncture holes results in luminal narrowing. Treatment is indicated by PTA, graft curettage, or partial graft replacement. Initial success rates of 73% and primary patency rates of 32% and 26% at 1 and 3 months, respectively, have been reported¹⁰⁶⁻¹⁰⁸. When endovascular treatment fails or is not possible, surgical thrombectomy may be performed with a Fogarty catheter. On-table DSA should be performed after completion of thrombectomy of both arterial and venous limbs of the graft.

Aneurysms

Aneurysm formation within the VA conduit can be induced by elevated intraluminal pressures in combination with a weakened venous wall¹⁰⁹. Both AVF's and AVG's are at risk for aneurysm formation due to repetitive large bore cannulation which negatively influences the quality of the cannulation segment. Stenotic deformations in the venous outflow trajectory are often responsible for the increase in luminal pressure¹¹⁰. Therefore, in patients with evident aneurysms, vascular imaging techniques should be employed (Figure 20). Treatment of the stenosis might stop aneurysm expansion: a single study reports that in 73% of the patients, development of venous outflow stenoses is in line with development of aneurysms¹¹⁰.

Figure 20: Aneurysmatic dilatation of an arteriovenous fistula due to repetitive cannulation in the same segment (area-technique): A) photograph, and B) corresponding DSA

Aneurysms in the VA conduit are at risk for thrombosis due to high residence time of blood and accordingly higher risk of platelet aggregation. Aneurysms are detected by inspection and confirmed by either DUS or DSA. Surgical correction of aneurysms is indicated when the diameter of the aneurysm is 2 times the diameter of the cannulation segment, a very superficial location of the aneurysm results in an increased chance of rupture, infectious parameters are present, the aneurysm is painful or increases in size, or when an obstructive intraluminal thrombus is present

Treatment of VA aneurysms depends on the type of aneurysm (true or false), the type of VA (AVG or AVF), and the location of the aneurysm. For aneurysms near the arteriovenous anastomosis, surgical correction is the treatment of choice¹¹¹. When possible, the anastomosis should be proximalized in order to save the VA conduit. In case a longer segment is compromised, the diseased segment needs to be excised and replaced by an interposition graft. Recent literature also reports the possibility of endovascular exclusion of the aneurysm by means of a covered stent¹¹²⁻¹¹⁴. However, no studies have been performed to identify superiority of one technique over the other.

Hemodialysis access induced distal ischemia

Hemodialysis access induced distal ischemia (HAIDI) or steal syndrome arises from insufficient endogenous cardiovascular adaptation mechanisms following the creation of an AVF. The loco-regional drop in blood pressure near the anastomosis in combination with pre-existing atherosclerosis and vascular calcification may result in reduced perfusion pressures distally of the anastomosis and may become symptomatic (Figure 21).

Figure 21: Digital necrosis due to impeded perfusion of the tissue distally of the anastomosis: the most severe clinical manifestation of hemodialysis access induced distal ischemia (HAIDI).

Severe chronic distal ischemia after VA creation is a serious complication with an incidence between 2% and 8% in the HD population¹¹⁵. However, more than 75% of the dialysis patients reports one or more complaints: coldness, pain, weakness, pallor, and paresthesia¹¹⁶. These ischemic complaints can be objectivated by measuring digital blood pressure or transcutaneous oxygen pressure. Digital pressure can be interpreted as an absolute value or in relation to the contra-lateral brachial artery pressure: the digital to brachial index (DBI). Healthy individuals and asymptomatic patients with a VA have a DBI (Pdig / Psyst) > 0.8 while symptomatic patients often have a DBI <0.6 which increases during compression of the fistula¹¹⁷⁻¹¹⁹. When complaints, physical examination and finger pressure measurements indicate distal ischemia, classification should be performed; like the Fontaine classification for peripheral arterial occlusive disease, 4 separate stages have been defined¹²⁰ (Table 5).

Table 5: Classification of hemodialysis access induced distal ischemia.

HAI/DBI	Symptoms
Stage 1	Pale or blue hand without pain; no complaints
Stage 2	Complaints during HD or exercise: a) acceptable b) unacceptable
Stage 3	Ischemic complaints during rest
Stage 4	Ulceration, necrosis and gangrene

The treatment strategy depends on the etiology of the ischemia. Conservative treatment is indicated in patients with stage I and IIa and consists of heat application, adjustments in medication and exercise for improvement of collateral circulation¹²⁰. In patients with more advanced stages, diagnostic vessel imaging is needed to rule out any arterial inflow stenoses¹²¹. Therefore, a DSA can be performed after which hemodynamic significant arterial stenoses can be treated by PTA^{96,122}. Patients with stage IIb or higher, not responding to conservative and endovascular treatment, need to be evaluated for surgical intervention, aimed at reducing access flow. Flow reduction can be performed by either surgical ligation of the fistula, surgical ligation of side branches and banding of the AVF. Also, several bypass procedures are available to the surgeon which improve distal perfusion of the upper extremity. The results of these procedures are usually good, however, in some patients, AVF ligation and transition to chronic CVC dialysis or PD may be the only solution.

Cardiac failure

The decrease in the peripheral vascular resistance results in acute and prolonged increase of cardiac output^{123,124}. Cardiac failure results from incapability of the myocardium to adapt to the new situation where, besides the normal circulation, also a fistula circulation

must be provided while maintaining blood pressure. A study performed by Basile et al.¹²⁵ reported that patients with a fistula flow >2.2 l/min have a significantly higher mean cardiac output than patients with a fistula flow <2.2 l/min. In the same study, the ROC curve analysis identified that flow values >2.0 l/min predicts the occurrence of cardiac failure accurately with a sensitivity of 89%, a specificity of 100% and a curve area of 99%. The incidence of these high flow AVF's, is estimated around 4% of which the majority (95%) consists of native elbow fistulas. In case the heart has difficulty to comply, patients can experience symptoms of cardiac failure as classified by the American Heart Association¹²⁶. Regular access flow measurements are necessary to identify patients at risk. In case repetitive access flows of >2 L/min are measured, and the patient complains of dyspnea, additional examinations need to be performed: a thorough physical examination, ECG registration and echocardiography are mandatory. In symptomatic patients several treatment options exist and depend on the life expectancy and comorbidities of the patient. Conservative treatment can be attempted in patients with minor complaints and consists of correcting anemia, hypertension and electrolytes. Furthermore, blood supply to the heart may be improved by performing endovascular procedures to the coronary arteries. Surgery is performed in patients not responding to conservative treatment with an access flow >2 L/min or in patients with lower access flows but with significant symptomatology. Basically, to decrease the cardiac burden, fistula flow needs to be reduced (to a level where it still delivers an adequate fistula flow for HD). In order to achieve this, the clinician has the availability over the same procedures as in patients with HAIDI: ligation of the AVF, ligation of hemodynamic important side branches, narrowing the arteriovenous anastomosis, the RUDI-procedure or the banding procedure.

Central venous obstruction

Central venous obstruction is a complication which often results from previous indwelling CVC's or pacemaker leads. On average, 40% of the patients who have had a CVC in the subclavian vein develop a significant central venous stenosis, while CVC's in the internal jugular vein result in a central venous stenosis in 20% of the patients¹²⁷. Usually, such an obstruction is asymptomatic, however, when an AVF is created in the ipsi-lateral upper extremity, symptoms may develop as a result of flow increase, and consist of prolonged bleeding time, local swelling, edema or even venous ulcera. Patients with mild complaints benefit from conservative treatment. In case local swelling, venous ulcera or infection hamper fistula cannulation, vascular imaging needs to be performed: e.g. conventional phlebography visualizing the veins from the upper arm into the superior caval vein (Figure 13b). Symptomatic central venous obstructions can be treated by endovascular procedures¹²⁸, with an initial success rate of 95%. Primary patency however is relatively low (10-20% after 1 year): multiple re-interventions due to re-stenosis are necessary to maintain central vein patency¹²⁹. Some studies suggest better patency rates with additional stent placement over the stenotic segment^{130,131}.

If endovascular therapy has failed, a surgical intervention can be attempted and is performed according to the patient's condition, life expectancy and vascular pathology. Initially, a surgical bypass over the stenosed or occluded segment is indicated and can be directed to the contra-lateral side or even the lower extremity. When surgical bypass fails, ligation of the upper limb VA can be considered to relieve symptoms but requires an alternative VA for dialysis therapy.

FUTURE DIRECTIONS FOR VASCULAR ACCESS

Although great progress has been achieved over the last decades, VA creation and maintenance remains the Achilles heel of chronic HD treatment. Bearing in mind that the ESRD patient population will increase tremendously, will be older when the first VA procedure needs to be performed, and most likely suffers from multiple comorbidities that affect the quality of the cardiovascular system, alternative strategies need to be explored to tailor VA management to the individual patient in an effort to reduce short- and long-term AVF dysfunction.

It has been shown that a multi-disciplinary approach according to national and international guidelines has the potential to reduce VA related complications¹³². Essential in these guidelines is a shift from *management* of complications to *prevention* of complications: by detecting VA dysfunction at an early stage, preemptive treatment allows for improved patency rates. Within such a multidisciplinary team, the nephrologist, the vascular surgeon, the interventional radiologist and the dialysis nurse play an important role, and are responsible for providing pre-dialysis information and education, timely referral to the vascular surgeon for creation of the AVF, preoperative screening, observation of fistula maturation, repetitive cannulation of the AVF, postoperative monitoring of the AVF, and management and treatment of complications.

Another very promising strategy is the development of computational tools that allow for preoperative prediction of postoperative AVF function by simulating the cardiovascular effect of VA creation. Ultimately, such predictive tools should be able to identify the AVF configuration with the most optimal postoperative hemodynamic profile, resulting in the lowest postoperative complication rates.

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CHAPTER

3

Clinical study protocol for the ARCH project: Computational modeling for improvement of outcome after vascular access creation

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ABSTRACT

Despite clinical guidelines and the possibility of diagnostic vascular imaging, creation and maintenance of a vascular access (VA) remains problematic, and avoiding short- and long-term VA dysfunction is challenging. Although prognostic factors for VA dysfunction have been identified in previous studies, their potential interplay at a systemic level is disregarded. Consideration of multiple prognostic patient-specific factors and their complex interaction using dedicated computational modeling tools might improve outcome by enabling a better selection of VA configuration. These computational modeling tools are developed and validated in the ARCH project: a joint initiative of four medical centers and three industrial partners (FP7-ICT-224390). This paper describes the rationale behind computational modeling and presents the clinical study protocol designed for calibrating and validating these modeling tools. The clinical study is based on the preoperative collection of structural and functional data at vascular level, as well as VA functional evaluation during the follow-up period. Also, the strategy adopted for study conductance and data collection is described here.

INTRODUCTION

End-stage renal disease (ESRD) is a major and growing social healthcare problem associated with substantial costs^{1,2}. It is to be expected that by the end of 2010 the global patient population requiring chronic renal replacement therapy (RRT) exceeds 2 million of which approximately 90% will depend on hemodialysis (HD) therapy^{3,4}. To facilitate adequate HD therapy a reliable vascular access (VA) is mandatory and can be provided by either creation of a native arteriovenous fistula (AVF), a prosthetic arteriovenous graft (AVG) or a central venous catheter (CVC). Guidelines by the National Kidney Foundation (NKF K/DOQI Guidelines), the Vascular Access Society (Good Nephrological Practice Guidelines) and the European Dialysis and Transplant Association (European Best Practice Guidelines on HD) advocate the implementation of an all-autologous policy to maximize the use of AVF over AVG and CVC because AVF have the best long-term patency, fewer complications and require less interventions once fully matured⁵.

Although the implementation of preoperative duplex ultrasonography (DUS) reduced the total number of early AVF failure by improved selection of the most suitable site for AVF creation, short- and long-term AVF dysfunction remains the major cause of morbidity and hospitalization in HD patients, and is therefore the major limitation of HD treatment^{6,7}. This dysfunction is usually associated with nonmaturation of the newly created AVF or the formation of neointimal hyperplasia (NIH) which potentially results in decreased flow and eventual thrombosis⁸. On the other hand, the low resistance trajectory via the AVF may lead to impeded perfusion of the extremity distally of the anastomosis, while the large extra AVF flow may lead to the development of left ventricular hypertrophy^{9,10}, both with severe consequences.

Numerous studies have investigated alternative preoperative mapping criteria for further reduction of AVF related complications^{9,11-15}, however, current clinical use of these individual parameters does not take into account their potential interplay at a systemic level. Consideration of multiple prognostic parameters within a single patient is likely more valuable to improve outcome; tailoring the AVF to the individual patient.

A possible solution to deal with multiple independent prognostic factors is by implementation of a predictive computational tool that accounts for individual differences in anatomical, physiological, demographical and hemodynamic parameters. More importantly, by taking their complex interplay into consideration, simulation of outcome after AVF creation is at hand. Given the high inter-subject variability these modeling tools need to be patient-specific for reliable prediction. Patient data on vascular and cardiac adaptation are of major importance, but until now complete datasets containing the required data for modeling are not available, pointing out the need for a clinical study on ESRD patients undergoing AVF creation for HD treatment, and their systematic prospective longitudinal follow-up.

Aim of this paper is to describe the rationale behind VA computational modeling and,

subsequently, to introduce the ARCH clinical study, which has been designed within the ARCH FP7 ICT project (ARCH; patient-specific image-based computational modeling for improvement of short- and long-term outcome of vascular access in patients on hemodialysis therapy). Within the current clinical study, longitudinal collection of cardiovascular data takes place with the intention to develop, calibrate and validate patient-specific modeling tools for surgical planning and assistance in the management of complications arising from AVF creation. Given the difficult and heterogeneous target population, the study protocol has been designed in such way that pre- and post-operative imaging could be performed strictly, aiming at complete datasets of structural, functional and demographical data. Following the validation of the computational model, a proposal for a large-scale randomized observational study, aiming at evaluating the potential beneficial effect of the use of computational tools in reducing AVF-related clinical problems, will be designed.

RATIONALE FOR VASCULAR ACCESS COMPUTATIONAL MODELING

Modeling has become a well-accepted approach to analyze cardiovascular hemodynamics. Ever since Grodins et al.¹⁶ created the first global dynamic model of the circulation using a mathematical approach, major improvements in medical imaging as well as advances in numerical methods and increased computational capabilities, have facilitated the development and use of image-based modeling technologies, which already have been used to investigate hemodynamics in aortic aneurysmal disease¹⁷⁻²⁰ as well as in cerebral^{21,22} and coronary artery^{23,24} disease. Besides investigating global and local hemodynamic parameters in cardiovascular diseases associated with atherosclerosis and aneurysm growth, recent modeling efforts are put into prediction of outcome after surgical and interventional procedures²⁵.

In order to be suitable for application in clinical practice, a model has to be accurate, predictive, economical, and useful²⁶. Only if predicted values reliably correspond with measured values, they provide additional insight into the physiological processes associated with pathology at individual patient level. For this, different mathematical models have been employed which are capable of describing cardiovascular mechanical properties at various levels of detail: lumped parameter models, one-dimensional (1D) wave propagation models and three-dimensional (3D) numerical models. For a detailed description of these modeling techniques the reader is referred to a recent review by Taylor et al.²⁷

Before patient-specific cardiovascular modeling can take place, several criteria have to be met. First, it is essential to obtain patient-specific anatomical information by either 'non-invasive' imaging techniques i.e. computed tomography (CT), magnetic resonance angiography (MRA), and DUS, or by invasive methods in the form of digital subtraction

angiography (DSA). The standard of reference for non-invasive diagnostic vessel imaging, contrast-enhanced (CE) MRA, is particularly suited for the acquisition of vascular geometry and depiction of vascular pathology because of its capability to obtain high-resolution 3D images. Subsequently, the anatomical information can be used for extraction of geometric models by making use of vascular segmentation techniques²⁸. For simulating hemodynamic conditions related to the geometric model, physiological data needs to be collected. In order to calibrate the model to the individual patient, vessel diameter and flow profile need to be measured at specified locations. Total cardiac output (CO) and blood pressure (BP) distribution over the vascular tree are important quantities as they define the boundary conditions of the model. To acquire these physiological data, blood pressure measurements, DUS evaluation, as well as phase-contrast MRA of the arteries, veins and heart are available in the clinical setting. As a result, hemodynamic models can be adapted to simulate the preoperative condition, as well as to simulate a surgical procedure and its consequences on global and local hemodynamics.

Computational modeling is potentially valuable to gain insight into the mechanisms responsible for short- and long- term AVF failure. Currently, postoperative changes in local hemodynamic profile are believed to be accountable for AVF failure by inducing vascular wall changes which potentially result in insufficient venous dilatation, or via the development of NIH with important alteration in pressure and flow distributions^{8,29}. In particular, the geometric configuration of the anastomosis is considered to have profound influences on postoperative hemodynamics (flow, pressure, and wall shear stress [WSS] distribution) and thereby plays an important role in AVF associated complications²⁵. Furthermore, connecting an artery with a vein induces remodeling of the vessels in effort to keep the WSS within a physiologic range, as is evidenced by Enelordache and colleagues who identified an important role for peak WSS levels as a determinant for arterial vessel remodeling^{30,31}.

Within the ARCH project, patient-specific computational modeling tools for short- and long-term prediction of cardiovascular hemodynamic changes in patients with ESRD awaiting AVF creation, are under development. These tools are currently being calibrated and validated, based on patient-specific anatomical, physiological and clinical data that are being collected in the prospective clinical study described in this paper.

STUDY DESIGN

The described prospective clinical study is being performed as part of the ARCH project and was designed to collect anatomical data (based on state-of-the-art, non-invasive medical imaging techniques), clinical data, and physiological data, in order to obtain information about the relations between anatomical and functional characteristics of individual patient vasculature and to provide information on vascular adaptation. These

datasets will be used for calibration and validation of the modeling tool by identification of sets of parameters with significant influence on postoperative functioning. Computational modeling aims to simulate hemodynamics for multiple AVF configurations in a single patient (e.g. upper arm, lower arm, end-to-side, side-to-side) and to allow for identification of the AVF configuration with the most favorable hemodynamic profile which might result in a lower probability of postoperative complications. For calibration and validation purposes, a total of 80 consecutive patients with ESRD awaiting VA creation will be enrolled in the four clinical partners of the project (Maastricht University Medical Center, The Netherlands; Univerzitetni Klinični Center Ljubljana, Slovenia; Ospedali Riuniti di Bergamo, Italy; Ghent University Hospital, Belgium). ESRD has been defined as either the time at which creatinine clearance falls below <25ml/min and referral to the department of vascular surgery for creation of a VA is indicated, or if there is an anticipated need for HD within 1 year. A subgroup of patients enrolled in Maastricht, undergoing wider investigations in addition to the standard protocol (as detailed in the following sections), is referred to as Subgroup 1, while all patients enrolled in Ghent, undergoing additional cardiac examinations, are referred to as Subgroup 2. Criteria for enrolment are listed in table 1. The medical ethical committees of all involved partners approved the contents of the study. Written informed consent was obtained from all individuals.

Table 1: Inclusion and exclusion criteria for participation within the study protocol	
Inclusion criteria	
Written informed consent	
Age > 18 years	
Patient in need of a vascular access in order to facilitate hemodialysis therapy	
Patient has entered the pre-dialysis program because of end-stage renal failure	
Treatment of first choice is creation of an native arteriovenous fistula	
Exclusion criteria	
Contraindication for creating an native fistula	
Life expectancy less than 1 year	
Previous vascular access creation in the same arm	
Patient is not suitable for MRI examination (Subgroup 1 and Subgroup 2 only)	

Study protocol

The flowchart of this study is based on systematic acquisition of medical history and clinical data from examinations performed in agreement with the current clinical work-up as advocated by the NKF K/DOQI Guidelines, 2006. After patient enrolment, demographical and clinical factors are systematically collected together with blood pressure measurements. Subsequently, a peripheral DUS examination is performed to acquire a

Figure 1. Block diagram of actions to be taken according to possible events during the clinical study conduction.

complete upper extremity vascular map, including arterial and venous vessel diameters and blood flow values at different vascular locations. As shown in table 2, patients in Subgroup 1 (enrolled in Maastricht) are subjected to additional evaluations (advanced DUS and MRA) aimed at obtaining mechanical properties of the arterial wall as well as imaging the central and peripheral vasculature in detail. Subgroup 2 (enrolled in Ghent) is subjected to additional cardiac evaluations to investigate cardiac mechanics behind AVF creation.

Table 2: Summary table showing investigations performed in the whole study population and additional investigations performed in different subgroups of patients. Patients in Subgroup 1 were recruited in Maastricht, while those in Subgroup 2 were recruited in Ghent.

Whole study population	
Preoperative	
Patient demographics and clinical factors	
Standard peripheral ultrasound evaluation	
Blood pressure measurements	
Postoperative follow-up	
Subgroup 1	Subgroup 2
Advanced peripheral ultrasound evaluation	MRI flow
Finger pressure measurements	MRI heart
MRA peripheral vasculature	Cardiac ultrasound evaluation
MRI flow	

Table 3: Clinical study flowchart, showing follow-up visits scheduled in the study protocol. Time and details about investigations performed in each visit are shown.

Visit	V0	V01 BM	V02 BM	V03 BM	V01	V02
Time	Pre	< 6 h	1w	6w P	1st HD	2w
	OP	post OP	post OP	post OP	T=0	
Patient demographics and clinical factors	X					
Blood Analysis	X			X		
Blood pressure measurements	X	X	X	X		
Standard peripheral US	X	X	X	X		
Advanced peripheral US *	X			X		
Peripheral vascular MRA *	X			X		
Cardiac MRA **	X			X		
Cardiac US **	X	X		X		
VA function clinical follow-up					X	X

Abbreviations: BM = before maturation; Pre OP = preoperative, Post OP = postoperative; HD = hemodialysis treatment; hh = hours, w. = weeks, mo. = months. * investigations performed only for patients in Subgroup 1; ** investigations performed only for patients in Subgroup 2

After completion of preoperative data acquisition, the surgical VA procedure is performed which is followed by routine postoperative DUS examinations. After HD initiation, additional follow-up data are gathered from the vascular laboratory and the dialysis ward, as detailed in table 3. Figure 1 shows the individual patient flowchart and illustrates actions to be taken following possible events or complications occurring during the conduction of the study.

Study investigations

In this section we provide a detailed description of investigations performed within the study, focusing in particular on standard and advanced DUS examinations, pressure measurements, MRA of the peripheral vasculature and cardiac examinations.

Standard duplex ultrasonography:

For all patients, a preoperative DUS examination is performed in order to assess vascular diameters and flows as well as to identify potential vascular pathology. The complete standard DUS examination is performed by either an experienced employee of the vascular laboratory or the physician himself, with the patient in supine position. A DUS machine with at least a 7.5 MHz convex transducer and a 10.0 MHz linear transducer is used for the measurements. Venous evaluation comprises visualization of the cephalic vein from the wrist to the cephalic arch, as well as the basilic vein from the wrist until it joins the brachial vein in the upper arm, while making use of a proximal pressure cuff for congestion as described by Planken et al³². Short- and long-axis diameter measurements are carried out, and side branches are noted with their exact location and

V03 6w	V04 10w	V05 4 mo	V06 6 mo	V07 8 mo	V08 10 mo	V09 12 mo	V10 14 mo	V11 16 mo	V12 18 mo	V13 20 mo	ENDV 22 mo
					X						X
X		X			X			X			X
X		X			X			X			X
											X
					X						X
		X			X						X
X	X	X	X	X	X	X	X	X	X	X	X

diameter. Venous compliance is evaluated by monitoring the difference in venous diameter with and without venous congestion pressure at selected locations. Evaluation of the peripheral arterial vascular tree consists of diameter measurements and identification of vascular disease by measuring peak systolic velocity (PSV), end diastolic velocity (EDV), diameter and volume flow. Finally, the central arterial and venous vessels are imaged to rule out any stenosis or occlusion that might hamper postoperative fistula function. Standardization of this examination was performed according to modeling requirements and is schematically visualized in figure 2.

Figure 2. Schematic visualization of the preoperative duplex examination. Over the upper extremity multiple routine measurements are performed over the arterial and venous vascular tree, focusing on diameter, vascular pathology, flow and depth. Also the location of venous side branches has to be registered.

Advanced duplex ultrasonography:

Additional DUS measurements are performed in a subset of patients (Subgroup 1) in order to investigate mechanical properties of the brachial artery. To this end, the change in diameter of the brachial artery as a function of time is evaluated with a commercially available ECG triggered DUS system, equipped with 'Artlab' software (ESAOTE, Maastricht, The Netherlands). Continuous integrated pressure registration (Nexfin, BMEYE, Amsterdam, The Netherlands) allows determination of arterial distensibility, arterial compliance and pulse wave velocity.

Pressure measurements:

Bilateral blood pressure measurements are carried out on the upper arm. Systolic and diastolic pressures are recorded together with cardiac frequency. Patients in Subgroup 1 are also subjected to pressure measurements using the NexFin device (BMEYE, Amsterdam, The Netherlands). By means of a cuff around the third digit, arterial finger pressure is continuously measured and interpolated into a brachial pressure. Postoperatively, finger pressures are measured, with and without compression of the fistula, to objectivate the decrease in perfusion pressure which potentially results in the clinical manifestation of distal ischemia.

