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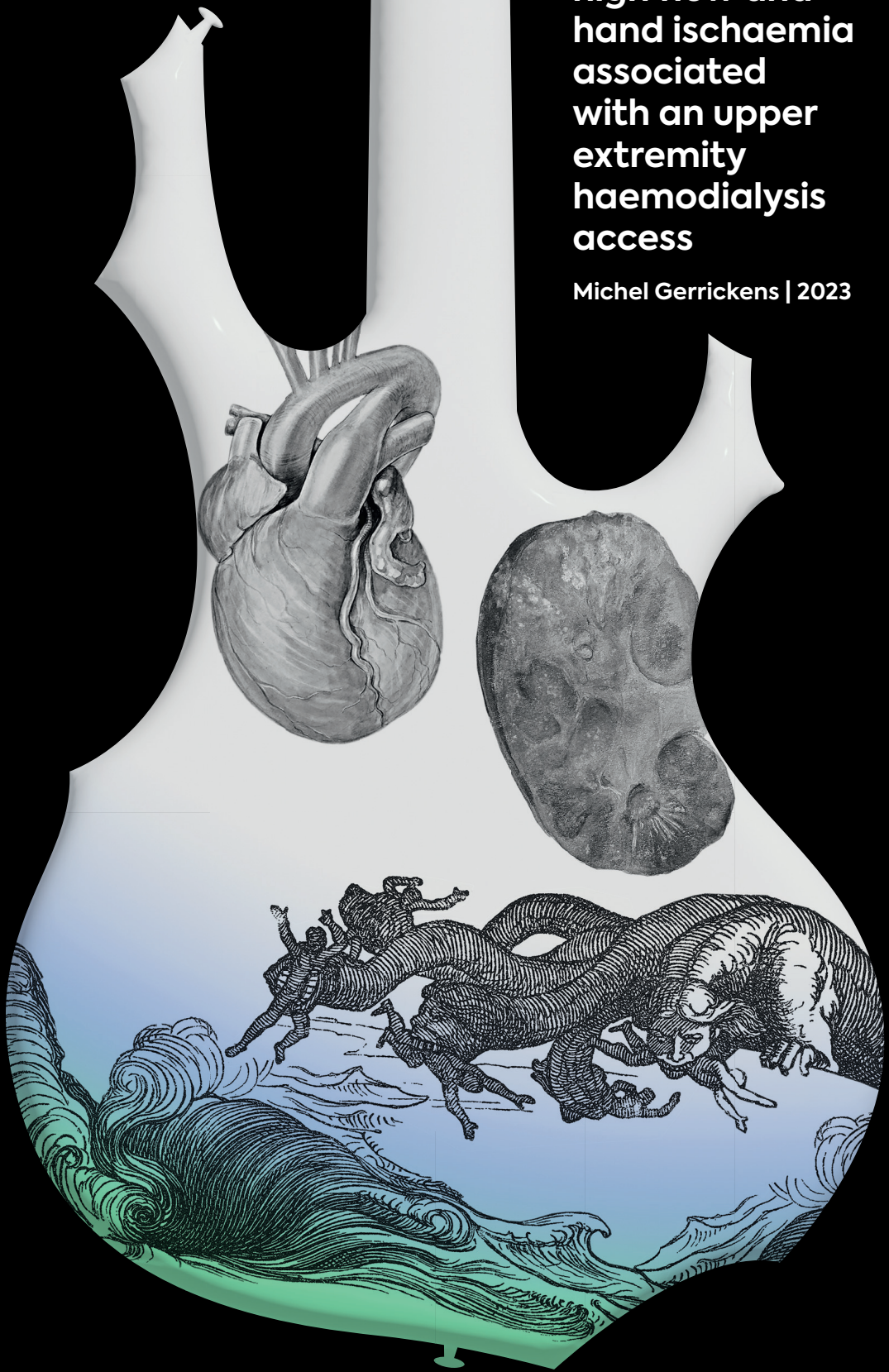
Michel Gerrickens | 2023



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Chapter 1

Introduction, aims and outline

Introduction

Dialysis is life-sustaining. At present, most patients suffering from end stage renal disease (ESRD) choose to receive intermittent haemodialysis (HD) rather than peritoneal dialysis (PD) as first mode of renal replacement therapy (RRT).[1] HD is possible by means of a central venous catheter (CVC) or an arteriovenous graft (AVG). However, using an arterialized vein following construction of an arteriovenous anastomosis (arteriovenous fistula, AVF) is the preferred choice for vascular access creation.[2] In 1966, Brescia, Cimino and Appel introduced the radio cephalic AVF (RC-AVF).[3] Since then, this wrist-based AVF continues to be the method of choice as recommended by both Dutch and international guidelines.[4-6] An alternative option is construction of an AVF at the elbow, using the brachial artery (BA-AVF) or proximal radial or ulnar artery as inflow source.[7]

Changing patient demographics

In the Netherlands, the prevalence of RRT is steadily increasing whereas the incidence per million inhabitants may be relatively stable. In the year of 2020, almost 80% (n=1285) of the incident Dutch ESRD patients started with HD. Overall, approximately 30% of the prevalent patients on RRT received haemodialysis (n=5260).[1] However, patient demographics have changed over the years as incidences of obesity, diabetes mellitus type 2, hypertension, peripheral arterial disease (PAD) and cardiac disease are increasing. Moreover, patients in the need of RRT are becoming older. As a consequence, vascular surgeons are forced to more often create a BA-AVF rather than a RC-AVF, as distal (forearm) vessels tend to be inadequate.[8] Maturation of a BA-AVF is frequently beneficial. However, such accesses are associated with an increased risk of the development of high flow (Qa) with or without cardiac complaints (high flow access, HFA), or haemodialysis access-induced distal ischaemia (HAIDI).[9-11]

Part I: High Flow Access (HFA)

Immediately following AVF construction, the acute decrease in local vascular resistance and the subsequent drop in the arm's arterial blood pressure signal for an increase in arterial flow rates in the arm. As a result, arm vessel endothelium releases factors such as nitric oxide leading to an increase in vessel diameter over time.[12] Meanwhile, the venous outflow tract 'arterializes', that is, it develops a thicker vessel wall. A minimal Qa of

400-600 mL/min through an arterialized vein is required for adequate HD.[4] In some cases however, ongoing AVF maturation may drive Qa values well above 1.5 L or even 2.0 L/min, leading to a HFA.[13] The incidence of HFA in general HD populations is thought to approximate 3-4%.[14]

The presence of a HFA is potentially harmful. For instance, Basile et al. reported an increased risk of high output cardiac failure (HOCF) resulting from Qa over 2.0 L/min, or a 'flow on cardiac output ratio' exceeding 0.3.[15] An earlier study from our department reported serious cardiovascular effects of a Qa exceeding 2.0 L/min.[16] Thus, persistent exposure to a high Qa may chronically overload the cardiovascular system and challenge cardiac function in the long term.[15,17] Additionally, a high Qa may lead to grossly dilated and even aneurysmatic arm veins (Figure 1). Risk factors associated with a HFA are largely unknown. However, HD-patients developing a HFA tend to be younger and less frequently suffer from diabetes mellitus compared with their peers not developing a high Qa.[18]

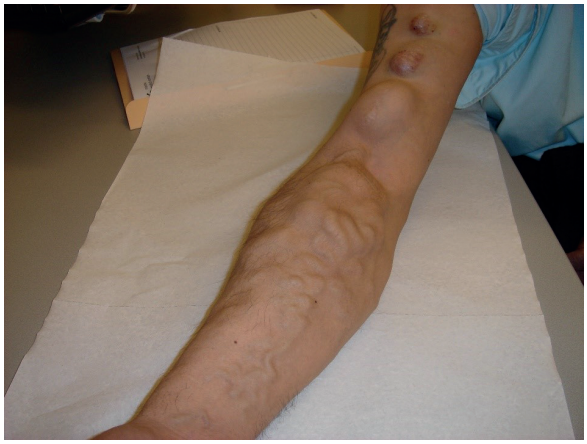

Figure 1. Grossly dilated and aneurysmatic arm veins in a patient with a high HFA (Qa >2 L/min).

Surgery for HFA

Therapy for HFA is initially conservative (correction of anaemia, electrolyte imbalances and hypertension). If unresponsive, a variety of surgical techniques are advocated. Banding is a technique that uses wrapping of the access' outflow vein by means of a circular band. By doing so, outflow resistance increases and Qa is reduced. This is the oldest and most widely used operation with acceptable short-term results (Figure

2). One year following this procedure however, >50% of banded patients developed a recurrent HFA in our department.[13] Complications such as 'overbanding' leading to access occlusion, band infection and erosion have been reported.[13,19,20] Revision using distal inflow (RUDI) was introduced as an alternative technique in the armamentarium for a brachial artery-based HFA. Following a RUDI-procedure, AVF inflow is no longer via a large diameter brachial artery but via a smaller calibre (proximal) radial artery by using a short stretch of interposition vein or graft. One year following RUDI, just 16% had developed a recurrent HFA. These results suggested that RUDI, although more complex to perform, might be superior to banding in terms of long term efficacy.[18] Longer term data on RUDI are scarce and the mechanisms driving HFA recurrence are poorly understood. Moreover, randomized trials comparing types of flow reductive surgery are lacking.

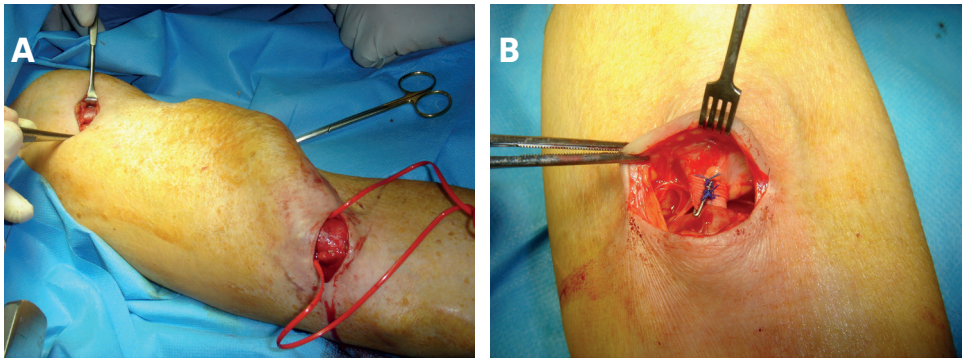

Figure 2. (A) Intra-operative view of an aneurysmatic outflow tract due to extremely high Qa (>4L/min). **(B)** Status following banding of the venous outflow tract.

Currently, it is unclear if and when to operate on a HFA whereas cut-off values are ill defined. Some authors advise surgery only in symptomatic patients. Others consider a HFA only if Qa exceeds 2.0 L/min and advise to perform an intervention, even if symptoms are absent. Overall, the need for Qa reductive surgery in some patients may intuitively seem clear, but there is no consensus on indications, timing and optimal technique.

Part II: Haemodialysis access-induced distal ischaemia (HAIDI)

Another, more commonly known long term complication of AVFs is haemodialysis access-induced distal ischaemia (HAIDI). Characteristic complaints are pain, coldness, cramps, paraesthesia or loss of strength in the hand of the dialysis arm. Rest pain and ulcerations may appear in

severe HAIDI.[21] HAIDI is thought to develop in approximately 5% of patients with a RC-AVF and in up to 9% of patients with a BA-AVF though higher percentages have been reported.[10,22] Risk factors are diabetes mellitus, female gender, previous access surgery and an access originating from the brachial artery rather than from a proximal or distal radial (or ulnar) artery.[9,23] At Máxima MC, the 'Hand Ischaemic Questionnaire' (HIQ) was developed to quantify a subjective symptom pattern enabling researchers and clinicians to identify potential patients and to monitor outcome following surgery in a standardized manner.[11,17,21,23-25] Physical examination might disclose a pale, cyanotic hand with diminished arterial pulsations and lowered capillary refill.[26] Moreover, finger plethysmography may reveal low digital systolic pressures (<50 mmHg) and a low digital brachial index <0.6 (DBI; index 'systolic finger pressure' on 'systemic systolic pressure measured in the contralateral brachial artery).[27-29] Following access compression, complaints such as coldness and pain may decrease while arterial pulsations return and DBIs normalise, indicating that the ischaemia is likely amendable to surgery.[26]

Pathophysiology of HAIDI

Generalized arterial stiffness and atherosclerosis combined with diminished arterial remodelling capacities due to uraemia, diabetes mellitus and increasing age may induce a gradient pressure drop along the heart-hand axis in some HD patients. An additional pressure drop arises following construction of an arteriovenous connection as in access surgery with turbulent flows at the anastomosis. Ongoing atherosclerosis and a possible haemodynamic significant stenosis may lead to even lower local/distal perfusion pressure.[26] Open venous side branches in proximity to the AVF's anastomosis were found to also contribute to the pressure loss.[21,24] Finally, (relative) systemic hypotension due to cardiac disease or antihypertensive agents may affect local perfusion.[26] It may well be that HAIDI occurs following a combination of these phenomena. Overall, HAIDI should be considered as a loco-regional manifestation of systemic arterial disease. It was suggested that patients developing HAIDI displayed limited survival.[30-32] Comparisons in survival between HD-patients with and without HAIDI are lacking. Furthermore, objective parameters prior to access construction predicting the onset of HAIDI following surgery are scarce.

Diagnostic pathway and treatment of HAIDI

In analogy to peripheral arterial occlusive disease, HAIDI was graded in mild ischaemia (grade I-IIa), and severe ischaemia (grade IIb-VI; Table 1). Invasive treatment of HAIDI type IIb-IV is advised. In case of rest pain (grade III) or tissue loss (grade IV), prompt intervention is indicated.[21,24,33] A thorough understanding of the pathophysiology is mandatory in order to decide on the appropriate treatment that should always be tailored to a patient's individual situation. The source of blood pressure loss must be identified in each patient with HAIDI. Duplex or angiography may reveal a haemodynamically significant proximal inflow stenosis requiring a percutaneous transluminal angioplasty (PTA).[26] Patent side branches near the anastomosis may require ligation, particularly if Duplex analysis demonstrates substantial flow.[21,24,34] When these steps are to no avail, one must focus on reducing the pressure drop due to the anastomosis. A decrease in Qa surely increases distal finger pressures. Therefore, treatment of a HFA combined with HAIDI is strongly advised, also as ischaemia may be abolished. For instance, both RUDI and banding for HFA reduction were found to effectively attenuate concomitant HAIDI.[11,35] In case of HAIDI in the absence of a high Qa (0.3-1.0 L/min), alternative procedures such as distal revascularisation and interval ligation (DRIL) or proximalization of arterial inflow (PAI) may be required. Surgical ligation of a HD access is deemed a last resort when all other treatment options have failed and ischaemia is progressive. When considering ligation for HAIDI, preoperative digital pressure measurements with open and clamped access are mandatory.[26] If digital pressures fail to rise following compression, ligation might prove ineffective.

Access surgery: Scylla and Charybdis?

Besides the risk of developing HFA or HAIDI, access surgery is characterized by the risk of thrombosis and occlusion. Thus, there is always a dilemma during the construction of an AVF. If one makes a wide anastomosis, an increased risk of high Qa and HAIDI is at hand. In contrast, a too narrow anastomosis might lead to thrombosis and access loss. As such, access construction is like navigating between Scylla and Charybdis. Building a solid body of evidence may aid in successfully treating, predicting and possibly even preventing the onset of HFA and hand ischaemia in future HD populations.

Table 1. Grade of haemodialysis access-induced distal ischaemia (HAIDI) in analogy to the Fontaine classification for peripheral arterial occlusive disease as described by our department and later adopted during a consensus meeting.[21,33]

HAIDI Grade	Description
I	Discrete signs of mild ischaemia may be observed: Slight cyanosis of nail beds, mild coldness of the skin of the hand, reduced arterial pulsations at the wrist. Reduced finger pressures. Conservative treatment may be indicated; otherwise, observation and review.
IIa	Complaints during dialysis sessions or intense use of the hand: Tolerable pain, cramps, paraesthesia, numbness or coldness. Pale or blueish nail beds, coldness of the skin of the hand, reduced arterial pulsations at wrist. Reduced finger pressures. Conservative treatment is indicated.
IIb	Complaints during dialysis or normal use of the hand: Intolerable pain, cramps, paraesthesia, numbness or coldness. Pale or blueish nail beds, coldness of skin of hand, reduced arterial pulsations at wrist. Reduced finger pressures. Combination of conservative and surgical treatment is indicated.
III	Rest pain or motoric dysfunction of fingers or hand. Pale or blueish nail beds, mild coldness of skin of hand. Reduced arterial pulsations at wrist and reduced finger pressures. Urgent invasive treatment supported by conservative measures is indicated.
IVa	Limited tissue loss (necrosis, ulceration). Complaints of rest pain, paraesthesia, motor and sensory loss. Reduced finger pressures. Urgent invasive treatment supported by conservative measures is indicated.
IVb	Irreversible tissue loss of the hand or even proximal parts of the extremity. Impossibility to preserve clinically significant hand function. Amputation is required. Urgent invasive treatment to prevent ongoing ischaemia is required.

Aim of thesis

Aim of this thesis is to study various aspects of the pathophysiology, treatment and prognosis of high Qa and hand ischaemia in haemodialysis patients having an upper extremity arteriovenous access.

Specific aims

1 To study the long-term efficacy of a flow reducing technique termed RUDI in terms of high Qa recurrence and to evaluate its effect on the local vasculature of the haemodialysis arm.
2 To assess the association between various characteristics of Qa and (cardiovascular) mortality.
3 To perform a literature study on the current body of evidence regarding treatment and indication for surgery for high Qa.
4 To evaluate the potential positive effects of a technique termed basilic vein transposition on hand ischaemia.
5 To compare survival in haemodialysis patients with and without HAIDI.
6 To study the possible predictive values of finger pressure measurements during an Allen test prior to access creation in the face of the development of HAIDI.

Outline

Part I

Several techniques are available for the treatment of both high Qa and HAIDI including RUDI (revision using distal inflow) but long-term data are scarce. Patency and high Qa recurrence rates within three years following RUDI using a greater saphenous vein as interposition graft are studied in **Chapter two**. As the response of the local vasculature as well as flow characteristics in the haemodialysis arm following RUDI may provide insight in factors driving recurrence of high Qa, results of a one-year Duplex follow-up study were reported in **Chapter three**.

There is an ongoing debate on the definition of HFA and on when and how to treat this entity. In **Chapter four**, a scoping review is provided studying the variety in definition, indication for surgery and efficacy of various existing Qa reducing techniques.

Most studies on high Qa are based on a single or a couple of Qa measurement(s). Although one intuitively might assume that a high Qa poses an increased cardiac workload and thus cardiac risk, data are ambivalent. **Chapter five** reports on the association between Qa and cardiovascular mortality, using a joint modelling approach considering the time effect of long-term exposure to high Qa.

Part II

In some patients, the cephalic upper arm outflow vein of a BA-AVF is of insufficient length for adequate two-needle dialysis. A basilic vein transposition may be performed to obtain an adequate needle access segment. In **Chapter six** the beneficial effects of this operation on HAIDI complaints and finger pressures were reported.

As HAIDI is a local manifestation of generalized atherosclerosis, one might hypothesize that patients with HAIDI display worse survival compared with peers without HAIDI. **Chapter seven** reports on survival rates of three categories of patients having mild, severe and absent HAIDI.

Historically, the Allen test was used to subjectively assess the perfusion pattern of the hand in patients who were to receive cardiac catheterisation or construction of a vascular access. We studied the possible predictive properties of a preoperative Allen test regarding the development of HAIDI later on in **Chapter eight**.

In **Chapter nine**, a summarizing discussion is provided. **Chapter ten** covers future perspectives followed by an impact section in **Chapter eleven**. A Dutch summary is provided in **Chapter twelve**. Finally, a list of presentations, acknowledgements and a curriculum vitae of the author are included.

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Chapter 2

Three-year patency and recurrence rates of revision using distal inflow with a venous interponate for high flow brachial artery-based arteriovenous fistula

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Abstract

Objectives Upper arm arteriovenous fistulas (AVF) occasionally develop high flow. Revision using distal inflow (RUDI) effectively reduces flow of high flow accesses (HFA) in the short-term and is also popularized for treatment of hemodialysis access-induced distal ischemia (HAIDI). The long-term efficacy is unknown. Aim was to report on three-year RUDI patency and recurrence rates for HFA with and without HAIDI.

Design *Retrospective cohort.*

Material & Methods Patients with a HFA with or without HAIDI undergoing RUDI using greater saphenous vein (GSV) interposition between March 2011 and October 2017 in three facilities were studied retrospectively. AVFs were termed HFA if flow volumes exceeded 2 L/min on two consecutive measurements using dilution techniques. HAIDI was diagnosed as recommended. Following RUDI, follow-up was not different from standard care in AVF-patients. Data on postoperative flows and re-interventions were extracted from electronic patient files. Loss to follow-up was nihilated. Rates of patency and HFA-recurrence were analysed using Kaplan-Meier analysis.

Results During the observation period, 21 patients were studied (7 females, 54 years ±3). Fourteen had uncomplicated HFA whereas seven had additional HAIDI. Immediately postoperative, flows decreased threefold (3120 mL/min ±171 vs. 1170 mL/min ±87, P<.001). Overall three-year primary patency was 48% ±12 (HFA, 55% ±15 vs. HAIDI/HFA, 29% ±17, P=.042). Secondary patency was identical in both groups (overall, 84% ±9). Interventions were percutaneous transluminal angioplasty (n=12, 9 patients), thrombectomy (n=7, 3 patients) and revision with new interponates (n=3). After three years, 51% ±12 were free of high flow (HFA, 32% ±13 vs. HAIDI/HFA, 100%, P=.018). High immediate postoperative access flow predicted recurrence (OR 1.004 [1.000-1.007], P=.044). Patients with recurrence were 12 years younger than those without (P=.055).

Conclusion RUDI with GSV-interposition for HFA offers acceptable patency rates after three years although re-interventions are frequently required. High immediate postoperative flows and young age are associated with recurrent high flow.

Introduction

Up to 4% of an average hemodialysis (HD) population harbouring autologous arteriovenous fistulas (AVFs) develops a high flow access (HFA, >2 L/min) over time. Furthermore, hemodialysis access-induced distal ischemia (HAIDI) is not infrequently occurring in the presence of a HFA.[1] Considering the ongoing shift from radial to brachial artery-based AVFs, HFA-incidence is expected to rise as elbow-based accesses are associated with increased risk on unacceptably high flows compared to accesses originating from smaller calibre forearm arteries.[2-5] It is thought that HFAs often remain asymptomatic.[6] However, increasing evidence shows that HFAs may contribute to heart failure development in HD-patients.[6-8] If flow reduction is indicated, various surgical procedures are available. In distal radial artery-based HFAs, proximal radial artery ligation (PRAL) might be considered.[9] In contrast, brachial artery-based HFAs may undergo venous outflow banding, effectively decreasing flow in the short term.[10] Although, median-term results demonstrated recurrent high flow in up to half of the banded patients within one year.[11,12]

An alternative method for flow reduction is termed revision using distal inflow (RUDI). This approach is popularised treating both HFA and HAIDI in brachial artery-based AVFs.[13] During RUDI, an interposition graft -e.g., greater saphenous vein (GSV) or polytetrafluorethylene (PTFE)- anastomosed to a forearm artery reduces access flow.[14] RUDI effectively reduced flow after one year follow-up, unless a basilic vein interponate was used.[15] Long-term efficacy and patency are unknown. The present study aimed to report on three-year RUDI patency and recurrence rates for HFA with or without HAIDI using GSV-interposition.

Material & Methods

Patients undergoing RUDI using GSV for a HFA in the upper arm with or without HAIDI in three Dutch hospitals (Máxima Medical Centre, MMC, Veldhoven; Maastricht University Medical Centre, Maastricht; Radboud University Medical Centre, Nijmegen) between March 2011 and October 2017 were studied retrospectively. One-year results of a part of the patients who underwent RUDI using different interponates (n=13) were published previously.[15] In the present cohort, RUDI was performed for three types of upper arm HFAs (brachiocephalic, BC-AVF; brachiobasilic, BB-AVF; Gracz-AVF).

Patients were included if they harboured a brachial artery-based AVF for HD with access flows exceeding 2 L/min on at least two consecutive measurements (or >1.5 L/min with overt signs of venous congestion or cardiac failure), and if they had received RUDI using GSV-interposition. Exclusion criteria were RUDI using non-venous interposition grafts, or radial artery transposition for HFA.

Each HFA-patient was additionally screened for signs of concomitant ipsilateral hand ischemia. A history and physical examination at the outpatient vascular department were performed including hand inspection and palpation of the radial and ulnar artery. When the presence of hand ischemia was likely, finger plethysmography was conducted (Vasoguard Nicolet 8 MHz, Scimet, Bristol, UK). HAIDI was diagnosed when one or more of the characteristic complaints (coldness, pain, cramps, loss of sensibility, diminished strength)[16,17] were reported and when the digital brachial index (DBI; ratio finger pressure to systemic pressure) was <0.6.[17-19] Unreliable DBI-values due to incompressible arteries were omitted. Hand ischemia was considered reversible (thus amendable to treatment) when access compression increased radial artery pulsations whereas DBI-values breached the ischemic threshold (DBI > 0.6).[20] HAIDI was graded in analogy to the Fontaine-classification as proposed in a recent consensus meeting.[21,22]

In one hospital (MMC), patients completed a hand ischemic questionnaire (HIQ). This questionnaire scores severity (0, none – 10, extreme) and frequency (0, never – 10, always) of the five cardinal symptoms of hand ischemia on a visual analogue scale. Subsequently, frequency and severity score per item are multiplied after which the five numbers are added up. Overall HIQ-scores range from 0 (no symptoms associated with hand ischemia) to 500 (maximal symptoms). HAIDI-patients often score >100 points whereas HIQ-scores are <50 in average HD-populations without ischemia.[23] Additional studies indicated that HIQ-scores reflect grade of ischemia and effectiveness of surgical HAIDI-revision.[10,24-26] In the present study, mean HIQ-scores per group (HFA vs. HAIDI/HFA) were calculated after the diagnosis HAIDI was confirmed or rejected by physical examination, medical history and DBI-measurements.