MRA examination of peripheral vasculature:

3D acquisition of the vascular anatomy in ESRD patients poses difficulties. CE-MRA, has been associated with the development of nephrogenic systemic fibrosis (NSF)^{33,34}, which can result in serious complications³⁵. Therefore, non contrast-enhanced (NCE) MRA techniques for depiction of vascular pathology and identification of arterial and venous geometry have attained renewed interest³⁶. However, there is a scarcity of publications beyond proof of concept studies, and little is known about the feasibility and diagnostic accuracy of these NCE-MRA techniques for imaging the upper extremity vascular tree. Therefore, part of this study is to assess the feasibility of a novel state-of-the-art NCE-MRA technique and to compare this technique with the current standard of reference for diagnostic vessel imaging, CE-MRA.

MR acquisitions in Subgroup 1 are performed with a clinically available 1.5T MR scanner (Gyroscan Intera, software release 11.3.1, Philips Medical Systems, Best, The Netherlands) using the Synergy Flex-L surface coil for the distal upper extremity and the Synergy Body coil for the proximal upper extremity and chest acquisitions.

For NCE-MRA acquisitions, a modified version of the balanced turbo-field echo (bTFE) as described by Gjesdal et al is used³⁷. The bTFE pulse sequence produces images with increased signal from fluid, analogous to T2 weighted sequences, along with retaining T1 weighted tissue contrast (Figure 3). These acquisitions are compared to CE-MRA, which consist of a multiphase T1-weighted gradient recalled echo sequence. According to recent guidelines³⁸, patients who are already dependent on intermittent HD therapy

Figure 3: Maximum intensity projection of a typical NCE-MRA acquisition of the distal upper extremity with corresponding cross-sectional reformations; Despite both arteries and veins are depicted in the NCE-MRA dataset, arteries and veins can easily be differentiated in the axial source images because of the high spatial resolution.

by means of a CVC are scheduled to undergo a complete 4 hour dialysis session directly after the MR acquisition, followed by regular HD sessions two and four days later. Despite the fact that we use a stable, macrocyclic GBCA, every patient is monitored for symptoms related to NSF at regular intervals.

Cardiac examinations:

In order to obtain longitudinal data regarding cardiac function and cardiac adaptation after AVF creation, patients of subgroup 2 are scheduled to undergo echocardiography and MR cardiography examinations in the pre- and postoperative setting (Table 3). The

echocardiography examinations (Vivid 7, GE Healthcare, Milwaukee, USA) provide standardized and reproducible measurements obtained from parasternal long- and short-axis, apical and subcostal views. Anatomical as well as functional parameters can be generated, and include velocities, flows, time intervals, pressures, volumes, diameters, masses and derived indexes.

MR cardiography (Avanto 1.5T, Siemens AG, Munich, Germany) consists of conventional flow and volume assessment of the left and right ventricular volumes as well as determination of the ventricular mass, the regional wall motion, the myocardial thickness and functioning of the cardiac valves by making use of NCE trueFISP (balanced SSFP) and phase-contrast MRA sequences.

Data management

Since this clinical investigation involves four centers distributed in different European countries, the study is conducted using secured, web-based, electronic case report forms (e-CRF's) to facilitate on-site computer-based collection of socio-demographic data, clinical data and DUS measurements. All data is obtained in accordance with current good clinical practice (GCP) guidelines. E-CRF's were generated using an open source, web-based software platform, Openclinica (Akaza Research, Boston, USA), which supports clinical data entry and management in compliance with GCP. Personal data entry access was provided to investigators from all involved clinical centers. A computer-generated patient number and a local identifier uniquely identify patients enrolled in the study, ensuring full anonymity. The raw, anonymized, image data (MRI examinations, standard DUS images and advanced DUS datasets) are stored on a secured FTP server of the ARCH project (ARCHClient), and are accessible to all partners of the ARCH Project Consortium.

DISCUSSION

The study protocol here described allows implementation of a clinical investigation on a difficult target: the evaluation of structural and functional cardiovascular changes that take place during and following AVF creation. Patients requiring a VA for HD treatment that undergo native AVF creation are exposed to potential dangerous complications which may hamper continuation of dialysis therapy. The heterogeneous characteristics of individual patients make systematic observations at population level very difficult. Despite it is generally accepted that the massive increase in blood flow and blood pressure at the site of the arteriovenous anastomosis are responsible for venous wall remodeling (adaptation), it is not easy to obtain detailed information on patient-specific hemodynamic changes induced by AVF creation. Computational tools have the potential to help the physician to study in more detail the local hemodynamic conditions of

individual patients and may be of crucial importance for AVF planning and postoperative management. As previously described in detail, development, calibration and validation of these computational tools must be performed based on extensive clinical observations. Within the ARCH project we designed a prospective clinical study to collect structural and functional data of patient vasculature, as well as clinical observations, before and after AVF surgery. The protocol of this study has been successfully implemented in four clinical centers and the study is currently being conducted.

Implementation of this protocol provides a detailed and controlled dataset (i.e. demographical data, dimensions of the arterial and vascular tree, geometry of the vascular network, mechanical properties of the vessel wall, boundary conditions for numerical simulations) which will be available for sensitivity analysis to identify the most relevant model parameters. After this, calibration and validation of the computational tool allows for best fitting of measured preoperative hemodynamics. Moreover, the acquired datasets will be analyzed to derive short- and long-term patency rates, and relate AVF function and postoperative complications to preoperative vascular geometry and flow distribution. Eventually, model-based evaluation of AVF surgery has to generate detailed information regarding the relation between hemodynamic changes and vascular changes with the aim to predict AVF dysfunction (i.e. nonmaturation, steal syndrome, cardiac failure, or the development of NIH with subsequent flow reduction and risk of thrombosis) in advance.

The electronic data input in web-based CRFs allows timely monitoring of patient enrollment and data collection. Image storage on a FTP server allows efficient centralization of study documentation and data exchange among scientific and technical partners that are involved in modeling tool development.

In conclusion, AVF surgery remains to be prone to complications despite the current preoperative clinical work-up and practice according to clinical guidelines. Outcome may improve with a more in depth evaluation of structural and functional changes in the upper extremity circulation as well as by taking into account multiple prognostic parameters and their interaction. Our study protocol intends to gain insight in short and long-term cardiovascular changes upon AVF surgery and to facilitate the development, calibration and validation of computational modeling tools in the field of VA surgery.

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APPENDIX

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CHAPTER

4

Feasibility of non contrast-enhanced magnetic resonance angiography for imaging upper extremity vasculature prior to vascular access creation

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ABSTRACT

Objectives: Preoperative mapping of arterial and venous anatomy helps to prevent postoperative complications after vascular access creation. The use of gadolinium in contrast-enhanced magnetic resonance angiography (CE-MRA) has been linked to nephrogenic systemic fibrosis in patients with end-stage renal disease (ESRD). The purpose of this study was to evaluate non contrast-enhanced magnetic resonance angiography (NCE-MRA) for assessment of upper extremity and central vasculature, and to compare it with CE-MRA.

Methods: NCE and CE-MRA images were acquired in 10 healthy volunteers and 15 patients with ESRD. In each dataset, two observers analyzed 11 arterial and 16 venous segments with regard to image quality (0-4), presence of artifacts (0-2) and vessel-to-background ratio.

Results: More arterial segments were depicted using CE-MRA compared to NCE-MRA (99% vs. 96%, $p=0.001$) with mean image quality of 3.80 vs. 2.68, ($p<0.001$) and mean vessel-to-background ratio of 6.47 vs. 4.14 ($p<0.001$). 91% of the venous segments were portrayed using NCE-MRA versus 80% using CE-MRA ($p<0.001$). Mean image quality and vessel-to-background ratio were 2.41 vs. 2.21 ($p=0.140$) and 5.13 vs. 3.88 ($p<0.001$), respectively.

Conclusions: Although arterial image quality and vessel-to-background ratios were lower, NCE-MRA is considered a feasible alternative to CE-MRA in patients with ESRD who need imaging of the upper extremity and central vasculature prior to dialysis access creation.

INTRODUCTION

The global patient population with end-stage renal disease (ESRD) increases rapidly. Presently, the annual growth rate lies at about 8%, resulting in an estimated 7.1 million patients depending on renal replacement therapy by the year 2030¹⁻³. A substantial number of these patients will be treated by hemodialysis (HD) for which a functional vascular access (VA) is mandatory.

Guidelines of the National Kidney Foundation and the Vascular Access Society as well as numerous clinical trials have emphasized the relevance of vascular assessment using imaging techniques prior to creation of a VA⁴⁻⁷. However, despite preoperative duplex ultrasonography (DUS), the number of complications (nonmaturation, distal ischemia and cardiac failure) remains high⁸. In an effort to reduce these complications and improve long-term patency, the 'patient-specific image-based computational modeling for improvement of short- and long-term outcome of vascular access in patients on hemodialysis therapy' (ARCH) project consortium (7th Framework European collaborative project), investigates alternative preoperative imaging modalities and develops predictive models to aid clinical decision-making⁹, similar to those already used in other fields of vascular surgery^{10,11}.

Earlier studies of our group have established contrast-enhanced magnetic resonance angiography (CE-MRA) to be of additional value in the preoperative work-up of patients awaiting VA creation. For instance, CE-MRA may identify arterial and venous stenoses not detected by DUS, which are associated with VA early failure and nonmaturation¹². Furthermore, CE-MRA enables luminal diameter measurements over the entire arterial inflow and venous outflow trajectory, including the central vessels. Therefore, a more comprehensive assessment of upper extremity vasculature can be performed, compared to selective diameter measurements using DUS. In addition, CE-MRA facilitates extraction of complete upper extremity vascular geometry, which may be of additional value in patient-specific modeling. However, recently it has become clear that administration of gadolinium-based contrast agents (GBCA) in patients with ESRD may result in the development of nephrogenic systemic fibrosis (NSF)^{13,14}, which is a potentially serious complication¹⁵.

In effort to preserve the potential diagnostic advantages of preoperative MRA in patients with ESRD, we developed a non-contrast enhanced magnetic resonance angiography (NCE-MRA) technique for the upper extremity, based on a modified balanced turbo field echo (bTFE) sequence introduced by Gjesdal et al¹⁶. The purpose of this study was to assess the feasibility of this NCE-MRA technique and to compare objective and subjective image quality with CE-MRA, which served as the standard of reference.

MATERIALS AND METHODS

The current study was performed as part of the ARCH project (ICT-224390). For the complete clinical study protocol the reader is referred to Bode et al⁹.

Study population

For evaluation of upper extremity vasculature NCE-MRA was compared to CE-MRA in ten healthy subjects (5 female, 5 male, mean age ($\pm$ SD): 26.2 ($\pm$ 4.2) years) without any known cardiovascular disease or diabetes mellitus. After having established the initial feasibility of the technique in the healthy subjects, fifteen patients with ESRD (7 female, 8 male, mean age ($\pm$ SD): 61.5 ($\pm$ 15.9) years, mean eGFR¹⁷ ($\pm$ SD): 9.3 ($\pm$ 4.0) ml/min) awaiting their first VA creation were enrolled.

A random upper extremity was imaged in healthy subjects while in patients the extremity was chosen in which the preoperative DUS was performed. The study was approved by the local medical ethical committee. After explanation of the potential risks and benefits (including NSF), written informed consent was obtained prior to enrolment in the study.

MR imaging technique

All MR acquisitions were performed with a clinically available 1.5T MR scanner (Gyrosan Intera, software release 11.3.1, Philips Medical Systems, Best, The Netherlands) using the Synergy Flex-L surface coil for the distal upper extremity and the Synergy Body coil for the proximal upper extremity and chest acquisitions. The subject was put in a semi-oblique supine position with an IV-needle in the contra-lateral dorsum of the hand. The vasculature in the distal upper extremity was always imaged first, followed by the proximal upper extremity and chest. For each station, first the NCE-MRA sequence was performed, followed by the CE-MRA acquisition.

NCE-MRA

For NCE-MRA acquisitions a modified version of the balanced turbo-field echo (bTFE) sequence as described by Gjesdal et al.¹⁶ was used, which produces images with increased signal from fluid, analogous to T2 weighted sequences, along with retaining T1 weighted tissue contrast. Detailed image parameters are listed in table 1.

CE-MRA

CE-MRA acquisition consisted of dynamic, multiphasic T1-weighted gradient recalled echo sequences of the distal upper extremity (first acquisition), followed by the proximal upper extremity and the chest (second acquisition). A macrocyclic contrast agent (Gadovist, BayerSchering Pharma, Berlin, Germany), for which no unconfounded cases of NSF have been reported in patients with renal failure, was administered via a contralateral intravenous cannula. Contrast medium was diluted using saline in a 1:1

Table 1: Sequence parameters of NCE-MRA and CE-MRA

	NCE-bTFE			CE-MRA	
	Central	Proximal	Distal	Proximal	Distal
Repetition time (msec)	4.5	5.6	5.8	5.4	5.4
Echo time (msec)	2.2	2.8	2.9	1.61	1.55
Flip angle (degrees)	90	90	90	40	40
Number of stacks	1	2	2	1	1
Field of view (mm)	300	175	175	430	325
Rectangular field of view (%)	65	65	55	85	25
Matrix (scan/reconstruction)	244/384	224/512	224/512	432/512	432/512
Number of slices	125	120	120	90	125
Slice thickness	0.79	0.79	0.79	1.25	0.84
Acquired voxel size	1.34x0.84x0.78	0.78x0.78x0.79	0.78x0.78x0.79	1.00x1.81x2.50	0.75x1.38x1.68
Reconstructed voxel size	0.78x0.78x0.78	0.34x0.34x0.79	0.34x0.34x0.79	0.84x0.84x1.25	0.63x0.63x0.84
Scan duration	4:45	5:48	4:54	1:52	0:45
Number of phases acquired	1	1	1	4	4

ratio (10 ml Gadovist and 10 ml saline) and administered in two separate injections of 10 ml each for the distal and proximal acquisitions, respectively.

As advocated by recent guidelines, patients already dependent on HD therapy were scheduled to undergo a complete 4 hour dialysis session directly after the MR acquisition, followed by regular dialysis sessions two and four days later¹⁸⁻²⁰. The relevance of these recommendations is underscored by the study of Prince et al²¹, who identified a decreased risk for the development of NSF in patients in whom a non-macrocyclic GBCA was administered with an estimated glomerular filtration rate (eGFR) lower than 15ml/min and underwent post-procedural HD. All Patients were monitored for symptoms related to NSF at regular intervals: in HD patients a physical examination was performed every week, while pre-dialysis patients were examined every six weeks during regular follow-up of their residual renal function.

MR IMAGE ANALYSIS PROTOCOL

The obtained datasets were reviewed by two experienced radiologists (NP and TL with 8 and 15 years of experience in reading cardiovascular MR images, respectively) in a blinded fashion. For both NCE-MRA and CE-MRA, the reviewers evaluated all source images and had the possibility to create maximum intensity projections (MIP's) and multi-planar reformations (MPR's).

The upper extremity vascular tree was divided in 11 arterial and 16 venous segments

(Figure 1), which were assessed for image quality and artifacts as described in table 2. In addition, a single observer (NP) calculated vessel-to-background contrast ratio's for the main arteries and veins in the upper extremity by measuring signal intensity within the lumen of the vessel segment and dividing this value by the standard deviation of signal intensity of muscle adjacent to the lumen.

Subsequently, the presence of stenoses and occlusions was evaluated with both techniques. A five point ordinal scale was used for grading: 0 for 0-19% stenosis, 1 for 20-49% stenosis, 2 for 50-74% stenosis, 3 for 75-99% stenosis, and 4 for occlusion²². The degree of stenosis was calculated by dividing the smallest in-plane diameter of the vessel at the site of the stenosis by the diameter of the closest normal appearing vessel segment. A stenosis grade of 50% or more was considered hemodynamically significant. The potential of NCE-MRA for detection of stenosis was compared to CE-MRA, which was used as the standard of reference.

Statistical analysis

For both techniques the total number of visible segments, the mean artifact scores, as well as the vessel-to-background ratio's were compared using the non-parametric McNemar and Wilcoxon signed ranks tests for paired samples. Interobserver agreement regarding diagnostic image quality (image quality ≥ 2) was assessed by the Cohen test (<0 indicating no agreement and 0 – 0.20 as slight, 0.21 – 0.40 as fair, 0.41 – 0.60 as moderate, 0.61 – 0.80 as substantial, and 0.81 – 1 as almost perfect agreement)²³. In all statistical analyses, p-values <0.05 were considered to be statistically significant. All statistical analyses were performed using SPSS 17.0.0 (SPSS Inc, Chicago, IL) for Windows (Microsoft, Redmond, WA).

Table 2: Subjective parameters for image analysis

Assessment	Score
Image Quality (IQ)	Score 0: Not assessable; vessels not visible or diagnostic information not obtained Score 1: Poor; vessels visible but suboptimally depicted due to incomplete filling, blurring or other artifacts Score 2: Moderate; vessels visible with low signal intensity but the complete course identifiable despite artifacts Score 3: Good; vessels visible with high signal intensity with minimal artifacts Score 4: Excellent; vessels visible with high signal intensity without artifacts
Artifacts	
Flow artifacts	Score 0: None
Black-banding artifacts	Score 1: Minor artifacts, not hampering image interpretation
Compression artifacts	Score 2: Major artifacts hampering image interpretation

Figure 1: Segmentation of the vascular tree for image analysis: The following segments were evaluated in the distal upper extremity: proximal, middle and distal segments of the radial artery, ulnar artery, cephalic vein and basilic vein. In the proximal upper extremity and chest the following segments were evaluated: proximal, middle and distal segments of the brachial artery, cephalic vein and basilic vein and proximal and distal segments of the subclavian artery, cephalic vein and subclavian vein.

RESULTS

All CE-MRA and NCE-MRA examinations were performed successfully. No side effects after GBCA administration were noted. None of the patients developed any symptoms of NSF (mean follow-up: 586 ± 100 days).

Healthy subjects

Results of objective and subjective image quality are listed in table 3A. Typical examples of CE-MRA and NCE-MRA acquisitions are shown in figures 2 and 3. For the arterial vascular tree CE-MRA resulted in superior image quality and less artifacts due to flow or magnetic field inhomogeneity, compared to NCE-MRA. In addition, CE-MRA provided a better vessel-to-background ratio. On the other hand, for the venous system NCE-MRA resulted in visualization of more vessel segments, better image quality and higher vessel-to-background ratio compared to CE-MRA. However, NCE-MRA examinations were prone to more flow- and magnetic field inhomogeneity artifacts. In healthy volunteers there was moderate interobserver agreement regarding the determination of diagnostic image quality in NCE-MRA and CE-MRA sequences. Kappa values were 0.50 and 0.58, for NCE-MRA and CE-MRA, respectively.

Patients

In the ESRD patient population we found superior arterial depiction with CE-MRA compared to NCE-MRA, as well as less artifacts related to flow or magnetic field inhomogeneity. On the other hand, more venous segments were visualized using NCE-

Table 3A: Results in healthy volunteers (N=10)

	Observer	Arterial vascular tree			Venous vascular tree		
		NCE-MRA	CE-MRA	P-value	NCE-MRA	CE-MRA	P-value
Visible segments with	1	107/110 (97)	110/110 (100)	NA	150/155 (97)	125/155 (81)	<0.001
Image Quality >0 (%)	2	108/110 (98)	110/110 (100)	NA	150/155 (97)	131/155 (85)	<0.001
Image Quality (0-4)	1	3.19 (± 0.94)	3.99 (± 0.10)	<0.001	2.86 (± 1.22)	2.44 (± 1.60)	0.003
	2	3.38 (± 0.82)	3.95 (± 0.27)	<0.001	2.90 (± 1.13)	2.14 (± 1.31)	<0.001
Flow artifacts (0-2)	1	0.49 (± 0.80)	0.11 (± 0.65)	<0.001	0.49 (± 0.72)	0.13 (± 0.62)	0.002
	2	0.41 (± 0.60)	0.07 (± 0.54)	<0.001	0.43 (± 0.65)	0.16 (± 0.63)	<0.001
Magnetic field inhomogeneities artifacts (0-2)	1	0.10 (± 0.39)	0.00 (± 0.00)	0.009	0.20 (± 0.56)	0.00 (± 0.00)	0.004
	2	0.10 (± 0.30)	0.00 (± 0.00)	0.001	0.31 (± 0.59)	0.00 (± 0.00)	<0.001
Compression artifacts (0-2)	1	0.01 (± 0.10)	0.00 (± 0.00)	0.317	0.23 (± 0.62)	0.33 (± 0.72)	0.380
	2	0.00 (± 0.00)	0.00 (± 0.00)	1.000	0.28 (± 0.68)	0.32 (± 0.69)	0.083
Vessel-to-background ratio		4.55 (± 1.36)	6.01 (± 2.39)	0.001	5.41 (± 2.00)	4.53 (± 2.82)	0.012

Figure 2: Composite whole volume maximum intensity projection of typical NCE-MRA acquisition with corresponding cross-sectional reformations; 1) central vessels, 2) upper arm, 3-4) lower arm. Despite both arteries and veins are depicted in the NCE-MRA dataset, arteries and veins can easily be differentiated in the axial source images because of the high spatial resolution. Note high signal intensity due to presence of synovial fluid.

Figure 3: Composite whole volume maximum intensity projection of typical CE-MRA acquisition in arterial phase (A) and venous phase (B) with corresponding cross-sectional reformations.

MRA. Image quality for veins was comparable with the two sequences (table 3B). Flow- and black-banding artifacts were not present in the CE-MRA images. There was moderate interobserver agreement regarding the determination of diagnostic image quality in NCE-MRA ($\kappa = 0.51$), and a good interobserver agreement in CE-MRA ($\kappa = 0.64$).

Table 3B: Results in ESRD patients (N=15)

	Observer	Arterial vascular tree			Venous vascular tree		
		NCE-MRA	CE-MRA	P-value	NCE-MRA	CE-MRA	P-value
Visible segments with	1	157/165 (95)	163/165 (99)	0.109	219/240 (91)	197/240 (82)	<0.001
Image Quality >0 (%)	2	154/165 (93)	164/165 (99)	0.006	198/240 (83)	180/240 (75)	0.015
Image Quality (0-4)	1	2.25 (± 0.97)	3.53 (± 0.69)	<0.001	2.19 (± 1.16)	2.22 (± 1.40)	0.701
	2	2.30 (± 1.12)	3.81 (± 0.55)	<0.001	2.01 (± 1.35)	2.09 (± 1.53)	0.358
Flow artifacts (0-2)	1	0.34 (± 0.59)	0.00 (± 0.00)	<0.001	0.29 (± 0.54)	0.07 (± 0.34)	<0.001
	2	0.31 (± 0.94)	0.00 (± 0.00)	<0.001	0.30 (± 0.57)	0.04 (± 0.24)	<0.001
Magnetic field inhomogeneities artifacts (0-2)	1	0.59 (± 0.77)	0.04 (± 0.19)	<0.001	0.57 (± 0.80)	0.05 (± 0.25)	<0.001
	2	0.59 (± 0.86)	0.00 (± 0.00)	<0.001	0.53 (± 0.84)	0.00 (± 0.00)	<0.001
Compression artifacts (0-2)	1	0.02 (± 0.13)	0.00 (± 0.00)	0.083	0.15 (± 0.48)	0.17 (± 0.54)	0.444
	2	0.01 (± 0.16)	0.01 (± 0.08)	0.655	0.21 (± 0.59)	0.33 (± 0.72)	0.001
Vessel-to-background ratio		3.87 (± 3.67)	6.77 (± 3.56)	<0.001	4.93 (± 3.20)	3.42 (± 1.47)	<0.001

Blinded review of the CE-MRA and NCE-MRA datasets resulted in the identification of six low-grade stenoses (grade 0 and I) in the subclavian artery (2), the radial artery (3), and the ulnar artery (1) using CE-MRA, and three low-grade stenosis in the subclavian artery (1), and the radial artery (2) with NCE-MRA. Two out of three stenoses identified with NCE-MRA corresponded with CE-MRA findings. In one case, irregularities in the subclavian artery as seen with NCE-MRA were not seen with CE-MRA. Conversely, at CE-MRA four non-significant stenoses were visualized which were classified as normal with NCE-MRA. None of these stenoses were depicted in the preoperative DUS examination.

DISCUSSION

In this study we found that upper extremity vasculature can be depicted relatively adequately by using a bTFE NCE-MRA sequence. Nevertheless, with the described image protocol, CE-MRA remains superior in terms of total number of visible arterial segments and overall image quality. However, NCE-MRA was of diagnostic quality (image quality ≥ 2) in the vast majority arterial segments (82%). For depiction of venous structures, on the other hand, we found NCE-MRA to be superior to dynamic CE-MRA because of the high intrinsic vessel-to-background contrast, regardless of the presence of contrast material.

In clinical routine, DUS is the method of choice in the preoperative workup of patients with ESRD. DUS is a highly valuable imaging modality and its use has been associated with significant reductions in postoperative access related complications²⁴⁻²⁶.

Nevertheless, postoperative access failure rates remain unacceptably high⁸, which have sparked the search for alternative techniques of preoperative vascular assessment. Prior work by our group found CE-MRA to yield additional insights in vascular geometry, vascular dimensions and the presence of pathology, particularly on locations where DUS examination lacks diagnostic accuracy (e.g. the central arteries and veins). Moreover, MRA enables time-efficient interrogation of the entire upper extremity vascular tree, instead of just several discrete locations. The present study was motivated because there is a paucity of data on the clinical feasibility and accuracy of novel NCE-MRA techniques for evaluation of upper extremity vasculature.

Unlike the lower extremity, reports on NCE-MRA protocols for depiction of upper extremity vasculature are scarce, particularly in patients awaiting VA creation. Most of these publications deal with either outdated NCE techniques suffering from major artifacts, limited field of views (FOV) or long acquisition times²⁷⁻²⁹. Moreover, although local venous anatomy could be identified, more proximal and central vessels were not be depicted because of limited surface coil coverage and difficulties in patient positioning.

The recently described lower extremity NCE-MRA protocol of Gjesdal and colleagues¹⁶ was adapted in such way that it facilitated depiction of the upper extremity vascular tree. Despite the excellent results in the lower extremities, we found our sequence to be prone to artifacts, as was reflected in lower image quality and higher artifact scores. Most likely, this is induced by the off-center positioning of the upper extremity inside the bore of the MR, where magnetic field inhomogeneities are more pronounced³⁰. Nevertheless, diagnostic images were obtained in the vast majority of subjects.

In the patient population, six low-grade stenoses (grade 0 and I) were detected using CE-MRA compared to three low-grade stenoses with NCE-MRA. In the three remaining cases the narrowing's were not seen with NCE-MRA. Although these stenoses were not hemodynamically significant, they were not found in the preoperative DUS examination, emphasizing the potential additional value of obtaining complete vascular geometry for diameter measurements over the complete arterial and venous vascular tree. In this limited sample, both MRA techniques excluded the presence of significant (>50% luminal narrowing) stenoses, thus confirming findings at DUS. The most likely explanation for the minor mismatches is the better spatial resolution of the NCE-MRA data, which is less prone to partial volume effects. Our results reflect those of Gupta et al. who found that bTFE is capable of accurately detecting stenoses³¹.

What is the potential additional value of MRA in clinical practice considering the higher costs and lower availability in the era of widespread DUS usage? With regard to the current results, we hypothesize that routine preoperative assessment using the described NCE-MRA sequence is potentially beneficial in all patients prior to dialysis access creation because vascular pathology overlooked with DUS may be identified and anticipated on, and non-invasive extraction of vascular geometry for patient-specific

computational modeling becomes feasible. Nonetheless, until its clinical relevancy has been established in a large clinical trial, NCE-MRA should always be performed as a supplementary examination to DUS, and therefore will result in additional costs in the preoperative work-up. To what extent these additional costs may be compensated by a reduction in the management costs of postoperative complications needs to be elucidated in further studies. For that reason, one might argue to perform NCE-MRA only in patients with a high probability of vascular pathology or postoperative fistula dysfunction (e.g. patients with marginal duplex findings, patients with multiple previous failures, or patients with multiple previous central venous catheters).

This study has limitations. First, we compared high spatial resolution NCE-MRA images with slightly lower resolution CE-MRA images. This discrepancy was unavoidable because both the arterial and venous systems needed to be depicted with a limited dose of non-bloodpool macrocyclic contrast agent. Because of the difference in voxel size between CE-MRA and NCE-MRA, we did not compare vascular diameter measurements between the two techniques. Nonetheless, we believe that NCE-MRA images can be used for accurate appraisal of vascular diameters due to the high spatial resolution, bearing in mind our prior study which found lower spatial resolution CE-MRA diameter assessment to correspond reasonably well with DUS assessment and intra-operative measurements³². Secondly, acquisition of distal, proximal and central stations required repositioning of the patient using multiple surface coils. Future work should be aimed at the 'real world' value of a NCE-acquisition of the complete upper extremity, preferably within a single acquisition using large coverage coils in combination with continuously moving table techniques³³. Furthermore, there was no comparison with intra-arterial digital subtraction angiography, which is the established reference standard with the highest spatial resolution. Finally, we have not investigated the impact of NCE-MRA on clinical outcome, but this was not the objective of this study.

In conclusion, we have demonstrated that bTFE NCE-MRA is a feasible alternative to CE-MRA for depiction of upper extremity vasculature. NCE-MRA has the potential to also provide valuable complementary information to CE-MRA. Future studies are needed to investigate the value of NCE-MRA prior to VA creation, as well as the potential of patient-specific modeling using patient-specific geometry obtained by NCE-MRA.

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CHAPTER

5

Preoperative assessment of upper extremity vasculature using non contrast-enhanced magnetic resonance angiography: A technical note on clinical value and modeling perspectives

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ABSTRACT

Purpose: To describe a non contrast-enhanced magnetic resonance angiography (NCE-MRA) technique for the assessment of upper extremity vasculature prior to vascular access creation. By using this technique, a more complete interrogation of upper extremity arteries and veins (including the central vessels) can be performed compared to discrete diameter measurements when employing duplex ultrasonography. Furthermore, the process of extracting patient-specific vascular geometry is described, which can subsequently be used for personalized computational modeling of the intended vascular access procedure.

INTRODUCTION

Despite a thorough upper extremity vascular assessment by means of duplex ultrasonography (DUS), early failure and nonmaturation remain frequent complications following vascular access (VA) surgery¹⁻³. In an effort to reduce these flow related complications, two additional preoperative modalities have been investigated: magnetic resonance angiography (MRA) and patient-specific computational simulation.

The potential of contrast-enhanced magnetic resonance angiography (CE-MRA) was established in a previous study of our group, and resulted in improved depiction of the most suitable site for VA creation, by identifying stenoses and occlusions not visualized with DUS^{4,5}. However, since administration of gadolinium-based contrast agents (GBCA) has been associated with the potential risk of nephrogenic systemic fibrosis (NSF)^{6,7}, non contrast-enhanced (NCE) MRA techniques became of interest^{8,9}. By adapting the recently described NCE balanced turbo field echo (bTFE) MRA sequence of Gjesdal and colleagues¹⁰, a continuous vascular diameter assessment of the chosen upper extremity can be performed¹¹, instead of selective diameter measurements when utilizing DUS. More importantly, NCE-MRA allows for a detailed assessment central vasculature, a region where DUS lacks diagnostic accuracy¹².

Patient-specific computational simulation can be used to tailor arteriovenous fistula (AVF) surgery to the individual patient by predicting postoperative flow enhancement for multiple AVF configurations^{13,14}. In order to personalize the predictive model, acquisition of patient-specific vascular geometry is advantageous.

Here we describe the NCE-MRA protocol utilized for evaluation of upper extremity vasculature prior to VA creation, as well as the process of extracting patient-specific vascular geometry to be used in personalized computational modeling, by subjecting the obtained NCE-MRA images to vascular segmentation tools.

Non contrast-enhanced balanced turbo field echo MRA

The NCE-MRA protocol for depiction of upper extremity vasculature is based on the bTFE sequence as described by Gjesdal et al. who used it for imaging the lower extremity vasculature¹⁰. In short, the bTFE pulse sequence produces images with increased signal from fluid, analogous to T2 weighted sequences, along with retaining T1 weighted tissue contrast. Consequently, arterial and venous information is obtained in a single acquisition. Detailed sequence parameters are listed in table 1.

Because of the large field of view, 3 separate scan volumes over the upper extremity have been defined: the lower arm, the upper arm, and the chest. For each of these stations, surface coils are utilized for the acquisition (e.g. Flex-L surface coil for the lower arm and Sense Body surface coil for the upper arm and central vasculature). In order to avoid artifacts arising from magnetic field inhomogeneities, the subject needs to be positioned in a semi-oblique supine position with the target arm as central as possible within the bore

Table 1: Sequence parameters of NCE-MRA and CE-MRA

	NCE-bTFE			CE-MRA	
	Central	Proximal	Distal	Proximal	Distal
Repetition time (msec)	4.5	5.6	5.8	5.4	5.4
Echo time (msec)	2.2	2.8	2.9	1.61	1.55
Flip angle (degrees)	90	90	90	40	40
Number of stacks	1	2	2	1	1
Field of view (mm)	300	175	175	430	325
Rectangular field of view (%)	65	65	55	85	25
Matrix (scan/reconstruction)	244/384	224/512	224/512	432/512	432/512
Number of slices	125	120	120	90	125
Slice thickness	0.79	0.79	0.79	1.25	0.84
Acquired voxel size	1.34x0.84x0.78	0.78x0.78x0.79	0.78x0.78x0.79	1.00x1.81x2.50	0.75x1.38x1.68
Reconstructed voxel size	0.78x0.78x0.78	0.34x0.34x0.79	0.34x0.34x0.79	0.84x0.84x1.25	0.63x0.63x0.84
Scan duration	4:45	5:48	4:54	1:52	0:45
Number of phases acquired	1	1	1	4	4

Figure 1: Patient positioning. Surface coils are applied over the complete upper extremity and thorax. The contrast pump is connected to a contra lateral intravenous cannula on the dorsum of the hand. Please note the slightly semi-oblique supine position for reduction of artifacts in NCE-MRA acquisition.

of the MR (Figure 1). The examination starts with the distal acquisition, while, after patient repositioning, the upper arm and central vasculature can be imaged. Total examination time, including patient preparation, patient repositioning and image post-processing, is approximately 30 minutes. A typical example of a NCE-MRA acquisition is shown in figure 2. Although the simultaneous depiction of both arteries and veins results in confusing maximum intensity projections, axial source images can be used to easily differentiate between arteries and veins, and facilitate diameter assessment over the complete arterial inflow and venous outflow tract by using the full width half maximum (FWHM) algorithm¹⁵. Next to diameter measurements, the location of the brachial artery bifurcation, venous side branches in the outflow tract, and the presence of stenoses or occlusions can be identified.

Segmentation of upper extremity vasculature using NCE-MRA

To allow for personalized computational modeling, a patient-specific vascular network that is able to anticipate on postoperative flow redistribution, is desirable, and can be obtained by employing the NCE-MRA sequence described above. For AVF surgery, vascular segmentation initially should focus on relevant vessels of the arterial inflow and venous outflow trajectories (e.g. subclavian artery, axillary artery, brachial artery, radial artery, ulnar artery, cephalic vein, basilic vein, subclavian vein), and their sidebranches. Owing to the large number of arteries and veins depicted in NCE-MRA images, and to the occasional presence of artifacts

Figure 2: Typical example of a NCE-MRA merged maximum intensity projection of the three separate scan volumes (distal, proximal and central vessels) of the left upper extremity. Note the visibility of both arteries and veins without making use of a contrast agent.

leading to signal drop and image inhomogeneity, computer-assisted interactive vessel tracing is the most suitable form of segmentation for extracting upper extremity vascular geometry.

To this purpose, an interactive 3D editor, integrated with the open source Vascular Modeling Toolkit software (www.vmtk.org)¹⁶, allows to selectively extract upper extremity vessels by placing seed spheres on images which, subsequently, are spline interpolated and visually represented as a translucent tube, as shown in figure 3A. Firstly, all arteries and superficial veins relevant for AVF surgery are identified and extracted, after which their sidebranches are evaluated for their continuity with more proximal veins as well as the central venous system. Secondly, the deep venous system can be subject of interrogation. Once all relevant upper extremity vessels have been traced in the image space, the center and radius of tube functions are automatically optimized on the imaging grid using a deformable model algorithm (Figure 3B)¹⁷. Finally, the obtained tube network can be integrated in a computational representation of the systemic vascular system (figure 4A), where physical laws are used to describe the distribution of flow preoperatively, as well as to predict postoperative flow redistribution after creation of an arteriovenous anastomosis on multiple locations (Figure 4B)¹⁴.

Figure 3: Segmentation of arteries and veins on a NCE-MRA image, distal station. **A)** Interactive initialization of tubes by placement of individual spheres along the vessels; **B)** final segmentation of major arteries and the cephalic vein after automated optimization.

Figure 4: Generation of computational models from segmentation. **A:** Integration of the arterial network for the distal upper extremity depicted in Figure 3B with a pre-existing model of systemic circulation; **B:** Simulation of postoperative configuration through an end-to-side anastomosis of the cephalic vein, extracted in Figure 3B, to the radial artery.

DISCUSSION

In clinical practice, vascular assessment with DUS is considered the standard of reference for preoperative workup in patients awaiting VA creation¹⁸. DUS is a highly valuable imaging modality and its use has been associated with significant reductions in postoperative access related complications¹⁹. Nevertheless, postoperative access failure rates due to either insufficient or excessive flow enhancement remain unacceptably high, and sparked the search for alternative modalities of preoperative assessment. In this context, the use of CE-MRA has been addressed in previous studies and was associated with an improved depiction of the most suitable site for VA creation by identifying vascular stenoses, not visualized with DUS⁵. Unfortunately the use of GBCA has been associated with a potential risk for NSF in patients with end-stage renal disease. Therefore the feasibility of an alternative NCE-MRA techniques has been addressed in previous work¹¹.

In the preoperative work-up of patients awaiting AVF surgery, NCE-MRA enables time-efficient interrogation of the entire upper extremity vascular tree, instead of just several discrete locations as is achieved with DUS. However, the question remains to what extent

a more costly NCE-MRA examination results in fewer postoperative complications. Compared to routine preoperative DUS examination, the entire upper extremity vasculature, including central vessels, is subjected to a thorough assessment of arterial and venous diameter, pathology and side branches. Moreover, NCE-MRA allows for extraction of patient-specific vascular geometry which can be used for personalization of computational modeling tools.

By adapting generic computational models to patient-specific conditions (anatomical characteristics, geometrical characteristics and mechanical characteristics) a more accurate prediction of postoperative flow enhancement can be obtained for multiple AVF configurations (e.g. radiocephalic AVF, brachiocephalic AVF, brachio basilic AVF) in the selected upper extremity¹⁴. As a result, in order to avoid postoperative AVF failure, a tailored procedure can be suggested to patients who have been evaluated on beforehand for insufficient or excessive postoperative flow enhancement. The most simple approach to personalize these generic modeling tools is by allocating the discrete arterial and venous flow and diameter measurements, as performed with DUS, to specific generic vessel segments in the computational modeling tool. Over the last couple of years, these modeling tools have proven to predict postoperative flow enhancement rather accurately¹⁴, however, an important shortcoming of this approach is the lack of alternative venous return pathways considered in the model, as venous sidebranches of the main outflow tract are completely neglected. With the introduction of a non-invasive NCE-MRA examination that enables personalizing the computational modeling tool with a patient-specific, instead of generic, vascular geometry, the model is expected to yield more reliable predictions, now the influence of alternative return pathways and venous sidebranches can be investigated as well²⁰. Moreover, sidebranches responsible for altered flow redistribution over the venous outflow trajectory can be taken into account in deciding the most suitable location for repetitive cannulation. Randomized controlled trials are currently being performed to address the value of these fully personalized models in clinical practice.

In conclusion, NCE-MRA facilitates the acquisition of a detailed map of the upper extremity vasculature and provides additional information regarding arterial and venous diameter, vascular pathology, continuity, and side branches compared to discrete DUS evaluation. In addition, NCE-MRA is a feasible modality to extract a patient-specific vascular network of the upper extremity arteries and veins to be used for personalized computational modeling, thereby allowing the determination of personalized pressure-flow relationships over all vascular segments.

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CHAPTER

6

Determination of brachial artery stiffness prior to vascular access creation: Reproducibility of pulse wave velocity assessment

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ABSTRACT

Background: Despite routine ultrasound mapping of upper extremity arteries and veins, early thrombosis and nonmaturation remain frequent complications following vascular access (VA) surgery. Besides vascular diameters, brachial artery stiffness is assumed to play an important role; however, reproducibility of measurements has never been established. The purpose of this study was to determine within-session and between-session variability of pulse wave velocity (PWV) assessment by using ultrasonography and blood pressure registration.

Methods: Beat-to-beat changes in brachial artery diameter and pressure were obtained in 21 subjects in measurement sessions on day 1 and day 3. Each session consisted of 3 acquisitions. For each acquisition systolic and diastolic diameter and pressure were determined and used for calculation of brachial artery PWV. Within-session variabilities of diameter and pressure, as well as the estimated PWV were expressed using the intraclass correlation coefficient (ICC) with corresponding coefficients of variation (CoV). Between-session variability was reported using Bland-Altman analysis in combination with CoV analysis.

Results: Significant agreement ($P < 0.001$) was obtained for all diameter and pressure measurements obtained on day 1 and day 3. Within-session CoV of pulse pressure, diastolic diameter and distension was 7.0%, 1.6%, and 18.3%. Subsequent estimation of local PWV resulted in a CoV of 10.6%. Between-session CoV was 15.1%, 3.8%, and 18.9% for pulse pressure, diastolic diameter and distension, respectively. For PWV estimation this resulted in a CoV of 13.5%.

Conclusions: Diameter and pressure can be recorded accurately over the cardiac cycle, and calculations of distensibility, pulse pressure and PWV show a slight to moderate degree of variation. Larger studies elaborating on inter-individual differences need to determine the clinical efficacy PWV measurements prior to VA creation.

INTRODUCTION

In patients with end-stage renal disease (ESRD) who require hemodialysis (HD) therapy, a well functioning upper extremity vascular access (VA) is crucial and determines the success of treatment. Based on the reduced incidence of complications, lower management costs, and decreased morbidity and mortality, an arteriovenous fistula (AVF) is the preferred VA for chronic HD, compared to arteriovenous grafts (AVG) and central venous catheters (CVC)¹.

In order to facilitate AVF creation in the majority of patients, a thorough preoperative vascular evaluation is advocated by both American and European guidelines in which duplex ultrasonography (DUS) plays a central role^{1,2}. With DUS, diameter of upper extremity arteries and veins can be appraised which are currently the primary determinant for VA configuration in the individual patient. Although diameter thresholds are believed to be of great importance for the short- and long term success of the vascular accesses, early postoperative thrombosis and nonmaturation remain a clinical problem³. As such, other factors should be taken in to consideration in an effort to reduce the number of failing fistulas.

One of the factors assumed to play a role in postoperative flow enhancement is vascular stiffness: more compliant vessels result in a larger postoperative dilatation with subsequent flow enhancement. Unfortunately, only few studies have addressed the relevancy of measuring local vascular mechanical properties prior to AVF creation^{4,6}. Quantification of venous compliance was attempted by Planken et al, however, the substantial intra-individual variation of venous diameter over time hampered implementation of routine venous compliance measurements prior to AVF surgery⁴. Arterial mechanical properties have been investigated in patients awaiting VA creation as well^{5,6}. Although these studies emphasize the potential benefit of measuring brachial artery stiffness, issues regarding reproducibility and intra-individual variation are not addressed.

The purpose of the present study was to assess within-session and between-session variability of non-invasive brachial artery stiffness measurements by estimation of the local velocity of the pressure pulse (pulse wave velocity, PWV)⁷. To this end, beat-to-beat variation in brachial artery diameter, pressure and PWV are obtained in a heterogeneous population, and investigated for their reproducibility.

METHODS

The current study was performed as part of the 'patient-specific image-based computational modeling for improvement of short- and long-term outcome of vascular access in patients on hemodialysis therapy' (ARCH) project, which is a 7th Framework European collaborative project with the aim to develop predictive tools and

methodologies to aid clinical decision-making and to improve the success after AVF creation (ARCH Project, ICT-224390).

Study design and demographics

For this prospective observational study, a heterogeneous target population was obtained by recruiting healthy volunteers without any known cardiovascular risk factors (hypertension, diabetes mellitus, and hypercholesterolemia) and patients with ESRD awaiting their first VA creation, from October 2010 through January 2011. Prior to enrolment, all subjects were subjected to a short DUS assessment of the brachial artery to rule out a variation in anatomy, for instance a high brachial bifurcation. A total of 21 subjects participated, 12 healthy volunteers and 9 patients. Demographical and clinical factors of these subjects are listed in table 1. The institutional ethics committee approved the study. Written informed consent was obtained from all subjects prior to enrolment.

Table 1: Demographical data of participants

	Total population	Healthy volunteers	Patients
Number of participants	21	12 (57%)	9 (43%)
Age (years $\pm$ SD)	44 ($\pm$ 25,6)	24 ($\pm$ 2,6)	71 ($\pm$ 14,2)
Male participants	13/21 (62%)	5/12 (42%)	8/9 (89%)
Length (cm $\pm$ SD)	173 ($\pm$ 8,8)	171 ($\pm$ 8,5)	175 ($\pm$ 8,6)
Weight (kg $\pm$ SD)	73 ($\pm$ 17,7)	65 ($\pm$ 9,0)	82 ($\pm$ 22,0)
Smoking	6 (29%)	2 (17%)	4 (44%)
Diabetes	4 (19%)	0 (0%)	4 (44%)
Hypertension	9 (43%)	0 (0%)	9 (100%)
MDRD (ml/min $\pm$ SD)*	NA	NA	19,8 ($\pm$ 3,7)

* MDRD: Estimation of the glomerular filtration rate by using the Modification of Diet in Renal Disease (MDRD) formula.

Experimental setup

In order to evaluate the variability of PWV, accurate and reproducible measurements of diameter and pressure in both the systolic and diastolic phase of the cardiac cycle are mandatory. In the study population, all measurements were performed between 7:30 am and 12:00 pm in a temperature controlled room (range 21-23 °C). Every participant was subjected to two measurement sessions (day 1 and day 3), each consisting of 3 acquisitions. Before each session, subjects were instructed to fast and abstain from exercise, nicotine, caffeine and alcohol in the 12 hours preceding the examination. Subjects were placed in supine position with the arm next to the body at heart level. Total session time was 30 minutes including patient preparation, acclimatization and image acquisition.

Patient preparation consisted of the following: firstly, a 3-lead ECG was connected to the patient in order to obtain information on the cardiac cycle. Secondly, a NexFin device (BMEye, Amsterdam, The Netherlands) was used to noninvasively obtain beat-to-beat brachial artery pressure. Thirdly, brachial artery diameter measurements were performed 5 cm proximal of the elbow fold with a MyLab70 ultrasound scanner (ESAOTE Europe, Maastricht, The Netherlands) equipped with a 23 mm linear multi frequency probe (5-13MHz) set at a frequency of 13 MHz. All measurements were performed in a longitudinal plane using B-Mode and were done by the same physician (AB), yielding a six-second registration at 60 frames/sec. Using ART.LAB software (ESAOTE Europe, 2010) diameters were determined in a selected region of interest of 12 mm in width (=footprint). Care was taken to visualize a straight segment for the measurement and to avoid compression of the vessel. ECG and blood pressure registrations were directly transferred into the ultrasound scanner and simultaneously stored in a file together with the diameter measurements (LOG-file).

Data analysis

The LOG-files were analyzed using an in-house written Matlab-script (Matlab, Mathworks Inc, Massachusetts, United States), which was capable of composing a diameter and pressure waveform for each cardiac cycle, together with corresponding absolute values for maximum, minimum and mean pressure and diameter. In figure 1 the flowchart from acquisition to data analysis is schematically visualized.

To determine within-session and between-session variability of brachial artery PWV estimation, maximum, minimum and mean pressure and diameter were calculated for every acquisition (session 1: three acquisitions, session 2: three acquisitions). Firstly, pressure and diameter measurements were analyzed for their variability. Subsequently, the obtained pressure and diameter data were used for calculation of PWV by making use of the following formula⁸:

$$PWV = \sqrt{\frac{D^2 \cdot \Delta p}{\rho \cdot (2 \cdot D \cdot \Delta D + \Delta D^2)}}$$

PWV: pulse-wave velocity, D:diastolic diameter, ΔD : distension, Δp : pulse pressure, ρ : density of blood (1055 kg/m³)

The present study was initiated to investigate the reproducibility of the measurement method, and was therefore not designed, or powered, to detect differences in the measured parameters between healthy volunteers and patients with ESRD. Nonetheless, in order to exclude the presence of a measurement bias, a sub-group analysis (Independent-Samples Mann-Whitney U Test) was performed to see whether the obtained datasets from healthy volunteers and patients with ESRD allowed for data pooling prior to further statistical assessment.

Figure 1: Schematic visualization of data acquisition and processing.

Statistical analysis

To assess within-session variability of brachial artery diameter, pressure, and PWV, the intraclass correlation coefficients (ICC) for average measures and absolute agreement were calculated, together with the coefficient of variation (CoV). ICC values range between 0 and 1, with values approaching 1 indicating stronger agreement between measurements. Between-session variability in pressure, diameter, and calculated PWV was visualized with Bland-Altman plots⁹, with the bias expressed as the mean difference and reproducibility of the obtained measurements expressed by two standard deviations (95% confidence interval). Correlation coefficients were acquired by linear regression analysis. Statistical analyses were performed using SPSS (SPSS Inc. Chicago, IL, version 15.0). Differences with $P < 0.05$ were considered statistically significant.