Each HFA-patient was discussed in a multidisciplinary meeting with a nephrologist, vascular laboratory technician, vascular surgeon, radiologist, and access-nurses. When required, a cardiologist was consulted. Once

the team decided upon performing RUDI, patients were informed on the procedures' specifics and consented verbally and in writing. The MMCs' ethics committee deemed that evaluation of the protocol was unnecessary as the study's aim was auditing of surgical results.

Operative protocol

GSV suitability was determined preoperatively using Duplex-analysis (diameter >3 mm). RUDI was essentially performed as suggested.[14] Patients underwent surgery in a day care setting under general anaesthesia. The AVF's venous portion on the upper arm was dissected close to the elbow anastomosis. A portion of the radial or ulnar artery at the proximal forearm was identified through a separate 5cm longitudinal incision. A 5-10 cm segment of the upper leg GSV was harvested. Some 2-4 cm downstream from the brachial artery anastomosis, the venous portion of the AVF was transsected. The venous stump on the brachial artery's side was ligated using 5.0 Prolene. The GSV was subsequently tunnelled as interposition graft between the radial (or ulnar) artery (end-to-side, 6.0 or 7.0 Prolene) and the upper arm access vein (end-to-end or end-to-side, 5.0 Prolene). The distance between the newly constructed arteriovenous anastomosis and the brachial artery bifurcation was approximately 4-6 cm.

Data collection, definitions, statistical analysis

Two groups of HFA-patients were identified. The HFA-group demonstrated access flows >2 L/min without evidence of concomitant hand ischemia. Conversely, the HAIDI/HFA-group showed subjective signs of hand ischemia with a DBI <0.6 in the presence of flows >2 L/min.

Data on demographics, initial AVF-type, surgery-associated complications, access flows, and re-interventions were obtained from local electronic patient files (EZIS 5.2, ChipSoft B.V., Amsterdam, the Netherlands; SAP 7.30, SAP SE, Walldorf, Germany; EPIC Hyperspace 2017, Epic Systems Corporation, Verona, USA; Diamant, Diasoft B.V., Leusden, the Netherlands; ProDB, MedVision Ag., Unna, Germany). This approach may have introduced selection bias as patients who refused RUDI or were considered unfit for surgery due to additional comorbidity were not studied.

Postoperative follow-up (FU) was standardly performed at the dialysis facilities by serial flow measurements (HD03, Transonic Systems IN, New York, USA) every 4-6 weeks as indicated by KDOQI.[27] Patients were discussed

in weekly multidisciplinary meetings as dictated by possible complications such as substantial changes in access flows or in case of complaints. If required, Duplex-sonography (e.g., in case of flow decrease) or Seldinger-angiography (if stenosis was likely) was performed or the patient was invited to visit the outpatient vascular department. Essentially, FU in RUDI-patients was identical to standard AVF-care.

To approximate potential loss to FU possibly introducing attrition bias, a follow-up index (FUI) was calculated following recent recommendations.[28] A complete FU-period lasted for three years. RUDI-status was determined at the end of October 2017. FU was terminated three years after RUDI-surgery or in case of secondary patency failure, death, AVF ligation or at October 31, 2017. Patients who had moved to another dialysis facility within the observation period were contacted and asked for permission to obtain data. Access flows depicted as >4 L/min (maximum of HD03 Transonic System) were scored as such.

Primary, assisted and secondary patency rates were defined as recommended.[29] An access was deemed 'recurrent HFA' when two consecutive flow measurements were >2 L/min. Time to recurrence was defined as number of weeks between RUDI and the first of two high flow measurements.

Statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Parameters were tested for normality and expressed as mean ±standard error of the mean (SEM). Survival was determined using Kaplan-Meier analysis and differences were analysed using Log Rank Mantel-Cox test. Group differences were determined using Mann-Whitney U test. Wilcoxon Log-Rank test was used for paired comparisons. Kruskal-Wallis was used for multiple group comparisons. Using binary logistic regression, possible predictors of recurrent high flow (recurrence yes/no) were identified. Proportions were compared using Fisher Exact-test and risk was expressed as odds ratio (OR) [95%-confidence interval]. P-values <.05 were deemed significant.

Results

Each of the three facilities accommodates between 85-110 chronic HD-patients and performs 100-200 access-related operations annually. During the observation period, 29 RUDI-procedures were conducted. Eight patients were excluded (interposition of PTFE, n=2 or cephalic vein, n=1; radial artery

transposition, n=3; HFA used for total parenteral nutrition, n=1; HAIDI with flow <2 L/min, n=1). Prior to RUDI, six patients had undergone unsuccessful revision for HFA or HAIDI (banding, n=3; side branch ligation, n=3).

The study population thus consisted of 21 patients undergoing RUDI using a GSV-interponate (7 females, mean age 54 years ±3; Table 1). Nineteen patients had flows >2 L/min whereas two had flows >1.5 L/min in presence of venous congestion. All but one were on HD >3 months whereas one patient was in pre-dialysis stage. Prior to RUDI, access flows of BC-AVF (n=8, 3230 mL/min ±363), BB-AVF (n=6, 3130 mL/min ±299) and Gracz-AVF (n=7, 2970 mL/min ±215) did not differ (P=.61).

Fourteen patients showed access flows >2 L/min without signs of HAIDI whereas seven had concomitant hand ischemia. Following AVF-compression, DBI-values of the HAIDI/HFA-group breached the ischemic threshold in all (DBI_{open} .48 ±.04 vs. $DBI_{compressed}$ .96 ±.07, P=.028; n=6, incompressible arteries n=1). Furthermore, the HFA-group displayed lower HIQ-scores compared to the HAIDI/HFA-group (HIQ_{HFA} 27 ±14, n=8 vs. $HIQ_{HAIDI/HFA}$ 115 ±30, n=7, P=.015). Age, gender, comorbidity rates, initial AVF-type or time between initial AVF-construction and RUDI were similar (Table 1).

In total, fifteen patients (71%) reported complaints possibly associated with the HFA (e.g., throbbing headaches with palpitations, exertional dyspnoea, hand ischemic complaints). Echocardiography was performed in seven of these. Only one patient with very mild symptoms showed dilated atria and decreased left ventricular ejection fraction (40%) possibly related to cardiac overload due to the AVF. Additionally, five showed evidence of left ventricular hypertrophy.

Table 1. Demographics of patients undergoing revision using distal inflow (RUDI) for high flow access (HFA) alone or combined with hemodialysis access-induced distal ischemia (HAIDI/HFA).

	Overall (n=21)	HFA (n=14)	HAIDI/HFA (n=7)	P-value
Age (years, mean ±SEM)	54 ±3	50 ±4	58 ±6	.30
Gender (male/female)	14/7	10/4	4/3	.64
Diabetes mellitus (%)	2 (10)	1 (7)	1 (17)	1.00
Peripheral arterial occlusive disease (%)	1 (5)	0 (0)	1 (14)	.33
Hypertension (%)	11 (52)	7 (50)	4 (57)	1.00
Coronary artery disease (%)	5 (24)	3 (21)	2 (29)	1.00
Type of AVF (BC/BB/Gracz)	8/6/7	7/4/3	1/2/4	N.A.
Time between AVF construction and RUDI (months, mean ±SEM)	44 ±12	44 ±11	43 ±30	.25
HAIDI grade (2a/2b/3/4)	N.A.	N.A.	4/2/1/0	N.A.

SEM, Standard error or the mean; AVF, Arteriovenous fistula; BC, brachiocephalic; BB, brachiobasilic; Gracz, outflow via both cephalic and basilic vein; N.A., Not applicable.

RUDI-configurations (artery-vein) were radio-cephalic (n=12), radio-basilic (n=5), ulnar-cephalic (n=2), ulnar-basilic (n=1) and brachial-cephalic (n=1). Immediately postoperative, flows were 2 L/min lower (3120 mL/min ±186 vs. 1170 ±87 mL/min, P<.001). Both pre- and postoperative flow in the HFA-group were higher than in the HAIDI/HFA-group (P<.05; Figure 1).

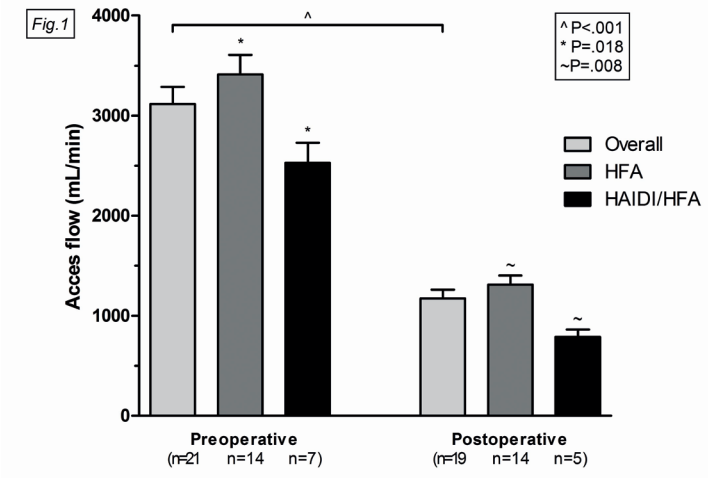

Figure 1. Mean access flows prior to revision using distal inflow (RUDI) and within 1 week after RUDI for high flow access (HFA, n=14) and high flow access with concurrent haemodialysis access induced distal ischaemia (HAIDI/HFA, n=7). Missing post-operative flows HAIDI/HFA group: failed RUDI, n=1; pre-dialysis patient n=1.

Three accesses (14%) occluded in the first postoperative week. Two were successfully revised using the GSV of the contralateral leg and by thrombectomy, respectively. The third was abandoned. Two others developed a hematoma at the GSV donor-site that healed conservatively. Wound infection or skin necrosis were absent. All patients were able to resume HD without temporary indwelling lines. One month after RUDI, one aneurysm of a venous stump was excised.

Overall primary patency rates after one, two, and three years were 71% ±10, 54% ±11, and 48% ±12, respectively. Rates differed between the HFA-group (93% ±7, 67% ±14, and 55% ±15) and the HAIDI/HFA-group (29% ±17 at each time point, P=.042; Figure 2A). One-, two, and three-year assisted patency rates were 76% ±9, 71% ±10, and 71% ±10 and differed between groups (HFA 100%, 92% ±8, and 92% ±8 vs. HAIDI/HFA 29% ±17, 29% ±17, and 29% ±17, P<.001).

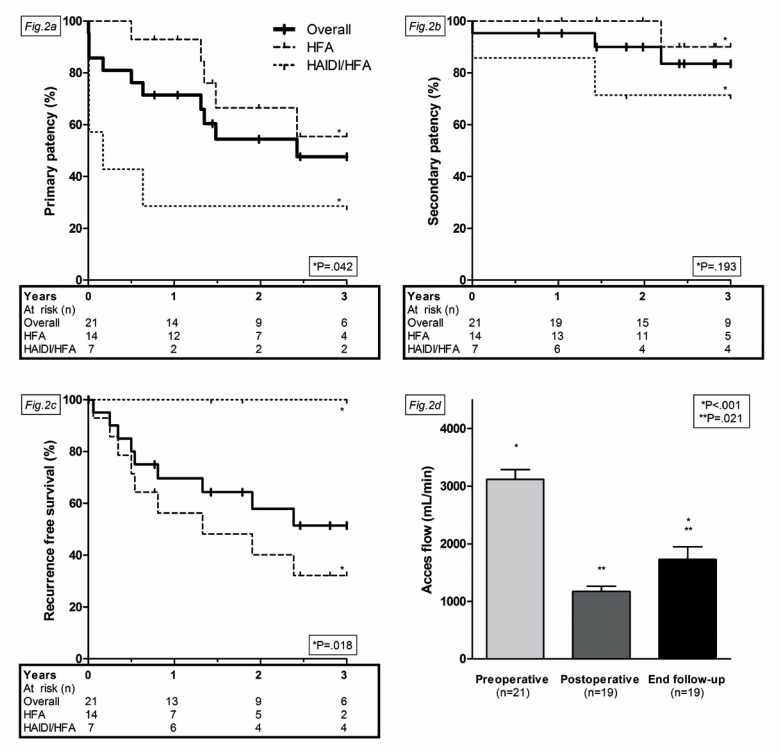

Figure 2. Kaplan-Meier analysis of patency and recurrence rates and flow development over time in 21 dialysis patients that underwent revision using distal inflow (RUDI) for high flow access (HFA) with or without hemodialysis access induced distal ischaemia (HAIDI/HFA). **(A)** Primary patency. **(B)** Secondary patency. **(C)** Recurrence free survival. **(D)** Mean access flow prior to RUDI, within 1 week after RUDI and at the end of follow up of secondary patency 28 months ±2 after the procedure.

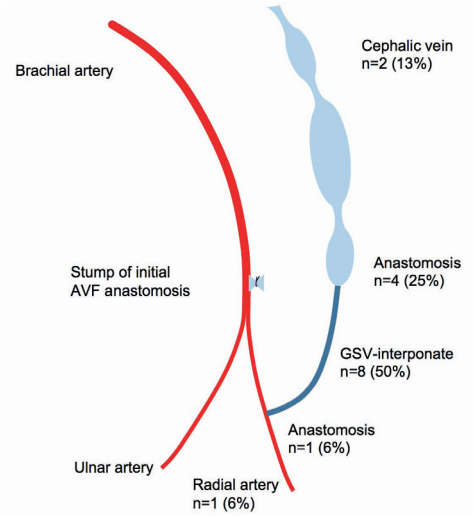

Figure 3. Schematic view of location of dilated stenosis sites, as seen during percutaneous transluminal angiography of arteriovenous fistulas (AVFs) after revision using distal inflow with greater saphenous vein (GSV) interposition.

Secondary patency rates (overall 95% ±5, 90% ±7, and 84% ±9) were similar (Figure 2B). During twelve angiographies in nine patients, sixteen percutaneous transluminal angioplasties (PTA) of significant stenotic lesions were performed. Half of these were found in the GSV-interposition conduit without involvement of either one of the two anastomoses (Figure 3). Furthermore, three patients underwent seven thrombectomies. In two of these, the GSV was replaced by PTFE-interposition during follow-up. Patients in the HFA-group had similar risks of undergoing PTA (HFA 5/14 vs. HAIDI/HFA 4/7; OR .42 [.07-2.66], P=.397) or thrombectomy (HFA 1/14 vs. HAIDI/HFA 2/7 OR .19 [.01-2.62], P=.247) compared to the HAIDI/HFA-group.

Recurrence free survival over three years (overall 70% ±10, 58% ±12, and 51% ±12) differed among both groups. The HFA-group showed rates of 56% ±14, 40% ±14, and 32% ±13 while no patient in the HAIDI/HFA-group developed recurrent high flow (P=.018; Figure 2C). After 28 ±2 months of FU, flows were 1400 mL/min lower compared to preoperative values (P<.001) but >500 mL/min higher than directly postoperative (P=.021; Figure 2D). Seven of nine patients with a recurrence were asymptomatic whereas the eighth patient developed severe cardiac failure following myocardial infarction. This patient chose to cease HD. The ninth patient with initial flows >4 L/min, high postoperative flow, and an early recurrence suffered from cardiac failure. His AVF was ligated but cardiac complaints did not diminish thereafter.

Gender, initial AVF-type, and comorbidities did not influence patency or recurrence of high flow (data not shown).

Patients with a recurrence demonstrated higher immediate postoperative access flows (1390 mL/min ±114 vs. 980 mL/min ±95, P=.016) and were 12 years younger than the non-recurrence group (46 ±3 years vs. 58 ±5 years, P=.055). Following correction for age (OR .951 [.878-1.030], P=.220), postoperative flow (OR 1.004 [1.000-1.007], P=.044) predicted onset of recurrence (R^2=.48) in a binary regression model (recurrence yes/no). Six of seven HAIDI/HFA-patients reported total recovery of hand ischemia after the procedure.

Due to complete data search, loss to follow-up was nihilated. Of the twelve patients with a FU shorter than 3 years, two had died with patent accesses, RUDIs failed in three additional patients whereas three others underwent ligation after successful renal transplantation. The final four patients underwent RUDI after October 2014, thus FU was terminated at October 31, 2017. Therefore, a FUI of 1.0 was attained with a mean FU of 28 ±2 months.

Discussion

Numbers of hemodialysis (HD) patients with an autologous arteriovenous fistula (AVF) developing a high flow access (HFA, >2 L/min) are expected to rise due to a contemporary shift favouring upper arm over wrist AVFs.[2] Flow reduction is advised as the systemic effects of HFA-induced cardiovascular overload may occasionally be detrimental. Banding, a previously recommended flow-reducing technique, is beneficial on the short term but high flow often recurs.[12] Most patients undergoing revision using distal inflow (RUDI) were still free of high flow after one year[15] but the efficacy of this technique is unknown beyond this time period. Aims of the present study were to investigate long-term rates of access patency and high flow recurrence after RUDI. To our knowledge, it is the first to report on these rates in a homogenous group of HD-patients harbouring an upper arm HFA undergoing RUDI using only the greater saphenous vein (GSV) as interposition conduit.

There is increasing evidence suggesting that RUDI offers optimal patency rates in treating both hand ischemia and HFA. For instance, one study demonstrated 78% three-year patency rates in patients with hand ischemia.[30] A second study found one-year 87% secondary patency

rates in 29 patients with hand ischemia or HFA.[13] A third study using PTFE-interponates reported 77% secondary patency rates after 16 months.[5] Conversely, one study in seven patients with hand ischemia showed failure rates well above 40% within eight months.[31] Our results indicate that the overall mid-long term (three year) access patency of RUDI for HFA using GSV is fairly good and well over 80%. However, as in all HD-patients harbouring an AVF, RUDI-patients require ongoing close flow surveillance as only half remained free of (endovascular) interventions.

It is unclear whether venous conduits used for RUDI are at risk for stenosis development. One study in maturing radiocephalic-AVFs indicated that most stenoses occur in the anastomotic area.[32] In brachiocephalic-AVFs, only 4% of stenoses occurred at the anastomosis itself while almost one quarter developed in the portion of the cephalic vein directly adjacent to the anastomosis.[33] In the present study, over 40% of the patients developed a stenosis. Moreover, half of these stenoses developed in a portion of the GSV away from both anastomoses. Furthermore, almost 40% occurred in the upper arm venous outflow tract including its anastomosis. Conversely, the arterial anastomosis was seldomly affected. If flow reduction occurs following RUDI, Duplex-analysis should especially focus on the GSV-interponate.

One may question whether performing RUDI for asymptomatic high flows (>2 L/min) without standardly examining cardiac function is indicated. However, ejection fractions may be preserved even in the presence of extremely high flows (>10 L/min).[34] Additionally, several studies showed that flows >2 L/min or a 'flow to cardiac output ratio' >0.3 are important predictors for the development of high-output cardiac failure[6,35] and that flows >2 L/min might confer serious hemodynamic consequences.[36] As a portion of our patients did report symptoms that were likely related to systemic overload, we feel that a quite aggressive attitude towards high flows was indicated.

HD-populations tend to have higher death rates compared to groups on peritoneal dialysis.[37] Furthermore, myocardial perfusion is chronically reduced in HD-groups.[38] Moreover, left ventricular hypertrophy was attenuated after AVF ligation in patients who successfully underwent renal transplantation.[39,40] During our study period, one patient with recurrent HFA suffered a myocardial infarction and heart failure leading to death after HD-cessation. This sequence of events can be regarded

as circumstantial evidence of the importance of durable flow reduction. Conversely, AVF ligation after transplantation in another patient with recurrent HFA and signs of heart failure did not alleviate symptoms of dyspnoea and orthopnoea. One might speculate that the heart failure did not exist -solely- due to the HFA. Alternatively, cardiac reserves may have been exhausted already due to very high flows prior to RUDI, a relative high postoperative access flow and early recurrence. Interestingly, none of the other seven patients with recurrent HFA developed cardiac overload. As the mean age of the recurrence group was relatively low, it is likely that it takes time before a HFA exhausts cardiac reserves.

A limited number of techniques are promoted for flow reduction of HFAs. Banding is suggested as a minimal invasive treatment option for high-output heart failure occurring in presence of high flow.[10] Unfortunately, half of the banded patients demonstrated recurrent high flow after one year.[12] The present one-year results demonstrate a two-third recurrence free survival indicating that RUDI does perform better at this time point, although direct comparisons are absent. However, one recurrence for every two RUDIs after three years is disappointing. Immediate high postoperative flow and young age, factors also identified in a previous study, predicted recurrence.[12] It may be concluded that the optimal flow reducing technique resulting in durable stable access flows is yet to be discovered.

Several limitations should be addressed. The study is relatively small and retrospective. Furthermore, the generally accepted 0.6 DBI ischemic threshold was challenged in a recent consensus meeting proposing a threshold of 0.4.[22] Patients who refused surgery or were considered unfit may have introduced selection bias, possibly leading to under- or overestimation of outcome measures. Moreover, the upper limit of our access flow equipment is 4 L/min, precluding accurate determination in some patients possibly having higher access flows. Finally, potential loss to follow-up may introduce attrition bias distorting results.[28] However, a follow-up index of 1.0 was attained in this retrospective study minimizing the risk on this type of bias.

In conclusion, the RUDI-technique using a portion of GSV offers favourable long term patency in HD-patients harbouring a brachial artery-based AVF with high flow but meticulous follow-up and maintenance are required. High immediate postoperative access flows and young age are associated with recurrent high flow.

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Chapter 3

Revision using distal inflow for high flow hemodialysis access alters arterial flow characteristics in the dialysis arm

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Abstract

Objectives Revision using distal inflow (RUDI) is currently proposed in patients on hemodialysis having a high flow access (HFA; >2 L/min) or hemodialysis access-induced distal ischemia (HAIDI). However, a recurrence of high flow or hand ischemia is not unusual in the years after RUDI. The aim of the present study was to describe changes in flow characteristics and arterial diameters in the dialysis arm after RUDI for HFA.

Methods Volume flow, diameter, peak systolic velocity and end diastolic velocity of the brachial artery (BA) were studied 2 and 12 months after RUDI using duplex imaging. In a portion of patients, these characteristics were also assessed at proximal and distal portions of radial and ulnar arteries (proximal forearm radial artery, distal radial artery, ulnar artery, and distal ulnar artery), and in the greater saphenous venous interponate. HFA patients were grouped according to presence of concomitant hand ischemia (HFA-HAIDI) or absence (HFA).

Results Fifteen patients (54 ±16 year old; 10 males; HFA-HAIDI, n=6; HFA, n=9) with a BA HFA (flow volume, 2740 ±322 mL/min) undergoing RUDI were studied between March 2011 and October 2016 in two Dutch hospitals. After 2 months, flow volume had decreased (1180 ±189 mL/min), but again increased at 12 months (1520 ±217 mL/min; P<.001). BA diameters did not change (7.4 ±0.5 mm), but proximal forearm radial diameters doubled (overall 2.6 ±0.2 mm to 5.4 ±1.0 mm; P<.001), albeit less prominent in HFA-HAIDI (+80%) than in HFA (+130%; P=.019). During follow-up, the distal ulnar artery peak systolic velocity in HFA-HAIDI (83 ±10 cm/s) was higher compared with the HFA group (54 ±5 cm/s; P<.01). Dilatation was not present in the greater saphenous venous interponate.

Conclusions RUDI for HFA reduction does not reverse BA dilatation, suggesting irreversible structural arterial wall damage possibly contributing to recurrent high flow. Radial artery remodelling is attenuated in HFA patients previously reporting concurrent hand ischemia diminishing the likelihood of high flow recurrence in this subgroup.

Introduction

Brachial artery-based arteriovenous fistulas (BA-AVFs) in hemodialysis (HD) patients occasionally develop high flow (high flow access [HFA]; >2 L/min) challenging cardiac function in the long term.[1,2] Ongoing high flows may also progressively compromise HD hand perfusion, leading to hemodialysis access-induced distal ischemia (HAIDI).[3] Current guidelines advise flow reduction by revision using distal inflow (RUDI) or venous outflow banding, particularly if cardiac complaints or HAIDI are present.[4] During RUDI procedures, access flow is diminished by inserting a piece of vein or graft that is connected to a proximal portion of a forearm artery.[5] Although RUDI is an effective flow-reducing technique in the short term,[5-7] follow-up studies found that flows tended to increase over time. After 3 years, one-half of the RUDI patients demonstrated recurrent high flow mandating lifelong access surveillance. However, patients with HFA and HAIDI did not develop recurrent HFA in 3 years.[8]

The processes playing a role in HFA recurrence after RUDI are poorly understood. Relatively high access flows directly after flow-reducing surgery and young age were associated with early recurrences.[8,9] Increased wall shear stress affecting the new inflow artery leads to nitric oxide release and vascular dilatation promoting flow augmentation. This vicious circle may sooner or later result in HFA recurrence.[10-12]

It is unknown to what extent RUDI influences flow characteristics in the HD arm. The aim of the present study was to describe changes in flow velocities and diameters of the arterial vasculature of the HD arm in the first year after RUDI. Studying these phenomena may aid in understanding the mechanisms contributing to HFA recurrence. We hypothesized an initial decrease of BA blood flow accompanied by flow-mediated diameter decrease, possibly followed by slight increases in both parameters. Additionally, gradual increases of inner lumen diameters of both proximal radial artery and greater saphenous venous (GSV) interponate were hypothesized.

Methods

The study was performed in two Dutch hospitals (Máxima Medical Centre, Veldhoven; Maastricht University Medical Centre, Maastricht). Approximately 100 patients receive chronic HD in each facility.

When construction of a radiocephalic AVF is deemed impossible as judged by preoperative duplex imaging, a BA-AVF is created following recommendations.[4] To prevent HFA development, efforts are made to limit the BA-based arteriovenous anastomosis,[13] ideally not >5 mm. Access flows are routinely monitored using two-needle dilution techniques every two months (HD03, Transonic Systems Inc, New York, NY).[14]

Patients were recruited between March 2011 and October 2016. They were considered eligible if they had a BA-based HFA, defined as an access with dilution flows exceeding 2 L/min on two or more consecutive measurements (or >1.5 L/min with signs of cardiac failure) and if they underwent a technically successful RUDI using a stretch of GSV. Patients who received RUDI using non-venous interposition grafts were excluded because an anticipated dilation of the GSV with subsequent changes in arterial flow characteristics upstream would be absent in a graft, potentially introducing bias. Radial artery transpositions were also excluded.

Patients were additionally screened for symptoms (coldness, pain, loss of strength, cramps and/or sensibility changes) and signs (diminished radial artery pulsations returning after access compression) associated with HAIDI at the outpatient vascular clinic. Digital brachial index (DBI) analysis using digital plethysmography was performed and DBIs of less than 0.6 were considered consistent with HAIDI.[15-18] Furthermore, patients completed a hand ischemic questionnaire (HIQ) which scores frequency (from 0 [never] to 10 [always]) and severity (from 0 [none] to 10 [extreme]) of the five cardinal symptoms using a numeric rating scale (from 0 [no ischemia] to 500 [maximal ischemia]). Scores of greater than 60 are associated with HAIDI.[15,19] Successful flow reducing surgery in HAIDI patients with mean scores of 153 ±33 resulted in scores of less than 60,[10] values also obtained in a general HD population not reporting hand ischemia.[15] Moreover, HIQ scores were inversely related to DBIs.[20] In this study, HIQ scores per subgroup were calculated after the diagnosis HAIDI was rejected or confirmed (and graded) based on medical history, physical examination and DBI measurements. HAIDI was graded according to the modified Fontaine classification as proposed by Inston et al following a consensus meeting.[21,22] Two groups were formed according to presence or absence of HAIDI. The first group had a HFA with concomitant HAIDI whereas the second group had a HFA without hand ischemia.

Each HFA patient was discussed in a weekly multidisciplinary meeting attended by nephrologists, a radiologist, vascular surgeon, vascular laboratory technician, and access team nurses. Once decided on performing RUDI, patients were informed on the operative specifics and consented verbally and in writing. All study procedures were in accordance with the ethical standards of our institutional research committees and with the declaration of Helsinki. The rules laid down in the Medical Research Involving Human Subjects Act did not apply to the study protocol as duplex analysis is considered a stress-free non-invasive imaging modality. The present analysis was considered auditing of surgical results.

Operative protocol

Suitability of the GSV (diameter >3 mm) and proximal radial (or ulnar) artery (diameter ≥2 mm) was determined using duplex analysis. Surgery was performed in a daycare setting under general anesthesia as reported elsewhere.[5,6] A portion of the radial artery in the proximal forearm was identified through a 5-cm longitudinal incision. A 5- to 10-cm long segment of upper leg GSV was harvested and anastomosed to the radial artery. The upper arm venous portion of the BA- AVF was dissected close to the elbow anastomosis (Figure 1A). Approximately 2 to 4 cm downstream from the original anastomosis, the AVF's venous portion was transsected followed by ligation of the venous stump on the BA side (Figure 1B). The GSV was subcutaneously tunnelled as an interposition graft between radial artery (end-to-side) and the upper arm access vein (spatulating end-to-end; Figure 1C). The distance between the newly constructed arteriovenous anastomosis and the BA was between 4 and 6 cm. The 3-year patency and HFA recurrence rates in a portion of these patients were reported elsewhere.[8]

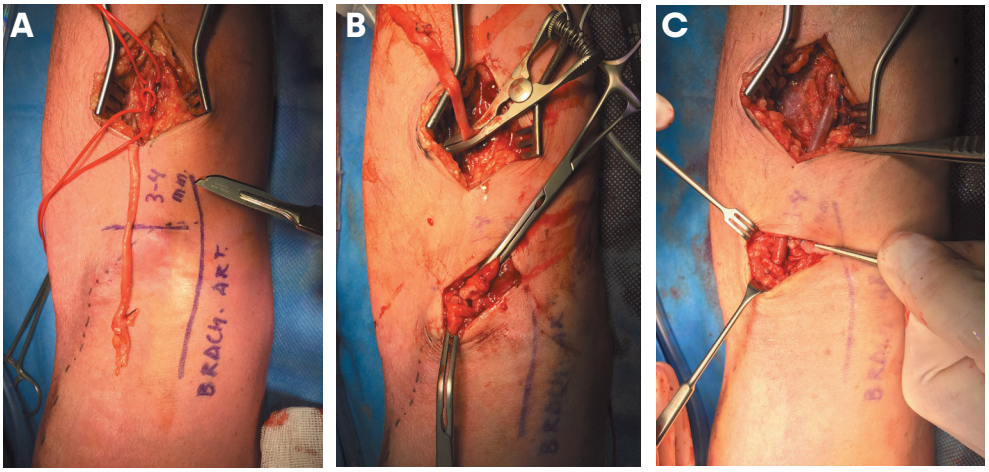

Figure 1. Revision using distal inflow (RUDI), operative procedure. **(A)** The greater saphenous vein is harvested and **(B)** anastomosed to the dissected radial artery. The venous portion of the initial arteriovenous fistula (AVF) is transected through a separate incision and the venous stump on the brachial artery (BA) is ligated. **(C)** The greater saphenous vein is tunnelled and anastomosed to the original venous outflow tract.

Serial duplex analysis

Duplex sonography (Aplio-XG Diagnostic Ultrasound System SSA-790A; Toshiba America Medical Systems, Inc, Tustin, Calif) was performed before HD sessions at room temperature by one highly experienced vascular technician per facility. Patients were seated in upright position, the arm on a cushion and the elbow at a 45° angle. The probe was aligned longitudinally in a 60° angle relative to the midarm BA point. Peak systolic velocity (PSV) and end diastolic velocity (EDV) were obtained using dedicated settings of the duplex device. Inner arterial lumen diameter was determined with the probe perpendicularly and transversally relative to the vessel. Flow volume was calculated using standard formulas.

In a portion of patients, the PSV, EDV, and diameter of the proximal forearm radial artery (P_{RAD}) and ulnar artery (P_{ULN}) were obtained, approximately 3 cm distal to the elbow-fold. Similar measurements were obtained at the distal radial (D_{RAD}) and distal ulnar artery (D_{ULN}) 3 cm proximal to the wrist fold. Measurements were repeated about 2 and 12 months after RUDI. P_{RAD} data were then obtained just upstream from the newly constructed RUDI anastomosis.

Statistics

Statistical analyses were performed using SPSS 24.0 (IBM-SPSS Inc, Chicago, Ill). Baseline characteristics were displayed as mean ±standard deviation or counts (percentages). Study parameters were tested for normality and expressed as mean ±standard error of the mean. Antegrade flows were displayed as positive values, retrograde flow as negative values. Missing values were imputed using stochastic single imputation for parameters of which at least one follow-up measurement was performed. Imputation prevents lack of precision and decreases likelihood of biased estimates. Patterns of changes in flow volume, flow velocity, and diameter were analysed using repeated measures analysis of variance, as were group differences (HFA-HAIDI vs. HFA) over time. Bonferroni correction was used for multiple pairwise comparisons. The Fisher exact test was used to address differences in group proportions. Mann-Whitney U test was used to analyse possible group differences when analysis of variance was not feasible. A P value of less than .05 was considered significant.

Results

Eighteen HFA patients underwent a successful RUDI procedure during the 5.5-year inclusion period (Máxima Medical Centre, n=13; Maastricht University Medical Centre, n= 5). Duplex studies were performed in 15 individuals (10 males [54 ±16 years]; refused participation, n=3; Table 1). Fourteen were on active HD. Patient 15 was in a predialysis stage. Six HFA patients were diagnosed with concomitant HAIDI (HFA-HAIDI group), nine only had HFA (HFA group). Three HFA-HAIDI-2a patients suffered from congestion and/or palpitations with fatigue, respectively. Four of nine HFA patients had congestion, chest tightness, and/or exertional dyspnea while access flows ranged from 3.5 to greater than 4.0 L/min. Two other patients (HFA-HAIDI, n=1; HFA, n=1) had undergone cardiac surgery after a myocardial infarction in the past (access flows of 2.9 and >4 L/min, respectively). The remaining four HFA patients did not report cardiac symptoms but displayed flows well above 2 L/min.

Table 1. Characteristics of patients undergoing revision using distal inflow (RUDI) for high flow access with hemodialysis (HD) access-induced distal ischemia (HFA-HAIDI) or without (HFA).

	HFA-HAIDI (n=6)	**HFA** (n=9)	**Total** (n=15)
Age (yr, ±SD)	60 ±17	51 ±16	54 ±16
Gender (Male / Female)	3 / 3	7 / 2	10 / 5
Hypertension (%)	5 (83)	5 (55)	10 (67)
Diabetes Mellitus (%)	1 (17)	1 (11)	2 (13)
Peripheral Arterial Occlusive Disease (%)	2 (33)	0 (0)	2 (13)
Coronary Artery Disease (%)	1 (17)	1 (11)	2 (13)
Type of index fistula (BB / BC / Gracz)	3 / 2 / 1	2 / 4 / 3	5 / 6 / 4
AVF-age at RUDI (months, ±SD)	45 ±63	37 ±36	41 ±47
HAIDI-Grade 2a/ 2b/ 3/ 4	4 / 1 / 1 / 0	N.A.	N.A.
HAIDI-questionnaire score (±SEM)	100 ±31	3 ±2 *	61 ±24
Digital brachial index (±SEM)	.48 ±.04	.72 ±.06 *	.60 ±.05

*P≤0.01. No significant differences among other parameters. SD, standard deviation; BB, brachiobasilic; BC, brachiocephalic; N.A., not applicable

Preoperative echocardiography was performed in 7 of 15 patients. One displayed a diminished left ventricular ejection fraction (LVEF) while congestive complaints were mild. Unfortunately, this patients' LVEF deteriorated further during follow-up. Echocardiography in a second asymptomatic patient having a flow of 3.4 L/min demonstrated globally attenuated pump function. In a third patient with fatigue and palpitations, the cardiologist deemed that complaints were likely related to the hyperdynamic circulation without the presence of structural deviations. In the other 12 patients, neither cardiac nor pulmonary pathology was present after a workup performed at the nephrologists' discretion. No patient other than the one with ongoing deterioration of LVEF reported cardiac complaints within 1 year of RUDI. Dialysis efficacy was not adversely affected. Temporary indwelling lines were not required. RUDI configurations were radiocephalic (n=10), radiobasilic (n=4), and ulnar-cephalic (n=1). Data of the first two study points (before RUDI, 2 months postoperatively) were complete in all. However, 1-year duplex measurements were missing in three patients (renal transplantation, moved away, refused; all n=1). All patients underwent duplex BA measurements and 10 also underwent lower arm arterial and GSV measurements.

Mid-upper arm BA

Before RUDI, BA volume flows were greater in HFA (3350 ±395 mL/min) compared with HFA-HAIDI (1820 ±270 mL/min). Two months post-operatively, flows had decreased in both groups followed by a gradual increase at 1 year (Figure 2A; P<.001). Similar patterns were observed in PSV and EDV (Figure 2B) without differences between HFA-HAIDI and HFA patients. BA diameters did not change (7.4 ±0.5 mm).

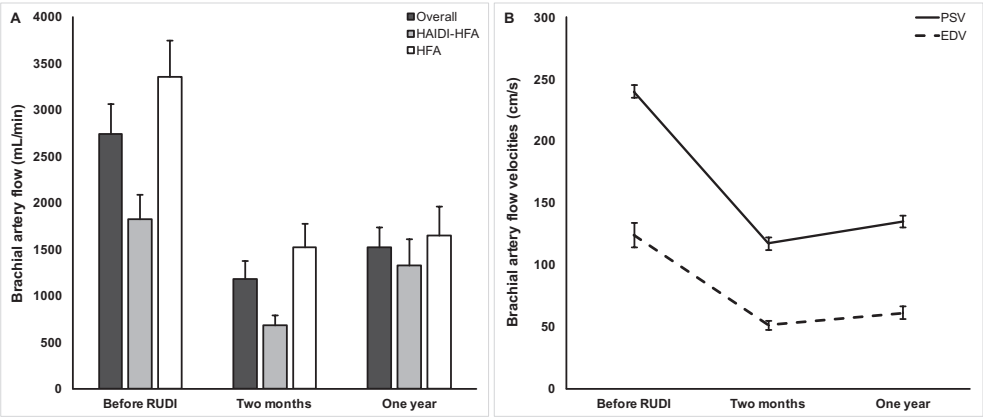

Figure 2. Volume flow and flow velocities in the brachial artery (BA) after revision using distal inflow (RUDI). **(A)** Patients with high flow access (HFA) with hemodialysis (HD) access-induced distal ischemia (HFA-HAIDI) displayed lower BA flows compared with patients without presence of concomitant hand ischemia (P=.015). Overall, follow-up values both differed from baseline measurements (P<.050) but not from each other (P=.053). **(B)** Peak systolic velocity (PSV) and end diastolic velocity (EDV) in the BA before and following RUDI displaying a pattern comparable to volume flow over time (both P<.001) without difference between HFA-HAIDI and HFA patients.

Proximal forearm arteries

After RUDI, both P_{RAD}-PSV and P_{RAD}-EDV greatly increased and stabilized (Figure 3A; both P=.002) without a difference between HFA-HAIDI and HFA patients. The P_{RAD} diameter increased, but a significant difference (P=.019) between the groups indicated that the remodelling capacity was less in patients with concomitant hand ischemia (Figure 3B). In one HFA-HAIDI patient, duplex imaging displayed radial arterial calcifications. In contrast, evidence of intimal thickening or calcification was not observed in the other 14 patients during duplex imaging or surgery.

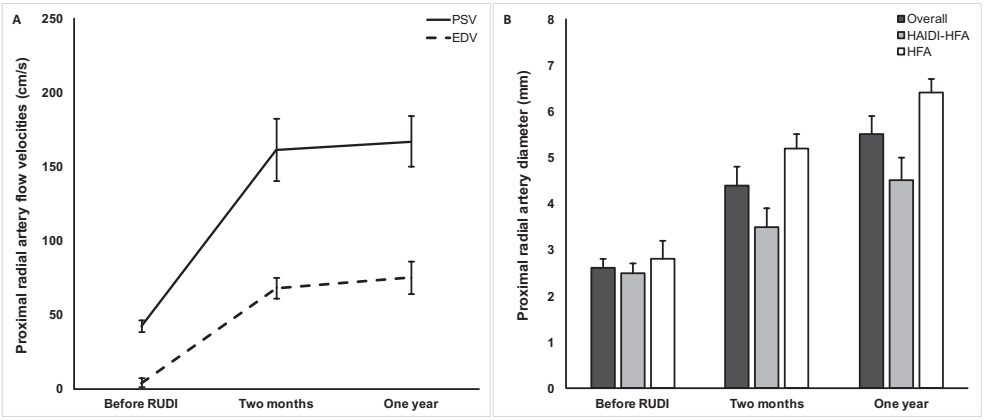

Figure 3. Proximal radial artery peak systolic velocity (PSV), end diastolic velocity (EDV), and diameter after revision using distal inflow (RUDI). **(A)** Increases in PSV end EDV (both P=.002) were similar between high flow access (HFA) with hemodialysis (HD) access-induced distal ischemia (HFA-HAIDI) and patients without presence of concomitant hand ischemia. **(B)** Inner lumen diameter continued to rise significantly (P<.001), although patients with HFA-HAIDI showed less increase compared with patients with HFA (P=.019).

Before surgery, one HFA-HAIDI patient demonstrated alternating flows (antegrade PSV, toward the hand; retrograde EDV, toward the elbow) in P_{ULN} and PRAD and a second HFA-HAIDI patient displayed alternating flows in P_{ULN} and absent flow in D_{ULN}. In a third HFA-HAIDI patient, both proximal arteries showed antegrade flows while no flow was found in the D_{ULN}. All other 12 patients had antegrade flows in the proximal forearm arteries. P_{ULN}-PSV (before RUDI 51 ±8 cm/s) tended to increase at 2 months (75 ±10 cm/s) and to decrease after 1 year (64 ±9 cm/s; P=.176). P_{ULN}-EDV followed a similar although significant pattern (Figure 4). Retrograde P_{ULN}-EDV in two patients became antegrade after RUDI. P_{ULN}-diameter remained stable in both groups (3.3 ±0.4 mm).

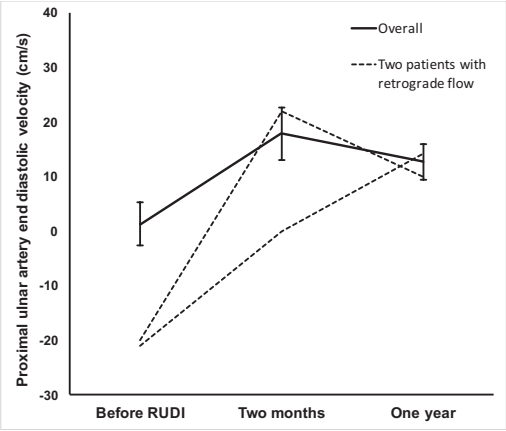

Figure 4. Proximal ulnar artery end diastolic velocity (EDV) after revision using distal inflow (RUDI) showed a significant increase, after which it remained stable (P=.021). Dashed lines represent two patients with previous retrograde EDV. Differences between high flow access (HFA) with hemodialysis (HD) access-induced distal ischemia (HFA-HAIDI) and patients without presence of concomitant hand ischemia were absent (P=.603).

Distal forearm arteries

Mean D_{RAD}-PSV and D_{RAD}-EDV remained unchanged. However, four of six HFA-HAIDI patients demonstrated retrograde PSV somewhere during follow-up compared with none of the HFA patients (P=.076). No HFA-HAIDI patient reported recurrent symptoms of ischemia, whether or not they had retrograde flow in D_{RAD}. When D_{RAD}-PSV was retrograde, D_{ULN}-PSV was higher (99 ±16 cm/s vs. 59 ±5 cm/s; P<.01) compared with time points when D_{RAD}-PSV was antegrade. D_{RAD}-diameter increased from 1.9 ±0.1 mm to 2.4 ±0.1 mm at 1 year (P=.035) without group difference (P=.309).

Both D_{ULN}-PSV and -EDV first increased, followed by a slight decrease (Figure 5). During follow-up, D_{ULN}-PSV was higher in HFA-HAIDI patients (83 ±10 cm/s) compared with HFA patients (54 ±5 cm/s; P<.01). Flow in D_{ULN} was absent in two HFA-HAIDI patients before RUDI but emerged during follow-up. D_{ULN} diameters tended to increase gradually (before RUDI, 1.6 ±0.3 mm; at 1 year, 2.4 ±0.2 mm; P=.251) without differences between groups (P=.109). An overview of the most important changes in the arterial system of the HD arm following RUDI is shown in Figure 6.

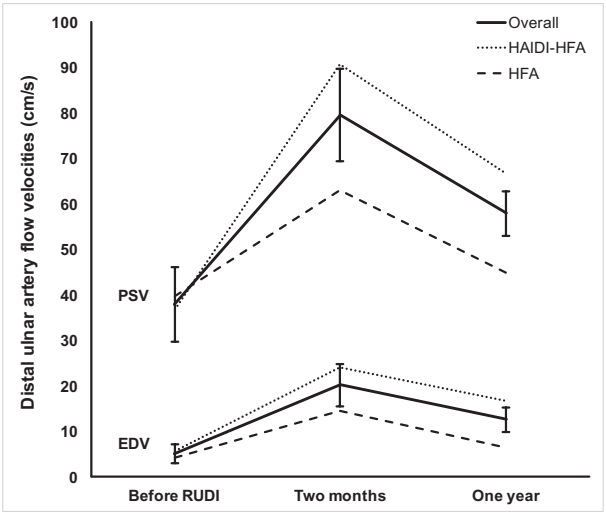

Figure 5. Distal ulnar artery flow velocities both increased after revision using distal inflow (RUDI) followed by a slight decrease (peak systolic velocity [PSV] and end diastolic velocity [EDV]; both P <.02).

GSV interponate

Intense turbulence precluded reliable flow velocity measurements at the GSV interponate. The PSV varied between 100 and 500 cm/s and the EDV between 50 and 350 cm/s. GSV diameters were stable over the year (4.0 ±0.2 mm). Aneurysmatic degeneration of the venous conduit or at anastomoses was not observed clinically at the 1-year follow-up or beyond. An overview of most important study findings is listed in Figure 6.

Discussion

Recent guidelines advise flow reduction for HFA patients who suffer from cardiac complaints or HAIDI.[4] Several studies documented the short term effect of RUDI for reduction of high flow (>2 L/min) BA-AVFs.[5-7] The long-term efficacy of RUDI and other techniques are questioned. For instance, within 1 year, high flow was again observed in one-half of banded AVFs.[9] RUDI performed slightly better because HFA recurrence was demonstrated in one-half of the patients after 3 years.[8] Driving processes of recurrent high flow after flow- reducing surgery are unknown. The aim of this study was to describe patterns of flow velocities and diameters in the arterial vasculature of a HD arm after RUDI. Studying these phenomena may aid in understanding the mechanisms contributing to recurrent high flow.

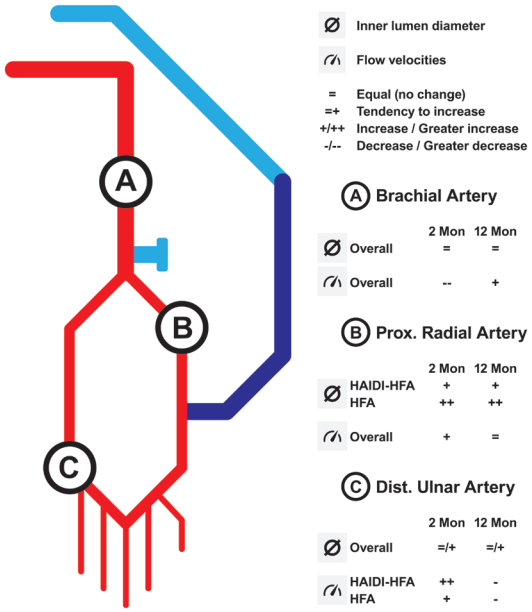

Figure 6. Changes in arterial diameters and flow velocities 2 and 12 months following revision using distal inflow for high-flow hemodialysis access. HFA, High flow access; HAIDI-HFA, high flow access with hemodialysis access induced distal ischemia.

Immediately after AVF construction, the acute decrease in local vascular resistance and the subsequent decrease in the arm's blood pressure signals for an increase in BA flow rates. The vascular endothelium releases nitric oxide and other endothelium-dependent relaxing factors dilating BA aimed at normalizing augmented levels of local shear stress.[23] In one study, 6 months after AVF construction, BA flows were 13 times higher compared with preoperative values and BA diameters had dilated by 50% from 4.3 to 6.4 mm.[24] In the present population of HFA patients, which was studied more than 3 years after AVF creation, BA diameters had almost doubled to more than 7 mm. It was hypothesized that RUDI would lead to a reversal of these events resulting in BA diameter reduction because flow, and thus wall shear stress, would decrease.[25,26] In contrast, BA diameters remained stable, suggesting an irreversibly exhausted capacity for remodelling of the BA wall. Earlier reports described ongoing enlargement in arteries feeding accesses that were not being used for HD anymore, even more than 10 years after transplantation. BA expansion was progressive even in patients with spontaneously occluded accesses, albeit at lower rates.[27] Additionally, it was demonstrated that aneurysmatic degeneration of the

BA might be stimulated by access ligation, possibly owing to increased peripheral vascular resistance.[28,29] Studies on traumatic and congenital AVFs showed that closure of longstanding fistulas did reverse cardiac enlargement, but not arterial dilatation.[30-32] AVFs existing more than 1 to 2 years were found to exhaust the remodelling capacity of the proximal arterial segment. Surgical correction was no longer likely to reverse this dilatation,[30,33] probably owing to irreversible fragmentation of elastic fibers by metalloproteinases, leading to ongoing degeneration of the arterial wall.[30-32] A possible relation between height of AVF flow and the rate at which the remodelling capacity is exhausted has yet to be established. If higher flows are more potent in diminishing the arterial walls' capacity to shrink compared with lower flows, one may argue that flow reduction could be advised at an earlier stage. This is even more imminent if a similar phenomenon of impeded remodelling capacity holds for other arteries, such as the coronary vasculature in these HFA patients.