RESULTS

All measurements were performed successfully and resulted in a total of 126 files for analysis (21 subjects, 6 LOG-files each). During post-processing of these datasets 4 LOG-files appeared to be of non-diagnostic quality due to subject movement and were therefore excluded from further analysis. In these subjects (N=4) session variability was calculated using at least 2 measurements. There were no significant differences in the within-session and between-session PWV CoV between healthy volunteers and patients with ESRD ($p = 0.570$ [day 1], 0.177 [day 3], and 0.522 , respectively), and therefore allowed to pool the data for the subsequent statistical analyses on reproducibility of the measurement method. Furthermore, there were no significant differences in mean systolic, diastolic, and pulse pressure as well as in systolic and diastolic diameter (table 2).

Table 2: Average pressure and diameter measurements

		Diastolic pressure	Systolic pressure	Pulse pressure	Diastolic diameter	Systolic diameter
Measurement moment		mmHg (std. error)			mm (std. error)	
Day 1	1	60,4 (2,71)	121,8 (6,84)	61,3 (5,35)	4,12 (0,21)	4,27 (0,22)
	2	62,8 (2,92)	125,3 (6,82)	62,5 (5,72)	4,14 (0,21)	4,29 (0,22)
	3	63,5 (2,54)	126,2 (6,50)	62,7 (5,71)	4,18 (0,20)	4,31 (0,21)
Day 3	4	60,0 (3,02)	115,1 (5,79)	55,1 (5,21)	4,26 (0,21)	4,41 (0,23)
	5	60,7 (2,59)	114,8 (5,35)	54,1 (5,04)	4,25 (0,22)	4,41 (0,23)
	6	62,0 (2,85)	118,4 (6,03)	56,4 (5,43)	4,27 (0,23)	4,42 (0,24)
P-value*		0,134	0,092	0,206	0,270	0,647

* Wilks'-Lambda (multivariate test)

Table 3: Coefficients of variation and intraclass correlation coefficients of the measurements obtained in a single session

	Day 1		Day 3	
	CoV (%)	ICC (95% CI)	CoV (%)	ICC (95% CI)
Diastolic diameter	1,6	0,997 (0,994 – 0,999)*	1,5	0,998 (0,996 – 0,999)*
Systolic diameter	1,6	0,997 (0,994 – 0,999)*	1,4	0,998 (0,996 – 0,999)*
Mean diameter	1,6	0,997 (0,994 – 0,999)*	1,4	0,998 (0,996 – 0,999)*
Diastolic pressure	4,1	0,973 (0,932 – 0,990)*	4,0	0,973 (0,943 – 0,988)*
Systolic pressure	3,6	0,986 (0,968 – 0,994)*	3,8	0,981 (0,960 – 0,960)*
Mean pressure	3,1	0,990 (0,978 – 0,996)*	6,8	0,977 (0,951 – 0,990)*
Pulse pressure (mmHg)	7,0	0,984 (0,965 – 0,994)*	5,8	0,984 (0,967 – 0,993)*
Distension	18,3	0,908 (0,801 – 0,963)*	17,1	0,956 (0,908 – 0,981)*
PWV	10,6	0,919 (0,821 – 0,967)*	10,4	0,894 (0,780 – 0,955)*

CoV: Coefficient of variation, ICC: Intraclass correlation coefficient, CI: Confidence interval. *P-value <0,001

Reproducibility of diameter and pressure

Within-session ICC's for pressure and diameter measurements are displayed in table 3, together with their corresponding CoV: in both sessions, significant agreement between measurements is obtained ($P < 0.001$). In table 4 results are listed of the analysis of variation for all individual subjects. Average CoV on group level on day 1 for pulse pressure, diastolic diameter and distension, were 7.0%, 1.6% and 18.3%, respectively. Similar values are obtained regarding the variation of pressure and diameter measurements on day 3: 5.8%, 1.5%, and 17.1%, respectively (source data not shown). Between-session variability of systolic and diastolic brachial artery diameter as well as distension yielded a mean variation of $0.12 (\pm 0.26)$, $0.12 (\pm 0.26)$, and $0.001 (\pm 0.051)$ mm, respectively, resulting in CoV of 3.6%, 3.8%, and 18.9%, respectively. For systolic,

Table 4: Variation in measured parameters on day 1 for each participating individual

Subject	Pulse Pressure (mmHg)		Diastolic Diameter (mm)		Distension (mm)		PWV (m/s)	
	Average ($\pm$ sd)	CoV	Average ($\pm$ sd)	CoV	Average ($\pm$ sd)	CoV	Average ($\pm$ sd)	CoV
1	75 ($\pm$ 0,1)	0%	5,28 ($\pm$ 0,06)	1%	0,198 ($\pm$ 0,021)	10%	11,18 ($\pm$ 0,53)	5%
2	123 ($\pm$ 2,1)	2%	5,23 ($\pm$ 0,03)	0%	0,147 ($\pm$ 0,030)	20%	16,73 ($\pm$ 1,75)	10%
3	80 ($\pm$ 12,6)	16%	4,63 ($\pm$ 0,04)	1%	0,231 ($\pm$ 0,060)	26%	10,12 ($\pm$ 1,93)	19%
4	65 ($\pm$ 3,9)	6%	4,11 ($\pm$ 0,01)	0%	0,131 ($\pm$ 0,026)	20%	11,38 ($\pm$ 1,36)	12%
5	81 ($\pm$ 2,9)	4%	4,11 ($\pm$ 0,13)	3%	0,154 ($\pm$ 0,019)	13%	11,63 ($\pm$ 1,15)	10%
6	44 ($\pm$ 4,9)	11%	5,25 ($\pm$ 0,02)	0%	0,162 ($\pm$ 0,015)	9%	9,41 ($\pm$ 0,11)	1%
7	78 ($\pm$ 2,8)	4%	4,55 ($\pm$ 0,06)	1%	0,306 ($\pm$ 0,026)	8%	8,42 ($\pm$ 0,26)	3%
8	88 ($\pm$ 4,4)	5%	5,14 ($\pm$ 0,05)	1%	0,205 ($\pm$ 0,005)	2%	11,68 ($\pm$ 0,17)	1%
9	42 ($\pm$ 0,6)	1%	5,45 ($\pm$ 0,04)	1%	0,143 ($\pm$ 0,053)	37%	10,31 ($\pm$ 1,92)	19%
10	63 ($\pm$ 5,1)	8%	4,32 ($\pm$ 0,03)	1%	0,082 ($\pm$ 0,014)	17%	14,56 ($\pm$ 0,92)	6%
11	39 ($\pm$ 2,4)	6%	3,24 ($\pm$ 0,03)	1%	0,134 ($\pm$ 0,016)	12%	7,65 ($\pm$ 0,24)	3%
12	62 ($\pm$ 1,0)	2%	3,26 ($\pm$ 0,06)	2%	0,139 ($\pm$ 0,009)	7%	9,49 ($\pm$ 0,31)	3%
13	52 ($\pm$ 1,8)	4%	4,28 ($\pm$ 0,17)	4%	0,119 ($\pm$ 0,016)	14%	10,83 ($\pm$ 0,64)	6%
14	56 ($\pm$ 5,7)	10%	3,28 ($\pm$ 0,11)	3%	0,088 ($\pm$ 0,028)	31%	11,65 ($\pm$ 2,11)	18%
15	50 ($\pm$ 10,4)	21%	3,96 ($\pm$ 0,09)	2%	0,075 ($\pm$ 0,026)	35%	13,27 ($\pm$ 3,90)	29%
16	69 ($\pm$ 6,9)	10%	4,18 ($\pm$ 0,12)	3%	0,278 ($\pm$ 0,115)	42%	8,50 ($\pm$ 2,73)	32%
17	50 ($\pm$ 2,7)	5%	3,98 ($\pm$ 0,05)	1%	0,041 ($\pm$ 0,006)	15%	17,57 ($\pm$ 1,40)	8%
18	57 ($\pm$ 2,3)	4%	2,97 ($\pm$ 0,08)	3%	0,086 ($\pm$ 0,033)	38%	11,36 ($\pm$ 1,71)	15%
19	34 ($\pm$ 3,6)	11%	3,13 ($\pm$ 0,04)	1%	0,061 ($\pm$ 0,002)	3%	10,34 ($\pm$ 0,67)	6%
20	47 ($\pm$ 2,4)	5%	2,83 ($\pm$ 0,03)	1%	0,135 ($\pm$ 0,025)	19%	7,90 ($\pm$ 0,67)	8%
21	46 ($\pm$ 5,7)	13%	3,03 ($\pm$ 0,06)	2%	0,086 ($\pm$ 0,007)	8%	10,00 ($\pm$ 0,69)	7%
Average		7.0%		1.6%		18.3%		10.6%

CoV: Coefficient of variation; PWV: Pulse wave velocity

diastolic and pulse pressure measurements the mean variation was $9.49 (\pm 20.24)$, $3.13 (\pm 14.12)$, and $6.43 (\pm 14.91)$ mmHg, respectively, resulting in CoV of 9.3%, 11.0%, and 15.1% (figures 2 & 3).

Figure 2: Between-session variability of diameter measurements. Linear regression analysis and corresponding Bland-Altman plot showing differences in A) mean, B) systolic, and C) distension between day one and day three. In the Bland-Altman plots, the solid lines represent the mean value, while the dotted lines correspond with 2 standard deviations of the difference.

Figure 3: Between-session variability of pressure measurements. Linear regression analysis and corresponding Bland-Altman plot showing differences in A) mean, B) systolic, and C) pulse pressure between day one and day three. In the Bland-Altman plots, the solid lines represent the mean value, while the dotted lines correspond with 2 standard deviations of the difference.

Arterial stiffness

PWV calculation demonstrates an ICC agreement of 0.919 and 0.894 on day 1 and 3, respectively (table 3). Table 4 shows the individual CoV of PWV calculation: mean CoV regarding PWV calculation on day 1 is 10.6%. Similar analysis for day 3 resulted in a CoV of 10.4% (source data not shown).

Between-session variability of PWV measurements shows a higher degree of variation, as is evidenced by the linear regression and Bland-Altman analysis (figure 4). Mean variation of PWV between day 1 and 3 was 0.21 (± 2.62) m/s, resulting in a CoV of 13.5%. Pearson correlation analysis revealed that variation in distension has the largest impact on PWV variation (table 5).

Figure 4: Between-session variability of PWV estimation. Linear regression analysis and corresponding Bland-Altman plot showing differences in PWV calculation between day one and day three. In the Bland-Altman plots, the solid lines represent the mean value, while the dotted lines correspond with 2 standard deviations of the difference.

Table 5: Correlation between the variation in PWV and variations of the measured values

	Variation in PWV vs. variation in pulse pressure	Variation in PWV vs. variation in diastolic diameter	Variation in PWV vs. variation in distension
Pearson correlation coefficient day 1	0,496*	0,344	0,895**
Pearson correlation coefficient day 3	0,384	-0,162	0,935**
Pearson correlation coefficient Total	0,385	0,040	0,647**

* Correlation significant at $\alpha : 0,05$ level

** Correlation significant at $\alpha : 0,01$ level

DISCUSSION

In the current study we present within-session and between-session variability of brachial artery diameter and pressure measurements which are subsequently used for estimation of local arterial stiffness by calculating PWV. Although within-session variability of systolic, diastolic and mean diameter as well as pressure showed relatively low CoV and good ICC values, within-session variability of PWV is slightly larger when these measurements are used for its calculation: there is an effect from diameter variability but also from pressure variability in the calculation of PWV. Reproducibility of measurements over time showed to be more susceptible to intra-individual variation: here we report a between-session CoV for systolic, diastolic and delta diameter of 3,6%, 3,8%, and 18,9%, respectively. For systolic, diastolic and pulse pressure larger CoV were depicted: 9,3%, 11,0%, and 15,1%, respectively. Ultimately, for PWV calculation, this results in a CoV of 13,5%.

Arterial stiffness parameters can be measured using a variety of techniques^{10,11}. According to the Expert Consensus Document⁷, quantification of aortic-femoral PWV is considered the 'gold standard' measurement for determination of arterial stiffness given the simple, non-invasive, and reproducible method. More importantly, when measured over the aortic-femoral tract, it provides a patient-specific risk estimation for cardiovascular mortality¹¹⁻¹⁵. However, this predictive power cannot readily be translated to arteries outside the aortic tract because of a profound heterogeneity in the molecular, cellular and histological structure of the arterial vascular tree¹⁵. Therefore, only a limited number of studies exist which elaborate on determination of local arterial stiffness¹⁵⁻¹⁹. Nevertheless, these studies emphasize that measurement of local arterial stiffness might have a predictive value in the development of cerebral ischemia and peripheral arterial disease when measured in the carotid-, and femoral artery, respectively.

In patients awaiting VA creation, arterial stiffness might play a role in fistula maturation as well: increased vascular stiffness hampers postoperative dilatation of the inflow artery, thereby limiting flow enhancement and increasing the risk of fistula failure^{5,6}. In an attempt to identify patients with an increased risk for fistula failure, Malovrh et al. identified the resistance index (RI) at reactive hyperemia (RH) as a prognostic parameter, and concluded that a RI at RH > 0.7 was associated with an increased risk of fistula failure⁵. The recent study of Kheda and colleagues concluded that patients showing nonmaturation generally had a lower small artery elasticity index compared to patients with matured fistulas. Surprisingly, no significant differences in large artery elasticity index could be identified⁶.

The acquisition technique used in our study consists of longitudinal echo tracking of the brachial artery lumen with simultaneous ECG and pressure registration. This technique, firstly described by Brands et al²⁰, is well validated for determination of arterial stiffness parameters in the carotid artery, but has never been utilized in other vascular beds. Although systolic, diastolic and mean brachial artery diameter and pressure measurements

showed good reproducibility, both within-session and between-session variability of PWV measurements were significantly larger. This might be due to the relatively large variation in distension and pulse pressure values, derived from the raw acquisition. A possible explanation for this variation might be found in the presence of heart rate variability, resulting in differences in stroke volume, thereby affecting beat-to-beat variability in distension and pulse pressure.

Also, the CoV for distension measurements reported in this study is larger than the one established by Brands et al²⁰. This discrepancy is most likely induced by the substantial smaller diameter of the brachial artery compared to the carotid artery, being closer to the resolution of the wall tracking algorithm of the ultrasound system. In an effort to reduce the variability in PWV estimation, the use of high frame rate B-mode (fast-B-mode, FBM) instead of B-mode ultrasound could be considered. FBM uses phase information of the echo signal for tracking the wall more accurately and, consequently, allows to obtain more functional characteristics of the arterial wall (e.g. perpendicular vessel wall velocity during systole).

For acquisition of systolic diastolic and mean brachial artery pressure we used the BMEye NexFin device, which is able to produce a continuous pressure waveform on a beat-to-beat basis. This approach might be superior to the technique used by Simova et al¹⁹, who used incident upper arm blood pressure measurements for the calculation of the stiffness parameters. We believe that detection of beat-to-beat fluctuations in blood pressure result in more accurate estimation of PWV and therefore our study was able to provide an acceptable CoV regarding brachial artery PWV measurements using a single observer.

As a limitation of this study we should point out the lack of an inter-observer comparison of the obtained measurements. However, given the fact that this issue has been satisfactory addressed by previous studies using similar echo tracking techniques^{21,22}, in combination with the simple nature of experimental setup and its measurements this was deemed unnecessary. As a further limitation of this study one might consider the pressure registration using a finger cuff. Though not measured at the exact same location as the ultrasound acquisition, the extrapolation algorithm for finger-to-brachial pressure in the NexFin system is well validated²³. Moreover, this method is considered non-invasive and facilitates acquisition of the complete pressure waveform, in contrast to earlier performed studies in which pressure registration was performed once per session, or in limited intervals.

In conclusion: we investigated the reproducibility of brachial artery diameter and pressure acquisitions, as well as the reproducibility of PWV estimation in healthy volunteers and patients with ESRD. Both diameter and pressure can be recorded accurately over the cardiac cycle, and calculations of distensibility, pulse pressure and PWV show a slight to moderate degree of variation. Inter-individual differences, as well as the relation between preoperative PWV and postoperative flow enhancement determine the clinical efficacy of preoperative PWV measurements, being susceptible to a CoV of 13%. These issues are currently being investigated.

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CHAPTER

7

A pulse wave propagation model to support decision-making in vascular access planning in the clinic

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ABSTRACT

The preferred vascular access for hemodialysis is a native arteriovenous fistula (AVF) in the upper extremity: a surgical connection between an artery and a vein. In clinical practice, the surgeon selects the preferred AVF location based on experience and preoperative diagnostic modalities. Nonetheless, 20-50% of all lower arm AVF's are dysfunctional due to insufficient postoperative flow enhancement, whereas complications associated with excessive flow enhancement are observed in 20% of all upper arm AVF's. We hypothesize that a patient-specific pulse wave propagation model has the ability to assist the surgeon in selecting the optimal AVF configuration by predicting direct postoperative flow.

Previously, a 1D wave propagation model was developed in which an approximated velocity profile was assumed based on the boundary layer theory. In the current study, we developed a distributed lumped parameter implementation of that model in which the elements of the electrical analog are based on the approximated velocity profiles derived from the Womersley number. Furthermore, we present the application of this lumped parameter pulse wave propagation model to vascular access surgery, and show how patient-specific modeling is able to predict the hemodynamical impact of AVF creation.

The lumped parameter pulse wave propagation model was able to select the same AVF configuration as an experienced surgeon in nine out of ten patients. In addition, in six out of ten patients predicted postoperative flows were in the same order of magnitude as measured postoperative flows. Future research should quantify the uncertainty in both clinical measurements and model based predictions.

INTRODUCTION

In Europe, more than 500.000 patients with end-stage renal disease (ESRD) are dependent on hemodialysis (HD) treatment¹; a number that is expected to increase by approximately 8% each year^{2,3}. To enable chronic HD therapy, a functional vascular access (VA) is required. Such a VA needs to provide a high flow and should have a caliber that enables repetitive cannulation^{4,5}. Since the human body has no vessels that meet all these requirements, a VA is surgically created. By surgically connecting an artery with a vein the peripheral resistance is bypassed, which results in a significant flow increase and vessel remodeling. Such an arteriovenous fistula (AVF) is considered suitable for HD if postoperative flow >600 ml/min, the proximal vein has a diameter >6 mm, and the cannulation segment is located <6 mm deep^{4,5,10,12,13}.

An AVF can be created on several locations in the upper extremity, and is a trade-off between initial and long-term access patency, complication rates, and saving potential access sites for future procedures⁶⁻⁹. For the former reasons, an AVF at wrist level is preferred over more proximal AVF's. Despite the expertise of the surgeon and the extensive preoperative work-up^{5,10,11}, nonmaturation occurs in up to 50% of all newly created lower arm AVF's^{4,5,7,12}. On the other hand, complications associated with too high flows are observed in 20% of all upper arm AVF's^{4,5,7,10}. Low flow measured directly after surgery is indicative for nonmaturation^{12,14}, while a high postoperative flow (> 30% of the cardiac output) increases the risk on cardiac failure and hand ischemia⁶⁻⁹. Preoperative prediction of postoperative flow might enable an improved selection of the most suitable AVF configuration. We hypothesize that a patient-specific computational model is able to predict the direct postoperative flow by considering multiple factors that influence VA flow (e.g. diameter, accessory veins and vessel distensibility) and their mutual dependency.

Computational models with various degrees of complexity have been used to study (patho)physiology of the cardiovascular system¹⁵⁻²². Although 3D models enable studying local flow phenomena, they are less suitable for predictive surgery because of their high computational cost. Pulse wave propagation models on the other hand are appropriate for predictive vascular surgery, because they can be used to calculate the distribution of pressure and flow throughout the vascular system within minutes. Besides, pulse wave propagation models are easier to adapt to patient-specific conditions than 3D methods and allow incorporation of nonlinear equations describing the relation between cross-sectional area and pressure^{24,26-29}, or the additional pressures drops resulting from stenoses, curvature and anastomoses²⁶⁻²⁹. Although some previous studies have described the use of pulse wave propagation models to predict hemodynamic changes after creation of femoro-popliteal²⁶, thoraco-thoraco aortic^{27,28}, and aorto-femoral bypasses²⁸, the use of predictive models is not common in clinical practice yet.

In pulse wave propagation models the vascular system is divided into segments that

represent local blood and vessel wall properties. All segments are serially connected based on the anatomical configuration. For each segment the relation between pressure and flow is described by the 1D momentum and continuity equations derived by Hughes and Lubliner³⁷. In addition, a constitutive law is used to describe wall behavior. The resulting equations can be solved for pressure and flow by several numerical techniques like the spectral element method^{24,25}, the finite element method^{27,28}, and the method of characteristics^{30,33}, resulting in one-dimensional (1D) pulse wave propagation models. Pulse wave propagation models in which segments are lumped (spatial information within each segment is lost) into an electrical analog are also used^{23,34,35}, and are here referred to as distributed lumped parameter pulse wave propagation models.

In the momentum equation, approximations for wall shear stress and the convective acceleration term are needed. These terms can be estimated from a large variety of velocity profiles based on Poiseuille^{27,28}, Witzig-Womersley theory for pulsatile flow³⁰, the Young and Tsai formulation³¹, and approximated velocity profiles^{24,29}. Bessems et al. used an approximated velocity profile based on boundary layer theory and solved the resulting set of equations in time domain by using spectral elements^{24,25}.

Previously, we showed that after neglecting the nonlinear convection term, it is possible to derive a lumped parameter segment to describe the pressure-flow relation in each vascular segment based on the set of equations used by Bessems without losing accuracy^{24,38}. Neglecting the convection term is reasonable, as in the application in this study this term is expected to be relatively small compared to the inaccuracy of the flow predictions resulting from inaccuracies in input parameters^{32,36}. Numerical implementation of a wave propagation model consisting of lumped parameter segments is straightforward. This method defines flow positive when directed into the segment and therefore no coupling equations are needed. Furthermore, the lumped parameter wave propagation model simplifies coupling of other lumped segments (e.g. for windkessels or for nonlinear elements like the anastomosis) to wave propagation segments because they have the same format and can be assembled together. In addition, the lumped parameter wave propagation implementation is, in our experience, robust. A lumped parameter description is intuitive and comprehensible, as the lumped parameter segment is build of three types of elements; resistors representing resistance to blood flow, inductors related to the force that is needed to accelerate blood and capacitors representing the storage capacity of the blood vessel. We thus expect that a lumped parameter pulse wave propagation model will be more readily implemented and used in clinical practice. In this study we derive and present a lumped parameter pulse wave propagation model and, in addition, we show how the model can be made patient-specific and might be used for VA surgery planning. The difference between the lumped model approach in this study and the one in for example Westerhof et al.²³ is that our electrical elements are based on an approximated velocity profile, which result in Womersley number dependent resistors and inductors. Another main difference is that

we allow for vessel diameter tapering within one segment.

We will first describe the mathematical approach of the pulse wave propagation model and the modeling of the feeding artery, the anastomosis and the outflow veins of the AVF complex. Next to the mathematical description, the interpretation of the different elements is given to improve the understanding of the model's background. Subsequently, the model is applied to VA surgery and we examine whether the model is able to delineate flow increases in upper arm and lower arm AVF's. Finally, we will compare simulations results of flow after VA creation with flows observed in a clinical setting.

METHODS

The mathematical model

For modeling the effect of VA creation on blood pressure and flow distribution, segments are needed that represent arteries, veins and the anastomosis. By combining these segments, different vascular topologies, with or without an AVF, can be constructed. Before describing the patient-specific topologies in detail, the physical and mathematical background of the different segments are presented.

Governing equations

The relation between pressure p and flow q for each vascular segment is derived from conservation of mass and the momentum equation by assuming fully-developed incompressible Newtonian flow in a straight vessel^{24,37}. The mass equation is further simplified by assuming a compliance C_0 per unit length, resulting in

$$C_0 \frac{\partial p}{\partial t} + \frac{\partial q}{\partial z} + \Psi = 0 \quad (1)$$

with

$$C_0 = \left. \frac{\partial A}{\partial p} \right|_{p=p_0} \quad (2)$$

in which p_0 is the mean pressure, A is the cross-sectional area and Ψ the flow per unit length distributed to small side-branches that are not separately modeled by vascular segments. The momentum equation is given by

$$\frac{\partial q}{\partial t} + \frac{\partial}{\partial z} \left(\int_A v_z^2 dA \right) + \frac{A}{\rho} \frac{\partial p}{\partial z} - A f_z - \frac{2\pi a_0}{\rho} \tau_w = 0 \quad (3)$$

in which A is the cross-sectional area, v_z the local axial velocity, a_0 the vessel radius at mean pressure, τ_w the wall shear stress, ρ the blood density and η the dynamic blood viscosity. In momentum equation (3), the convection term and the effect of body forces ($A f_z$) are neglected because their contributions are expected to be small compared to the other terms.

ted to be small in the arm vasculature, which are the most important vessels in the application for VA planning^{32,36}. Neglecting the convection term is allowed as long as in $\frac{V}{c} \ll 1$ which V is the blood velocity and c the wave speed⁵⁵. This holds in the arm vasculature and by approximation in the aorta.