In RUDI, a proximal portion of the radial artery is used as the preferential inflow source of the disconnected upper arm venous outflow tract of the HFA.[5-7] The present study hypothesized that the anastomosis between this artery and the GSV interponate would result in loss of blood pressure along the radial artery due to decreased resistance. Subsequent augmented flows and shear stress were thought to dilate this artery.[34] One year after RUDI, PSV was three to four times higher and P_{RAD} diameters had indeed more than doubled compared with preoperatively. Interestingly, this increase in diameter was significantly attenuated in HFA patients with concomitant HAIDI compared with HFA patients without hand ischemia (+80% vs. +130%; P<.05). This difference occurred independent of risk factors associated with HAIDI (e.g., diabetes mellitus, peripheral arterial occlusive disease) because these rates were similar in the two groups. Low numbers of diabetes in our sample suggest a protective effect of this metabolic disorder for high flow development, as suggested elsewhere.[3,9,35] One might question why some patients did develop HAIDI in the first place, because rates of known risk factors were surprisingly low. HAIDI may exist due to an imbalance between protecting factors (e.g. younger age, smaller calibre arteries) and predisposing factors (e.g., diabetes mellitus, female sex, BA-AVF) leading to digital hypoperfusion.[21] Moreover, HFA-HAIDI patients may have harboured stiffer, less compliant arteries (e.g., owing to smoking, tendency to older age, physical inactivity,[36] hyperlipidemia, or higher uraemia levels).[37,38] Combined with high flows, this stiffness might have

led to impaired perfusion of the HD hand.[18] The diminished forearm artery capacity to adapt to increasing flows and thus, in turn, lower rates of high flow recurrence in HFA-HAIDI patients compared with HFA-only patients[8] might also be a consequence of such stiffer arterial walls. However, neither arterial compliance nor stiffness measurements (e.g., brachial-ankle pulse wave velocity or radial arterial applanation tonometry) were performed.[36]

RUDI is predominantly advocated for HFA, but is also proposed in patients with HAIDI.[39] The most important mechanism explaining an improved hand perfusion after RUDI is distalization of the anastomosis toward the radial artery restoring flow into the ulnar artery. Additionally, the blood pressure loss at the radial artery anastomosis in the proximal forearm after RUDI is smaller when compared with the loss of blood pressure at the BA anastomosis. The role of reversal of blood flow direction (steal) in forearm arteries as potential cause of HAIDI owing to BA-AVFs is controversial. Duplex analysis in patients with severe HAIDI found lower PSV and EDV in radial arteries compared with controls without hand ischemia. However, whether radial arterial flow was antegrade or retrograde was irrelevant with respect to HAIDI.[40] The present study sought to determine if RUDI resulted in altered blood flow direction in the forearm vasculature. In HFA-HAIDI patients with a previous antegrade flow in the distal radial artery, PSV in the distal ulnar artery more than doubled to 90 cm/s at 2 months after RUDI, most likely to compensate for an imminent loss in hand perfusion after compromised radial artery perfusion pressures and possible retrograde D_{RAD} flow. Recurrent HAIDI was not reported by any during follow-up. It is concluded that RUDI for HFA patients with hand ischemia is effective in reversing HAIDI, but only if the ulnar artery is likely patent as demonstrated by preoperative duplex scanning, possibly after access compression. The role of the interosseous artery as a potential collateral was not determined.

In our experience, flow reduction for HFA using banding occasionally resulted in dilatation of a portion of the venous outflow in proximity to the anastomosis. This dilatation was progressive in some patients, leading to unacceptably high flow recurrence rates and aneurysms requiring surgical excision. In the present study, it was questioned if recur- rent high flow after RUDI was possibly due to dilatation of the GSV interponate. However, GSV diameters remained stable in the first postoperative year. Aneurysmal deformation was also not detected in any of the patients. Because flow

in the GSV interponate was very turbulent, this portion of the access is at risk for stenosis. If access flow is rapidly decreasing in patients after RUDI, duplex should especially focus on the GSV interponate.[8]

One may argue that performing RUDI for asymptomatic HFA is not indicated, especially when echocardiographic imaging is not performed. However, access flows of greater than 2 L/min may confer serious hemodynamic consequences,[3] whereas several studies showed that such flows or access flow to cardiac output ratios of greater than 0.3 are important predictors of high-output cardiac failure,[1,2,12] which is associated with limited survival.[41] Furthermore, echocardiography may be entirely normal, even with extremely high flows (>10 L/min).[42] Because flow-reducing surgery attenuates HAIDI,[3,13] its presence may tip the balance toward opting for surgery in HFA patients. Because several of our patients did suffer from complaints likely related to the HFA, we were convinced that an aggressive strategy toward high flows was justified at the time of study. Recent articles suggest that flows may be indexed to estimate the risk of high-output cardiac failure and mortality. One could, for example, correct for cardiac output,[43] height$^{2.7}$ or body surface area.[44] In the current study which started in 2011, access flows were not indexed nor were cardiac output measurements performed standardly. Although we believe indexing access flow is key in HFA management, especially in asymptomatic patients, the best indexing method is yet to be determined.

The present prospective study suffers from shortcomings including small sample size and low statistical power. HFA controls not receiving surgery were not included. Some data points were missing (<10%) requiring statistical imputation. Postoperative measurements of DBI would have allowed for determining relationships with altered flow velocities but were not included. Furthermore, the 0.6 DBI cut-off value was challenged in a recent consensus meeting proposing a threshold of 0.4.[22] Standardized collection of data on cardiac function and dialysis efficacy before and after RUDI would have been of added value, but are lacking. However, all patients continued HD uninterruptedly, and temporary indwelling lines were not required indicating that dialysis performance was not affected. Cardiac output measurements with open and compressed access were not performed, but may prove useful in future studies. In hindsight, RUDI using a graft (n=2 during the study period) could have been included, but at the expense of risk of bias.

Conclusions

One year after RUDI for flow reduction of an elbow-based autologous HFA, brachial arteries were still dilated, re-establishing earlier reported permanently impaired remodelling capacity. Radial artery dilatation following RUDI is slower in HFA patients also suffering from HAIDI. RUDI increases flow rates in the ulnar artery compensating for an imminent loss in hand perfusion after the loss of radial artery perfusion pressure.

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Chapter 4

Access flow volume (Qa) and survival in a haemodialysis population: an analysis of 5208 Qa measurements over a 9-year period

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Abstract

Objective Aim of the study was to determine associations between characteristics of arteriovenous access (AVA) flow volume (Qa, mL/min) and four year freedom from cardiovascular mortality (4yr-CVM) in hemodialysis (HD) patients.

Methods HD patients who received a primary AVA between January 2010 and December 2017 in one center were analysed. Initial Qa was defined as the first Qa value obtained in a well-functioning AVA by a two-needle dilution technique. Actual Qa was defined as access flow at a random point of time. Changes in actual Qa were expressed per 3-month periods. CVM was assessed according to the ERA-EDTA classification. The optimal cut-off point for initial Qa was identified by a receiver operating characteristic curve. A joint modelling statistical technique determined longitudinal associations between Qa characteristics and 4yr-CVM.

Results A total of 5208 Qa measurements (165 patients, male n=103; age 70±12 years, autologous AVA n=146, graft n=19) were analysed. During follow-up (Dec 2010-Jan 2018, median 36 months), 79 patients (48%) died. An initial Qa <900 mL/min was associated with an increased 4y-CVM risk (HR: 4.05; 95% CI [1.94-8.43], P<0.001). After 4 years, freedom from CVM was 34% lower in patients with a Qa <900 mL/min (53 ±7% vs. Qa ≥900 mL/min: 87 ±4%, P<0.001). An association between increases in actual Qa over 3-month periods and mortality was found (HR: 4.48 per 100 mL/min, 95% CI [1.44-13.97], P=0.01) indicating that patients demonstrating increasing Qa were more likely to die. By contrast, actual Qa per se was not related to survival.

Conclusions Studying novel arteriovenous access Qa characteristics may contribute to understanding excess CVM in HD patients.

Introduction

A minimum of 400-600 mL/min flow volume (Qa) is required in an arteriovenous vascular access (AVA) for effective hemodialysis (HD) in patients with chronic kidney disease (CKD) requiring renal replacement therapy (RRT).[1] In some patients, serial surveillance measurements of Qa ('actual' Qa) may detect values >1500 mL/min occasionally leading to a high flow AVA.[2] Persistent exposure to high Qa may possibly overload the cardiovascular system and challenge cardiac function.[3,4] Conversely, Qa reductive measures may attenuate these potential detrimental sequelae.[5]

Survival of a HD population is limited due to excessive rates of cardiovascular mortality (CVM).[6] One may hypothesize that long term exposure to a high actual Qa may contribute to inappropriately high CVM rates, but the available data are contradictory. For instance, an association between high output cardiac failure (HOCF) and presence of a AVA was suggested.[7] Another study found that HD patients demonstrating an actual Qa >1000 mL/min had a lower death rate compared to patients with a Qa <1000 mL/min.[8] Moreover, a possible relation between a first Qa ever measured in a matured AVA ('initial' Qa) and CVM is unknown. Therefore, associations between Qa and freedom from CVM are complex and currently unclear.[9]

KDOQI guidelines advise to routinely check the status of an AVA by physical examination supplemented by actual Qa surveillance.[1] Most authors investigating possible associations with CVM used just one (or a limited number of) actual Qa reading(s).[8,10] However, efforts towards identifying potential relationships between serial actual Qa or additional Qa characteristics and CVM are not reported yet. Recently, longitudinal–survival statistical models were found to have a great potential for evaluating relations between response to a drug and the risk of developing side effects.[11] By applying this joint modelling technique, we aimed to unveil possible associations between initial Qa, actual Qa and its changes over 3-month periods, and CVM in a HD population.

Materials and methods

General information

The present retrospective cohort study was performed in Maxima Medical Center (MMC), a Dutch hospital accommodating approximately 110 chronic HD patients. CKD patients choosing HD or peritoneal dialysis are

referred by nephrologists to our department of vascular surgery. If an AVA is preferred, advise on type and location is determined by history, physical examination and vascular Duplex mapping of the arm.[1,2] Cannulation is initiated when HD is necessary and the AVA is considered sufficiently mature as advised.[2] Study specifics were in accordance with the ethical standards of our institutional research committee and with the declaration of Helsinki. The rules laid down by the Medical Research Involving Human Subjects Act (Dutch WMO) did not apply to the study protocol.

Study criteria

Adult CKD patients who received a primary AVA between January 2010 and December 2017 in MMC and who were on chronic (>3 months) HD were considered eligible. Patients were followed until 31 December 2018. Patients were excluded if the AVA was received elsewhere, or if just one Qa value was obtained.

Qa definitions and measurements

Three different characteristics of Qa were studied. Initial Qa was defined as the first Qa value obtained from a functional AVA after the patient successfully started two needle AVA cannulation. Some suggested a 1000 mL/min initial Qa cut-off point predicting mortality.[8,10] Actual Qa was defined as the access flow volume that was routinely obtained once every 1-2 months for AVA surveillance. Changes in actual Qa were analysed over 3-month periods.

All Qa values were measured using a two-needle dilution technique (HD03, Transonic Systems Inc, New York, USA) during the first 30 minutes of the HD session as recommended.[1] Two measurements were standardly obtained during a monitoring session. The mean was calculated if these two readings differed <15%. If ≥15%, a third measurement was performed and the average of the two closest measurements was calculated. If all 3 measurements differed >15%, an average of all three was used. For actual Qa >4000 mL/min (maximum of the Transonic monitoring system), a value of 4000 mL/min was used. If a patient was on interim HD using a central venous catheter (CVC) in temporary absence of a patent AVA, Qa was set at 0 ml/min during this period. Qa values were corrected for body surface area (BSA) that was calculated from length and weight.[12]

Data collection

All Qa readings were extracted in September 2020 from our HD department's data management system (FinProDB 7.9, MedVision AG, Unna, Germany). Demographics, etiology of CKD, comorbidities, smoking status, body mass index, BSA and number of percutaneous transluminal angioplasties (PTA) for AVA maturation or maintenance (if present) were retrieved from electronic patient files (HiX 6.1, ChipSoft B.V., Amsterdam, The Netherlands).

Primary outcome

Primary outcome was cardiovascular mortality (CVM) as dictated by the ERA-EDTA classification (codes 11, 14-16, 18, 22-26, 29). Non-cardiovascular death was classified as HD discontinuation, infection, cancer, or other causes.

Flow reduction surgery (FRS)

A small portion of study patients (n=10, 6%) underwent flow reducing surgery (FRS) during the 9-year observation period. Criteria for FRS were at least two actual Qa >2000 mL/min. A portion of data on short and long term effects of FRS were published previously.[13,14]

Statistical analysis and joint modelling

Patient characteristics were reported as mean and standard deviation (SD), or as count and percentage. Follow-up (FU) time was expressed as median and first and third quartile. FU started at the date of first HD session and ended following death, or at December 31, 2018. Patients who moved to another HD facility were considered loss to FU and 'date last known alive' was used as censoring date. Survival was depicted using the Kaplan-Meier (KM) method and expressed as median and 95% confidence interval (CI). The association between initial Qa and 4y-CVM was estimated using Cox proportional hazards regression and KM-curves. A receiver operating characteristic (ROC) analysis determined the most optimal cut-off point for initial Qa.

Associations between longitudinal measurements of Qa and 4y-CVM were analyzed based on a joint modelling approach.[15] This statistical approach considers possible associations of values of actual Qa (and its changes) with CVM at any time during follow-up. Longitudinal changes in Qa are first modelled using a linear mixed-effects regression model.

Thereafter, the joint model takes the results of this longitudinal model as predictors of survival using Cox proportional-hazards regression. Potential associations were determined with and without adjustment for confounders, except for the rate of change over time, as this represents a within-patient parameter. A priori selected confounders were age, gender, diabetes, cardiovascular disease (CVD) and BSA.[16] All associations were expressed as hazard ratio (HR) including the 95% CI. P-values ≤0.05 were considered statistically significant. All analyses were performed using R version 3.6.1 (R Project for Statistical Computing).[15]

Results

A total of 309 patients were on chronic HD between January 2010 and December 2018 at our institution. As 144 patients were excluded (AVA constructed before 2010 or in 2018, n=129; AVA received elsewhere, n=11; just one Qa reading, n=4), 165 patients fulfilled inclusion criteria. Median follow-up was 36 months (1st and 3rd quartile, 14 and 57 months). The ROC-analysis identified 900 mL/min as the most optimal cut-off value of initial Qa (sensitivity 71%, specificity 68%, PPV 37%, NPV 90%). The area under the curve (AUC) was 0.71 ±0.05 (CI 0.62-0.80, P<0.001; Figure S1). Table 1 compares patient groups according to this 900 mL/min threshold value. Patients in the <900 mL/min group were 8 years older and more often had CVD prior to AVA construction compared to the ≥900 mL/min group (63% vs. 44%, P=0.018). Other demographic characteristics were not different (Table 1). Mean time between AVA construction and initial Qa was 31 ±3 weeks. HD on the first AVA was possible in 125 patients (76%) whereas 40 patients (24%) received more than 1 AVA during the observation period (HD initiated via second AVA, n=35; third AVA, n=4; fourth AVA, n=1).

A total of 79 patients (48%) died during the 9 years of observation. Median survival was 57 months (95% CI: 47-63 months). Mortality was due to CVD (n=46; 58%), infection (n=10; 13%), HD discontinuation (n=9; 11%), cancer (n=5; 6%) or other causes (n=9; 11%).

Initial Qa and cardiovascular mortality (CVM)

After four years, freedom from CVM was 34% lower in patients with an initial Qa <900 mL/min (53 ±7%) vs. Qa ≥900 mL/min (87 ±4%, P<0.001; Figure 1). Following correction for age, sex, diabetes mellitus, history of CVD and BSA, the increased CVM risk in patients having an initial Qa <900

mL/min was maintained (unadjusted HR: 4.05; 95% CI, 1.94 to 8.43, P<0.001; adjusted HR: 2.77; 95% CI, 1.29 to 5.97, P=0.009; Table 2).

Actual Qa and cardiovascular mortality (CVM)

A total of 5208 Qa measurements were available for longitudinal modelling (n=165 patients, median 23 values per patient). Substantial heterogeneity in Qa trajectories was found (Figure 2A). Actual Qa decreased slightly but significantly over the years after the initial Qa (-37.6 mL/min per year, 95% CI, 0.25 – 75.0, P=0.047; Figure 2B). This association remained significant after correcting for confounders (-41.6 mL/min per year, 95% CI, 3.0 to 80.2, P=0.035). Curves of patients who died (n=79) and who survived (n=86) were different (P=0.005, Figure 2B).

In the longitudinal model, an association between actual Qa increase over a 3-month period and increased risk of CVM was observed (HR: 4.48 per 100 mL/min increase per 3 months, 95% CI, 1.44 to 13.97, P=0.010). For six months periods, an elevated risk for CVM was also found, albeit less prominent (HR: 2.11 per 100 mL/min increase per 6 months, 95% CI: 1.20 to 3.73, P=0.010). In contrast, single values of actual Qa were not related to 4yr-CVM (HR: 0.94, 95% CI, 0.87 to 1.02, P=0.146). Correction for confounders did not alter this insignificant relationship (HR: 0.96, 95% CI, 0.88 to 1.05, P=0.361).

Table 1. Characteristics of patients (n=165) demonstrating initial Qa <900 mL/min (n=67) or ≥900 mL/min (n=98).

Characteristic	**Initial Qa <900 mL/min** N=67	**InitialQa ≥900 mL/min** N=98	**P**
Age (years, ±SD)	75 ±10	67 ±13	**<.001**
Male gender (%)	41 (61)	62 (63)	.787
Diabetes Mellitus (%)	29 (43)	34 (35)	.265
Cardiovascular disease (%)	42 (63)	43 (44)	**.018**
Hypertension (%)	56 (84)	83 (85)	.847
Etiology of renal disease (%)			n/a
- Glomerulonephritis/sclerosis	15 (22)	18 (18)	
- Pyelonephritis	1 (2)	1 (1)	
- Hypertension	6 (9)	10 (10)	
- Renal vascular disease	5 (8)	6 (6)	
- Diabetes	22 (33)	20 (20)	
- Polycystic	0 (0)	0 (0)	
- Miscellaneous	16 (24)	35 (36)	
- Unknown	2 (3)	8 (8)	
Smoking (%)	32 (48)	55 (56)	.282
- Former	23 (34)	31 (32)	
- Active	9 (13)	24 (24)	
Type of constructed AVA (%)			.198
- Wrist-based AVA	25 (37)	25 (26)	
- Elbow-based AVA	35 (52)	62 (63)	
- AVG	6 (9)	10 (10)	
- Leg AVA	1 (1)	1 (1)	
Temporary CVC (%)	14 (21)	24 (24)	.935
Body-mass Index (mean ±SEM)	27 ±0.7	27 ±0.6	.669
Body surface area (mean ±SEM)	1.89 ±0.02	1.96 ±0.03	.084
Time AVA construction – initial Qa (weeks)	31 ±4	32 ±4	.841
Initial Qa (mL/min, mean ±SEM)	531 ±26	1582 ±65	**<.001**

SD, standard deviation; SEM, standard error of mean; AVA, arteriovenous access; AVG, arteriovenous graft; CVC, central venous catheter; Body-mass index is weight (kg) divided by square of height (m). Boldface P-value represents statistical significance.

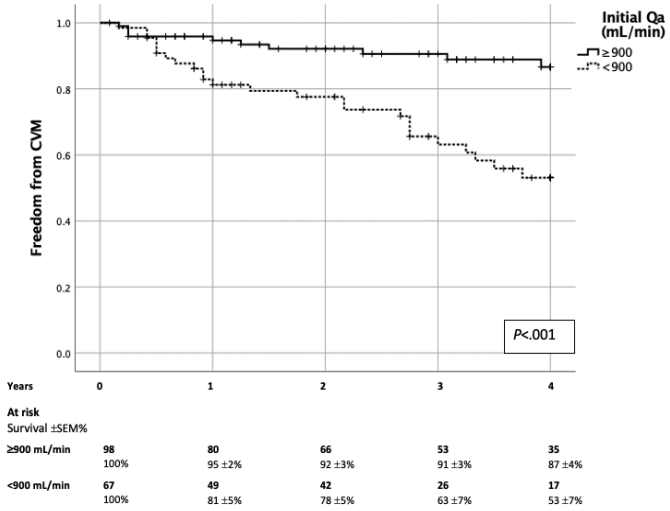

Figure 1. Freedom from CVM and initial Qa ≥900 mL/min (n=98), or <900 mL/min (n=67).

Table 2. Factors determining 4-yr CVM in HD patients undergoing initial Qa analysis.

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age	1.05	1.02-1.09	**.003**	1.04	1.00-1.08	**.040**
Female sex (vs. male)	0.86	0.43-1.72	.663	0.62	0.28-1.38	.241
Diabetes Mellitus	1.73	0.89-3.36	.108	1.53	0.75-3.11	.240
Cardiovascular disease	2.31	1.15-4.66	**.019**	1.60	0.77-3.32	.206
BSA	0.61	0.14-2.56	.495	0.59	0.10-3.43	.555
Initial Qa <900 mL/min ≥900 mL/min	4.05	1.94-8.43	**<.001** Ref.	2.77	1.29-5.97	**.009** Ref.

Cox proportional hazards model, CI, confidence interval; HR, hazard ratio; BSA, Body-surface area; Boldface P-value represents statistical significance; Ref., reference.

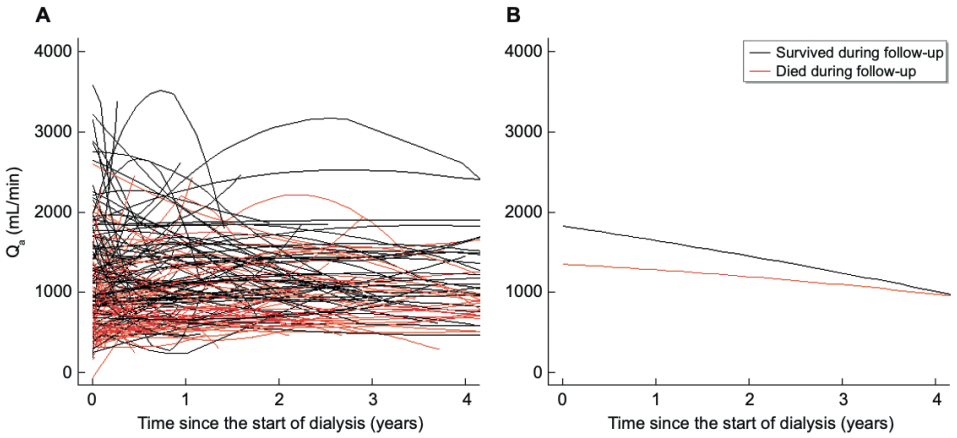

Figure 2. (A) Qa over time of individual patients and entire study cohort (n=165) **(B)** Curves of patients who survived (upper black line, n=86) and who died (lower red line, n=79) are significantly different (P=.005).

Percutaneous transluminal angioplasty (PTA)

A total of 274 PTA's were required for AVA stenosis reflected by diminishing actual Qa values (n=69 patients, 42%). Rate of freedom from CVM in patients undergoing a PTA was not different from patients who did not (PTA+ 71% vs. PTA- 73% P=0.521). Neither PTA (yes/no) nor number of PTA's increased the risk of CVM (HR 1.05, 95% CI, 0.59 to 1.88, P=0.862; HR 1.00, 95% CI, 0.93 to 1.07, P=0.992, respectively).

Flow reduction surgery (FRS) and 4-year mortality

During the 9-year observation period, flow reducing surgery (FRS; revision using distal inflow RUDI, n=9; access banding n=1) was executed in 10 patients. FRS patients had a mean 542 ±229 mL/min Qa increase over a 12 ±4 months period since their initial Qa. Following FRS, actual Qa dropped from 2617 ±245 to 1053 ±167 mL/min. Four year survival was 100% compared to 55% in the population who did not undergo FRS (P=0.020; Figure S2). A sensitivity analysis excluding these 10 FRS patients found a similar association between Qa increase over 3-months periods and 4yr-CVM (HR: 3.89 per 100 mL/min increase per 3 months, 95% CI, 1.20 to 12.58, P=0.023).

Discussion

Incidence of HD patients with a high Qa AVA is rising due to a contemporary trend favoring brachial artery based AVA over radial artery based AVA.[17] A high Qa AVA is thought to possibly overload the cardiovascular system with detrimental sequelae in the long term.[3,4] However, reports on the association between actual Qa and survival are conflicting.[8,9] We studied the role of actual Qa but also focused on other characteristics of Qa including initial Qa, and periodical changes in actual Qa. The results indicate that single values of actual Qa were not associated with cardiovascular mortality (CVM). However, an increasing actual Qa over 3-month periods conferred a higher CVM risk. In addition, HD patients having a <900 mL/min initial Qa were almost four times more likely to die from a cardiovascular event in the first four years after receiving an AVA compared to the population with an initial Qa >900 mL/min. It is concluded that studying these novel Qa characteristics may contribute to understanding excess CVM in HD patients.

According to earlier KDOQI guidelines, a high flow access (HFA) is an AVA having an actual Qa of 1000-1500 mL/min, or when the Qa is >20% of the cardiac output.[1] However, this definition is challenged.[1,3,4,18-20] Apart from controversies defining HFA, it is largely unclear if a HFA is beneficial (as cannulation and HD sessions often occur smoothly), or hazardous (due to potential systemic overload). Basile et al. found that HOCF could occur with an AVA having an actual Qa >2000 mL/min.[3] Wu et al. reported that survival was better in populations with an actual Qa >1000 mL/min AVA.[8] Similarly, Al-Ghonaim et al. found that patients having an AVA with an actual Qa ≥1000 mL/min did not have a higher mortality risk.[10] However, these studies did not utilize ROC techniques for objectively determining the optimal cut-off value for initial Qa. Guidelines and studies on HFA were hitherto based on the analysis of single actual Qa values at random time points using standard statistical methods. The current study focuses on alternative qualities of Qa using a sophisticated joint modelling technique.

The role of an initial value of Qa with reference to long term survival is largely unclear. Immediately following AVA creation, a cascade of events will lead to a Qa increase within the first 24 hours, whereas a plateau is reached after 6-8 weeks that may consolidate over the following 6 months.[21-23] A favorable systemic hemodynamic environment including sufficient blood pressure and arterial remodelling characteristics are

crucial factors determining successful AVA maturation. These findings suggest that a relatively high initial Qa might be considered as a surrogate marker of better cardiovascular health.[10,20,24-30] The present study found a direct relationship between initial Qa and freedom from CVM. Moreover, a 34% difference in CVM after 4 years of HD sessions was found if a 900 mL/min initial Qa threshold value was considered. The current analysis studied initial Qa values that were obtained using a two needle dilution technique after a mean of 7 months after AVA construction. Future studies using serial Duplex analysis of a maturing AVA should focus on the first 6 months after construction.

This study is the first to suggest an association between an increase in actual Qa over 3-month periods and a higher risk of CVM. A sound pathophysiological explanation is currently absent. Previous literature reported that a high Qa may promote ventricular dilation and that exceptionally high Qa levels may lead to HOCF over time.[4,18,31-34] Malik et al. discussed the role of natriuretic peptides (ANP and BNP) release after AVA creation. High concentrations of these substances may possibly be regarded as an early warning sign reflecting non-physiologically hemodynamic adaptations.[35] Our sensitivity analysis of 155 patients who did not receive flow reducing surgery (FRS) indicated that an increase in Qa over a relatively short period of time may be related to an adverse cardiovascular event. These phenomena may also be found after long term high-volume high intensity exercise in healthy athletes.[36-39] An increase of actual Qa over a 3-month period may reflect progressive failing of homeostatic mechanisms in frail HD patients who are already in a (latent) state of compensated cardiovascular disease. Future cardio-physiological and imaging studies combined with monitoring serial biochemical markers may contribute to the understanding of this complex pathophysiology.

It is unlikely that higher rates of CVM are due to an increase in actual Qa following percutaneous transluminal angioplasty (PTA). Actual Qa may temporarily be elevated after PTA but often do not attain previous values later on.[40-43] For instance, Bacchini et al. reported that AVA's with a baseline Qa of 809 mL/min that had dropped to 468 mL/min just before PTA increased to 820 mL/min after a successful endovascular intervention. One month later however, Qa again had decreased to 754 mL/min.[40] Other studies focusing on cardiovascular effects of percutaneous interventions for AVA also did not find higher all-cause mortality rates.[44-46] Therefore, it is

likely that lower survival rates in HD populations are not caused by adverse cardiovascular effects of a PTA for AVA maintenance.

Previous guidelines advise to consider flow reducing surgery (FRS) in selected patients with a persistently high actual Qa so the irreversible consequences of cardiovascular overload are possibly avoided. Optimal timing of surgery is unknown but may depend on patient characteristics, cardiac imaging and clinical judgement.[1] Revision using distal inflow (RUDI) and banding resulted in good AVA patency but suboptimal long term Qa control.[13,14,47,48] However, it is unknown whether FRS optimizes patient survival. Interestingly, our 10 eligible patients demonstrated a mean 542 mL/min actual Qa increase in the 12 months prior to the decision to undergo FRS. Surprisingly, all patients who underwent FRS demonstrated substantial lower actual Qa and were free of CVM after 4 years compared to just 55% of patients not undergoing FRS. Further research should focus on FRS timing and potential long term protective effects.

Several limitations of this study need to be addressed including a limited patient number and a nonexperimental retrospective study design. Risk factors known to partially determine HD patient survival such as cardiopulmonary performance, blood pressure, URR (urea reduction ratio) and blood chemistry were not considered, since these were only available in a small portion of the population.[16] Since some individual Qa trajectories display considerable fluctuations over longer (than 3 month) periods, it was decided to adhere to Qa change over a period of 3 months as one of our primary outcomes. Furthermore, a potential extra quantity of Qa that is shunted via possible venous side branches was not incorporated in the standard Qa measurement. Only values of Qa obtained by a dilutional method were included in the analysis. Qa values that were measured by Duplex scanning before and after PTA were not studied. As the analysis was based on a Qa-trajectory over time, rather than on a single Qa-measurement, the effect of outliers and in between dialysis session Qa variability is mitigated. Last, serial cardiac echography may have provided information on long term impact of Qa but was not performed.

Conclusion

Studying novel Qa characteristics may contribute to understanding excess CVM in HD patients. The validity of these findings should be confirmed in a larger population.

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Supplemental material

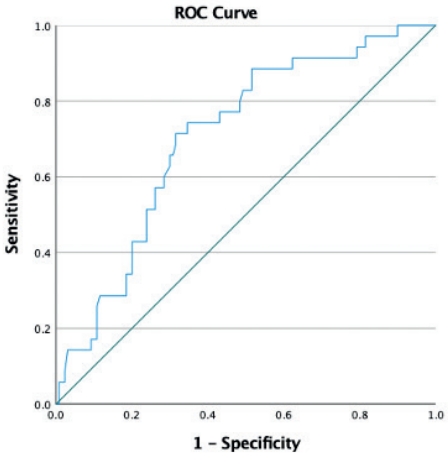

Figure S1. Receiver operating characteristic (ROC) analysis for the association between initial Qa and four-year cardiovascular mortality (CVM).

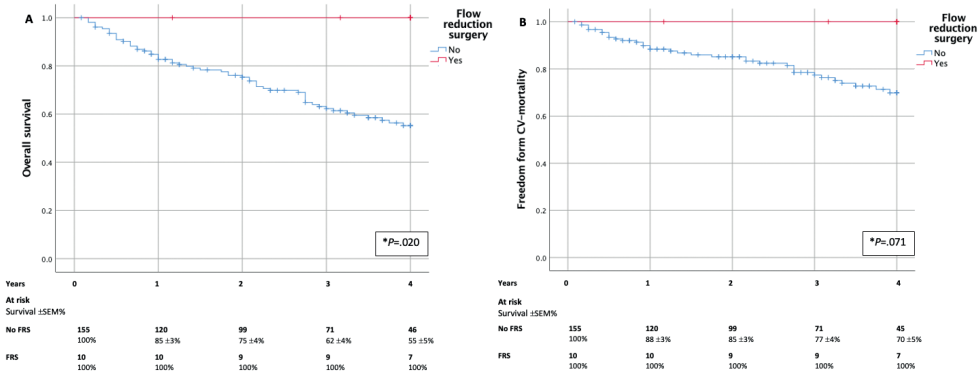

Figure S2. (A) Four-year overall survival and **(B)** freedom from cardiovascular mortality in patients undergoing FRS or not.

Chapter 5

A scoping review on surgical reduction of high flow arteriovenous haemodialysis access

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Abstract

Volume flow (Qa)>1.5-2 L in arteriovenous accesses may be associated with high flow related systemic or loco-regional complications. A variety of surgical techniques are advocated for Qa reduction. Aim of this scoping review is to provide an overview of available evidence regarding the efficacy of this broad spectrum of interventions for Qa reduction in patients with a high flow haemodialysis access.

PubMed and Embase were searched according to PRISMA-guidelines. Studies on invasive management of HFA were selected. Inclusion required an English description of surgical techniques in human HFA including pre- and postoperative access flow values.

Sixty-six studies on 940 patients (mean age 56 years [3-90 years], male 62%, diabetes mellitus 26%, brachial artery-based arteriovenous access 65%) fulfilled inclusion criteria. Performed techniques were banding (58%), revision using distal inflow (12%), plication/ anastomoplasty (10%), graft interposition (5%), proximal radial artery ligation (3%), aneurysm repair (4%), or miscellaneous other techniques (8%). Definition of HFA, work-up, indication for surgery and intraoperative monitoring were diverse. All techniques reduced access flow on the short term (mean drop 0.9-1.7 L/ min). Secondary access patency rates varied between 70 and 93% (mean follow-up, 15 [0-189] months). Definitions of success and recurrence varied widely precluding a comparison of efficacy of techniques. Patient specific factors legitimizing invasive treatment for HFA are discussed. Recommendations on reporting standards when dealing with HFA surgery are provided.

In conclusion, the present report on the current management of high flow access does not allow for drawing any definite conclusions due to a lack of standardization in definition, indications for surgical intervention and techniques. Randomized trials comparing different Qa reducing techniques in symptomatic patients are warranted, as are trials comparing a wait-and-see approach versus flow reduction in asymptomatic patients. As an overview of the variety of techniques was lacking, this scoping review might serve as a map for future researchers.

Introduction

Arteriovenous accesses (AVA) may occasionally develop severe blood flow related complications.[1] Haemodialysis access-induced distal ischaemia (HAIDI) might arise due to poor distal tissue perfusion or vasculopathy. Occasionally, HAIDI may be caused by a high flow (Qa) access.[2] A high flow access (HFA) possibly also leads to complications such as cardiac dysfunction.[3] Work-up and indications for interventions of HAIDI are relatively well specified.[2-5] In contrast, the approach of a HFA is a matter of debate.[6,7]

A Qa of approximately 300-400 mL/min (in an arteriovenous fistula, AVF) and 500-600 mL/min (in an arteriovenous graft, AVG) is considered adequate to provide haemodialysis. Occasionally, Qa in certain AVA's may be higher with values >1.5-2.0 L/min. Such Qa may be associated with flow related systemic or loco-regional complications.[3] Earlier studies reported an association between high Qa and the development of high output cardiac failure (HOCF).[8-11] Basile et al. reported that Qa values >2.0 L/min were predictive of the occurrence of HOCF in 10 elderly patients with stage C heart failure.[12] Additionally, abnormal turbulence caused by high Qa is suggested to be an aetiological factor in the development of local complications such as stenosis by promoting venous neo-intimal hyperplasia in the outflow veins.[13,14] Reduction of high Qa has been associated with a decrease in need for angioplasties due to a delay in progression of stenosis in the cephalic arch.[13] A relation between high Qa and central venous stenosis has also been suggested.[15]

In the current guidelines of the National Kidney Foundation (NKF), Qa related complications are acknowledged as important and are addressed as a separate topic. A Qa of 1.0-1.5 L/min or 'a flow to cardiac output ratio >20%' are suggested as threshold values defining HFA. Criteria mandating invasive treatment are not mentioned.[16] Access guidelines of the European Society for Vascular Surgery (ESVS) mainly focus on high Qa associated hand ischaemia and its treatment options. Regular monitoring of Qa if >1.5 L/min, an echocardiography and identifying signs of congestive heart failure is advised. Patients with progression of symptoms, progressive Qa increase or objective signs of heart failure should be considered for flow reduction.[15] In daily practice, these practical guidelines are more or less adhered to. However, the current approach is highly subjective and often based on the clinicians' best judgement.

An evidence based HFA monitoring scheme is lacking and consensus on management of (seemingly) asymptomatic HFA is absent. Several surgical techniques such as banding and revision using distal inflow (RUDI) have been proposed for symptomatic HFA treatment. However, the optimal operative method guaranteeing lower Qa with uninterrupted HD in symptomatic HFA has yet to be identified. In order to tailor treatment to the individual patient, it is crucial to understand differences in techniques and outcome. An overview of the variety of surgical techniques is currently lacking. Aim of this scoping review was to provide an overview of available evidence regarding the spectrum of surgical techniques for Qa reduction rather than critically appraise data and synthesize an answer to a clinical question.[17] This scoping review might serve as a map for clinicians and future research on HFA.

Methods

Both PubMed and EMBASE were searched according to PRISMA guidelines using terms comprising haemodialysis, high flow and associated complaints and types of surgery. In PubMed, specific MeSH-terms 'dialysis, renal replacement therapies, arteriovenous fistula, cardiac failure, surgery, treatment, endovascular procedure and minimally invasive surgical procedures' were included. Specific EMBASE-terms were 'hemodialysis, renal replacement therapies, arteriovenous fistula, anastomosis, blood vessel shunt, heart failure, surgery, therapy endovascular surgery and vascular surgery'. The exact terms per database are displayed in supplemental file 1.

Titles and abstracts of English papers were scanned. If deemed pertinent, the publication was read in detail. Inclusion required a description of surgical technique and pre-and postoperative non-indexed Qa values. In case of overlapping patient populations, the article describing the largest cohort was included. Data regarding patient characteristics, AVA type, indication, Qa tool, pre- and postoperative Qa, complications, follow-up, patency and HFA recurrence were tabulated. Reviews, reports on AVA ligation and animal studies were excluded. When details on the performed surgical technique were unclear, authors were contacted with an inquiry for additional information. Reference lists of eligible articles were checked for additional literature. Two authors (MG, RY) independently performed the search and data extraction and discussed any disagreement. The senior author (MS) ultimately decided in case of ongoing disagreement.

Parameters, definitions and calculations

Age (years), Qa-values (L/min) and follow-up (months) were displayed as mean (range: minimum-maximum). If ranges were lacking, standard deviations or errors were depicted as published. Overall, mean parameter values were based on number of available entries rather than on initial numbers of patients per study preceding overestimation due to missing data. A HFA was considered symptomatic in case of presence of signs and/ or symptoms of cardiac origin and/ or distal ischaemic origin. If such complaints were absent, the HFA was considered asymptomatic. Qa thresholds were based on reported values but, if absent, on the patient with the lowest preoperative Qa per study. Postoperative complications included bleeding, infection, thrombosis, aneurysm and re-operation within one month. Recurrence of HFA or unremitting HFA (re-HFA) were based on study specific definitions or a Qa >1.5 L/min. Death rates were calculated as '1 death per X-observed patient years'. Patency was defined as percentage of patent accesses at the end of follow-up, with or without revision. Secondary patency was shown as reported and if absent, calculated based on available information.

Results

The search strategy yielded 2447 studies published between September 1973 and August 2021 (Figure 1). Sixty-six articles encompassing 940 patients fulfilled study criteria (mean age 56 years [3-90], male 62%).[5,6,13,18-81] Five articles described two or more surgical techniques in different patients.[44,48,51,64,67] One article added data to a second included article without adding new patients.[19,20] Diabetes mellitus (DM) was observed in 26% of patients and more commonly present in studies including HAIDI patients (58%) compared with studies in which HAIDI was absent (18%). The majority of patients (65%) harboured a brachial-artery based access. A total of 37 deaths occurred in 886 observed patient years (one death per 24 observed patient years).

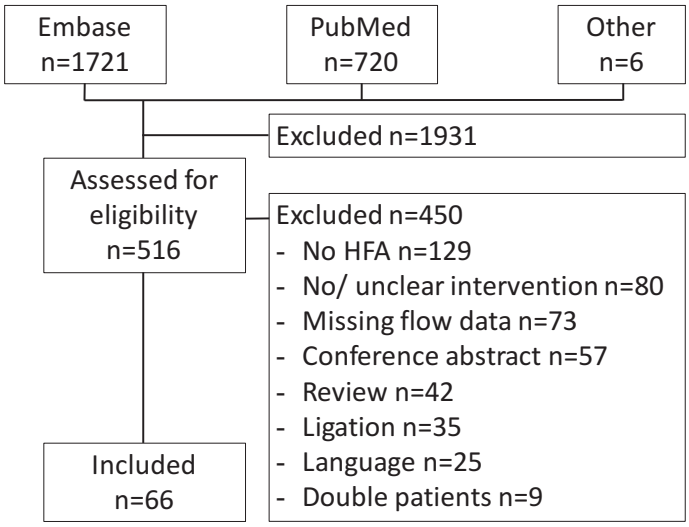

Figure 1. Study inclusion flow chart. HFA, High flow access.

Definitions and surgical workup

Definitions of HFA and indication for Qa reducing surgery varied greatly. For example, reported cut-off values ranged from 0.6 L/min to 2.0 L/min.[6,25] Some authors ignored Qa thresholds and executed Qa reduction when cardiac complaints or HAIDI were present.[44,62,75] One author stated that 'surgery was performed for high flow' but provided neither symptoms nor predefined threshold values.[46]

Echocardiography supporting a decision of Qa reduction was used in 24 articles describing 381 patients (41%).[6,22,23,29,30,32,36,38,45-49,51-53,59,68,72,74,76-78,80] Echocardiographic parameters reflecting HOCF in the presence of a HFA were not stated although left ventricular mass index (LVMi) decreased following surgery.[29,72] Changes in serum Brain Natriuretic Protein (BNP) and Atrial Natriuretic Protein (ANP), biomarkers linked to cardiac failure,[82,83] were measured in one study and decreased greatly following Qa reduction.[49]

Qa reducing techniques

Banding

Banding is used for all types of HFA involving the brachial (Figure 2A), radial (Figure 2B) and femoral artery. A band is wrapped around the venous outflow tract increasing AVA outflow resistance leading to a lower Qa and higher finger pressures (Figure 2C).[28] Several modifications were popularized.

During Minimally Invasive Limited Ligation Endoluminal-assisted Revision (MILLER), an angioplasty balloon (typically 4-5 mm) is temporarily inserted into the venous outflow tract to prevent 'over-banding' and consequent thrombosis.[84] T-banding includes wrapping of both venous outflow tract and feeding artery using a single T-formed band.[40] During External Dilator-Assisted Banding (EDAB) a dilator-device is temporarily placed at the exterior vessel wall. EDAB is used for both arterial and venous banding.[46]

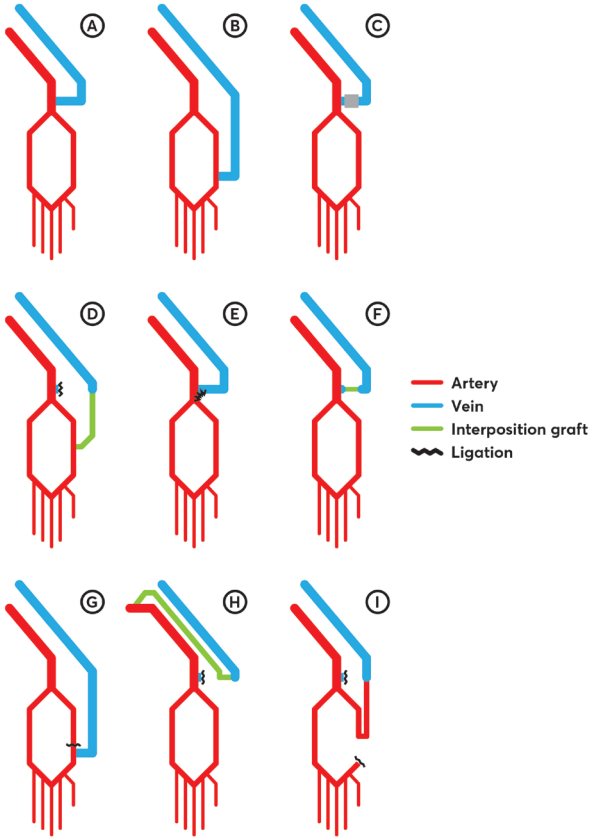

Figure 2. Schematic overview of different access flow (Qa) reducing techniques. **(A)** brachial artery based arteriovenous access (AVA); **(B)** radial artery based AVA); **(C)** Banding; **(D)** Revision using distal inflow (RUDI); **(E)** Plication/ anastomoplasty; **(F)** Graft interposition; **(G)** Proximal radial artery ligation (PRAL); **(H)** Proximalization of arterial inflow (PAI), a revascularization technique; **(I)** Radial artery transposition (RAT).

Banding with intraoperative Qa-tool

A total of 21 articles on banding with intraoperative Qa tools guiding surgery were included (n=378 patients, 61% male, mean age 55 [15-90]; Table 1).[13,18-37,56] One article provided additional data in a second article without adding new patients.[19,20]

Qa drop was 1.5 L/min (2.5 to 1 L/min). Complications were reported in 24 patients (6%) including access thrombosis/occlusion (n=14). Patency rate was 92% (mean follow-up 10 months, total 198 patient years). High Qa recurred or persisted in 50 patients (13%).

Banding without intraoperative Qa-tool

Fifteen articles reported on banding without an intraoperative tool (n=167 patients, 64% male, mean age 60 [18-89]; Table 2).[38-52]

Qa-drop was 1.1 L/min (2.1 to 1 L/min). Complications were reported in 27 patients (16%) including thrombosis/ occlusion (n=13). Patency rate was 86% (mean follow-up 12 months, total 107 patient years). High Qa recurred or persisted in 24 patients (14%).

Revision using distal inflow (RUDI)

RUDI is used for correction of brachial artery based HFA. A piece of vein or polytetrafluoroethylene (PTFE) graft is positioned between the radial (or ulnar) artery and the disconnected upper arm access outflow vein while the original brachial artery-located anastomosis is interrupted (Figure 2D). Qa reduction occurs as the access inflow is now provided by a smaller calibre artery.[61] RUDI is also advocated for HAIDI.[62] Some authors favour a short (5-8 cm) piece of vein, anastomosed to the proximal radial artery. Others make the anastomosis halfway down the forearm or even towards the wrist. One author constructed an anastomosis between the transsected and mobilised outflow vein and the proximal radial artery thus avoiding an interposition graft.[63] Ten articles reported on RUDI (n=110 patients, 62% male, mean age 57 [28-78]; Table 3). [6,51,57-64]

Qa drop was 1.7L/min (2.8 to 1.1 L/min). Complications were reported in 13 patients (12%), mostly thrombosis (n=9). Patency rate was 86% (mean follow-up 17 months, total 158 patient years). High Qa recurred or persisted in 23 patients (21%). RUDI using a basilic vein graft (n=4) was ineffective.[61]

Plication/ anastomoplasty

Plication and anastomoplasty are based on a banding principle as the anastomotic or outflow tract diameter is reduced leading to increased outflow resistance (Figure 2E). One author additionally placed a band around the plicated area to prevent postoperative dilatation.[85] Nine articles on plication/anastomoplasty were included (n=92 patients, 60% male, mean age 57 [9-86]; Table 3).[44,48,54,65-70]

Qa drop was 1.4 L/min (2 to 0.6 L/min). One complication (thrombosis, 1%) was reported. Patency rate was 93% (mean follow-up 12 months, total 68 patients years). High Qa recurred or persisted in 3 patients (3%).

Graft interposition technique (GIT)

During graft interposition, a portion of the outflow vein is replaced by a piece of vein or PTFE. The access outflow is diminished if the diameter of the interposition graft is less than the original outflow vein (Figure 2F). A variation is the graft inclusion technique, incorporating the graft into the outflow vein.[48] Data on both techniques were combined in this review. GIT is performed in both radial and brachial artery-based AVA. Seven articles reporting on graft interposition were included (n=46 patients, 64% male, mean age 60 [28-89]; Table 4).[48,64,67,71-74]

Qa drop was 1.6 L/min (2.9 to 1.3 L/min). Complications were reported in 7 patients (15%), mostly thrombosis (n=6). Patency rate was 78% (mean follow-up 39 months, total 147 patient years). High Qa recurred in 1 patient (2%).

Proximal Radial Artery Ligation (PRAL)

PRAL is used for radial artery-based HFA as the radial arterial segment just proximal to the anastomosis is ligated. The access is perfused via the ulnar artery and the palmar arch (Figure 2G). Preoperative imaging of these structures is required.[77] Theoretically, a PRUL (proximal ulnar artery ligation) may be used if the ulnar artery is the inflow vessel of the AVA although articles on PRUL were not found. Three articles reported on PRAL (n=31 patients, 55% male, mean age 45 [16-82]; Table 4).[75-77]

Qa drop was 1 L/min (1.8 to 0.8 L/min). Complications were absent. Patency rate was 81% (mean follow-up 19 months, total 49 patient years). High Qa recurred or persisted in 2 patients (6%). One other paper using an Amplatzer plug for proximal radial arterial occlusion (n=3) reported a 26-50% Qa-reduction but failed to state absolute values.[86]

Venous aneurysm repair

As a result of increased Qa through an AVA, veins may grossly dilate leading to venous aneurysms. Various options and techniques reducing aneurysm diameter are proposed. A reduction in Qa following aneurysm surgery is not uncommon. Depending on the performed technique, Qa reduction is likely due to a decreased vessel diameter or to a new (possibly smaller) anastomosis. The longevity of these operations (without an additional flow reduction technique) is unknown. Two articles reporting on different types of venous aneurysm repair fulfilled inclusion criteria (n=42 patients, 69% male, mean age 37 (18-60]; Table 4).[53,55]

Qa drop was 0.9 L/min (1.7 to 0.8 L/min). Complications were not reported. Secondary patency rate could not be calculated. Follow up was 27 months (mean, total 93 patient years). High Qa recurrence was not reported.