An expression for wall shear stress as function of p and q is derived from a time and frequency dependent approximated velocity profile which is based on boundary layer theory^{24,38}. The momentum equation then becomes

$$-\frac{\partial p}{\partial z} = \left[\frac{c_q}{2-c_p}\right]R_0 q + \left[\frac{1}{2-c_p}\right]L_0 \frac{\partial q}{\partial t} \quad (4)$$

in which R_0 is the Poiseuille resistance per unit length ($\frac{8\eta}{\pi a_0^4}$) and L_0 is the inertia per unit length ($\frac{\rho}{\pi a_0^2}$). Parameters c_p and c_q solely dependent on the Womersley number

($\alpha = a_0 \sqrt{\frac{\omega \rho}{\eta}}$ with ω angular frequency) and are given by Bessems et al²⁴.

$$c_p = 1 + \frac{\sqrt{2}}{\alpha} \left(1 - \frac{\sqrt{2}}{2\alpha}\right), \quad c_q = \frac{\alpha}{4\sqrt{2}} \left(1 - \frac{\sqrt{2}}{2\alpha}\right)^{-1} \quad \text{for } \alpha > \sqrt{2} \quad (5)$$

and

$$c_p = \frac{3}{2}, \quad c_q = \frac{1}{2} \quad \text{for } \alpha \leq \sqrt{2}. \quad (6)$$

A lumped parameter segment is derived that consists of a Womersley number dependent resistor per unit length R and a Womersley number dependent inductor per unit length L in series representing the momentum equation (Figure 1). The capacitor per unit length C and the resistor R_L of this lumped parameter segment represent the continuity equation. By evaluating c_p and c_q only for the characteristic frequency, this serial configuration fits Womersley theory better than the parallel configuration proposed earlier by us³⁸, whereas when all frequencies are considered they behave similar. By evaluating c_p and c_q only for the characteristic frequency, parameters L and R stem from momentum equation (4), which results in

$$-\frac{\partial p}{\partial z} = Rq + L \frac{\partial q}{\partial t} \quad (7)$$

with

$$R = \left[\frac{c_q(\alpha_0)}{2-c_p(\alpha_0)}\right]R_0 \quad \text{and} \quad L = \left[\frac{1}{2-c_p(\alpha_0)}\right]L_0 \quad (8)$$

herein, α_0 is the Womersley number corresponding to the characteristic frequency.

Figure 1: Lumped parameter model of a vascular segment (top) and a three-element windkessel model that is used to model branches that are truncated (bottom).

Vascular segment

For both arterial and venous segments, a lumped parameter segment with the serial arrangement of the resistor and inductor is used (Figure 1). For each segment total resistance and total inertance are obtained by integrating R and L over the segment length. The superficial veins that are used for venous drainage in an AVF can have an elliptical cross-sectional area and therefore different expressions for L_0 and R_0 are used, that apply to elliptical tubes. The Poiseuille resistance per segment length for an elliptical tube $R_{0,v}$ than given by Haslam et al⁴⁰.

$$R_{0,v} = \frac{8\eta(a_0^2 + b_0^2)}{2\pi(a_0^3 b_0^3)} \quad (9)$$

with a_0 and b_0 the major and minor radii at the mean pressure $p=p_0$. Note that equation (9) reduces to $R_0 = \frac{8\eta}{\pi a_0^4}$ (Poiseuille resistor) in case $a_0=b_0$. The venous inertance per unit length, $L_{0,v}$ is

$$L_{0,v} = \frac{\rho}{\pi a_0 b_0}. \quad (10)$$

To incorporate vessel compliance in the lumped parameter model, a capacitor is added to each side of the vascular segment (Figure 1), representing half of the total vascular compliance over that segment²³. Furthermore, it is assumed that the artery is a thick-walled linear elastic tube. The compliance per segment length is then given by Jager³⁵

$$C_0 = \frac{2\pi a_0^2 \left(\frac{2a_0^2(1-\mu^2)}{h_0^2} + (1+\mu) \left(\frac{2a_0}{h_0} + 1 \right) \right)}{E_0 \left(\frac{2a_0}{h_0} + 1 \right)} \quad (11)$$

with E_0 the Young's modulus, μ the Poisson ratio and h_0 the wall thickness. Veins can have an elliptical cross-sectional area, and therefore, instead of a_0 a weighted average radius ($\bar{a}_0 = \sqrt{a_0 b_0}$) is used in (11). Because veins are much thinner than arteries, the limit of (11) for $\bar{a}_0 \gg h_0$ is used for veins, resulting in

$$C_{0,v} = \frac{2\pi \bar{a}_0^3 (1-\mu^2)}{E_{0,v} h_0} \quad (12)$$

in which $E_{0,v}$ is the venous Young's modulus. Total compliance for each segment is determined by integrating C_0 or $C_{0,v}$ over the segment length. The distributed flow Ψ in (1) is captured by adding linear resistances in parallel to the capacitors (Figure 1).

Modeling the anastomosis

The anastomosis (Figure 2) cannot be modeled by linear segments because the radial velocity component is no longer infinitesimally small compared to the axial velocity and flow separation can occur in this region. The velocity profile can thus not be based on fully developed flow in straight vessels. Consequently, a special segment is created to model pressure losses over the anastomosis.

Due to complex flow patterns, resulting from the geometry at the anastomotic region and possible turbulence, there is no analytical relation that describes the pressure losses. Steele et al.²⁷ and Jones et al.⁴¹ have applied pressure loss relations for a T-junction to model the anastomosis of a thoraco-thoraco aortic bypass graft and a HD prosthetic graft, respectively. They both neglected the extra pressure drop due to unsteadiness of flow. This assumption seems reasonable as pulsatility in an AVF decreases with respect to the steady component and because the cross-sectional area of the vein is larger than the area of the anastomosis which results in deceleration of flow and thus an increase in pressure which might compensate for the extra pressure drop resulting from the unsteady flow. However, future research should investigate this statement. In this study, we therefore followed the same approach as Steele et al.²⁷ and Jones et al.⁴¹ to model the anastomosis of an AVF (Figure 3). Pressure in the proximal artery p_p minus pressure in the vein p_v and pressure in the proximal artery p_p minus pressure in distal artery p_d can be written as

$$p_p - p_v = K_v \frac{1}{2} \rho v_p^2 \quad (13)$$

and

$$p_p - p_d = K_d \frac{1}{2} \rho v_p^2 \quad (14)$$

Figure 2: A schematic picture of the torso and arm vasculature including the major arteries and the superficial veins (left). The procedure of creation of an arteriovenous fistula (permanent connection between the artery and the vein) in the upper (middle, top) and lower (middle, bottom) arm and the connection of the VA to the dialyzer are depicted. At the right the anastomosis is shown in more detail.

respectively^{27,42}. Herein v_p is the cross-sectional averaged blood velocity in the proximal artery, and K_v the loss coefficient from the proximal artery to the proximal vein, and K_d the loss coefficient from the proximal artery to the distal artery.

Gardel et al.^{43,44} experimentally derived semi-empirical relations for the loss coefficients K_v and K_d . The loss coefficients for an anastomosis are given by (dividing T-junction)

$$K_v = k_1(1 - q^*)^2 + q^{*2} \left[k_2 \cot \frac{\theta}{2} - k_3 + \frac{k_4 - k_5 A^*}{A^{*2}} \right] + k_6 q^*(1 - q^*) \left(1 + \frac{1}{A^*} \right) \cot \frac{\theta}{2} \quad (15)$$

$$K_d = k_7(1 - q^*)^2 + k_8 q^{*2} - k_9 q^*(1 - q^*) \quad (16)$$

in which q^* is the ratio between flow through the vein and flow through the proximal artery, A^* is the ratio between cross-sectional area of the vein and cross-sectional area of the proximal artery and θ is the angle between proximal artery and proximal vein (Figure 3)⁴²⁻⁴⁴. Empirical determined values for the constants k_1 to k_9 are given in table 1. By introducing flow $q_p = v_p A_p$ with A_p the cross-sectional area of the proximal artery, (13) and (14) can be rewritten to

$$p_p - p_v = K_v \frac{1}{2} \rho \frac{q_p^2}{q_v^2} \frac{1}{A_p^2} |q_v| q_v = R_v(q^*, A^*, \theta, q_v, q_p, A_p) q_v \quad (17)$$

and

$$p_p - p_d = K_d \frac{1}{2} \rho \frac{q_p^2}{q_d^2} \frac{1}{A_p^2} |q_d| q_d = R_d(q^*, A^*, \theta, q_d, q_p, A_p) q_d \quad (18)$$

The pressure drop in the anastomosis from the proximal artery to proximal vein and to distal artery is incorporated in the pulse wave propagation model by adding two resistors, R_v and R_d , that nonlinearly depend on flow.

Figure 3: The anastomosis incorporated in the lumped parameter pulse wave propagation model.

Table 1: Semi-empirical determined dimensionless constants k_1 to k_9 for equations (15) and (16)^{43,44}

k_1	k_2	k_3	k_4	k_5	k_6	k_7	k_8	k_9
0.95	1.3	0.3	0.4	0.1	0.4	0.03	0.35	0.2

Numerical scheme

After assembly of the segments and by using the (implicit) trapezoidal rule for time integration the following system of equations is derived

$$\underline{K}p^n = q_e^n + f^{n-1} \quad (19)$$

in which $\underline{K}$ is the system matrix, p^n is a column containing the nodal pressures that we calculate in the current time step n , q_e^n denotes the external nodal flows containing zero values for all nodes except the nodes on which external flow is prescribed, and f^{n-1} is the right hand side column vector resulting from time integration and matrix assembly. The system of equations is solved with a direct solver after defining boundary conditions as described in the next section. The flow through each segment is depicted by applying an analogue of Ohm's law. By incorporating flow dependent resistors (17) and (18) for the anastomosis, the system becomes nonlinear and is given by

$$\underline{K}_i(q_i^*, A^*, \theta, q_{vi}, q_{di}, q_{pi}, A_p)p_i^n = q_e^n + f^{n-1} \quad (20)$$

Boundary conditions

Prescribed flows

In our model aortic flow is prescribed at node $k=1$ and thus $q_e = [q_{aorta}, 0, \dots, 0]^T$. The aorta is part of the modeling domain to be able to predict the redistribution of flow through the body after AVF creation. Moreover, reflections at the inlet are better represented (closed aortic valve) than if we prescribe the flow at the arm.

Prescribed pressures

In addition, extravascular pressure p_e and venous pressure at the end of the venous branch p_v and at the end of the windkessel model $p_{v,wk}$ are prescribed.

Windkessel model

At arterial ends, arteries are terminated with a three-element Windkessel model (Figure 2) consisting of a characteristic impedance, Z_{wk} , a resistance, R_{wk} and a compliance, C_{wk} ¹⁹. The characteristic impedance is chosen such that reflections from high frequencies ($\omega C_{wk} R_{wk} \gg 1$) are attenuated¹⁹. The pressure drop over the characteristic impedance is then given by

$$p - p_s = Z_{wk}q \quad \text{with} \quad Z_{wk} = \sqrt{\frac{L}{C_0}} \quad (21)$$

in which Z_{wk} is the characteristic impedance for $\omega L \gg R$ and p_s a standard reference pressure. R , L and C_0 are, respectively, the resistance, the inertance and the compliance of the segment before the end-segment. The sum of the resistance R_{wk} and the characteristic impedance Z_{wk} is the total resistance R_p of the peripheral bed¹⁹:

$$R_p = Z_{wk} + R_{wk}. \quad (22)$$

R_p is defined as:

$$R_p = \frac{\bar{p}}{\beta \bar{q}} \quad (23)$$

with β the fraction of the cardiac output flowing through the peripheral bed and $\bar{p}$ the mean arterial pressure and $\bar{q}$ the cardiac output. The pressure wave decreases during diastole with a time constant that is equal to:

$$\tau = R_{wk} C_{wk} \quad (24)$$

If τ and R_{wk} are known, the compliance C_{wk} can be derived from (24). The parameter R_{wk} can be derived from equations (22) and (23), while τ can be obtained from the descending slope of the local pressure curve during diastole or can be based on literature. To adapt the model to patient-specific conditions, blood properties (viscosity, density), and geometrical (radius, wall thickness-to-radius ratio, vessel length, anastomosis angle) and mechanical vessel properties (Poisson ratio, Young's modulus) are needed. Additionally, patient-specific boundary conditions should be available.

Models for vascular access surgery

Ten patient-specific models were made using data from ten ESRD-patients awaiting VA creation to facilitate HD. For all patients the target extremity did not have an earlier VA. The study was approved by the Medical Ethical Committee of the Maastricht University Medical Center (MUMC) and all patients gave their written informed consent. Depending on the arm in which the VA is created, the left or right arm is modeled in detail. The

aorta, the vessels in the lower body, in the contralateral arm and in the head are only modeled partially and then closed by windkessel models. These arteries are included into the model to obtain the correct flow distribution over the vasculature as this is unknown after AVF creation. Postoperatively, an element that models the anastomosis and a venous branch are added to model the venous return of the AVF. For an upper arm AVF a single vein is added (basilic or cephalic vein), whereas for a lower arm AVF the distal cephalic vein, the median cubital vein and the proximal basilic vein are added. The computational domains of the preoperative situation, the lower arm configuration and the upper arm configuration are shown for the left arm in figure 4. In case of a right arm configuration, the computational domain is comparable; the left arm is truncated after the first edge (left subclavian artery A) and the right carotid artery and the right arm are added to the end of the innominate artery. The models are made patient-specific as described in the next paragraph.

Patient-specific input

Model geometry

All ten patients underwent a preoperative DUS examination to determine vessel diameters as part of standard clinical health care. Diameters of the brachial, radial and ulnar arteries as well as the basilic, subclavian and cephalic vein were measured in the distal lower arm (a few cm proximal to the wrist joint), halfway the lower arm, in the proximal lower arm (a few cm distal to the elbow joint), at the elbow joint, in the distal upper arm (a few cm proximal to the elbow joint), halfway the upper arm and in the proximal upper arm (a few cm distal to the axilla). In addition, diameters of the subclavian artery and the median cubital vein

Figure 4: The computational domains for the preoperative situation, with an upper arm and with a lower arm AVF in the left arm. The arterial tree (red) and the included veins (blue) are divided in edges. The arterial edge numbers refer to the edges in Table 3. The venous edges for the lower arm AVF represent the distal cephalic vein (#14), the median cubital vein (#15), the proximal cephalic vein and the distal axillary vein (#16), the basilic vein (#17) and the proximal axillary and subclavian vein (#18). The venous edges for the upper arm AVF represent the proximal cephalic vein and the distal axillary vein (#14) and the proximal axillary and subclavian vein (#15). The light blue circles indicate the locations on which diameter measurements are available.

Table 2: Physiological and geometrical data of the arterial tree based on Stergiopulos et al.³¹ This table contains the segment length l , the proximal radius a_p , the distal radius a_d , the wall thickness h and the elastic Young's modulus (E).

Edge nr.	Arterial edge name	l [10^{-2} m]	a_p [10^{-2} m]	a_d [10^{-2} m]	h [10^{-3} m]	E [10^6 Pa]
1	ascending aorta	4.00	1.47	1.44	1.63	0.40
2	aortic arch A	1.00	1.12	1.12	1.26	0.40
3	aortic arch A	1.00	1.12	1.12	1.26	0.40
4	innominate	3.40	0.62	0.62	0.80	0.40
5	aortic arch B + thoracic aorta	9.10	1.07	0.999	1.13	0.40
6	left carotid	4.10	0.370	0.370	0.63	0.40
7	left subclavian A	3.40	0.423	0.423	0.66	0.40
8	left vertebral	4.90	0.188	0.186	0.45	0.80
9	left subclavian B + axillary + brachial	44.3	0.403	0.236	0.67	0.40
10	left radial	23.5	0.174	0.142	0.43	0.80
11	left ulnar proximal	6.70	0.215	0.215	0.46	0.80
12	left interosseus	7.90	0.091	0.091	0.28	1.60
13	left ulnar distal 1	5.70	0.203	0.188	0.46	0.80

were determined (Table 3). Prior to measurement of the distal venous diameters a tourniquet was applied around the upper arm to induce venous dilatation and to increase the reproducibility of the measurement^{47,48}. Arterial and venous diameters were measured in B-mode, both in longitudinal and transversal imaging plane using an electronic caliper with an accuracy of 0.1 mm. Because the ultrasound examination supplies diameters on discrete locations (Figure 4), a linear inter- and extrapolation was performed within each vascular edge to obtain diameter-length relations for each vascular edge. All edges were then divided in vascular segments. For diameters of the other vessels, data from Stergiopulos et al.³¹ was used (Table 2) after applying a patient-specific scaling factor, determined from the ratio between the measured arm diameters and arm diameters from literature³¹. Also the arterial lengths were based on Stergiopulos et al. Venous lengths were assumed equal to the arteries at the same anatomical level. Generic values for vessel lengths were taken as Leguy et al. showed that the mean flow is not sensitive to uncertainties in the lengths of the vessels and for AVF creation mean flow is the most important outcome⁴⁹. However, note that for other output parameters like the transit time of the waveforms this does not hold. In that case, the vessel lengths should be determined patient-specifically.

The wall thickness to radius ratio in the subclavian, axillary and brachial artery were set to 0.15, in the ulnar, interosseus and radial artery a ratio of 0.20 was taken⁵⁰⁻⁵². For all other arteries data from Stergiopulos³¹ were used (Table 2). For veins a ratio of 0.10 was assumed. The anastomosis angle is unknown prior to surgery but has influences the pressure drop over the anastomosis. It was therefore varied between 30 and 60 degrees.

Table 3: All patient-specific data that is measured within the clinic for each individual patient.

	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
Arterial diameters [mm]										
Subclavian artery	6.6	9.0	7.3	6.9	7.7	6.3	8.0	6.3	8.4	6.2
Brachial artery proximal	4.4	5.1	4.5	5.2	5.7	5.5	4.8	2.8	5.2	4.2
Brachial artery in the middle	3.4	4.3	3.7	4.9	4.6	4.2	4.8	-	4.1	3.8
Brachial artery distal	3.8	4.2	4.1	5.9	5.4	4.6	6.1	4.2	4.6	3.9
Radial artery proximal	2.3	3.3	3.6	2.8	4.2	2.6	-	-	2.6	3.0
Radial artery in the middle	2.2	2.7	2.5	2.3	2.2	2.4	-	2.6	2.0	2.0
Radial artery distal	1.5	1.7	2.1	2.2	2.5	2.4	2.6	2.4	2.2	2.1
Ulnar artery proximal	2.7	-	4.4	-	3.6	3.5	2.9	2.6	2.4	2.0
Ulnar artery in the middle	2.5	1.9	1.8	2.0	1.1	2.6	1.8	1.6	1.7	2.0
Ulnar artery distal	1.5	1.8	1.4	1.8	1.4	2.1	1.7	1.3	2.2	2.1
Minor axis venous diameters [mm]										
Cephalic vein distal	1.4	3.4	1.3	2.0	2.5	1.7	2.9	2.0	2.1	1.7
Cephalic vein in the middle of the lower arm	2.0	3.9	2.3	4.3	2.0	2.3	2.7	3.2	1.8	3.2
Cephalic vein at the elbow	3.7	5.0	2.7	4.2	3.5	5.0	3.1	3.5	2.5	3.3
Cephalic vein in the middle of the upper arm	-	3.1	2.3	3.4	2.4	4.9	-	3.2	3.1	4.0
Cephalic vein at shoulder level	-	3.5	2.3	2.2	1.7	3.8	-	4.6	2.4	-
Basilic vein distal	-	2.5	-	1.0	1.2	4.2	-	1.8	-	3.0
Basilic vein in the middle of the lower arm	1.3	3.3	1.1	0.7	1.8	3.5	1.5	2.5	-	3.7
Basilic vein at the elbow	3.4	3.8	2.0	3.1	4.0	-	2.0	2.4	2.7	4.4
Basilic vein in the middle of the upper arm	3.6	7.2	2.9	4.4	5.3	5.1	6.0	5.4	6.0	5.0
Basilic vein before entering the deep venous system	-	6.4	2.9	-	6.8	4.2	6.4	6.8	5.8	3.5
Median cubital vein	2.2	5.9	4.2	3.5	5.5	4.7	5.6	7.2	2.0	4.9
Subclavian vein	9.0	9.0 ^a	-	6.9	7.7 ^a	6.8	8.0	9.5	9.3	8.4
Major axis venous diameters [mm]										
Cephalic vein distal	1.5	4.8	1.5	2.1	2.8	1.7	2.9	3.1	2.3	1.8
Cephalic vein in the middle of the lower arm	2.2	4.9	2.9	4.8	2.7	3.7	2.7	4.5	2.2	3.5
Cephalic vein at the elbow	4.6	6.2	3.4	4.6	3.5	5.9	3.3	4.1	2.8	4.0
Cephalic vein in the middle of the upper arm	-	3.1	2.9	3.6	2.8	5.3	-	4.5	3.7	4.3
Cephalic vein at shoulder level	-	3.5	4.1	2.4	2.0	4.0	-	4.8	2.5	-
Basilic vein distal	-	2.6	-	1.4	1.4	4.7	-	2.6	-	3.7
Basilic vein in the middle of the lower arm	1.4	3.6	1.5	1.1	1.8	4.3	2.1	4.2	-	3.8
Basilic vein at the elbow	3.8	4.0	2.8	3.4	4.2	-	2.4	3.5	3.2	4.5
Basilic vein in the middle of the upper arm	4.0	8.2	3.4	5.3	6.1	5.3	6.1	2.8	6.5	5.3
Basilic vein before entering the deep venous system	-	7.6	3.1	-	7.4	4.9	7.3	7.1	6.0	4.0
Median cubital vein	2.5	9.6	5.1	3.9	7.1	6.7	5.9	7.2	2.1	6.2
Subclavian vein	9.0	9.0 ^a	-	6.9	7.7 ^a	6.8	8.0	9.5	9.4	9.4
Mean pressure [mmHg]										
Brachial artery	102	115	124	104	88	105	64	113	98	76
Mean flow [ml/min]										
Ascending aorta	5.3	4.9	6.4	4.7	4.8	3.9	4.9	7.1	4.9 ^b	4.9 ^b
Axillary artery in the middle	20 ^c	190	125	147	111	192	108	164	247	87 ^c
Radial artery in the middle	8	20	7	31	24	50	41	79	79	44
Ulnar artery in the middle	8	28	8	32	11	44	31	18	57	39
Distensibility [10^{-6}pa^{-1}]										
Brachial artery	6.8	4.6	6.4	4.5	4.5	6.1	6.7	3.4	7.0	6.7

A) The subclavian vein diameter is not measured here and therefore assumed to be equal to the diameter of the subclavian artery. **B)** The mean aortic flow is not measured with MR flow for this patient but assumed to be equal to patient #2. **C)** The mean axillary artery flow is not measured with MR flow for this patient, therefore the preoperative Doppler US flow is used.

Elastic properties

For each patient the distension (change in diameter d) of the brachial artery was measured with ultrasound (Picus with ART.LAB functionality, ESAOTE B.V. Europe). Simultaneously, the brachial pressure p_b was assessed from real-time noninvasive finger pressure measurements (NexFin, BMEYE B.V., The Netherlands). From the distension Δd and the brachial pulse pressure Δp_b the distensibility D can be assessed from

$$D \approx \frac{1}{\pi a_0^2} \frac{\Delta A}{\Delta p_b} \approx \frac{a_{sys}^2 - a_{dia}^2}{a_0^2 \Delta p_b} \quad (25)$$

in which a_{sys} and a_{dia} are the systolic and diastolic radii. The determined distensibilities are given in table 3. By assuming a thick-walled tube formulation and a wall thickness to radius ratio of 0.15, the Young's modulus of the brachial artery was determined from (11). This estimate for the (patient-specific) Young's modulus was also taken for the subclavian, axillary, ulnar, radial and interosseus artery. The Young's modulus for veins was assumed to be $1.2 \cdot 10^5$ Pa and derived from Huberts et al.⁵³ by applying (12) and a wall thickness to radius ratio of 0.10.

Constants

In all simulations blood density, blood viscosity, and the Poisson ratio were chosen to be $1.05 \cdot 10^3$ kg/m³, $3 \cdot 10^{-3}$ Pa · s, and 0.5 [-] respectively²³.

Boundary conditions

Prescribed flows

As input the aortic flow waveform is used that is preoperatively determined by means of phase-contrast magnetic resonance angiography (PC-MRA) for each patient. In table 3 the time-averaged aortic flow is given, whereas in the figures 5 and 6 an example of a patient-specific aortic flow waveform is presented.

Prescribed pressures

The extravascular pressure p_e was assumed to be 0 mmHg. The venous branch that represents the AVF's draining vein was closed with a venous pressure p_v of 10 mmHg whereas the windkessels were closed with a venous pressure $p_{v,wk}$ of 0 mmHg.

Windkessel parameters and distributed flow to small side-branches

The time constant τ was set to 1.1 seconds according to data from Leguy et al⁴⁹. The peripheral resistance of an end-segment, R_p , was determined by (23). The mean arterial pressure was assessed from finger pressure measurement (table 3). Flow waveforms through the axillary, ulnar and radial artery were determined by PC-MRA and the time-averaged flows were used to calculate peripheral resistance. By assuming that the interosseus artery and ulnar artery are subjected to equal Poiseuille wall shear stress

(Murray's law⁵⁴), the mean flow through the interosseus artery $\bar{q}_i$ can be determined by

$$\bar{q}_i = \left(\frac{a_{0,i}}{a_{0,u}}\right)^3 \bar{q}_u \quad (26)$$

in which $\bar{q}_u$ is the mean ulnar artery flow, $a_{0,i}$ the interosseus diameter and $a_{0,u}$ the distal ulnar diameter. Furthermore, it was assumed that 0.5% of the cardiac output flows through the end-segment of the vertebral artery, while 7% flows to the left and 7% to the right carotid artery, and that preoperatively, the flow to both arms is the same. The remaining cardiac output flows through the thoracic aorta. Blood flow through small side branches that were not modeled separately, was only applied in the axillary and brachial artery and represents the blood that flows to the muscles in the upper extremity. This amount of flow distributed for each patient was assessed from the difference between the time-averaged axillary artery flow and the sum of the time-averaged radial, ulnar and interosseus flows as determined by PC-MRA and (26).

Numerical constants

In all simulations the time step Δt was set at 5 ms and the convergence criterium $\epsilon=10^{-5}$ m³/s was used. The simulations were stopped if the relative difference of mean pressures between two consecutive cardiac cycles was smaller than 10^{-5} .

Simulations and analysis

Before application of the lumped parameter implementation to patient-specific VA planning, we benchmarked our lumped parameter implementation with the spectral element implementation of Bessems et al.²⁴ on a generic arterial tree.

Ten patient-specific lumped parameter pulse wave propagation models were used to simulate the effect of VA creation on the hemodynamics in the arm. First, pressure and flow waveforms in the brachial and distal radial artery are compared for both an upper and lower arm AVF creation to study the ability of the model to delineate flow increases and pressure changes resulting from an upper and a lower arm AVF creation. To demonstrate how a patient-specific lumped parameter pulse wave propagation model might be able to support in the decision-making of the AVF location, the direct postoperative flows for the lower arm AVF were compared to a threshold of 400 ml/min; when a flow larger than 400 ml/min was predicted for the lower arm AVF, a lower arm AVF was suggested, otherwise an upper arm AVF was indicated. The suggested AVF configuration was compared to the configuration that has been independently selected and created by a vascular surgeon with ample experience and expertise in creating VA for HD (more than 1000 AVF's created).

Finally, simulated mean brachial artery flows for the established AVF configurations were compared to the direct (within one week) postoperative mean brachial artery flows determined by DUS. Mean brachial artery flows were determined by measuring the time-

averaged maximum blood flow velocity with Doppler ultrasound and multiplying this with the cross-sectional area depicted from B-mode imaging, thus assuming a flat velocity profile. However, in reality the velocity profile will differ from a flat profile. The actual velocity profile within the brachial artery can be calculated from Womersley theory³⁹ in the case of fully developed flow. However, the high mean Reynolds numbers postoperatively ($O(600-2000)$) will result in large entrance lengths ($O(20-70\text{ cm})$ for a diameter of approximately 6 mm) for the steady flow component and therefore the flow is not necessarily fully developed. In addition, the peak Reynolds numbers might even be higher ($O(1500-6500)$) resulting in possible turbulent flow and thus more flat velocity profiles. For these reasons and, in addition, due to curvature, the real velocity profile is not exactly known. However, it is likely that the actual velocity profile is between a parabolic and a flat velocity profile. Therefore, we decided to correct for the velocity profile by a factor 0.75 and to define a range with as upper limit the flow determined with a flat profile and as lower limit the flow determined from a parabolic profile (corrected by 0.5).

RESULTS

No differences were found between the lumped parameter implementation in this study and the spectral element implementation of Bessems et al²⁴, demonstrating a correct realization of the proposed scheme.

Vascular access planning

Preoperative results

The model was adapted to mimic the patient-specific pressure and flow waveforms preoperatively. Figure 5 shows simulated and measured (with MRA) preoperative flow waveforms in the axillary, radial and ulnar artery for patient #2 as an example. This patient is chosen as representative for all patients. Results for the other patients were equally good, however, in two patients (#1 and #10) measurements of the axillary artery flow were missing. Preoperatively, the simulated mean flows are almost equal (i.e. 0.18 l/min versus 0.19 l/min for the axillary artery flow, 0.019 l/min versus 0.020 l/min for the radial artery flow and 0.025 l/min versus 0.028 l/min for the ulnar artery flow) to the measured mean flows. This is expected, since these data are used as input for the model. However, simulated and measured flow waveforms in the axillary, ulnar and radial artery are also quite similar, although the simulated artery flow waveforms are slightly more attenuated than the measured ones. In addition, there is a small time delay (25 ms) between the simulated and measured axillary artery flow, and reflections differ between the flow waveforms. This probably results from generic geometrical properties used as model input such as arterial lengths that influence wave propagation. The simulated mean arterial

pressure of 112 mmHg is close to the measured arterial pressure of 115 mmHg, which is also expected as it is used as model input. For all patients differences between simulated and measured mean pressure and flows were smaller than 5%.

Figure 5: The predicted (solid) and MR measured (dashed) axillary, radial and ulnar artery flows as function of time for patient #2.

Figure 6: The pressure and flow waveforms calculated by the model in the brachial artery and distal radial artery before surgery (solid), after the creation of a lower arm AVF (dashed) and after creation of an upper arm AVF (dotted) for patient #2. The anastomosis angle was set at 45 degrees.

Postoperative results: general effects

Changes in pressure and flow after AVF creation are discussed by again using the simulation results of patient #2. For all other patients, similar effects are observed. For this patient, the mean brachial artery flow increases from 0.12 l/min to 0.55 l/min after creation of a lower arm AVF (Figure 6) and to 1.9 l/min after creation of an upper arm AVF (brachio-basilic arteriovenous fistula; BB-AVF). The anastomosis angle was set to 45 degrees for these simulations. The negative peak (backflow), that is present in the brachial artery flow waveform preoperatively, disappears after creation of both a lower and upper arm AVF. The mean brachial pressure decreases more after creation of the upper arm AVF (from 112 to 61 mmHg) than after creation of the lower arm AVF (from 112 to 100 mmHg). The systolic and diastolic pressure also decrease postoperatively.

In the distal radial artery the mean flow decreases from 0.019 l/min to 0.011 l/min after creation of the lower arm AVF, whereas after creation of the upper arm AVF the radial

Figure 7: The pressure drop over the anastomosis from the axillary artery to the subclavian vein if no anastomosis element is incorporated (-) and with anastomosis element for an anastomosis angle of 30, 45 and 60 degrees. The systolic (solid), mean (dashed) and diastolic (dashed-dot) pressures are presented for patient #2 for the upper arm configuration (BB).

artery flow decreases to 0.011 l/min. The mean radial pressure decreases from 109 mmHg to 66 mmHg and 61 mmHg after creation of the lower and upper arm AVF, respectively. In the distal radial artery a backflow is observed in the diastolic phase both preoperatively and after creation of an upper arm AVF, whereas backflow disappears after the creation of a lower arm AVF.

In figure 7 the effect of the anastomosis model and the anastomosis angle is shown for an upper arm AVF configuration (BB-AVF) for patient #2. Neglecting the extra pressure drop over the anastomosis results in a very low mean arterial pressure (approximately 43 mmHg) after AVF creation and a very high flow (3.1 l/min). Incorporating the anastomosis model results in a more realistic AVF flow whereas pulsatility distally from the anastomosis decreases. Furthermore, it can be observed that an acute anastomosis angle gives a larger pressure drop than a wider anastomosis angle. The negative diastolic venous pressure, observed in figure 7, results from neglecting venous collapsibility.

Figure 8: The calculated brachial artery flows after the creation of a lower arm AVF for all patients. The values are presented for an anastomosis angle of 45 degrees and the error bars represent the variation in flow prediction due to a variation in anastomosis angle (± 15 degrees). The table shows the AVF configuration (U=upper arm, L=lower arm) based on the simulated postoperative flow and the AVF configuration selected by the surgeon. The superscript * indicates a different choice

Postoperative results: surgical planning

In figure 8 simulated brachial artery flow in case of a lower arm AVF is shown for all patients. In addition, the choice of the surgeon and the choice of the model are shown. The error bars on the simulated flows in this figure represent the influence of the anastomosis angle. With the current threshold of 400 ml/min in nine of the ten patients the surgeon and the model select the same AVF configuration (upper arm or lower arm AVF). The choice of the model and the surgeon differed in patient #7. Clinically, the AVF of patient #7 showed delayed maturation (three months) while all other AVF's matured within six weeks.

Figure 9 shows that the absolute values of model predictions are in the same order of magnitude as the measured postoperative flows in six out of ten patients, whereas in the other four patients there is no overlap.

Figure 9: The predicted brachial artery flows after the creation of the AVF configuration selected by the surgeon compared with the observed brachial artery flow for this AVF configuration directly after surgery (within 1 week). The error bars on the simulated flow represent the variation in flow prediction due to a variation in anastomosis angle (± 15 degrees), whereas the error bars on the measured flow represent the flow based on a parabolic velocity profile and a flat profile. In the table below the patient characteristics are given.

DISCUSSION

This study aimed to derive and present a lumped parameter pulse wave propagation model that is robust and easily applicable in a clinical setting. Additionally, we showed how a patient-specific computational model, that predicts the postoperative flow, might support the surgeon in selecting an AVF configuration (i.e. upper or lower arm). A lumped parameter pulse wave propagation model is presented with vascular segments based on an approximated velocity profile derived from the boundary layer theory²⁴. Pressure and flow waveforms calculated by the lumped parameter implementation are equal to the spectral element implementation of Bessems²⁴.

The lumped parameter pulse wave propagation model presented in this study is able to capture the pressure and flow changes after AVF creation. Both observed and simulated flow through the brachial artery increases significantly. Also a drop in blood pressure is observed after AVF creation. Additionally, the simulations show that the backflow normally present in the brachial artery disappears after AVF creation, as described in literature^{45,46}. The hemodynamical effects resulting from AVF creation were more pronounced in an upper arm AVF compared to a lower arm AVF, as is observed in clinical practice^{45,46}.

To demonstrate how the lumped parameter pulse wave propagation model might be able to assist in VA surgery planning, the model is used to simulate AVF creation in ten ESRD patients. The model accurately describes preoperative hemodynamics: simulated mean pressures and flows differ by less than 5% from measured values and the simulated and measured flow waveforms are similar. Small differences in amplitude, transition time and shape due to reflections between measured and simulated flow waveforms can be explained from input inaccuracies for geometrical and mechanical properties of the vessels (for example by using generic values) inducing differences in wave propagation. The lumped parameter pulse wave propagation model selects the same AVF configuration as the experienced surgeon in nine out of ten patients when using a threshold of 400 ml/min. In one of the patients (#7) the model suggested another AVF configuration. However, in this patient the maturation process was delayed (three months instead of six weeks) and the predicted low flow was possibly indicative for this. The threshold we used to select the optimal AVF is based on literature¹⁴. An AVF flow larger than 600 ml/min and smaller than 30% of the cardiac output after six weeks of maturation is generally accepted as a proper AVF flow^{8,9,12,13}. In a lower arm AVF the direct postoperative flow is on average 60% of the flow after maturation while in an upper arm AVF this is almost 80%¹⁴. To be on the safe side, in the simulations a threshold of 400 ml/min was used. However, changing this threshold will naturally result in different conclusions. To establish the correct threshold a larger study is required. The results of this preliminary study give us the possibility to further elucidate the power of the model in a larger population.

The predicted postoperative flows are in the same order of magnitude as the measured postoperative flows in six out of ten patients. In the other four patients the predicted and observed flows differ. In patient #3, the large difference can be explained from the fact that a major venous side-branch was not incorporated in the model, although this side-branch significantly influenced the resulting AVF flow. However, a comparison between measured and simulated flows is hampered by the inaccuracy in the flow predictions resulting from measurement inaccuracies in the input that is currently unknown. Hence in a future study, we need to perform an uncertainty analysis to determine the influence of input inaccuracies on our flow predictions. Furthermore, a sensitivity analysis needs to be performed to help to identify the parameters for which measurement improvements are necessary and most rewarding to further decrease the inaccuracy on the flow prediction, while less important parameters can be fixed and based on literature. The latter will result in parameter reduction and eases the adaptation of the model to patient-specific conditions and implementation in clinical practice potentially also. The comparison between measurement and simulations is also hampered by the accuracy of the measured mean brachial artery flow that is not exactly known. Next to the assumption of the velocity profile, is the uncertainty of Doppler flow measurements caused by measurements errors, like for example diameter measurement inaccuracy or an incorrect angle of the Doppler measurement. Therefore, in future research the inaccuracy of Doppler flow measurements should be determined and a method should be developed that is able to accurately measure the postoperative mean brachial artery flow, which will result in model and measurement comparisons that are more quantitatively.

In this study, we used a lumped parameter wave propagation model to predict the postoperative flows. Because the main output of interest was the mean brachial flow and the momentum and continuity equations were linearized, the wave propagation model can eventually be simplified to a model consisting of resistances only if a proper estimate for the anastomosis resistance is known. However, the anastomosis resistance is dependent on the flow and we therefore need, at least locally, a proper estimate of the flow waveform. In addition, to be able to incorporate, in future research, the nonlinear relation between the venous pressure and its cross-sectional area and adaptation laws, a wave propagation model is better suitable than a model consisting of resistances only. Especially, because the distributed locations where stenosis might develop can be of clinical interest.

In future research, the pressure-flow relation for the anastomosis that was assumed to be similar to a T-junction should be validated, for example by 3D computational fluid dynamic simulations of anastomoses. An extra pressure drop due to unsteadiness in flow should possibly be included. Incorporating these model improvements will result in less uncertainty in the model description and therefore better flow predictions, however, it will also increase the model complexity and number of model input parameters, hereby

increasing the effect of data uncertainty. Increasing the model complexity will thus not necessarily result in better flow predictions. Therefore, future research will first focus on the current model and applying this for prediction of flow including the reliability for a larger patient population.

CONCLUSION

In this study, we have presented a lumped parameter pulse wave propagation model that is easily implementable, robust, intuitive and comprehensible towards VA planning. Additionally, we showed that a patient-specific model can be used to simulate the hemodynamical effects after AVF creation and might assist in VA surgery planning. The advantage of such a model is that it allows for preoperative patient-specific simulations of multiple factors (e.g. diameters, accessory veins and the anastomosis) and their mutual influence on postoperative flow.

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CHAPTER

8

Patient-specific computational modeling of upper extremity arteriovenous fistula creation: Its feasibility to support clinical decision-making

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ABSTRACT

Introduction: Inadequate flow enhancement on the one hand, and excessive flow enhancement on the other hand, remain frequent complications of arteriovenous fistula (AVF) creation, and hamper hemodialysis therapy in patients with end-stage renal disease. In an effort to reduce these, a patient-specific computational model, capable of predicting postoperative flow, has been developed. The purpose of this study was to determine the accuracy of the patient-specific model and to investigate its feasibility to support decision-making in AVF surgery.

Methods: Patient-specific pulse wave propagation models were created for 25 patients awaiting AVF creation. Model input parameters were obtained from clinical measurements and literature. For every patient, a radiocephalic AVF, a brachiocephalic AVF, and a brachiobasilic AVF configuration were simulated and analyzed for their postoperative flow. The most distal configuration with a predicted flow between 400 and 1500 ml/min was considered the preferred location for AVF surgery. The suggestion of the model was compared to the choice of an experienced vascular surgeon. Furthermore, predicted flows were compared to measured postoperative flows.

Results: Taken into account the confidence interval (25th and 75th percentile interval), overlap between predicted and measured postoperative flows was observed in 70% of the patients. Differentiation between upper and lower arm configuration was similar in 76% of the patients, whereas discrimination between two upper arm AVF configurations was more difficult. In 3 patients the surgeon created an upper arm AVF, while model based predictions allowed for lower arm AVF creation, thereby preserving proximal vessels. In one patient early thrombosis in a radiocephalic AVF was observed which might have been indicated by the low predicted postoperative flow.

Conclusions: Postoperative flow can be predicted relatively accurately for multiple AVF configurations by using computational modeling. This model may therefore be considered a valuable additional tool in the preoperative work-up of patients awaiting AVF creation.

INTRODUCTION

Patients suffering from end-stage renal disease (ESRD) depending on hemodialysis (HD) therapy require a functional vascular access (VA)¹, which can be provided by creation of an arteriovenous fistula (AVF), creation of an arteriovenous graft (AVG), or the insertion of a central venous catheter (CVC). Since the use of prosthetic graft material (AVG and CVC) is associated with reduced patency rates and higher mortality rates^{2,3}, guidelines advocate the use of native vessels for VA creation⁴. However, an important downside of AVF creation is the significant probability of early thrombosis or nonmaturation (20-50%) due to insufficient flow enhancement, particularly in lower arm fistulas^{5,6}, and excessive postoperative flow enhancement resulting in steal syndrome and cardiac failure (up to 20%) in elbow fistulas^{7,8}. In an effort to limit these complications, an extensive preoperative duplex ultrasonography (DUS) evaluation of the upper extremity vascular tree is performed to select the most suitable site for AVF creation⁹. Unfortunately, flow related complications persist and additional interventions are often needed to make the AVF suitable for HD treatment¹⁰.

Following AVF surgery, flow enhancement is determined by multiple factors and thus differs between patients. Geometrical factors (e.g. vascular diameters, venous sidebranches), peripheral resistances, and structures such as stenoses and the anastomosis, all influence the resistance to blood flow, and are therefore believed to be accountable for the observed flow increase. Hence, the currently performed discrete diameter measurements of upper extremity vasculature only partially represent the hemodynamic resistances that influence flow enhancement.

Computational modeling allows to investigate patient-specific hemodynamics by employing physical laws for quantitative integration of the multiple prognostic factors, and has already proved to be of assistance in aortic aneurysmal disease^{11,12}, in cerebral disease^{13,14}, and coronary artery disease^{15,16}. Although models have been used previously to gain insight in VA hemodynamics and pathologies, or disease progression associated with it¹⁷⁻²⁰, predictive models, aiming for a more accurate risk-estimation regarding the development of flow related complications, have not been used.

Within the 7th Framework Program of the European Commission, a pulse wave propagation model has been developed that is able to capture pressure and flow changes after AVF creation. This pulse wave propagation model has been validated against a silicone model of the aorta, arm arteries and veins in which AVF procedures were mimicked²¹. Here we have shown that the main features of experimental flow and pressure waveforms, both before and after AVF creation, were adequately simulated. A pilot study on a limited number of patients showed that the pulse wave propagation model, when adapted to patient-specific conditions, has the potential to suggest the most suitable AVF configuration by predicting postoperative flow²². However, to implement the model in the preoperative workup of patients awaiting AVF creation, the accuracy of

model predictions should be taken into account, as to personalize the model, a considerable number of input parameters needs to be obtained, which are subjected to biological variations and measurement inaccuracies.

The purpose of this study was to determine the accuracy of the patient-specific model and to investigate its feasibility to support decision-making in AVF surgery.

METHODS

Study population

Twenty-five consecutive patients suffering from ESRD awaiting their first VA creation were enrolled in this prospective observational study. The study was approved by the medical ethical committee of the Maastricht University Medical Center, and written informed consent was obtained from all individuals prior to enrolment in the study. All clinical investigations have been performed according to the principles expressed in the Declaration of Helsinki.

Pulse wave propagation model

The pulse wave propagation model used here, has been described in detail in previous work²². In short, the model simulates pressure and flow waveforms on several arterial and venous locations of the upper extremity. Depending on the site (left or right) and the AVF configuration (radiocephalic AVF [RC-AVF], brachiocephalic AVF [BC-AVF], brachiobasilic AVF [BB-AVF]), inflow arteries and outflow veins of interest were included in the computational domain (Table 1, Figure 1). Each vessel of the computational domain was divided into segments with a maximum length of 5 cm, describing the local relation between pressure and flow via a lumped parameter approach. Such a lumped segment consists of a resistor R representing the viscous resistance to blood flow through the vessel segment, a resistor R_L representing the resistance to blood flow through small sidebranches not modeled in detail, an inductor L representing the inertia of the blood and a capacitor C representing the vascular compliance (i.e. storage capacity of the vessel). For the anastomosis, a segment was used consisting of nonlinear resistors that depend on anastomosis angle and blood flow. Arteries not included in the computational domain as well as the peripheral vascular beds were modeled by windkessel elements with a specific resistance and compliance. As boundary conditions, an intravenous pressure was prescribed at the subclavian vein, whereas postoperative inflow was prescribed at the aorta. Since the latter is preoperatively unknown, the aortic flow was measured preoperatively and iteratively updated by scaling the preoperative waveform until the postoperative mean aortic pressure was restored to the preoperative level (baroreflex). All other preoperative model parameters (e.g. peripheral resistances) were kept constant.

Table 1: The names of all vessels included in the computational domains.

Number [-]	Vessel name [-]	Number [-]	Vessel name [-]
1	Ascending aorta	11	Distal Ulnar artery
2	Aortic arch A1	12	Interosseus artery
3	Left Carotid artery	13	Left Subclavian artery
4	Aortic arch A2	14	Innominate artery
5	Thoracic aorta	15	Right carotid artery
6	Right subclavian artery	16	Distal cephalic vein
7	Vertebral artery	17	Median Cubital vein
8	Axillary and Brachial artery	18	Proximal Cephalic vein
9	Radial artery	19	Basilic vein
10	Proximal Ulnar artery	20	Axillary and Subclavian vein

Figure 1: Left arm vasculature divided into arterial, venous and anastomosis segments (middle). These segments locally describe the relation between pressure p and flow q via a lumped parameter approach (right), and consists of a resistor R (viscous resistance to blood flow), a resistor R_L (viscous resistance of blood flow to small side-branches), an inductor L (blood inertia) and a capacitor C (vascular compliance). The anastomosis is modeled with two nonlinear resistors R_V and R_D . The windkessels consist of two resistors, Z_{WK} and R_{WK} (together the peripheral resistance) and a capacitor C_{WK} (peripheral compliance). This figure is adapted from Huberts et al.

Personalization of the pulse wave propagation model

To personalize the input parameters of the pulse wave propagation model, patient-specific anatomy (vessel length, vessel diameters, vessel wall thickness) and mechanical characteristics of the vessels (vascular compliance) were mandatory. Furthermore, information on anastomosis configuration (location, angle), windkessel parameters, blood properties (density and dynamic viscosity), intravenous pressure and preoperative aortic flow waveform were required. However in clinical practice, it is impossible to assess all these parameters for every patient. Fortunately, not all parameters are equally important for the prediction of postoperative flow enhancement; model parameters that need to be measured patient-specifically opposed to model parameters that can be estimated from literature, were identified previously in a sensitivity analysis²³.

Model parameters were therefore chosen as follows. Arterial lengths were based on a generic geometry taken from Stergiopoulos et al²⁴. Venous lengths are considered equal to arterial lengths on the same anatomical location. Upper extremity vascular diameter measurements were obtained patient-specifically on discrete locations by performing an extensive preoperative DUS examination which was already part of clinical routine in our hospital, and is described in detail in Bode et al²⁵. Missing diameters of the arm vasculature were obtained by linear inter-, or extrapolation. Diameters of the aorta and its primary branches were based on literature and scaled according to upper extremity arterial diameters²⁴. Vessel wall thicknesses were derived from wall thickness-to-radius ratios: a ratio of 15% was used for the subclavian, axillary and brachial artery, whereas a ratio of 20% was used for the radial, ulnar and interosseus artery²⁶⁻²⁸. The ratios of all other arteries were based on literature²⁴. For veins a ratio of 10% was chosen²⁹.

Mechanical properties of the upper extremity vessels were characterized by vascular compliance. For this, in addition to wall thickness and diameter, the Young's modulus was required^{22,30}. The Young's modulus of the brachial artery was determined via arterial distensibility, which was assessed by a Picus ultrasound machine equipped with ARTLAB software (ESAOTE, Maastricht, The Netherlands). For each patient, vessel wall distension over the cardiac cycle was measured using a wall-tracking technique in combination with continuous, non-invasive pressure registration (NexFin, BMEye, Amsterdam, The Netherlands). The Young's modulus of the brachial artery was applied for the compliance of all arterial arm segments, whereas for the aorta and veins Young's moduli were based on literature^{22,24}.

The location of the anastomosis was set to 5 cm proximal to the wrist in case of a lower arm AVF and 5 cm proximal to the elbow bifurcation in case of an upper arm AVF. The angle of the AVF between the proximal artery and the vein was set to 45 degrees.

Windkessel parameters were personalized by using mean arterial pressure and mean arterial flows in the aorta, brachial, radial, and ulnar artery. Mean flows were obtained by preoperative MR flow measurements (Philips Healthcare, Best, The Netherlands), whereas mean arterial pressure was assessed by using the NexFin.

Blood was considered to behave as an incompressible Newtonian fluid with a density of $1 \times 10^3 \text{ kg/m}^3$ and a dynamic viscosity of $3 \times 10^{-3} \text{ Pa}\cdot\text{s}$. Intravenous pressure at the subclavian vein was set to 10 mmHg³¹.

In table 2 an overview of all the measurements performed on each patient and their required examination time are presented. The measurements consist of clinical routine advocated by guidelines and additional measurements performed in the context of this study.