Miscellaneous techniques

Radial artery transposition (RAT) depends on a transposed radial artery as the new inflow artery for a brachial artery-based AVA resulting in a Qa drop of approximately 1.1 L/min (1.7 to 0.6 L/min; Figure 2I) in 47 patients.[78]

In 12 patients with cardiac complaints, arterial banding and ligation led to a mean 0.8 L/min drop in Qa (1.4 to 0.6 L/min).[44]

Transposition of the basilic vein (BVT) reduced mean Qa by 0.6 L/min (1.8 to 1.2 L/min) in 10 patients with HAIDI and an inadequate needle access segment precluding two-needle dialysis.[5]

One author proposed an endovascular technique using an hourglass shaped stent-graft in the venous outflow tract of 3 brachial artery-based AVA. Qa decreased 0.7 L/min (1.7 to 1.0 L/min).[79]

Whenever the radial artery had developed a hairpin formed turn due to a long-standing radial artery-based HFA, re-implantation resulted in a Qa drop of 1.7 L/min (2.3 to 0.6 L/min).[80]

An 'Endo-RUDI' was described for a failed graft interposition in a brachiocephalic HFA. A side-to-side anastomosis was created between the radial vein and artery distal to the access. The interposed graft was removed and the artery was repaired using a transverse running Prolene suture. Qa was reduced by 1.4 L/min (2.2 to 0.8 L/min).[81] An overview of miscellaneous techniques is listed in Table 4.

Table 1. Publications on banding of high flow accesses guided by a flow tool.

Author, year	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Qa-method pre
De Palma, '73 Banding[18]	C+/ H±/ As- ≥1.3	3	48 (21-62)	0	0	FA-AVA -Bovine (67) - GSV (33)	EM-probe
Anderson,'75'76 Banding[19,20] *	C+/ H-/ As- ≥1.4	3	48 (45-51)	67	0	RA-AVF (100)	EM-Probe
Fee, '76 Banding[21]	C+/ H-/ As- ≥1.6	4	41 (20-60)	25	25	FA-AVF - Bovine (75) - GSV (25)	Catheter
Isoda, '94 Banding[22]	C+/ H-/ As- 3.7	1	52	100	0	RA-AVF (100)	Ultrasound
Murray, '04 Banding[23]	C-/ H-/ As+ 5.2	1	60	100	0	BA-AVF (100)	Dilution
Thermann, '07 Banding[24]	C-/ H+/ As- ≥0.6	15	68 (46-84)	47	47	BA-AVF (87) BA-AVG (13)	Ultrasound
Miller, '10 MILLER[13]	C+/ H±/ As- ≥1.5	69	56	62	33	BA-AVF (86) RA-AVF (9) BA-AVG (6)	Dilution
Jennings, '12 MILLER[25]	C-/ H-/ As+ ≥0.9	22	43 (22-73)	59	32	NR	Ultrasound
Nickel, '13 Banding[26]	C+/ H-/ As- ≥3.4	1	22	100	0	BA-AVF (100)	Ultrasound
Gkotsis, '15 Banding[27]	C+/ H-/ As- ≥1.1	12	42 (15-73)	75	NR	NR	Ultrasound
Vaes, '15 Banding[28]	C±/ H-/ As+ ≥1	50	51 ±14	60	6	BA-AVF (96) RA-AVF (4)	Dilution
Balamuthusamy, '16 Banding[29]	C+/ H-/ As- ≥2	12	65 ±14	NR	83	BA-AVF (100)	Ultrasound
Teixeira, '17 Banding[30]	C+/ H-/ As- >1.5 C-/ H+/ As- NR	55 64	56 (21-87) 66 (22-90)	64 58	24 56	BA-AVF (95) RA-AVF (5) BA-AVF (86) RA-AVF (8) BA-AVG (6)	Ultrasound
Baker, '17 Banding[31]	C-/ H+/ As- ≥2.4	1	34	0	100	BA-AVF (100)	Ultrasound
Letachowicz, '18 EDAB[32]	C+/ H-/ As- ≥0.9	5	63 (40-77)	60	0	RA-AVF (100)	Ultrasound
Mallios, '18 Banding[33]	C-/ H-/ As+ ≥2	1	75	100	0	BA-AVF (100)	Ultrasound

Qa pre L/min mean (range)	Qa post L/min mean (range)	Qa tool Intra	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
2.6 (1.3-4.0)	0.6 (0.6-0.7)	EM-probe	0	NR	NR	0	NR
2.1 (1.4-2.9)	0.6 (0.5-0.7)	EM-probe	0	9 (8-10)	0	0	100
3.1 (1.6-4.9)	0.9 (0.2-2.2)	Catheter	Thrombosis (1)	5 (0.5-12)	1	1	75
3.7	1.4	EM-probe	0	42	0	0	100
5.2	3	Catheter	0	12	1	0	100
1.5 (0.6-2.8)	0.8 (0.3-1.5)	Dilution	0	18 (6-70)	1	3	91
2.6	1.3	Dilution	Thrombosis (1)	11 (0-37)	4	2	89
1.6 (0.9-4.2)	0.8 (0.4-2.1)	Ultrasound	0	8 (3-24)	0	0	91
3.4	1.7	EM-probe	0	1	0	0	100
2.2 (1.1-3.3)	0.6 (0.5-0.9)	Ultrasound	0	12 (1-18)	0	0	100
3.1 ±0.1	1.5 ±0.1	Ultrasound Transit time	Thrombosis (1) Infection (1)	6 (1-12)	26	3	100
3.7 ±0.8	1.1 ±0.4	Ultrasound	0	6	0	0	100
2.4 ±0.7 1.7 ±0.7	1.0 ±0.2 0.7 ±0.2	Ultrasound	Thrombosis (10) Rupture (3) False aneurysm (1)	NR	6	NR	91
2.4	0.8	Ultrasound	0	12	0	0	100
1.4 (0.9-2.5)	0.5 (0.4-0.6)	Ultrasound	0	0	0	0	NR
2.5	1.0	Ultrasound	Wall rupture & aneurysm (1)	2	1	0	100

Table 1 continues on the next page.

Table 1 continued.

Author, year	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Qa-method pre
Kahraman, '19 Banding[34]	C±/ H-/ As+ ≥1.2	10	48 ±11	40	30	NR	Ultrasound
Lee, '20 Dynamic band[35]	C±/ H-/ As± ≥2	5	60 (16-80)	NR	0	RA-AVF (40) RA-AVG (40) BA-AVF (20)	Ultrasound
Turner, '20 Banding[36]	C+/ H-/ As- ≥5	1	53	100	0	BA-AVF (100)	Ultrasound
Wan, '20 MILLER[37]	C+/ H-/ As- ≥1.5	1	65	100	0	RA-AVF (100)	Ultrasound
Matoussevitch, Banding '21[56]	C±/ H±/ As± ≥1.5	42	49 (20-89)	72	5	BA-AVF (50) RA-AVF (50)	Ultrasound
Total N=21 publications		**378**	**55 (15-90)**	**61**	**30**	**BA-AVF (70) RA-AVF (13) BA-AVF (3) RA-AVG (1) FA-GSV (1) FA-Bovine (1) NR (11)**	

C, Cardiac complaints; H, Hand ischaemic complaints; As, Asymptomatic; N, Number; DM, Diabetes Mellitus; Qa, access flow; Pre, preoperative; Post, postoperative; Intra, intraoperative; FU, follow up; Re-HFA, recurrent or persistent high flow access; FA, femoral artery based; AVA, Arteriovenous access; Bovine, bovine shunt; GSV, Greater saphenous vein; EM-probe, electromagnetic probe; NR, not reported; RA, radial artery based; AVF, arteriovenous fistula; BA, brachial artery based; AVG, arteriovenous graft; MILLER, minimally Invasive limited ligation endoluminal-assisted revision; EDAB, external dilator assisted banding. *The second paper added data without adding new patients.

Qa pre L/min mean (range)	Qa post L/min mean (range)	Qa tool Intra	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
1.3 ±0.1	0.6 ±0.1	Ultrasound	0	0	0	0	NR
3.0 (1.3-4.5)	1.1 (0.5-1.2)	Ultrasound	0	12 (12-12)	0	0	100
5.0	1.2	Ultrasound	0	24	1	0	100
3.1	0.7	Ultrasound	0	6	0	0	100
2.6 (1.5-6)	0.7 (0.3-1.3)	Ultrasound	Bleeding (3) Thrombosis (1)	12 ±3	8	3	85
2.5 (0.6-6.0)	**1 (0.3-2.2)**		**Thrombosis (14) Rupture (4) Bleeding (3) (Pseudo) Aneurysm (2) Infection (1)**	**10 (1-70) Total 2377**	**50**	**12**	**92**

Table 2. Publications on banding of high flow accesses not guided by a flow tool.

Author, year	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Qa-method pre
Tzanakis, '99 Banding[38]	C+/ H-/ As- ≥1	1	48	100	0	RA-AVF (100)	Ultrasound
Malik, '03 Banding[39]	C-/ H+/ As- ≥1.5	2	NR	NR	0	NR	Ultrasound
Schneider, '06 T-Banding[40]	C+/ H-/ As- ≥1	22	63 (45-81)	73	0	BA-AVF (91) RA-AVF (9)	Ultrasound
Lombi, '10 Banding[41]	C+/ H-/ As- ≥2	1	61	0	0	RA-AVF (100)	Ultrasound
Rokosny, '14[52]	C±/ H±/ As+ ≥2.5	62	60 (28-81)	63	16	RA-AVF (65) BA-AVF (35)	Ultrasound
Ladenheim, '15 MILLER[42]	C-/ H+/ As- ≥1.3	1	63	0	0	BA-AVF (100)	Ultrasound
Shintaku, '15 MILLER[43]	C±/ H-/ As± ≥1.4	7	54	86	0	RA-AVF (100)	Ultrasound
Kanno, '15 Banding[44]	C+/ H-/ As- ≥0.6	37	64 (38-83)	62	19	BA-AVF (54) RA-AVF (46)	Ultrasound
Imran, '15 Banding[45]	C+/ H-/ As- ≥5	1	65	100	0	RA-AVF (100)	Ultrasound
Letachowicz, '16 EDAB[46] -Art. (9) -Ven. (3)	C+/ H-/ As- ≥1.5	12	54 (30-77)	42	NR	RA-AVF (75) BA-AVF (25)	Ultrasound
Ragupathi, '16 Banding[47]	C+/ H-/ As- ≥2	1	54	100	0	BA-AVF (100)	Ultrasound
Nojima, '18 Banding[48]	C±/H±/ As± ≥1.4	4	67 (50-89)	50	25	RA-AVF (75) BA-AVF (25)	Ultrasound
Warja, '20 MILLER[49]	C+/ H-/ As- ≥2.8	1	18	NR	100	BA-AVF (100)	Ultrasound
Cerqueira, '21 EDAB[50]	C±/ H+/ As- ≥1	6	61 (47-80)	33	50	BA-AVF (100)	Ultrasound
Malik, '21 Banding[51]	C+/ H-/ As- ≥1.5	9	57 (27-73)	78	0	RA-AVF (56) BA-AVF (44)	Ultrasound
Total N=15 publications		**167**	**60 (18-89)**	**64**	**16**	**BA-AVF (61) RA-AVF (39)**	

C, Cardiac complaints; H, Hand ischaemic complaints; As, Asymptomatic; N, Number; DM, Diabetes Mellitus; Qa, access flow; Pre, preoperative; Post, postoperative; FU, follow up; Re-HFA, recurrent or persistent high flow access; RA, radial artery based; AVF, arteriovenous fistula; NR, not reported; BA, brachial artery based; MILLER, minimally Invasive limited ligation endoluminal-assisted revision; EDAB, external dilator assisted banding; Art., arterial; Ven., venous.

Qa pre L/min mean (range)	Qa post L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
1.6	0.6	0	6	0	0	100
1.7 (1.7-1.7)	0.8 (0.8-0.8)	0	6 (6-6)	0	0	100
2.0 (1.3-3.2)	1.0 (0.6-1.4)	Hematoma (2) Thrombosis (2)	2 (1-3)	5	0	100
7	3	0	NR	1	0	NR
4 ±1.9	1.7 ±0.8	Bleeding (3) Infection (3) Thrombosis (1)	15 ±15	3	8	80
1.3	0.7	Pseudoaneurysm & band migration (1)	2	1	0	100
2.0 (1.4-2.6)	1.2 (0.9-2.0)	Thrombosis (1)	12	1	0	83
1.3 (0.6-4.6)	0.5 (0.2-1.3)	Thrombosis (9) Infection (2)	NR	7	NR	75
5.0	1.8	0	1	0	0	100
3.7 ±0.8	1.5 ±0.3	0	5 (1-10)	0	0	100
8	4.3	0	2	1	0	100
2.1 (1.8-3.0)	0.6 (0.4-0.7)	0	26 (4-60)	0	2	75
2.8	3.0	0	1	1	0	100
2.1 (1.6-30)	1.5 (1.2-1.8)	Infection (1) Aneurysm (1)	12	0	0	100
2.3 (1.3-3.9)	1.5 (0.7-2.5)	0	1.5	4	0	100
2.1 (0.6-8)	**1 (0.2-4.3)**	**Thrombosis (13) Infection (6) Bleeding (3) Haematoma (2) (Pseudo) aneurysm (2) Band migration (1)**	**12 (1-60) Total 1280**	**24**	**2**	**86**

Table 3. Publications on revision using distal inflow (RUDI) and plication for flow reduction of a high flow access.

Author, year RUDI	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Qa-method pre
Andrade, '04 PTFE[57]	C±/ H+/ As- ≥1	2	39 (29-48)	100	50	BA-AVF (100)	Ultrasound
Chemla, '07 PTFE[58]	C+/ H-/ As- ≥1.6	17	54 (31-76)	59	NR	BA-AVF (88) BA-AVG (12)	Dilution
Parmar, '09 GSV[59]	C+/ H-/ As- ≥10	1	50	100	0	BA-AVF (100)	Ultrasound
Beecher, '10 Vein[60]	C-/ H+/ As- ≥2	2	60 (56-64)	100	100	BA-AVF (100)	Ultrasound
Vaes, '15 Basilic vein[61]	C+/ H±/ As± ≥1.5	4	53 (38-64)	75	0	BA-AVF (100)	Dilution
Misskey, '16 PTFE (15) GSV (3)[62]	C-/ H+/ As- NR	20	64 ±15	55	85	BA-AVF (100)	Dilution
Loh, '16 Direct (17) Vein (1)[63]	C±/ H±/ As± ≥1.5	28	55 ±3	43	69	BA-AVF (96) BA-AVG (4)	Ultrasound
Gerrickens, '18 GSV[6]	C±/ H±/ As± ≥1.5	21	54 (28-75)	67	10	BA-AVF (100)	Dilution
Leskovar, '19 Cormatrix[64]	C-/ H-/ As+ ≥2	1	53	0	0	BA-AVF (100)	Ultrasound
Malik, '21 NR[51]	C+/ H-/ As- ≥1.5	14	62 (43-78)	71	0	BA-AVF (79) RA-AVF (21)	Ultrasound
Total N=10 publications		**110**	**57 (28-78)**	**62**	**44**	**BA-AVF (94) RA-AVF (3) BA-AVG (3)**	

Author, year Plication	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Qa-method pre
Shemesh, '99[65]	C-/ H+/ As-	1	65	0	0	BA-AVG (100)	Ultrasound
Schenk, '01[66]	C-/ H-/ As±	1	28	100	0	BA-AVF (100)	Ultrasound
Aschwanden, '03[67]	C-/ H+/ As-	2	72 (60-78)	100	0	BA-AVF (100)	Ultrasound
Tellioglu, '08 [68]	C±/ H±/ As-	30	48 (9-57)	53	0	AVF (83) AVG (17)	Ultrasound
Patel, '15 [69]	C-/ H+/ As-	26	58±15	58	62	BA-AVF (100)	NR
Kanno, '15[44]	C+/ H-/ As-	25	64 (29-86)	68	20	RA-AVF (72) BA-AVF (28)	Ultrasound
Ferrante, '16[70]	C-/ H+/ As-	1	86	100	0	RA-AVF (100)	Ultrasound

Qa pre L/min mean (range)	Qa post L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
1.2 (1.1-1.2)	0.6 (0.5-0.7)	0	6 (6-6)	0	1	100
3.1 (1.9-4)	1 (0.4-2.6)	Thrombosis (5)	16 (7-39)	1	0	77
10.4	3.6	0	7	1	0	100
2.5	1.1	0	24 (24-24)	0	0	100
3.2 (2.9-3.4)	1.8 (0.9-3.2)	0	8 (3-12)	3	0	100
1.9 ±0.5	0.9 ±0.2	Wound complication (1)	24 (0-48)	0	1	78
2.2 ±0.2	1 ±0.1	0	15 +2	4	0	87
3.1 (1.5-4)	1.2 (0.6-1.9)	Thrombosis (3) Haematoma (2) Pseudoaneurysm (1)	28 (0-36)	9	2	84
2.3	0.8	0	12	0	0	100
3.5 (1.7-7.5)	1.3 (0.6-2.0)	Thrombosis (1)	1.5	5	0	100
2.8 (1.1-10.4)	**1.1 (0.4-3.2)**	**Thrombosis (9) Bleeding (2) Pseudoaneurysm (1) Wound complication (1)**	**17 (0-48) Total 1892**	**23**	**4**	**86**

Qa pre L/min mean (range)	Qa post L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
1.2	0.9	0	28	0	0	100
5.8	1.9	0	1	0	0	100
1.5 (1.4-1.6)	0.5 (0.4-0.6)	0	8 (3-12)	0	0	100
2.7 (1.9-3.6)	0.6 (0.5-1)	0	12 (12-12)	0	0	97
2 ±0.8	0.6 ±0.5	0	12	NR	0	92
1.3 (0.6-2.4)	0.6 (0.3-1.1)	Thrombosis (1)	NR	1	0	96
2.1	1.1	0	2	0	0	100

Table 3 continues on the next page.

Table 3 continued.

Author, year	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Qa-method pre
Nojima, '18[48]	C±/ H±/ As±	5	72 (61-79)	60	40	BA-AVG (60) RA-AVF (40)	Ultrasound
Marumatsu, '18[54]	C-/ H-/ As+ ≥1.3	1	52	0	0	BA-AVF (100)	Ultrasound
Total N=9 publications		**92**	**57 (9-86)**	**60**	**39**	**BA-AVF (40) AVF (27) RA-AVF (23) AVG (5) BA-AVG (4)**	

C, Cardiac complaints; H, Hand ischaemic complaints; As, Asymptomatic; N, Number; DM, Diabetes Mellitus; Qa, access flow; Pre, preoperative; Post, postoperative; FU, follow up; Re-HFA, recurrent or persistent high flow access; RA, radial artery based; AVF, arteriovenous fistula; BA, brachial artery based; AVG, arteriovenous graft; NR, not reported; RUDI, revision using distal inflow; PTFE, polytetrafluorethylene; GSV, greater saphenous vein; Vein, venous graft; Direct, direct anastomosis without graft.

	Qa pre L/min mean (range)	Qa post L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
	1.4 (1.4-1.7)	0.5 (0.3-0.9)	0	19 (5-34)	2	1	60
	1.3	0.9	0	2	0	0	100
	2 (0.6-5.8)	**0.6 (0.3-1.9)**	**Thrombosis (1)**	**12 (1-34) Total 816**	**3**	**1**	**93**

Table 4. Publications on the graft interposition technique (GIT), proximal radial artery ligation (PRAL), venous aneurysm repair and miscellaneous other techniques for flow reduction of a high flow access (HFA).

Author, year GIT	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Qa-method pre
Rosental, '80[71]	C-/ H+/ As- ≥1.6	1	28	NR	100	Bovine (100)	EM-Probe
Aschwanden, '03[67]	C-/ H+/ As- ≥1.4	1	67	100	0	BA-AVF (100)	Ultrasound
Lubas, '13[72]	C+/ H-/ As- ≥2	1	48	100	0	BA-AVF (100)	Ultrasound
Kaneko, '18[73]	C+/ H-/ As- ≥2	1	55	0	0	RA-AVF (100)	Ultrasound
Nojima, '18[48]	C±/ H±/ As± ≥1.4	16	62 (37-83)	75	25	RA-AVF (69) BA-AVF (31)	Ultrasound
Leskovar, '19[64]	C-/ H-/ As+ ≥2	1	52	100	0	BA-AVF (100)	Ultrasound
Hashimoto, '20[74]	C+/ H-/ As- ≥1.5	25	61 ±13	56	20	RA-AVF (64) BA-AVF (36)	Ultrasound
Total N=7 Publications		**46**	**60 (28-89)**	**64**	**22**	**RA-AVF (62) BA-AVF (37) Bovine (2)**	

Author, year PRAL	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Qa-method pre
Smith, '08[75]	C+/ H-/ As- ≥1	1	32	0	0	RA-AVF (100)	Dilution
Oe, '09[76]	C+/ H-/ As- ≥2	1	68	0	0	RA-AVF (100)	Ultrasound
Bourquelot, '10[77]	C±/ H±/ As± ≥1	29	45 (16-82)	59	0	RA-AVF (100)	Ultrasound
Total N=3 Publications		**31**	**45 (16-82)**	**55**	**0**	**RA-AVF (100)**	

Qa pre L/min mean (range)	Qa post L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
1.6	0.9	0	NR	0	0	100
2.8	0.9	0	29	0	0	100
2.5	1.4	0	5	1	0	100
2.2	0.9	0	12	0	0	100
2.3 (1.4-3.6)	0.9 (0.6-1.2)	0	34 (1-68)	0	1	88
3.5	1.8	Thrombosis (1)	4	0	0	0
3.4 (1.8-6)	1.5 (0.5-2.2)	Thrombosis (5) Infection (1)	47 (1-112)	0	2	72
2.9 (1.4-6)	**1.3 (0.6-2.2)**	**Thrombosis (6) Infection (1)**	**39 (1-112) Total 1769**	**1**	**3**	**78**

Qa pre L/min mean (range)	Qa post L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
3	1.2	0	6	0	0	100
4.1	1.9	0	1	0	0	100
1.7 (1-3)	0.8 (0.5-1.6)	Thrombosis (1) Aneurysm (1)	20 (0-89)	2	0	78
1.8 (1-4.1)		**Thrombosis (1) Aneurysm (1)**	**19 (0-89) Total 587**	**2**	**0**	**81**

Table 4 continues on the next page.

Table 4 continued.

Author, year Aneurysm Repair	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Qa-method pre
Shah, '18[53]	C+/ H-/ As- ≥1.5	1	36	0	0	BA-AVF (100)	Ultrasound
Wan, '19[55]	C-/ H-/ As+ ≥1	41	37 (18-60)	71	10	RA-AVF (95) BA-AVF (5)	Ultrasound
Total N=2 publications		**42**	**37 (18-60)**	**69**	**10**	**RA-AVF (93) BA-AVF (7)**	

Author, year, technique Miscellaneous	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Qa-method pre
Bourquelot, '09[78] RAT	C±/H±/As± ≥0.8	47	44 (3-82)	53	11	BA-AVF (100)	Ultrasound
Kanno, '15[44] Art. Band & ligation	C+/ H-/ As- ≥0.6	12	72 (39-86)	50	8	RA-AVF (100)	Ultrasound
Gerrickens, '18[5] BVT	C±/ H±/ As- ≥0.8	10	61 (54-75)	80	40	BA-AVF (100)	Dilation
Hong, '20[79] Stent graft	C-/ H-/ As+ ≥1.5	3	62	NR	NR	BA-AVF (100)	Ultrasound
Katsui, '20[80] RAHT	C+/ H-/ As- ≥1.5	1	73	0	0	RA-AVF (100)	Ultrasound
Mallios, '20[81] Endo-RUDI	C-/ H-/ As+ ≥2	1	60	100	0	BA-AVG (100)	Ultrasound
Total N=6 Publications		**74**	**62 (3-86)**	**56**	**14**	**BA-AVF (81) RA-AVF (18) BA-AVG (1)**	

GIT, graft interposition technique; C, Cardiac complaints; H, Hand ischaemic complaints; As, Asymptomatic; N, Number; DM, Diabetes Mellitus; Qa, access flow; Pre, preoperative; Post, postoperative; FU, follow up; Re-HFA, recurrent or persistent high flow access; NR, not reported; Bovine, bovine shunt; EM-probe, electromagnetic probe; BA, brachial artery based; AVF, arteriovenous fistula; RA, radial artery based; PRAL, proximal radial artery ligation; RAT, radial artery transposition; Art. Band & ligation, arterial banding and ligation; BVT, basilic vein transposition; RAHT, re-implantation of an artery with a hairpin turn; Endo-RUDI, endovascular revision using distal inflow; AVG, arteriovenous graft; NA, not applicable.

Qa pre L/min mean (range)	Qa post L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
5.2	1.2	0	9	0	0	100
1.6 ±0.3	0.8 ±0.1	0	27 (12-43)	0	2	NR
1.7 ±0.3	**0.8 ±0.1**	**0**	**26 (9-43) Total 1116**	**0**	**2**	**NA**

Qa pre L/min mean (range)	Qa post L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
1.7 (0.8-3.0)	0.6 (0.2-1.9)	0	20 (0-189)	0	5	70
1.4 (0.7-2.5)	0.6 (0.3-0.8)	Infection (1)	NR	1	0	100
1.8 (0.8-2.1)	1.2 (0.7-1.9)	Pseudoaneurysm (1)	2 (2-2)	0	0	100
1.7 (1.5-1.9)	1 (0.9-1.1)	0	8 (6-12)	0	0	100
2.3	0.6	0	2	0	0	100
2.2	0.8	0	6	0	0	100
NA	**NA**	**Infection (1) Pseudoaneurysm (1)**	**15 (0-189) Total 792**	**1**	**5**	**NA**

Discussion

Indication, definition and work-up

Aim of this scoping review is to provide an overview of available evidence regarding the spectrum of surgical techniques for Qa reduction in a high flow access (HFA). The incidence of HFA may be up to 4% in general HD-populations.[7] Unfortunately, a universally accepted definition of HFA is lacking, hampering the initiation of high level evidence trials. Recent dialysis guidelines proposed a 1.0 to 1.5 L/min Qa-cut-off value.[15,16] However, indexing Qa is intuitively more appealing.[87] For instance, a man standing two-meter-tall likely suffers less from the cardiovascular effects of a Qa >2.0 L/min compared to a woman weighing 45 kg. Indexing may be based on body surface area, height$^{2.7}$ or cardiac output.[88,89] As the optimal method of indexing has yet to be established, publications only reporting corrected Qa values were excluded from this review.