Table 2: Patient-specific measurements performed in the context of the study

	Examination	Duration
Current clinical routine	Vessel mapping with DUS	60 min
	Postoperative flow measurements with DUS	10 min
Additional measurements	Fingerpressure and distensibility measurements	15 min
	Preoperative MR flow measurements	20 min

ANALYSIS

For every patient, three different AVF configurations were considered (RC-AVF, BC-AVF, BB-AVF), and evaluated with respect to their postoperative flow directly after surgery. In lower arm fistulas the immediate postoperative flow is approximately 60-70% of the flow after successful maturation³². Furthermore, postoperative flows larger than 30% of the cardiac output are associated with an increased risk for cardiac failure and distal ischemia^{7,8}. As a result, AVF configurations resulting in a predicted postoperative flow between 400 and 1500 ml/min were considered by the model as an option for AVF creation. When more AVF configurations resulted in a flow exceeding 400 ml/min, the sequential order of preference was RC-AVF, BC-AVF, and BB-AVF. To objectivate the model's capability to identify the optimal location for AVF creation, the suggested AVF configuration was compared with the choice of a surgeon with ample experience in VA surgery (more than 1000 AVF creations).

Subsequently, in order to quantitatively determine the accuracy of flow predictions, predicted flows of the created AVF configuration were compared with observed postoperative flows as measured with DUS one week after surgery. In this perspective, the uncertainty of the flow prediction resulting from input parameter uncertainty (summarized in Appendix 1) is evaluated by means of Monte Carlo simulations as described by Huberts et al²³, and expressed through the 25th-75th percentile interval.

RESULTS

ARTERIOVENOUS FISTULA CONFIGURATION

In 4 of 25 patients postoperative brachial artery flow could not be simulated for all three AVF configurations because the cephalic vein could not be visualized preoperatively due to pre-existing thrombosis (patient #19, #23, and #25) or because the computations did not converge for all Monte Carlo simulations (patient #24). As in these patients not all AVF configurations could be simulated by the model, they were excluded on beforehand regarding the AVF configuration analysis.

In the remainder of patients (N = 21), the model suggested an upper arm or lower arm AVF configuration in agreement with the choice of the surgeon for 16 patients (16/21: 76%). In five patients the suggestion of the model and the choice of the surgeon were

Figure 2: The predicted postoperative flows for a RCAVF, BCAVF and BBAVF configuration. The flows are presented as the median of all Monte Carlo simulations with their 25th and 75th percentile interval. In 4 patients postoperative brachial artery flow could not be simulated for all three AVF configurations because essential patient-specific data were missing due to thrombosis of the cephalic vein (patient #19, #23, and #25) or because the computations did not converge for all Monte Carlo simulations (patient #24). A * indicates the choice of the surgeon

different (Figure 2); in patients #6, #11, and #16 model predictions may have allowed for a lower arm AVF, while the surgeon created upper arm AVFs. Conversely, in patient #8 the surgeon created a lower arm AVF, while the model suggests to create an upper arm AVF. Also in patient #21 a lower arm AVF was created, whereas the model predicts a too low postoperative flow for all configurations. These low flow predictions might have been indicative for the early failure as observed in patient #21.

When differentiating between RC-AVF, BC-AVF, and BB-AVF, the model suggests the same AVF configuration as the surgeon in 12 patients (12/20: 60%) (Figure 2). For this analysis, one additional patient (#15) was excluded, because during the surgical

Figure 3: Schematic visualization of predicted and measured postoperative flows for the AVF configuration created by the vascular surgeon. The error bars in predicted flow are the result of inaccuracies in input parameters, while the error bars in postoperative flow are the result of measurement inaccuracies²². For patient #15 prosthetic graft material was used for VA creation. For patient #21 no postoperative flow measurements could be obtained due to immediate thrombosis. A green circle around the patient identification represents overlap between predicted and measured postoperative flow (16 patients). A red square around the patient identification represents a discrepancy between predicted and measured postoperative flow (7 patients). Note that patient #24 received an alternative AVF configuration (cephalic vein was anastomosed with the ulnar artery on the upper arm due to a high brachial artery bifurcation)

procedure immediate thrombosis occurred for the intended BB-AVF configuration and prosthetic graft material was used to create the VA. In addition to the five previously mentioned patients, there is a discrepancy between the suggested configuration of the model and the choice of the surgeon with respect to a BC-AVF or BB-AVF configuration in three patients (#1, #7, and #22).

Absolute postoperative flow prediction

Postoperative flow predictions could be compared to clinically measured flows in 23 of 25 patients. One patient (#15) was excluded from this analysis because graft material was used for creation of the VA conduit, which is not supported by the computational model. A second patient (#21) was excluded because of immediate thrombosis and, as a result, no postoperative flow measurement was available.

Figure 3 shows predicted flows versus measured flows one week after surgery. In addition, the flow measurement at six weeks is visualized to gain insight into flow enhancement during the maturation phase. At one week, predicted and measured flow show overlap in 16 patients (16/23: 70%). In patient #1, #6, #23, and #24 the predicted flow is an overestimation of the measured flow, while in patient #7, #18, and #22 the predicted flow is an underestimation of the measured flow. In patient #1 a significant hematoma was identified during the immediate postoperative DUS examination, whereas in patient #23 postoperative thrombosis was observed one week after surgery.

DISCUSSION

In this study we investigated the accuracy and feasibility of a pulse wave propagation model to support decision-making in AVF surgery by predicting postoperative brachial artery flow for multiple AVF configurations. By using the described model, postoperative brachial artery flow can be estimated relatively accurately without subjecting the patient to excessive additional preoperative measurements.

In clinical routine, preoperative mapping of upper extremity vasculature with DUS is considered the method of choice to identify the most suitable site for VA creation, and its clinical implementation has been associated with a significant reduction of postoperative failure rates^{33,34}. Nevertheless, complications related to either insufficient flow enhancement, particularly in lower arm fistulas, and to excessive flow enhancement, mainly in upper arm fistulas, remain responsible for AVF failure in a significant number of patients⁵⁻⁸. Therefore, alternative modalities to decrease the incidence of flow related complications have become of interest.

Pulse wave propagation models have been shown in both experimental setup and in vivo to be able to simulate pressure and flow waveforms on multiple locations^{35,36}. Some studies have reported the use of pulse wave propagation models for prediction of

outcome after vascular surgery^{37,38}. However, the application of predictive models is still in its infancy. Regarding AVF surgery, prior work of our group focused on the development and experimental validation of a pulse wave propagation model in which pressure and flow distributions in the upper extremity vasculature can be simulated²². This way, hemodynamic consequences of AVF creation can be evaluated by taking multiple prognostic factors, as well as their complex interplay into consideration, instead of focusing on discrete diameter measurements. As already indicated by a previous pilot study, the pulse wave propagation model showed potential to suggest the most suitable AVF configuration by patient-specifically predicting postoperative flow²². In this study, postoperative flow predictions of the model were subject of clinical validation.

By using the pulse wave propagation model, overlap between predicted and observed postoperative flow was observed in 70% of the patients. Predicted flows in 4 patients overestimate the flows measured with ultrasound at one week, while the predicted flows of 3 patients underestimate the measured flows. Overestimation of flow in patient #1 and #23 might be explained by the occurrence of a postoperative hematoma compressing the venous outflow trajectory, and by unexpected early thrombosis, respectively. Other possible explanations for overestimation of postoperative flow might be stenotic segments, curvature or kinking not detected with routine DUS examination. These vessels abnormalities are not included in the computational model but would increase the resistance to blood flow in the VA conduit. An improved depiction of such structures might further improve absolute flow predictions. A possible solution might be to perform a magnetic resonance angiography (MRA) of the upper extremity vasculature which allows for assessment of vascular diameter over the complete vascular trajectory, and for the identification of stenoses, curvature and kinking^{39,40}. In addition, MRA might be beneficial in patients in whom vascular anatomy has been influenced by previous VA creation. The model can easily be adapted to deal with resulting extra pressure drops and altered vascular geometries. Underestimation of postoperative flow might be caused by the lack of vascular adaptation laws in the computational model. In patient #7 and #22, this might be indicated by the large flow enhancement from week one to week six. In addition, flow mediated dilatation and autoregulation are not incorporated in the model. Although model improvements may result in a better description of postoperative hemodynamics, they also require more (advanced) patient-specific measurements to acquire all input parameters, and increase the burden on the patient.

According to the observations in the current study, the suggestion of the patient-specific wave propagation model for an upper or lower arm AVF configuration already corresponds to the selection of an experienced surgeon in 76% of the patients. In three patients the surgeon decided to create an upper arm AVF, whereas the model allowed for creation of a lower arm AVF. When this additional information would have been available to the surgeon at the time of VA planning, the surgeon might have considered to preserve proximal vessels for future VA procedures by primary creation of a lower arm

AVF. Conversely, upper arm AVF creation was suggested in two patients while a lower arm AVF procedure was performed. In one of these patients, immediate thrombosis was observed, while in the other patient the measured flow was slightly above the threshold of 400 ml/min, as was predicted by the model. This additional information might also have changed the surgeon's choice when known in advance. In this perspective, computational modeling might be considered a potential valuable tool in the preoperative work-up, in addition to the currently performed diameter measurements. However, a prospective randomized clinical trial is required to establish the additional value of the model in routine clinical practice.

Considering the differentiation between BC-AVF and BB-AVF, a discrepancy between model and surgeon was observed in three patients: two BC-AVFs were created where the model suggested a BB-AVF configuration, and one BB-AVF was created while a BC-AVF appeared to be feasible according to the model. Although the model might already be able to differentiate between an upper and lower arm AVF, it appears to be more difficult to distinguish between two upper arm AVF configurations. The most likely explanation for these inconsistencies is the uncertainty in venous input parameters used for modeling, and, possibly, the neglect of accessory veins and vascular adaptation in the model.

The study presented here has limitations. Firstly, a relatively small number of patients was enrolled. However, for assessing the feasibility of the model as well as evaluating the impact of model input uncertainties on the output, the number of enrolled patients suffices. Nonetheless, to determine the predictive value, sensitivity and specificity of the model as additional tool in the preoperative work-up in patients awaiting VA creation, a large prospective randomized clinical trial needs to be initiated. As a further limitation, one might consider the difficulty of model personalization, since in clinical practice not all input parameters can be obtained for each patient with sufficient accuracy (e.g. windkessels). The reason for this is the limited availability of measurement modalities, and moreover, because the additional burden on the patient should be minimized. Fortunately, the previous sensitivity analysis showed that some input parameters are more important than others²³. As a result, half of all input parameters could be derived from literature. To this end assumptions had to be made, for which additional sensitivity analysis showed that these do not significantly alter outcome.

In conclusion, we have demonstrated that a patient-specific pulse wave propagation model can be considered potentially beneficial in the preoperative work-up of patients awaiting VA creation, since postoperative flow can be predicted relatively accurately for multiple AVF configurations. Future effort should focus on acquiring a more detailed overview of patient-specific vasculature to capture vascular pathology and geometry, and for simulation of the maturation process, adaptation laws should be incorporated. To establish the additional value of modeling in clinical decision-making, a large prospective randomized clinical trial needs to be performed.

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APPENDIX 1

Monte Carlo simulations (see Robert et al.¹ for details about Monte Carlo simulations) are used to determine the uncertainty in model predictions resulting from uncertainty in the input parameters assessed by measurements or from literature by applying certain assumptions. The uncertainties in the model parameters and their motivation are shown below.

Measurements	Uncertainty	Based on
Vessel diameters upper extremity	$\pm 10\%$	2,3
Brachial distensibility	$\pm 20\%$	2
Brachial pressure	$\pm 10\%$	4
Axillary, radial and ulnar artery flow	$\pm 15\%$	5
Mean aortic flow	$\pm 10\%$	5

Assumptions	Uncertainty	Based on
Vessel lengths	$\pm 10\%$	Demographical data (http://www.cbs.nl)
Vessel diameter scaling factor	$\pm 20\%$	Retrospective patient cohort
Position of diameter measurements	± 3 cm	Clinical experience
Wall thickness-radius ratio	$\pm 40\%$	6
Generic arterial Young's modulus	$\pm 20\%$	2
Generic venous Young's modulus	$\pm 20\%$	Assumed equal to arterial Young's modulus
Anastomosis position	± 2 cm	Clinical experience
Anastomosis angle	$\pm 20\%$	7
Time constants	$\pm 30\%$	2
Intravenous pressure	$\pm 50\%$	8,9
Generic mean windkessel flow	$\pm 15\%$	10

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CHAPTER

9

Summarizing discussion, future perspectives and conclusions

For successful hemodialysis (HD) treatment reliable access to the circulation is mandatory. Such a vascular access (VA) is preferably provided by the surgical creation of a native arteriovenous fistula (AVF) that allows connecting the patient to an artificial kidney for blood withdrawal and extracorporeal purification^{1,2}. To select the most suitable site for AVF creation, patients are subjected to a preoperative physical examination, supplemented with duplex ultrasonography (DUS) assessment of the upper extremity arteries and veins^{1,2}. Nevertheless, even when carefully practicing according to widely accepted guidelines, many surgically created AVF's never become suitable for adequate HD treatment due to insufficient flow enhancement, or become dysfunctional due to excessive postoperative flow enhancement or the development of stenotic lesions in the VA conduit. Studies performed between 1977 and 2002 report a mean ($\pm$ SD) primary failure rate of 24% ($\pm$ 12%), and a one-year primary patency rate of 70% ($\pm$ 14%) following AVF surgery³. More recent studies are in line with these observations and present mean early failure and one-year primary patency rates of 21% ($\pm$ 13%), and 60% ($\pm$ 20%)⁴⁻¹¹, respectively. In order to reduce these persistent and unacceptably high failure rates, the VA community has become increasingly interested in alternative preoperative examinations that enable improved selection of the optimal AVF configuration. The purpose of the present thesis was to assess the clinical feasibility of non contrast-enhanced magnetic resonance angiography (NCE-MRA) and brachial artery stiffness measurements in patients awaiting AVF creation. Furthermore, in order to tailor AVF creation to the individual patient, the potential of a computational modeling tool, capable of considering *multiple* prognostic factors simultaneously, was investigated.

CURRENT CLINICAL PRACTICE

Chapter 2 provides an up-to-date overview of evidence-based medicine for treating patients with end-stage renal disease (ESRD) who require VA creation. From this chapter it has become clear that there are multiple options for VA creation that allow connecting the patient to an artificial kidney, and that, although best practice guidelines are taken into consideration, VA dysfunction continues to be the major limitation of chronic HD treatment.

When looking at factors associated with AVF dysfunction, patient characteristics (age, gender, race)¹²⁻¹⁵, vessel characteristics (arterial diameter, venous diameter, vascular compliance, arterial blood flow, the presence of vascular pathology, sidebranches)¹⁶⁻¹⁹, and postoperative changes in hemodynamic profile^{20,21}, all play an important role by influencing postoperative flow enhancement. Evaluation of patient characteristics and vessel characteristics is generally done by the surgeon by means of physical examination and preoperative imaging of upper extremity and

central thoracic vasculature. Imaging is of particular interest for its leading role in determination of the most suitable site for VA creation^{1,2}. Improvement in preoperative imaging modalities might therefore result in reduced complication rates. On the other hand, postoperative changes in hemodynamic profile, which are believed to be accountable for AVF dysfunction by inducing vascular wall changes that may result in insufficient vessel dilatation, insufficient flow enhancement, or the development of neointimal hyperplasia, are much more difficult to anticipate because they are the result of multiple etiologies. Prior studies have tried to investigate these hemodynamic consequences of AVF creation. However, most of this prior work has focused on the predictive value of a single parameter, thereby ignoring the complex interplay between the multiple variables that are known to influence AVF outcome.

A very promising approach to deal with multiple patient-specific prognostic factors as well as to investigate cardiovascular hemodynamics is by using computational modeling tools. Previously such tools have mainly been used to *describe* hemodynamics²²⁻²⁴, or to elaborate on the relation between disease progression and alterations in hemodynamic profile²⁵⁻²⁷. However, until now, the clinical utility of predictive computational models that allow for a risk-estimation regarding flow related complications has not become a clinical reality yet. In order to develop such modeling tools as well as to investigate their clinical feasibility, the 'patient-specific image-based computational modeling for improvement of short- and long-term outcome of vascular access in patients on hemodialysis therapy' (ARCH) has been initiated.

Chapter 3 describes the clinical study protocol that has been implemented in the context of the ARCH project and focuses on determining the feasibility of NCE-MRA and brachial artery stiffness measurements in the preoperative workup of patients awaiting VA creation per se, and to evaluate their role as input parameter for computational modeling.

PREOPERATIVE IMAGING

Multiple modalities are available to the clinician to assess upper extremity vasculature prior to VA creation²⁸. For this purpose, DUS is the most widely used and recommended modality because of its non-invasiveness, widespread availability and low cost. However, complication rates remain unacceptably high and have sparked the search for other, alternative preoperative modalities that may allow for a better selection of the most suitable site for VA creation. Prior studies have identified contrast-enhanced magnetic resonance angiography (CE-MRA) of the upper extremity as such a tool²⁹⁻³¹. Unfortunately, this modality requires the

administration of a gadolinium-based contrast agent for adequate depiction of the vessels, which is contraindicated in patients with end-stage renal disease due to the recently described relationship between certain types of gadolinium-based contrast agents and the development of nephrogenic systemic fibrosis (NSF)^{32,33}.

In order to preserve the potential diagnostic advantages of MRA in the patient population suffering from ESRD, the MR community has shown renewed interest in NCE-MRA techniques. Whereas conventional NCE-MRA techniques, time-of-flight and phase-contrast, are known to suffer from artifacts and long acquisition times which limit their clinical use³⁴, novel NCE-MRA techniques are much more promising^{34,35}. **Chapter 4** reports on a comparison of a newly developed NCE-MRA protocol for depiction of upper extremity vasculature with the standard of reference for diagnostic vessel imaging, CE-MRA, regarding subjective and objective image quality. An important advantage of this new NCE-MRA approach is that both arteries and veins can be captured noninvasively in a single acquisition, whereas prior techniques only allowed for either selective arterial or venous depiction over a small field-of-view^{36,37}. Moreover, prior techniques often neglected the vessels that matter most in vascular access surgery: the central vessels. In this study, superior depiction of the arterial vascular tree is described when using CE-MRA. However, NCE-MRA images were of diagnostic quality in the vast majority of subjects. On the other hand, NCE-MRA was shown to be superior for depiction of the venous vascular tree. Although the utilized NCE-MRA protocol has some drawbacks in patient positioning and still remains susceptible to minor artifacts, it provides a feasible alternative to CE-MRA in patients in whom contrast administration is contraindicated.

The question remains to what extent a preoperative NCE-MRA examination contributes to reducing postoperative VA dysfunction. Therefore, a randomized clinical trial needs to be conducted. However, until such a study has established the additional value of routine NCE-MRA prior to VA creation, we believe that NCE-MRA should already be considered in patients with a high suspicion of vascular pathology or postoperative fistula dysfunction (e.g. multiple previous CVC's, marginal DUS findings, or multiple previous failures). When NCE-MRA is combined with conventional DUS evaluation in these patients, vascular pathology may be ruled-out with a greater degree of certainty, especially when is taken into consideration that NCE-MRA has a high negative predicting value³⁸. In patients in whom NCE-MRA yields either inconclusive images or identifies vascular pathology, alternative, more invasive techniques such as CE-MRA, conventional flebography and digital subtraction angiography can be considered, by making use of a variety of contrast agents³⁹⁻⁴⁴.

A second important application of NCE-MRA prior to AVF surgery is the ability to extract highly reliable information about vascular geometry in individual patients. By using these vascular networks in computational modeling tools, patient-specific

modeling becomes feasible. Over the years, many techniques have been described that allow for extraction of patient-specific vasculature⁴⁵⁻⁴⁸, however, most of these techniques have dealt with either arterial or venous images. In the described NCE-MRA imaging protocol both arterial and venous information is obtained in a single acquisition, which, although advantageous, poses some difficulties for automated vessel extraction. To facilitate extraction of relevant parameters, a semi-automated user interface was developed, which is described in **chapter 5**.

Next to a more thorough and comprehensive preoperative interrogation of the upper extremity vasculature by means of MRA, other characteristics of the vasculature have been subject of investigation to improve outcome. Similar to arterial stiffness being predictive for cardiovascular related mortality, previous studies have identified brachial artery stiffness as an independent prognostic factor for postoperative flow enhancement, which in turn is correlated with the risk for nonmaturation^{18,49}. Therefore, routine preoperative measurement of brachial artery stiffness might be worthwhile to identify patients with an increased risk for insufficient flow enhancement. However, before these measurements can be implemented in clinical practice, or can even be considered as input parameter for computational modeling, information regarding measurement reproducibility and intra-individual variation is of the utmost importance.

Chapter 6 describes a novel method to determine local brachial artery stiffness, quantified by pulse wave velocity (PWV) that is directly determined from the change in pressure driving the change in volume, by using DUS and continuous blood pressure measurements. Aim was to determine the within-session and between-session variability. In this study 21 subjects were evaluated for the reproducibility of systolic and diastolic brachial artery diameter and pressure measurements. Good intraclass correlation coefficients and a low coefficient of variation for measurements performed in a single session were found. However, when these measurements were used for the calculation of local pulse pressure, distension and PWV, coefficients of variation slightly increased. In addition, measurements performed over time were subject to moderate variability. Considering these results, future efforts should focus on inter-individual differences, as well as the relation between preoperative PWV and postoperative flow enhancement, in order to see whether clinical implementation of these measurements is feasible and of value in improving outcome.

COMPUTATIONAL MODELING

As discussed previously, AVF surgery can be performed at multiple locations in the upper extremity. Over the past years, deciding on the most suitable site for AVF creation has become a trade-off between the lowest chance of flow related

complications, the best long-term patency, and saving proximal vessels for future VA procedures. To optimally weigh these different factors, the results of preoperative physical examination and DUS are interpreted and put in perspective by the clinical experience of the surgeon.

Besides improving preoperative imaging modalities, decreasing the incidence of flow related complications might be achieved by preoperative prediction of postoperative brachial artery flow and distal perfusion pressures for multiple AVF configurations. Unfortunately, these hemodynamic parameters are difficult to predict since they are influenced by multiple factors (e.g. postoperative flow redistribution, mechanical characteristics of the vessel, and the pressure drop over the anastomosis) that are subject to significant inter-individual differences. By employing patient-specific computational tools, multiple prognostic factors can be considered simultaneously by means of physical laws, and may allow for personalized prediction of these postoperative hemodynamic parameters.

In a joint effort by the members of the ARCH project consortium to reduce postoperative flow related complications, the lumped parameter pulse wave propagation model as described in **chapter 7** was developed. In such models, segments are defined that represent the central and upper extremity arteries and veins involved in the VA conduit, as well as the anastomosis. By adjusting the configuration and characteristics of these segments, different, patient-specific, vascular topologies can be constructed, and subsequently investigated for hemodynamic changes after creation of the fistula.

In a small feasibility study (N=10) we adapted this model to patient-specific conditions for comparison of measured and simulated pressure and flow waveforms. Preoperatively, simulated mean pressures and flows differ by less than 5% from measured values and the simulated and measured flow waveforms were found to be similar, thereby confirming the models' capability to simulate cardiovascular hemodynamics under physiological circumstances. Subsequent analysis of the ability of the model to correctly differentiate between an upper and lower arm AVF configuration, as was chosen by the experienced surgeon, showed that the suggestion of the model is similar in 90% of the subjects. Although these results look promising, relatively large inaccuracies in absolute postoperative flow predictions were observed.

To further improve model based predictions, a sensitivity analysis was performed by Huberts et al. to identify the input parameters associated with significant convergence of predicted versus postoperatively measured flow⁵⁰. For prediction of mean brachial artery flow, it was observed that more accurate diameter measurements of the arterial inflow and venous outflow trajectory potentially result in more precise postoperative flow predictions. Furthermore, mean aortic flow, radial artery peripheral resistance, radial artery peripheral compliance, intravenous

pressure and distributed flow were identified as significant influential model parameters. More accurate determination of these parameters will probably improve model based flow predictions. A second sensitivity analysis was aimed at identifying input parameters that were not rewarding to be determined patient-specifically⁵¹. These parameters could be set to a generic value based on literature. For implementation of the computational model in clinical practice these results imply that a significant number of input parameters can be obtained from literature, while parameters with a significant influence on postoperative flow enhancement can be measured more accurately. This would significantly simplify the personalization of the pulse wave propagation model, and thus the clinical applicability of the model. In **Chapter 8** we present the results of a longitudinal observational study in which insights for improvement of the pulse wave propagation model, obtained by the sensitivity analyses^{50,51}, have been implemented. In 25 patients awaiting primary AVF creation, a radiocephalic, a brachiocephalic, and a brachio basilic AVF configuration were simulated using generic vascular geometry. With appropriate confidence intervals taken into consideration, we found that the model was able to predict the actual measured flows in 70% of the patients. When differentiating between the exact fistula configuration, the choice of the model coincides with the choice of the surgeon in 60% of all cases, while differentiation between upper and lower arm AVF configuration matched in 76% of all patients. In this study, an important benefit of computational modeling is illustrated in three patients, where the surgeon had chosen to create an upper arm AVF while model based predictions may have also allowed for a lower arm configuration, thereby preserving proximal vessels for future AVF procedures. Moreover, early failure might have been avoided in a single patient in whom the vascular surgeon decided to create a radiocephalic fistula. In this patient, insufficient postoperative flow enhancement resulted in thrombosis, as was predicted by the model. With absolute flow predictions in the same order of magnitude as the measured postoperative flow, computational modeling can be considered a potential valuable tool in the preoperative workup of patients awaiting AVF creation, in order to reduce flow associated complications. Nonetheless, although these initial results are promising, a randomized controlled trial is required to establish the added value of patient-specific preoperative model based analysis in clinical routine.