The roles of patient history and physical examination in HFA management are unclear. Dyspnea, tachypnea, peripheral edema, systolic bruits, a gallop rhythm and hand ischaemia may reflect a symptomatic HFA.[7] Serial use of a validated heart failure questionnaire (e.g., Minnesota questionnaire) may identify progressive cardiac overload contributing to a decision to intervene.[90] The current review confirms a diversity in HFA work-up and criteria for Qa reduction. The role of echocardiography should standardly be studied, appreciating that 75% of ESRD patients already demonstrate left ventricular hypertrophy prior to hemodialysis initiation.[91,92] Left ventricular mass significantly increased at one, three and twelve months after AVA creation, even in the absence of high Qa.[82,93] The present review found that just 41% of operated HFA patients received a preoperative echocardiographic evaluation. Biomarkers such as brain natriuretic peptide or atrial natriuretic peptide in maturing AVA and before and after Qa reduction deserve further study.

Based on the current findings of this overview, several practical recommendations can be made in the face of a decision to perform Qa reducing surgery or not. Factors such as extremely high Qa, the presence of cardiac or hand ischaemia or a history of myocardial infarction support a decision towards surgery. In contrast, short life expectancy, a single measurement of high Qa or stable renal transplant function and a wish for access ligation may aid in the decision not to operate. Number and weight of factors potentially guiding invasive HFA treatment are listed in Figure 3.

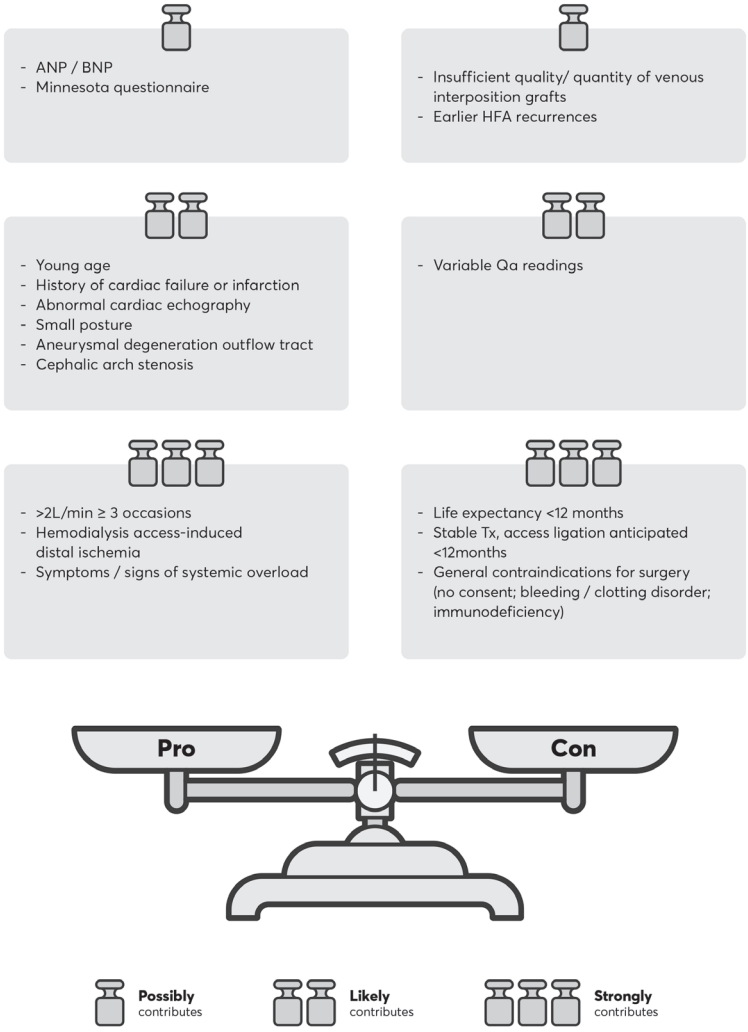

Figure 3. Factors that may contribute to the decision to reduce access flow (pro, left colomn) or conversely, not to reduce access flow (con, right colomn); ANP, Atrial Natriuretic Protein; BNP, Brain Natriuretic Protein; HFA, high flow access; Qa, access flow; Tx, renal transplantation.

Techniques

A range of surgical techniques reducing Qa were introduced in recent years. However, most experience is gained with banding which was introduced in the 1970's.[8] Efficacy and patency rates of banding are acceptable. It is relatively simple to perform and re-perform in case of a recurrence. Furthermore, it can be executed under local, regional and general anaesthesia. High Qa recurrence rates following banding (overall <20% in this review) differed greatly among publications with one study reporting rates as high as 52% (>2 L/min) within one year.[28] The vast variety of banding techniques and different intraoperative Qa measurement tools possibly explain why the use of an intraoperative Qa technique did not seem to improve success rates in comparison to studies in which no intraoperative Qa tool was used. This variation highlights the need for standardization of both surgical technique and intraoperative Qa measurement tools in order to optimize outcome following banding.

RUDI and PRAL were recently promoted for HFA reduction but long term data are scarce.[6,77] A 1-year follow-up study indicated that a recurrence occurred just once after RUDI (6%).[61] After three years however, HFA had recurred in 50% of the patients.[6] Both RUDI and PRAL are only feasible in patients having a defined type of vascular anatomy. RUDI can be performed in brachial artery based AVAs only and is relatively complicated to perform requiring extensive surgery.[6] PRAL can only be executed in a forearm AVA.[77] In both techniques, the ulnar and radial artery as well as the palmar arch should be intact to preserve distal perfusion.[77,87]

Resection of venous aneurysms, known to occur in up to 17% of AVA's,[15] was found to lead to a (mild) drop in Qa.[53,55] However, most studies on aneurysm resection in high Qa states additionally perform a secondary technique (e.g. banding or plication) in order to maintain an acceptable Qa.[52,54] As the longevity of aneurysm resection for Qa reduction without these co-interventions is questioned and long term data are scarce, one may argue that aneurysm repair in itself cannot be termed a flow reductive technique.

As the aim of this overview was to describe surgical techniques for Qa reduction, studies on proximalization of arterial inflow (PAI; Figure 2H), a revascularization technique popularized for the treatment of HAIDI, were excluded. Interestingly however, a slight decrease in Qa (0.5 L/min) on a group level was found following PAI, but only in patients with brachial artery based access.[94,95]

Asymptomatic HFA

It may be intuitive that a symptomatic HFA requires treatment. Conversely, management of -seemingly- asymptomatic HFA remains controversial. Earlier studies suggested an association between an AVA with inappropriately high Qa and HOCF.[8-11] A Qa >2.0 L/min was predictive of HOCF in 10 patients with stage C heart failure.[12] Yadav et al. recently showed that an initial access Qa <0.9 L/min was associated with an increased risk of cardiovascular mortality. Conversely, values of Qa that are standardly obtained for access monitoring were of little relevance with respect to survival. Qa increases over 3 month periods as calculated using a joint-modelling technique did show a significant association with cardiovascular mortality.[96] It remains uncertain whether AVA reduction in HFA patients decreases (cardiovascular) mortality. Interestingly, four year survival in 10 patients undergoing Qa reductive surgery was 100% compared to 55% in 155 patients who did not.[96] Whether these patients were symptomatic or not was not reported. Is there other circumstantial evidence supporting surgical Qa reduction in asymptomatic HFA? The present review identified just 37 deaths during 886 observed patient years (1:24) in both symptomatic and asymptomatic patients. In contrast, a recent publication on the natural history of a general HD ward reported 21 deaths during 148 observed patient years (1:7). However, mean age in the latter population was substantially higher and diabetes more common.[97] It is concluded that the slim body of evidence on Qa reduction and its effect on mortality in both symptomatic and asymptomatic HFA patients does not allow for firm conclusions.

Limitations

This review suffers from shortcomings that are inherent to limited volumes of patients, lack of randomized controlled trials, diversity in work-up and broad range of surgical techniques. Publication bias may have led to overestimation of effectiveness and access patency rates. Conference abstracts were excluded, possibly leading to exclusion of newer or yet less-accepted methods of Qa reduction. However, it must be appreciated that the aim of this scoping review was to offer an overview of the surgical management of HFA possibly aiding future researchers and clinicians alike.

Future directions

Are there any future directions in HFA management? The present review identified controversies that must be considered in order to optimize management of HFA in both symptomatic and asymptomatic HFA patients. An important step is the conduction of large scale prospective studies comparing different interventions in symptomatic HFA patients, ideally following randomization and considering multiple Qa measurements using a statistical joint modelling technique. Suggested primary outcome parameters are resolution of concomitant cardiac and HAIDI related complaints, long-term efficacy, cardiac events and mortality. Secondary outcomes should encompass echocardiographic parameters, cardiac biomarkers and quality of life. Randomized controlled trials on asymptomatic HFA comparing 'watchful waiting' and 'preventive surgery' on matters of survival, cardiac events and quality of life are warranted to elucidate whether early interventions are indicated. Future trials should standardly include echocardiographic findings and ultra-sonographic measurement of pre- intra- and postoperative brachial arterial Qa. Additionally, a specification of the used definition of HFA (or high Qa) is required. This also holds true for recurrent HFA or recurrent high Qa. Ideally, cardiac biomarkers and digital pressures are considered as well as means to quantify high Qa related complaints of cardiac origin (e.g., Minnesota questionnaire),[90] and hand ischaemia (e.g., the Hand ischaemic questionnaire).[5,97]

Conclusion

In conclusion, the present scoping review evaluates the reported experience on invasive treatment of high Qa arteriovenous haemodialysis accesses. However, the optimal sequence of management steps is unknown due to a lack of standardisation of definitions, diagnostic work-up and surgical techniques. There is an urgent need for RCTs to determine if - and if so, which – HFA patients benefit from access Qa reduction.

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Chapter 6

Basilic vein transposition for unsuitable upper arm hemodialysis needle access segment may attenuate concurrent hand ischemia

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Abstract

Introduction

Some hemodialysis patients with a brachial arteriovenous fistula (AVF) have an unsuitable upper arm needle access segment (NAS) necessitating basilic vein transposition (BVT). It was frequently observed that a portion of these patients spontaneously experienced a warmer and less painful dialysis hand after BVT. Aim of this study was to determine whether BVT for an inadequate NAS attenuated hemodialysis access-induced distal ischemia (HAIDI) in patients with a brachial AVF.

Methods

Patients with a brachial AVF and an unsuitable NAS also reporting hand ischemia and scheduled to undergo BVT between 2005 and 2016 in a single facility were studied. Hand ischemia was graded as proposed in a 2016 consensus meeting. Hand ischemic questionnaire (HIQ-) scores (0 points, no ischemia – 500 points, maximal ischemia), digital brachial index (DBI, ischemia <0.6) and access flow (mL/min) before and after BVT were compared. The cephalic vein and all side branches of the basilic vein were ligated during the BVT.

Results

Ten patients were studied (8 males, 61 [54-75] years). BVT was performed 8 [4-10] months following the initial AVF construction. HIQ-scores dropped from 220 [71-285] to 9 [0-78] (P=.043) postoperatively, whereas DBI increased from 0.51 [0.39-0.67] to 0.85 [0.68-0.97] (P=.012). DBI and HIQ-scores were inversely correlated (R^2=71%, P=.001). Access flows dropped significantly ($Flow_{pre}$ 1120 mL/min [1100-2300] versus $Flow_{post}$ 700 mL/min [600-1760]; P=.018). Surgery-associated complications were absent and dialysis continued uninterruptedly. Eight patients reported total recovery from hand ischemia six weeks postoperatively.

Conclusions

Basilic vein transposition for an unsuitable upper arm needle access segment may attenuate hand ischemia in patients with a brachial AVF previously reporting hemodialysis access-induced distal ischemia.

Introduction

Due to aging populations and associated higher incidences of diabetes mellitus and atherosclerosis, the rate of brachial artery-based arteriovenous fistulas (AVFs) in patients requiring hemodialysis (HD) will rise at the expense of radial artery based AVFs.[1] The upper arm needle access segment (NAS) of some brachial artery-based AVFs does not mature adequately and may remain too short, too deep or too curved precluding two needle placement. Upper arm cannulation options may then be optimized by a basilic vein transposition (BVT).[2,3]

Over time, a brachial artery-based AVF may lead to complications including hand ischemia (hemodialysis access-induced distal ischemia, HAIDI).[4] Several studies suggest that HAIDI is caused by a loss in perfusion pressure along the arterial heart-arm axis.[5,6] Diagnostic efforts are therefore directed towards identifying sources of blood pressure loss. If inflow arteries are patent, HAIDI may in part be caused by the arteriovenous anastomosis' pressure sink and/or lower arm atherosclerosis.[7] Recent studies demonstrated that patent venous side branches (SB) of a brachial artery based AVF also may lead to blood pressure loss and may contribute to hand ischemia. Moreover, side branch ligation (SBL) mitigated signs and symptoms of HAIDI.[8,9]

A BVT procedure includes ligation of the basilic vein's SBs as well as the cephalic vein. We incidentally observed that patients who underwent a BVT for an insufficiently matured NAS spontaneously reported a warmer and less painful dialysis hand after the operation. Aim of the study was to determine whether BVT attenuated signs and symptoms of hand ischemia in patients having an unsuitable upper arm NAS and who were also reporting coincident HAIDI.

Material and methods

General information

At present, approximately 110 patients receive HD in Máxima Medical Centre (MMC), Veldhoven, The Netherlands. Furthermore, about 100 AVF-related operations are performed annually. If construction of a radio-cephalic (RC-) AVF is deemed impossible as judged by preoperative Duplex imaging, our preferred technique is the creation of a brachial artery based AVF termed a Gracz fistula. This type of AVF entails mobilizing of the median

cubital vein or a deep perforating venous branch that is subsequently connected to the brachial artery some 2 cm distal to the elbow fold. Using this technique, outflow is usually via upper arm cephalic and basilic veins and their SBs.[10,11]

Inadequate needle access segment and HAIDI

Access flow of our HD population is standardly measured in duplicate every two months as suggested by KDOQI[12] using a standard two-needle dilution technique (HD03, Transonic Systems Inc, New York, USA). Each patient with structurally complicated HD sessions is discussed in a weekly multidisciplinary meeting attended by a nephrologist, vascular surgeon, interventional radiologist, vascular laboratory technician and nurses of the shunt team. If the upper arm access segment of an elbow-based AVF is considered inadequate for placement of two needles leading to a suboptimal dialysis, a Duplex is performed for access imaging and flow measurement. Conversion to a BVT is discussed if the basilic vein is considered of sufficient diameter (> 3-4 mm) and length (> 10 cm).

The multidisciplinary team has a special interest in the management of hand ischemia. Each patient reporting symptoms possibly associated with ischemia is also discussed in the weekly meeting. If the history suggests HAIDI (pain, cramps, coldness, loss of strength and/or diminished sensibility), a questionnaire scores symptomatology (hand ischaemic questionnaire, HIQ). Scores range from 0 (no symptoms associated with ischemia) to 500 (maximal symptoms of ischemia) [4]. Several studies have indicated that a HIQ-score reflects grade of ischemia and may be used to determine efficacy of remedial surgery.[4,6,8,9,13,14] For instance, access outflow banding diminished HIQ scores from 153 ±33 to 42 ±15 whereas ischemia was largely abolished.[13] Moreover, SBL in another population of HAIDI patients decreased HIQ scores from 184 ±21 to 60 ±5.[9] Conversely, HIQ scores in a random HD-population not reporting hand ischemia were predictably <50 using this 0-500-point scale.[15]

If HAIDI is suspected on the basis of history and HIQ scores, a physical examination at the outpatient vascular department is performed including hand inspection and radial artery palpation. Compression of upper arm cephalic and basilic veins is performed to test reversibility of ischemia. An index finger plethysmography with and without AVF compression is executed (Vasoguard Nicolet 8 MHz, Scimet, Bristol, UK). A <50 mmHg

finger pressure (P_{dig}) or a <0.6 digital brachial index (DBI) are accepted cut-off points of hand ischemia.[16-18] The degree of HAIDI was scored as advised in a recent consensus document.[19] Additional imaging using a Seldinger or MR-angiography is indicated if patients suffered from a grade 2b, 3 or 4 HAIDI, unless an arterial stenosis is deemed highly unlikely as in very young HD patients.

Some patients with a brachial AVF having an unsuitable upper arm NAS also report symptoms of HAIDI. Patients were included in the present study if they harboured a brachial artery based AVF, if they had an unsuitable NAS - defined as repetitive faulty and problematic two needle cannulation due too inadequate length, excessive depth or tortuosity as deemed by the nurses of the shunt team and discussed in the multidisciplinary team - that would benefit from a BVT, and if they suffered from at minimal grade 2a HAIDI. They were excluded if there were signs of impaired mental capacity or a language barrier or if a simultaneous additional (endo) vascular procedure for HAIDI was conducted. Patients were informed on the nature of the operative procedure and consented to its specifics verbally and in writing. Our ethics committee deemed that evaluation of the study protocol was not necessary, since the present analysis was considered auditing of surgical results and evaluation of patient-reported outcome measures (PROM).

Operative protocol

Each patient was operated under general anaesthesia using a standard protocol. Serial monitoring of finger pressures under strict sterile conditions in patients suffering from a minimal 2b HAIDI was performed (P_{dig} in mmHg, index finger of the hemodialysis hand; VasoGuard Nicolet, 8 Mhz, Scimed Ltd, Bristol, UK). Serial measurements of heart rate (HR, beats/min), blood pressure (SBP, systolic blood pressure; DBP, diastolic blood pressure, mmHg) were obtained from the contralateral arm at regular intervals via an on-line electrocardiogram and a sphygmomanometer. The basilic vein was disconnected from the arterial anastomosis in the elbow area and dissected via 2-3 separate incisions (Figure 1A). All of its SBs including the distal basilic vein, perforating veins and upper arm cephalic vein were ligated. Special care was taken not to damage the accompanying medial brachial cutaneous nerve (Figure 1B). The basilic vein was superficially rerouted along the anterolateral aspect of the biceps muscle and re-anastomosed to the brachial artery (Figure 1C). Intraoperative success

was determined by a combination of palpable thrill, increased radial artery pulsations, a warmer hand and increase in DBI. Single access needling was allowed immediately on the day of surgery or on the first postoperative day followed by a two-needle regimen from day 14 on.

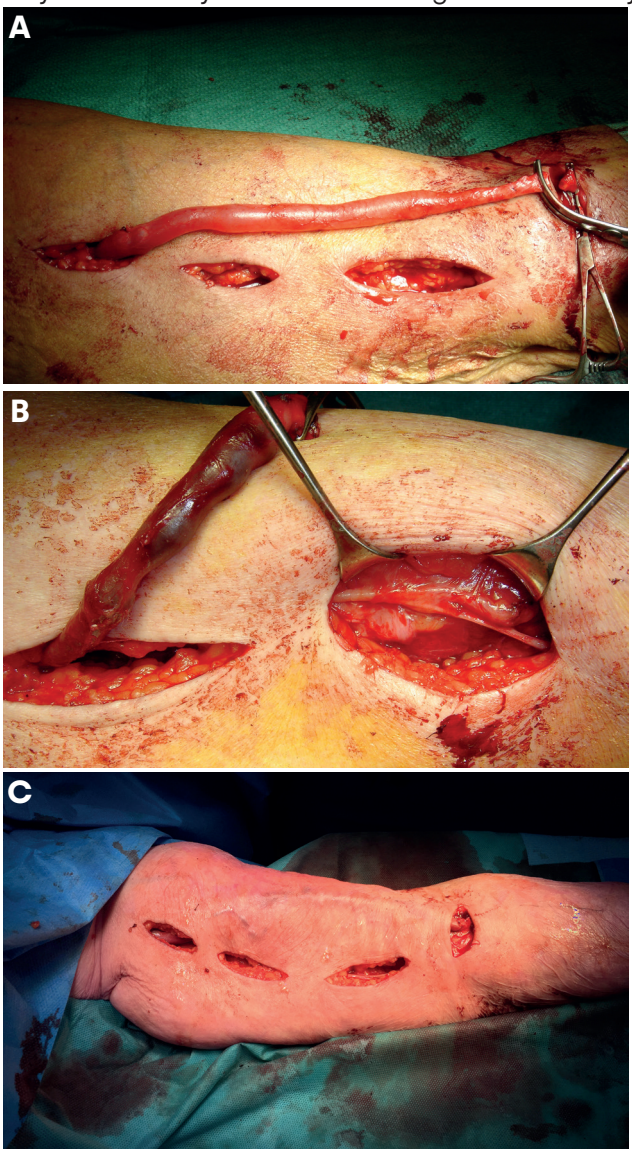

Figure 1. **(A)** Basilic vein transposition procedure. The upper arm basilic vein is disconnected from the original anastomosis and freed from its surroundings using three separate incisions. **(B)** The medial brachial cutaneous nerve is located in close relation to the basilic vein. **(C)** The vein is rerouted superficially along the anterolateral aspect of the biceps muscle and re-anastomosed.

Follow up and definitions

A history and physical examination were obtained regarding signs and symptoms of hand ischemia in each patient at the outpatient vascular department approximately six weeks postoperatively. Access flows and HIQ-scores were measured during the first three months after BVT. Data were recorded from local electronic patient files (EZIS 5.2, ChipSoft B.V., Amsterdam, the Netherlands). Values of P_{dig} that were faulty or not obtainable due to incompressible digital arteries were omitted from analysis. Questionnaires that were incompletely filled out by the patient and HIQ scores that were considered extreme, defined as exceeding three times the interquartile range while not congruent with history or findings at physical examination, were also deleted.

Statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Parameters were tested for normality. A Wilcoxon-signed rank test was used to determine the effect of BVT on DBI, HIQ-scores and access flow. Possible correlations between DBI and HIQ scores were analysed using linear regression. Results were expressed as median (interquartile range) or mean (±standard error of the mean; SEM) when appropriate. A P-value <.05 was considered significant.

Results

During the 11-year observation period, 60 BVTs were performed in our institution. In 21 patients, the indication for BVT was an inadequate NAS after earlier elbow AVF-construction. Eleven patients reported coincident hand ischemia and thus were eligible for the present study. One patient was excluded because of an additional banding procedure intraoperatively. Therefore, the study population consisted of ten patients (median age 61 years, 8 males, Table 1). In all ten, preoperative vein mapping precluded construction of a RC-AVF due to inadequate vein diameter necessitating the construction of brachial artery based AVF. Eight of these ten patients currently used their access for hemodialysis. However, one patient preferred dialysis via central venous lines due to fear of needles whereas the tenth patient was still in a pre-dialysis stage.

Table 1. Demographics of patients undergoing basilic vein transposition (BVT) for an unsuitable upper arm needle access segment and concurrent hand ischemia.

N	10
Age (years, median ±interquartile ranges)	61 [54-75]
Gender (male/female)	8 / 2
Diabetes mellitus (%)	4 (40)
Peripheral arterial occlusive disease (%)	4 (40)
Hypertension (%)	7 (70)
Coronary artery disease (%)	3 (30)
AVF (Gracz/ Brachiobasilic)	9 / 1
Time between AVF construction and BVT (months, median ±interquartile ranges)	8 [4-10]
HAIDI grade (2a/ 2b/ 3/ 4)	2 / 3 / 5 / 0

AVF, arteriovenous fistula; HAIDI, hemodialysis access-induced distal ischemia.

Prior to BVT, compression of the access' outflow demonstrated more prominent radial artery pulsations suggesting reversible hand ischemia in all ten patients. Reversibility of ischemia was likely as manual compression increased DBI well above the ischemic threshold of 0.6 (n=8, DBI_{open} 0.47, [0.10-0.56] vs. $DBI_{compressed}$ 0.89, [0.76-0.99], P=.012, missing n=2; Figure 2).

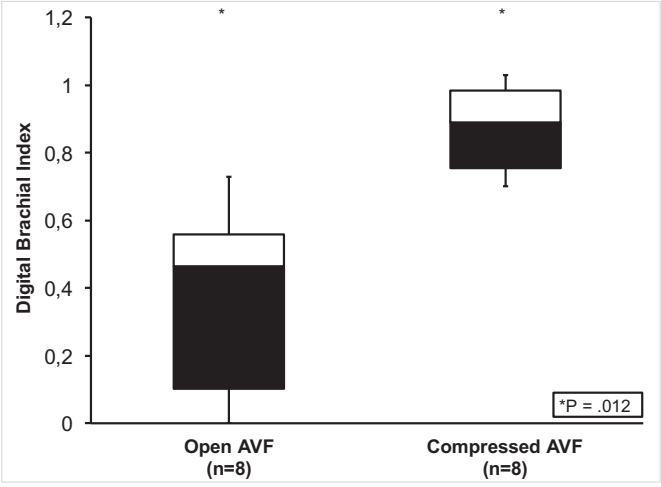

Figure 2. Digital Brachial Index (DBI) in patients with an unsuitable upper arm needle access segment and hand ischemia, open versus compressed arteriovenous fistula (AVF).