FUTURE PERSPECTIVES

An important reason to perform the work as described in this thesis is that the exact mechanism of VA dysfunction is still not fully understood. Strategies to improve outcome after VA creation have been the main subject of studies that have been

done over the past few years. The studies performed in the context of this thesis were initiated to further elucidate the mechanisms underlying VA failure and to establish the feasibility of alternative preoperative diagnostic modalities such as MRA and distensibility measurements, as well as patient-specific computational modeling tools that can take into account multiple prognostic factors and their complex interactions.

Preoperative imaging

Regarding the MRA developments as described in this thesis, NCE-MRA is already considered a feasible alternative to the CE-MRA protocol described by Planken et al³¹ for depiction of upper extremity vasculature without risking the induction of NSF. However, the technique as proposed in this thesis has some shortcomings that should be addressed in future work. Firstly, the described technique requires multiple acquisitions to cover the entire upper extremity, and necessitates patient repositioning and change of surface coils halfway the exam. Future effort should focus on adapting the image protocol so that the entire upper extremity can be imaged in a single acquisition, similar to the procedure that is performed for the lower extremity, for example by means of continuous moving table techniques⁵². In order to achieve this, imaging protocols need to be developed that take advantage of recently produced digital surface coils that enable imaging of upper extremity vasculature over a large field of view. Secondly, the utilized balanced TFE technique obliges patient positioning as central as possible within the bore of the MRA in order to reduce magnetic field inhomogeneity artifacts⁵³. An unwanted side-effect of the described subject positioning is potential compression of the central vessels due to the slightly sideways positioning, particularly in obese patients. Upcoming studies should focus on improving the bTFE acquisition protocol so that image quality improves while image interpretation is not hampered by subject positioning. The recent introduction of 70-cm magnet bore size and the concomitant increase in field-of-view may ameliorate this concern. Finally, to what extent a preoperative NCE-MRA examination contributes to actually reducing postoperative failure rates remains to be elucidated. A randomized controlled clinical trial elaborating on these matters is currently being conducted.

Regarding brachial artery stiffness, future research activities should address three issues. Firstly, now that we have established the variability of measurements within a single individual, future studies should focus on inter-individual differences, and, subsequently, correlate these differences to observed postoperative flow enhancement. Secondly, since variability in PWV is the direct consequence of variability in both beat-to-beat diameter and pressure measurements, improvement of either one of these, would decrease the variability. For example, by changing the ultrasound acquisition from B-mode to fast-B-mode, a more accurate determination of diameter measurements over the complete cardiac cycle might be achieved, and

may result in less variability between measurements. Nonetheless, regardless of the improvement in this non-invasive acquisition protocol, intra-individual biological variation in pressure will, most likely, always keep hampering the reproducibility of PWV assessment. Finally, besides using clinical observations to investigate the influence of arterial stiffness on postoperative flow enhancement, model based predictions should be considered for experimental validation.

Computational modeling

Although the efforts of the ARCH project consortium have resulted in a feasible pulse wave propagation model regarding prediction of postoperative flow enhancement, technical refinements of the model will most likely result in more accurate predictions.

Currently, a generic model of vascular geometry is personalized by means of patient-specific DUS measurements and MR flow measurements, after which the anastomosis is modeled as a T-junction^{54,55}. By using patient-specific vascular geometry for defining vascular segments of the model, as well as by implementing a more physiological segment representing the anastomosis, important model improvements might be made in future studies. Moreover, the use of patient-specific vascular geometry may also enable computational analysis of 'difficult' patients undergoing secondary or tertiary procedures, instead of the effect of primary VA creation thus far. Finally, by also taking into account the process of cardiovascular adaptation and remodeling following VA creation, long-term flow prediction may be evaluated as well. Although model improvements should be aspired, they most likely require additional patient-specific measurements. In clinical practice however, performing these additional measurements is not always possible without putting an additional burden on the patient. If this is the case, there is a trade-off between the beneficial effect of modeling and the burden on the patient, as well as hospital resources. Nonetheless, regardless of model improvements, inaccuracies in postoperative flow predictions are likely to persist due to limitations in physical laws, physiology or measurement modalities.

Conditional upon technical refinements of the model, future studies should also aim at prediction of other pathological conditions associated with VA surgery. To this end, the development of stenoses in the VA conduit, the development of distal ischemia, as well as remodeling of the myocardium can be investigated. Since stenoses mostly tend to develop within the first few centimeters after the anastomosis, computational fluid dynamics might be of assistance in describing flow-patterns and wall shear stress distribution in this area^{22-24,47}. Molecular insights in the development of neointimal hyperplasia might subsequently be coupled to these model based predictions^{24,56,57}. Finally, similar to silicone models²⁷, computational modeling tools may be used to simulate the effect of surgical procedures performed in order to reduce access flow

(e.g. banding, RUDI, DRIL)⁵⁸. Also, the effect of endovascular revascularization procedures such as thrombectomy and percutaneous transluminal angioplasty may be predicted by utilizing future modeling tools.

CONCLUDING REMARKS

In the context of the ARCH project we have investigated the feasibility of alternative preoperative imaging modalities and computational modeling tools with the aim to lower the persistently high VA failure rates. Although some significant hurdles have to be taken before these modalities are ready for implementation in clinical routine, we believe that future improvements herein have the potential to contribute significantly to reduction in postoperative VA failure rates.

Although model improvements are desirable, it will be practically impossible to obtain 100% accuracy for absolute postoperative flow predictions due to limitations in physical laws, biological variations within a single patient as well as inaccuracies in clinical measurement modalities. Nonetheless, in order to improve the model and achieve the best possible results, a close multidisciplinary collaboration between vascular surgeons, radiologists and qualified medical engineers is mandatory. With continued successful collaboration one can be confident that non contrast-enhanced MRA, brachial artery stiffness measurements and personalized pulse wave propagation models, utilized as an additional tool in clinical decision-making, can improve outcome after AVF creation.

CONCLUSIONS OF THIS THESIS

1. Despite good adherence to clinical practice guidelines, creation and maintenance of successfully functioning vascular access remains challenging.
2. In patients awaiting vascular access creation, non contrast-enhanced balanced turbo field echo MRA is considered a feasible alternative to contrast-enhanced MRA for depiction of upper extremity vasculature.
3. Non contrast-enhanced balanced turbo field echo MRA enables a thorough interrogation of the upper extremity vascular tree and allows to extract arterial inflow and venous outflow trajectories for personalization of computational modeling tools.
4. Repeated measurements of brachial artery stiffness show a moderate degree of variation. Inter-individual differences as well as their effect on postoperative flow enhancement determine their clinical efficacy.
5. Lumped parameter pulse wave propagation models allow for preoperative simulation of hemodynamic changes after creation of an arteriovenous fistula.
6. The described lumped parameter pulse wave propagation model predicts postoperative flow enhancement for multiple arteriovenous fistula configurations relatively accurately, and can therefore be considered a potential additional tool in the preoperative workup of patients awaiting VA creation.

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CHAPTER

10

Samenvatting (summary in Dutch)

SAMENVATTING

Terminaal nierfalen is een groeiend medisch probleem en resulteert in een toenemende vraag naar nierfunctie vervangende therapieën. Nierfunctie vervangende therapieën kunnen worden onderverdeeld in niertransplantatie, hemodialyse en peritoneaal dialyse. Het uitvoeren van een niertransplantatie heeft hierbij de voorkeur. Echter, een persisterend tekort aan donor organen maakt het gebruik van hemodialyse en/of peritoneaal dialyse in het merendeel van de patiënten noodzakelijk. In de meerderheid van de patiënten (69%) wordt hemodialyse gebruikt als behandelmethode.

Het principe van hemodialyse bestaat uit het zuiveren van bloed door middel van een kunstnier, welke zich buiten het lichaam bevindt. Om het bloed bij de kunstnier te krijgen en vervolgens weer terug te geven aan het lichaam moet er een toegang zijn tot de bloedsomloop van de patiënt. Voor succesvolle hemodialyse is het van belang dat deze toegang een voldoende hoge bloedstroom (flow) heeft en dat de diameter van de vaten voldoende is om eenvoudig aan te prikken. Aangezien het lichaam niet beschikt over een bloedvat wat aan deze eisen voldoet, dient er een chirurgische vaattoegang gecreëerd te worden alvorens hemodialyse gestart kan worden. Een chirurgische vaattoegang kan gerealiseerd worden door het plaatsen van een centraal veneuze catheter (CVC) in de bovenste holle ader of door het creëren van een shunt waarbij een ader en een slagader met elkaar verbonden worden. De kwaliteit en diameter van de bloedvaten van de patiënt bepalen of de shunt gemaakt kan worden door de ader en de slagader direct met elkaar te verbinden (=arterioveneuze fistel [AVF]) of dat er gebruik gemaakt moet worden van prothesemateriaal (=arterioveneuze graft [AVG]).

Bij het creëren van een toegang tot de bloedbaan gaat de voorkeur uit naar een directe verbinding tussen een ader en een slagader waarbij géén prothesemateriaal gebruikt wordt. Onderzoek heeft namelijk laten zien dat zowel het gebruik van CVC's als het gebruik van prothesemateriaal veelvuldig geassocieerd is met complicaties. Desalniettemin brengt het aanleggen van een fistel ook een aantal belangrijke risico's met zich mee: vanwege de initieel lage flow komt direct postoperatieve stolling relatief frequent voor. Daarnaast bestaat er bij het aanleggen van een fistel een kans op een slechte rijping (maturatie), gekarakteriseerd door onvoldoende toename van flow en diameter in de eerste weken na aanleg van de fistel, zodat efficiënte hemodialyse onmogelijk is. Tot slot bestaat er een risico op het ontwikkelen van een hoge postoperatieve flow, wat kan resulteren in hartklachten, danwel een doorbloedingsvermindering van de 'shunthand'. Om het risico op deze complicaties enigszins te beperken pleiten de huidige richtlijnen voor het uitvoeren van een preoperatief echo onderzoek van de aders en slagaders in de arm ten einde de meest geschikte locatie voor het aanleggen van een fistel te identificeren. Echter, ondanks deze richtlijnen is een aanzienlijk deel van de nieuw aangelegde fistels niet geschikt voor hemodialyse (24%) en worden klachten van doorbloedingsvermindering beschreven door 75% van de patiënten.

Teneinde fistelgerelateerde complicaties verder te reduceren is er een groeiende interesse in alternatieve preoperatieve beeldvormende technieken. Eerdere studies hebben namelijk laten zien dat er mogelijk een daling van het aantal postoperatieve complicaties bereikt kan worden wanneer het ultrageluid onderzoek (duplex) wordt aangevuld met een magnetische resonantie angiografie (MRA). Echter, het conventionele MRA onderzoek is gebaseerd op de toediening van gadolinium houdend contrastmiddel voor het afbeelden van de bloedvaten. Hiervan is recent gebleken dat toediening bij patiënten met een verminderde nierfunctie mogelijkserwijs kan leiden tot het ontwikkelen van nefrogene systemische fibrose, een zeer ernstige, potentieel dodelijke, aandoening. Een tweede mogelijkheid om het preoperatieve onderzoek uit te breiden is middels evaluatie van de mechanische eigenschappen van de betrokken bloedvaten. Hiervan wordt verondersteld dat zij voorspellend zijn voor het aanpassingsvermogen van de bloedvaten na de aanleg van een fistel. Eenduidige meetprotocollen hieromtrent ontbreken helaas nog altijd. Naast het uitbreiden van de diagnostische mogelijkheden bestaat er ook interesse in modaliteiten die de chirurg assisteren bij het interpreteren van de verkregen informatie. Computer simulatie modellen die het resultaat van een voorgenomen ingreep voorspellen lijken hierbij veelbelovend.

In dit proefschrift zijn de uitvoerbaarheid van een tweetal alternatieve preoperatieve beeldvormende technieken, te weten niet-contrast-versterkte magnetische resonantie angiografie (MRA) van de gehele arm en arteriële stijfheids metingen van de slagader in de bovenarm, onderzocht en beschreven. Daarnaast is de ontwikkeling van een patiënt-specifieke preoperatieve computer simulatie techniek beschreven. Van dit model is onderzocht of het in staat is de meest geschikte locatie voor fistel chirurgie te adviseren op basis van het voorspellen van postoperatieve flow per type fistel.

In **hoofdstuk 2** wordt een uitgebreid overzicht gegeven van de actuele literatuur met betrekking tot de vaattoegang voor hemodialyse. Hierin worden de verschillende opties voor preoperatieve diagnostiek besproken, evenals de diverse mogelijkheden voor het creëren van een vaattoegang en de complicaties die daarmee geassocieerd zijn. Veel van deze complicaties zijn terug te voeren op patiënt factoren (leeftijd, geslacht, bijkomende ziekten) en vaatkarakteristieken (diameter, vernauwingen, zijtakken). Een andere belangrijke rol lijkt te zijn weggelegd voor postoperatieve veranderingen in het stromingsprofiel van bloed (hemodynamisch profiel) op zowel lokaal, perifeer als systemisch niveau. Recente studies suggereren dan ook dat postoperatieve complicaties mogelijkserwijs beperkt danwel voorkomen kunnen worden wanneer een zo optimaal mogelijk hemodynamisch profiel wordt bewerkstelligd gedurende de operatieve ingreep. Om dit te bereiken is een patient-specifieke analyse, waarbij multi-pele factoren in ogenschouw genomen worden, noodzakelijk.

In **hoofdstuk 3** wordt het studieprotocol beschreven dat geïmplementeerd is in het kader van het ‘patient-specific image-based computational modeling for improvement of short- and long-term outcome of vascular access in patients on hemodialysis therapy’ (ARCH) project (7th Framework project van de Europese Commissie). Dit studieprotocol faciliteert de structurele acquisitie van patiëntgegevens teneinde de uitvoerbaarheid van alternatieve beeldvormende technieken (niet-contrast-versterkte MRA en arteriële stijfheidsmetingen) te onderzoeken en een voorspellend computer simulatie model te ontwikkelen, te kalibreren en te valideren.

Teneinde de potentiële voordelen van een preoperatief MRA onderzoek te behouden is in **hoofdstuk 4** de potentie van een nieuwe, *niet*-contrast-versterkte MRA sequentie onderzocht. In een onderzoekspopulatie bestaande uit 10 gezonde vrijwilligers en 15 patiënten met nierfalen is een niet-contrast-versterkte balanced turbo field echo (bTFE) MRA sequentie vergeleken met de huidige gouden standaard voor diagnostische vasculaire beeldvorming van de perifere vasculatuur, contrast-versterkte MRA. Uit de statistische analyse blijkt dat voor de arteriële vaatsegmenten de contrast-versterkte MRA sequentie superieur is wat betreft het aantal gevisualiseerde vaatsegmenten en beeldkwaliteit. Desalniettemin, de niet-contrast-versterkte acquisitie was van diagnostische kwaliteit in 82% van het totaal aantal arteriële vaatsegmenten. Voor het afbeelden van veneuze structuren in de arm bleek niet-contrast-versterkte MRA zelfs superieur gezien het grotere aantal afgebeelde vaatsegmenten en de hogere beeldkwaliteit. Gezien het feit dat met niet-contrast-versterkte MRA de vasculaire structuren in de arm adequaat afgebeeld kunnen worden zullen toekomstige studies uit moeten wijzen of klinische implementatie hiervan in de preoperatieve work-up ook daadwerkelijk bijdraagt tot een reductie van het aantal postoperatieve complicaties na vaattoegangschirurgie.

Naast het mogelijk maken van preoperatieve beoordeling van de bloedvaten in de arm kan het niet-contrast-versterkte MRA onderzoek ook gebruikt worden om patiënt-specifieke vasculaire netwerken te verkrijgen. Deze kunnen vervolgens gebruikt worden voor het personaliseren van voorspellende computer modellen. In **hoofdstuk 5** wordt een techniek beschreven die extractie van vasculaire netwerken uit niet-contrast-versterkte MRA datasets mogelijk maakt.

Naast geometrische factoren blijken ook mechanische factoren bepalend te zijn voor het slagen of falen van de operatieve ingreep. Over het algemeen wordt aangenomen dat de elasticiteit van een vat prognostisch is voor het postoperatieve adaptatievermogen. Tot op heden is er echter geen goede methode geïntroduceerd om de vasculatuur van de arm te beoordelen op zijn mechanische eigenschappen. **Hoofdstuk 6** beschrijft een niet-invasieve methode voor het bepalen van de polsgolf snelheid in de slagader van de bovenarm (arteria brachialis) aan de hand van druk en diameter veranderingen tussen de systolische en diastolische hartfase, en karakteriseert hiermee de lokale stijfheid van de slagader. Alvorens de prognostische

waarde van lokale polsgolf snelheid te bepalen was het noodzakelijk de variabiliteit en de reproduceerbaarheid van deze druk en diameter metingen te onderzoeken. In een studie onder 21 vrijwilligers was er een goede correlatie waarneembaar tussen de verschillende druk en diameter bepalingen binnen een meetsessie, met tevens weinig variatie. Echter, wanneer deze metingen gebruikt werden voor het bepalen van de lokale polsgolf snelheid ontstond er een grotere mate van variabiliteit. De variabiliteit van de polsgolf snelheid binnen een sessie is 10.6%, terwijl deze toeneemt tot 13.5% wanneer gemeten over meerdere dagen. Toekomstige studies die zich richten op de onderlinge verschillen tussen patiënten, alsmede het kwantificeren van het effect van stijfheid op postoperatieve flow zullen de klinische relevantie van het meten van de polsgolf snelheid in de arteria brachialis bepalen.

Hoofdstuk 7 beschrijft de mathematische en fysische achtergrond van het computer simulatie model wat ontwikkeld is in de context van het ARCH project. Dit pulse wave propagation model bestaat uit diverse segmenten die de arteriën en venen van de arm representeren. Door de configuratie en eigenschappen van deze segmenten aan te passen aan de verschillende patiënt-specifieke omstandigheden kunnen hemodynamische veranderingen als gevolg van fistel operaties reeds voor de operatie gesimuleerd worden. Op basis hiervan kan een operatie verricht worden die een zo gunstig mogelijk hemodynamisch profiel voor de patiënt als gevolg heeft, wat mogelijkwerijs kan leiden tot een vermindering van het aantal postoperatieve complicaties.

In een kleine studie onder 10 patiënten bleek het model in staat om de preoperatieve flow te simuleren met een afwijking van slechts 5% ten opzichte van de daadwerkelijk gemeten preoperatieve flow. Aansluitend is onderzocht of het model in staat was te differentiëren tussen een onderarms en een bovenarms fistel. Hiertoe is de operatie, uitgevoerd door de vaatchirurg, vergeleken met de uitkomst van het computermodel, welke gebaseerd is op de voorspelde postoperatieve flow. Hieruit bleek dat het model, ondanks de relatief grote foutmarges op absolute voorspelling van de flow, in 90% van de patiënten in staat was eenzelfde type fistel te suggereren als gekozen is door de chirurg.

In **hoofdstuk 8** worden de resultaten van de vervolg studie in het kader van het ARCH project gepresenteerd. Na optimalisatie van het computer simulatie model aan de hand van diverse gevoeligheidsanalyses zijn 25 patiënten met nierfalen geanalyseerd wat betreft postoperatieve flow toename voor 3 verschillende type fistels: de pols fistel, de elleboog fistel en de bovenarm fistel. In 70% van de patiënten kwam de voorspelde postoperatieve flow overeen met de daadwerkelijk gemeten postoperatieve flow. In 60% van de patiënten was de gesuggereerde fistel gelijk aan de keuze van de vaatchirurg. Echter, wanneer slechts gekeken werd naar een onderarm of bovenarm fistel kwam de suggestie van het model in 76% van de patiënten overeen met de keuze van de chirurg. In 4 patiënten werd een voordeel

van preoperatief modeleren gevonden: in 3 patiënten werd gesuggereerd een pols fistel aan te leggen terwijl de chirurg primair gekozen had voor een bovenarms fistel. Hiermee hadden mogelijkwerijs de vaten in de bovenarm gespaard kunnen worden voor toekomstige procedures. In een 4e patiënt suggereerde het model een bovenarms fistel terwijl de chirurg voor een pols fistel gekozen had. De aangelegde fistel bleek enkele dagen postoperatief gestold te zijn. Hoewel de eerste resultaten veelbelovend zijn moeten toekomstige gerandomiseerde studies de toegevoegde waarde van preoperatief patiënt-specifiek modeleren nog aantonen.

Hoofdstuk 9 geeft een samenvattende discussie over de bevindingen van dit proefschrift en plaatst deze in de context van de huidige literatuur. Vervolgens worden handreikingen gedaan ten einde preoperatieve beeldvorming met niet-contrast-versterkte MRA en computer simulatie modellen te optimaliseren alvorens deze in de kliniek te implementeren. Tot slot worden de belangrijkste conclusies uit dit proefschrift aangehaald.

CONCLUSIES UIT DIT PROEFSCHRIFT

1. Ondanks besluitvorming aan de hand van richtlijnen en protocollen blijft het bewerkstelligen en het onderhouden van een functionele vaattoegang voor hemodialyse een uitdaging.
2. In patiënten die in afwachting zijn van de aanleg van een vaattoegang vormt niet-contrast-versterkte balanced turbo field echo MRA een uitvoerbaar alternatief voor contrast-versterkte MRA voor het afbeelden van de bloedvaten van de arm.
3. Niet-contrast-versterkte balanced turbo field echo MRA maakt een betere preoperatieve afbeelding van de arm bloedvaten mogelijk en ondersteunt patiënt-specifieke input van slagaderlijke en aderlijke netwerken voor het maken van een computer simulatie.
4. Herhaalde stijfheids metingen van de slagader in de bovenarm laten een matige variabiliteit van de polsgolf snelheid zien. Onderlinge verschillen tussen personen, alsmede het effect op postoperatieve flow toename, bepalen de klinische relevantie van deze metingen.
5. Lumped parameter pulse wave propagation modellen voorzien in de mogelijkheid een preoperatieve simulatie van hemodynamische veranderingen na fistel aanleg te doen.
6. Het beschreven lumped parameter pulse wave propagation model voorspelt postoperatieve flow toename voor meerdere type fistels. Computer simulatie kan daarom beschouwd worden als een toegevoegde onderzoeksmethode in de preoperatieve work-up van patiënten die in afwachting zijn van een vaattoegang.

Dankwoord

... een wetenschappelijke verhandeling over een bepaald onderwerp danwel een samenvoeging van wetenschappelijke publicaties. Bij goedkeuring van het proefschrift door de promotor krijgt de promovendus, na een succesvolle verdediging tijdens de promotieplechtigheid, de graad van doctor.

Wikipedia

Mijn proefschrift ‘verhandelt’ over modaliteiten die mogelijkwerijs het aantal complicaties na vaattoegangschirurgie kunnen verminderen en bestaat uit een verzameling van wetenschappelijke publicaties die het resultaat zijn van studies uitgevoerd in het kader van een groot Europees onderzoeksproject. Het moge duidelijk zijn dat dit geen individuele prestatie geweest is. Dit proefschrift is tot stand gekomen met medewerking en steun van velen. Graag wil ik eenieder bedanken die een bijdrage heeft geleverd aan het eindresultaat, het boekje dat u hier voor ogen heeft. Een aantal mensen wil ik in het bijzonder noemen.

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Curriculum Vitae

Arie Simon (Aron) Bode was born on August 17, 1983 in Rotterdam, The Netherlands. He attended the 'Nassau Scholengemeenschap' in Breda, where he graduated in 2001. Immediately thereafter he started his medical training at the Maastricht University Medical Center (MUMC). After obtaining his 'doctoraal' in 2004 he started his medical internships, during which he participated in several research projects in the departments of Orthopedics, Urology, and Surgery. He obtained his MD degree (cum laude) in April 2008 after which he started his PhD research project at the Department of Vascular Surgery of the Maastricht University Medical Center under the supervision of prof. dr. P.J.E.H.M. Kitslaar, dr. J.H.M. Tordoir, and dr. T. Leiner. Until 2011 he worked in the context of a seventh Framework Program of the European Commission, the ARCH project, aiming at improving preoperative imaging modalities and the development of predictive computational modeling tools in the field of vascular access surgery, which resulted in the current thesis. He has presented original research and invited papers at many national and international meetings, and contributed to several educational courses for vascular surgeons and dialysis nurses. In January 2012 he started his surgical residency at the Atrium Medisch Centrum in Heerlen (dr. R.J.Th.J. Welten).

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