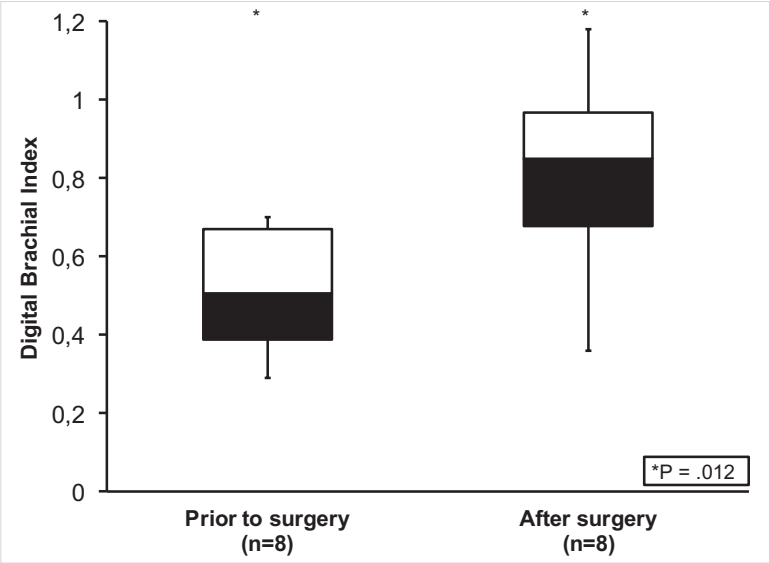

Figure 3. Digital Brachial Index (DBI) prior to and after basilic vein transposition for inadequate needle access segment.

No patient had evidence of arterial inflow stenosis on Duplex sonography (n=8) or Seldinger angiography (n=6; HAIDI 2a n=2, rejected Seldinger n=1, stenosis highly unlikely due to young age n=1). Furthermore, Duplex analysis (n=8) did not demonstrate a steal phenomenon distal to the brachial artery anastomosis as defined by retrograde flow in ulnar or radial artery forearm arteries in seven patients. However, one patient suffering from HAIDI 2a showed alternating flow directions (retrograde at end of diastole, antegrade in remainder of cycle) in both ulnar and radial arteries.

Following BVT, DBI values increased significantly (n=8, DBI_{pre} 0.51 [0.39-0.67] vs. DBI_{post} 0.85, [0.68-0.97], P=.012, intraoperative measurements; Figure 3). Moreover, access flows decreased slightly ($Flow_{pre}$ 1120 mL/min [1100-2300] vs. $Flow_{post}$ 700 mL/min [600-1760]; P=.018; N=7, missing N=3). Interestingly, DBI values and HIQ-scores were inversely correlated (n=12, R^2=71%, P=.001; preoperative measurements n=7, postoperative measurements n=5, missing n=8; Figure 4).

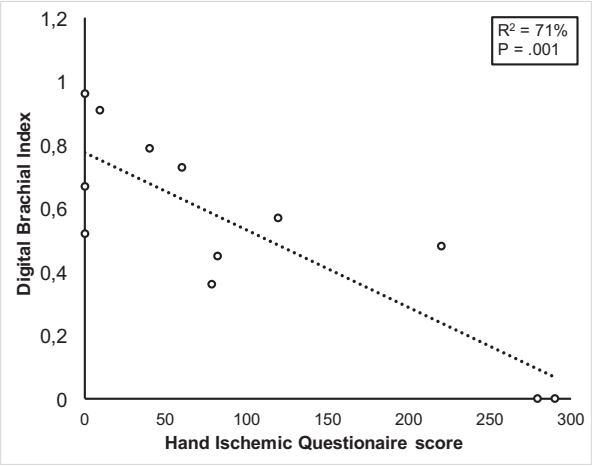

Figure 4. Correlation between hand ischemic questionnaire score and digital brachial index (pre-operative n=7, postoperative n=5, missing n=8).

All eight patients resumed HD sessions using one needle cannulation after BVT, either on the same or on the first postoperative day. Uncomplicated two needle HD regimens were possible from day 14 on in all. Patient nine continued HD via central venous lines duo to persisting fear of needles while the tenth patient remained in the pre-dialysis tract. Immediate postoperative complications such as wound infection, access thrombosis requirement of temporary central venous lines were not observed. One patient developed a pseudoaneurysm of the basilic vein in the presence of several puncture holes two weeks postoperatively necessitating successful surgery with uninterrupted dialysis. A percutaneous transluminal angioplasty was required in three patients because of access flow reduction due to a stenosis in the outflow tract within 3 months post-surgery followed by uncomplicated dialysis. Tissue loss due to previous hand ischemia was absent whereas additional surgery for recurrent HAIDI was not required.

At the six weeks follow up, eight patients reported total recovery from ischemia, whereas the ninth patient experienced an improvement. The tenth patient stated that BVT did not affect his hand ischemia, although specific history and physical examination suggested no signs of ischemia anymore. After renal transplantation, this patient demanded AVF-ligation. Overall HIQ-scores had dropped significantly (HIQ_{pre} 220 [71-285] vs. HIQ_{post} 9 [0-78], P=.043; n=5, incomplete questionnaire n=1, absent data n=3; extreme value without clinical evidence of ischemia n=1). A separate analysis of

the five cardinal symptoms associated with HAIDI demonstrated that pain was absent after the operation ($Pain_{pre}$ 42 [18-75] vs. $Pain_{post}$, 0 [0-0], P=.043). Coldness, sensibility change and loss of strength also diminished although statistical significance was not attained ($Coldness_{pre}$ 49 [2-67] vs. $Coldness_{post}$ 0 [0-0], P=.068; $Diminished\ sensibility_{pre}$ 56 [45-70] vs. $Diminished\ sensibility_{post}$ 0 [0-25], P=.066; $Loss\ of\ strength_{pre}$ 50 [0-65] vs. $Loss\ of\ strength_{post}$ 0 [0-35], P=.102). Cramps were not reported by any of the patients before or after the BVT.

Discussion

Several surgical techniques for the treatment of an inadequate upper arm NAS in the presence of a brachial artery based AVF are currently available. For example, suction-assisted lipectomy may lead to cephalic vein superficialization and easier puncturing in obese patients.[20] Furthermore, elevation and stretching procedures may effectively treat excessive depth and tortuosity of upper arm veins of a brachial artery based AVF. However, cephalic vein cannulation in these populations is advised not earlier than three to six weeks after these procedures due to issues of wound healing and insufficient arterialization.[21,22] Several studies on two-step BVT procedures show that cannulation was not performed earlier than four to seven weeks after the transposition step.[23,24] The BVTs in the current study can be regarded as delayed two-step procedures and the results indicate that a transposed basilic vein is safely cannulated from day one on precluding the use of temporary lines.

Rates of complications associated with autologous elbow AVFs such as hand ischemia (hemodialysis access-induced distal ischemia, HAIDI) are expected to rise.[4] Accepted invasive therapies for HAIDI include proximalization of arterial inflow (PAI), revision using distal inflow (RUDI) or distal revascularisation and interval ligation (DRIL) but these techniques require an extensive operative dissection. However, a minimally invasive technique of ligation of patent venous access side branches (SB) was also found to attenuate symptoms of hand ischemia in two recent studies,[8,9] as did coil embolization in another study.[25] A basilic vein transposition (BVT) procedure that is popularized for patients with an insufficient upper arm NAS may in essence be regarded as an extended version of SB ligation. Surely, the cephalic vein being a SB of the access itself, as well as all of the basilic vein's SBs are tied off during this operative procedure.

A comparison of HAIDI rates of several brachial artery-based AVF's including brachiobasilic, brachiocephalic, and Gracz was never performed. Intuitively one might speculate that a dual outflow tract of both a cephalic and a basilic vein as in Gracz-AVF leads to a higher risk on hand ischemia. In one retrospective study on brachial artery-based AVFs, 65% of patients that developed hand ischemia harboured a Gracz-type fistula compared to 41% of patients without ischemic complaints.[26] Interestingly, in one study on SB ligation, isolated ligation of the basilic vein sufficiently increased intraoperative DBI in only one patient whereas ligation of additional side branches was required in four patients.[8] As both cephalic vein as well as basilic vein side branches were ligated, the present study does not allow for the identification of the definite cause of the ischemia. It may also be that recovery from ischemia, apart from side branch ligation, is due to the creation of a possibly smaller anastomosis. However, the width of the new arteriovenous anastomosis was not measured in the present study.

A diagnosis of hand ischemia due to an HD access is suspected on specifics of the patient's history.[27,28] Pain, coldness and altered skin sensation in the ipsilateral hand as well as diminished strength and muscle cramps are often reported.[29,30] Moreover, these subjective symptoms may be provoked during HD as systemic blood pressure and peripheral perfusion pressures drop towards the end of a HD session.[15] Pain in the affected limb that occurs or aggravates during HD can be a hallmark of impending ischemia and should never be ignored.[31] The use of a hand ischaemic questionnaire (HIQ) allows for quantification of the five cardinal symptoms associated with hand ischemia.[4,8,9,13,14,15] Interestingly, HIQ scores and digital brachial indices, the latter generally accepted as the only parameter objectively reflecting hand ischemia, were inversely related underscoring the potential validity of a HIQ. It is probably worthwhile to standardly complete a HIQ in patients possibly suffering from HAIDI allowing for a comparison of HAIDI-rates in dialysis populations and efficacy of flow reducing therapies.

The role of a physical examination is pivotal in the diagnosis of hand ischemia. Pallor, muscle atrophy and ulcers may be observed.[18] Absent or weak radial artery pulsations in presence of these objective signs also point towards HAIDI. If manually compressing the AVF's outflow results in more prominent radial artery pulsations whereas coldness subjectively diminishes, reversibility of ischemia is likely.[5] In the current study, radial artery pulsations returned or were stronger after manual

access compression whereas finger pressures increased significantly prior to BVT. If this were not the case however, it must be questioned whether BVT or other flow reducing techniques are successful. Prior to embarking on any invasive surgical therapy, lower arm and hand vasculature require visualization using a selective Seldinger angiography with compressed AVF outflow. It is highly questionable whether (minimally) invasive therapy is beneficial if severe lower arm and hand atherosclerosis is demonstrated following imaging.

May BVT play a role in the armamentarium of therapies for HAIDI? Recent studies on SB ligation in hand ischemia hypothesized that it might be worthwhile to preoperatively determine flow in all venous outflow tracts of an AVF in combination with finger plethysmography.[8,9] If flow in one or more SB's is present as suggested by a thrill using physical examination or by a hand held Doppler system, the magnitude of flow may be quantified using Duplex analysis. If total flow over SBs including the basilic vein is substantial and the cephalic vein is suitable for needling, SB ligation might be a simple first line treatment. Flow rates of the basilic vein and its SBs were not standardly determined in the present population. However, the combined findings of patient history (symptoms of HAIDI), physical examination (too short upper arm NAS, weak radial artery pulsations), imaging (plethysmography, DBI <0.6 with open access, >0.6 following access compression; Duplex, flow in basilic vein and in its SBs) may aid in predicting whether a beneficial effect on hand ischemia is to be expected in patients requiring BVT. The present study also demonstrates that monitoring DBI during the operation is an important predictor of the efficacy of BVT in HAIDI.

This study suffers from potential limitations including small sample size, incomplete data sets, a short follow up period and absence of a control group. Patients that rejected invasive surgery were not registered possibly causing selection bias. Furthermore, the majority of the patients harboured a Gracz-type fistula, which might make the results less applicable for other types of brachial-artery based access. However, it must be appreciated that the aim of the study was to prove the validity of the concept of a BVT in the treatment of patients with hand ischemia. In conclusion, BVT in hemodialysis patients with an unsuitable upper arm needle access segment in presence of a brachial AVF may attenuate signs and symptoms of hand ischemia.

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Chapter 7

Severe hemodialysis access-induced distal ischemia may be associated with poor survival

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Abstract

Background Some hemodialysis (HD) patients develop hemodialysis access-induced distal ischemia (HAIDI) due to insufficient loco-regional perfusion pressure and consequent poor arterial flow. We hypothesized that patients with severe HAIDI had worse survival compared with patients with mild or no HAIDI.

Methods This single-centre retrospective observational cohort study included three groups of prevalent HD-patients with an upper extremity vascular access between 2006 and 2018. Symptomatic patients had signs and symptoms of HAIDI and low digital brachial indices (DBI <60%) and were divided into a mild (Grade I-IIa) and a severe HAIDI (IIb-IV) group. A control group consisted of HD-patients without signs of HAIDI with DBIs >60%. Factors potentially related to four-year survival were analysed.

Results Mild HAIDI-patients displayed higher DBIs (n=23, 41% ±3) compared with severe HAIDI-patients (n=28, 24% ±4), whereas controls had the highest values (n=48, 80% ±2; P<.001). Forty-four patients (44%) died during follow-up. DBI (HR 0.989 [0.979-1.000], P=.046) was related to overall mortality following correction for presence of arterial occlusive disease (HR 2.28 [1.22-4.29]), diabetes (HR 2.00 [1.07-3.72]) and increasing age (HR 1.03 [1.01-1.06]), as was digital pressure (HR 0.990 [0.983 - 0.998], P=.011). Overall survival was similar in mild HAIDI and controls (two-year 79% ±5; four-year 57% ±6, P=.818). In contrast, four-year survival was >20% lower in patients with severe HAIDI (two-year 62% ±10; four-year 34% ±10; P=.026).

Conclusions Presence of severe HAIDI may be associated with poorer survival in HD-patients. Lower DBI-values are associated with higher overall mortality, even following correction for other known risk factors.

Introduction

Hemodialysis (HD) using a surgically constructed arteriovenous fistula (AVF) or graft (AVG) is life-sustaining in patients with end-stage renal disease.[1] Occasionally, perfusion of the dialysis hand may progressively be compromised leading to hemodialysis access-induced distal ischemia (HAIDI). HAIDI develops due to blood pressure loss along the heart-hand axis, leading to insufficient loco-regional perfusion pressure and thus poor arterial flow. Rates of 4-9% have been reported in general HD-populations.[2,3] HAIDI incidence rates may rise in future populations as patients increasingly suffer from diabetes mellitus and atherosclerosis.[2] Moreover, the presence of a brachial artery-based AVF rather than a radial artery-based access is a risk factor for the onset of HAIDI.[4,5] Ongoing hand ischemia, if left untreated, may lead to progressive pain, wounds and loss of function of the hand of the dialysis arm.

In patients with peripheral arterial occlusive disease, low toe pressures reflecting impaired peripheral circulation have been found to predict overall and cardiovascular mortality.[6] Furthermore, an association between a decreased ankle-brachial index and mortality was also described in HD-patients.[7] Several case series in HD-populations suggested that patients with hand ischemia had a poor survival.[8,9,10] The aim of the present study was to determine whether survival is worse in HD-patients with severe HAIDI compared with patients with mild or no hand ischemia.

Methods

Approximately 110 patients receive maintenance HD in Máxima Medical Centre (MMC), Veldhoven/Eindhoven, the Netherlands. Some 100 access-related open and endovascular interventions are performed annually. Patients having complicated HD-sessions are discussed in a weekly multidisciplinary meeting attended by a vascular surgeon, interventional radiologist, nephrologist, vascular laboratory technicians and access nurses.

HAIDI Diagnosis and gradation

If HAIDI is suspected by dedicated access nurses, symptoms in the dialysis hand are assessed by a vascular surgeon during an outpatient clinic evaluation. These tracked cardinal symptoms are coldness, pain, changes in sensation, loss of strength, and cramps. The dialysis hand is

inspected for signs of ischemia such as pallor or wounds. Radial artery pulsatility with and without compression of the access' venous outflow is compared. Occasionally, patients experience a warmer hand during access compression. Moreover, radial artery pulsations may become more powerful suggesting a reversible type of ischemia.[2]

If HAIDI is likely based on clues in history and physical examination, the systolic pressure (P_{dig}) of the index (or middle) finger of the dialysis hand is measured with open and clamped access by a dedicated vascular laboratory technician using digital plethysmography (Vasoguard Nicolet 8 MHz, Scimet, Bristol, UK). A digital brachial index (DBI) is obtained by dividing the systolic finger pressure by the contralateral systolic brachial artery pressure. ∂DBI and ∂P_{dig} are calculated by subtracting values obtained from measurements with an open access from values with a clamped access. In our institution HAIDI is diagnosed if history and physical examination are consistent with hand ischemia in combination with a DBI <60% (or a P_{dig} <50 mmHg).[11,12,13] Grading is based on the (modified) Fontaine classification as proposed in 2009 by our department.[5] This gradation was adopted during a consensus meeting in 2016.[14] Based on this document, patients with Grade I or IIa HAIDI have a mild form that can be managed conservatively. In contrast, patients with a Grade IIb, III or IV HAIDI require imaging and (endo) vascular interventions including percutaneous transluminal angioplasty (PTA) for possible arterial inflow stenosis, side branch ligation (SBL), distal revascularization and interval ligation (DRIL), revision using distal inflow (RUDI), banding or other invasive techniques.

Hand ischemic questionnaire

In addition to the outpatient clinic visit, patients complete a hand ischemic questionnaire (HIQ). This in-house questionnaire scores frequency (0, never - 10, always) and severity (0, none - 10, extreme) of the five cardinal symptoms of HAIDI mentioned above using a numeric rating scale. Frequency and severity scores of each of the five items are multiplied and these numbers are added up to a total HIQ-score ranging from 0 (no symptoms associated with HAIDI ever) to 500 (maximal symptoms, always). HIQ-scores in HD-patients without ischemia are typically <60 while HAIDI-patients often score >100 points.[15,16] Various studies indicated that HIQ-scores reflect effectiveness of surgical revision for HAIDI.[17-19]

Patient selection

For this retrospective observational cohort study, three groups of HD-patients were studied. The first group was on maintenance HD, had an upper extremity access, had a DBI <60% (or P_{dig} <50 mmHg) and was diagnosed with Grade I or IIa HAIDI (mild). The second group was also on maintenance HD, harboured an upper extremity access, had a DBI <60% (or P_{dig} <50 mmHg) but were diagnosed with grade IIb, III or IV HAIDI (severe). Both HAIDI-groups were included between January 2006 and December 2018 in MMC. Exclusion criteria for both groups were earlier enrolment in another patient group, referral from another institution, or a language or cognitive impairment. The third group of patients served as controls. They were on maintenance HD, harboured an upper extremity access, and had undergone finger plethysmography of the dialysis hand between March and October 2013. Exclusion criteria were DBI <60% (or P_{dig} <50 mmHg), earlier enrolment in another study group, or a language or cognitive impairment.

The MMC's medical ethical committee deemed that evaluation of the study protocol was not necessary as measurements were considered stress- and risk-free whereas follow-up followed practice recommendations.[20] Parameters were considered patient-reported outcome measures (PROMs) and the study was deemed to be in accordance with the declaration of Helsinki.

Data accrual and definitions

Demographics and clinical data were obtained from surgical and nephrology electronic patient files (HiX 6.1, ChipSoft B.V., Amsterdam, The Netherlands; ProDB, MedVision Ag., Unna, Germany). These files were checked for presence of arterial occlusive disease (AOD; history of coronary artery bypass graft, percutaneous cardiac intervention, angina pectoris and/or PTA, peripheral bypass, carotid endarterectomy, radiological evidence of arterial stenosis -e.g. subclavian or renal artery stenosis-, or an ankle brachial index <90%), presence of diabetes mellitus and presence of hypertension (as diagnosed by an internist and/or use of blood glucose decreasing agents or antihypertensive agents, respectively). Time on HD and renal replacement therapy (RRT) were defined as time between start of maintenance HD or any RRT and inclusion date. DBIs were depicted as percentages.

Statistics

Statistical analyses were performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Parameters were tested for normality and expressed as mean ±standard deviation (SD) or standard error of the mean (SEM), or as proportions (percentages). Group differences were analysed using one-way analysis of variances (ANOVA) with a Bonferroni correction for pairwise comparisons, independent sample T-tests or Chi-square tests when appropriate. A possible relation between HIQ-score and DBI was addressed using linear regression analysis. Overall survival curves were compared using Kaplan Meier analysis and pairwise Log-Mantel Cox tests. In post-hoc tests, survival curves of mild HAIDI and controls were combined to assess whether severe HAIDI-patients displayed poorer survival. Univariate and -when appropriate- multivariate Cox regression analyses determined which factors were associated with overall and cardiovascular mortality. Outcomes were expressed as hazards ratios (HR [95%-confidence interval]). Cardiovascular mortality was defined according to ERA-EDTA codes 11, 14-16, 18, 22-26, and 29).[21] Survival follow-up (FU) was terminated in case of death, after four years of follow-up, at the end of December 2018, or when a patient was lost to follow-up ('date last known alive'). FU and FU-index were calculated following recommendations.[22] P-values ≤0.05 were considered significant.

Results

Between January 2006 and December 2018, 118 HD-patients were analysed for possible HAIDI by the senior author. 67 patients did not meet study criteria (no diagnosis of HAIDI n=31; no maintenance HD yet n=20; referral from other institution n=8; earlier enrolment n=7; lower extremity AVG n=1). Therefore, 51 unique HAIDI-patients were included (HAIDI I-IIa, n=23; HAIDI IIb-IV, n=28). A total of 101 control patients received HD between March and October 2013 in MMC. As 53 patients did not meet study criteria (no maintenance HD yet n=18; earlier enrolment in HAIDI-group n=13; no digital pressure measurement n=10; refused participation n=10; lower extremity AVG n=2), the control group consisted of 48 patients. No asymptomatic patients with DBIs <60% were found.

Patients with HAIDI IIb-IV and controls were some 8-10 years older than HAIDI I-IIa patients (P=.023). Rates of AOD were significantly lower in HAIDI I-IIa (30%) and controls (38%) compared to HAIDI IIb-IV patients (68%, P=.011).

In contrast, access age and time on HD were higher in controls compared to HAIDI IIb-IV patients (both P<.01). Time on any renal replacement therapy (RRT) was similar among groups (Table 1).

Table 1. Demographic characteristics in patients with HAIDI and controls.

Characteristics	HAIDI I-IIa (n=23)	HAIDI IIb-IV (n=28)	Control (n=48)	* P-value
Gender (male / female)	14 / 9	13 / 15	26 / 22	.585
Age (year, ±SD)	61 ±19	69 ±15	71 ±13	**.023**
Diabetes mellitus (%)	35	43	38	.827
Arterial occlusive disease (%)	30	68	38	**.011**
Hypertension (%)	78	93	85	.328
Wrist-based AVF / elbow-based AVF / PTFE-loop	1 / 20 / 2	1 / 26 / 1	18 / 21 / 9	**<.001**
Access age (months, ±SD)	21 ±32	11 ±16	36 ±29	**.001**
Time on hemodialysis (months, ±SD)	24 ±31	15 ±20	34 ±26	**.008**
Time on RRT (months, ±SD)	40 ±60	35 ±79	42 ±36	.877
Primary renal disease (%)				N.A.
Glomerulonephritis/sclerosis	4	21	25	
Pyelonephritis	9	4	10	
Hypertension	4	4	8	
Renal vascular disease	17	32	6	
Diabetes mellitus	13	25	8	
Polycystic kidney disease	9	0	8	
Miscellaneous	30	7	17	
Unknown	13	7	17	

SD, Standard deviation; AVF, arteriovenous fistula; PTFE, polytetrafluor-ethylene; RRT, renal replacement therapy; N.A., not applicable.

Finger pressures and HIQ-scores

P_{dig} with open access was higher in HAIDI I-IIa (57 mmHg ±5) compared with HAIDI IIb-IV (35 mmHg ±6; P=.009) while P_{dig} in controls was highest (110 mmHg ±3; P<.001). P_{dig} with clamped access also differed (HAIDI I-IIa 115 mmHg ±8; HAIDI IIb-IV 97 mmHg ±10; Controls 138mmHg ±4; P<0.001; Figure 1A). DBI showed similar differences (Figure 1B). Interestingly, ∂P_{dig} was twice as high in both HAIDI-groups (HAIDI I-IIa 59 mmHg ±7; HAIDI IIb-IV 62 mmHg ±8) compared with control patients (30 mmHg ±3; P<.001) as was ∂DBI (Figure 1).

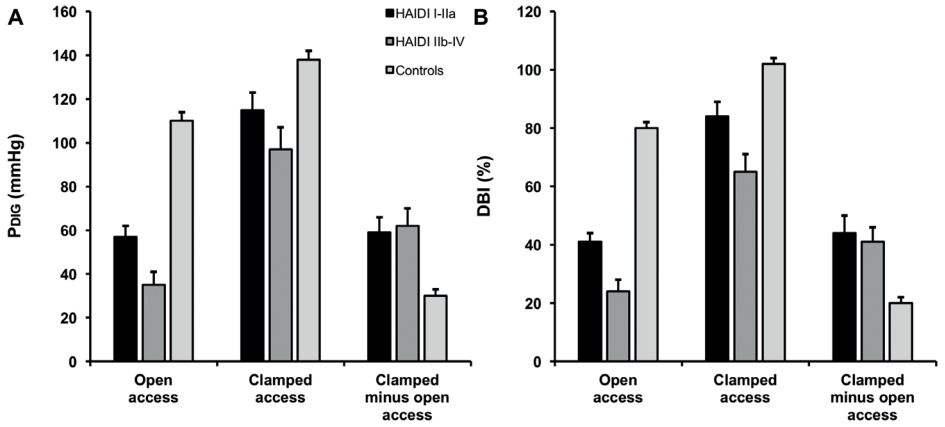

Figure 1. Mean values with standard errors of absolute digital pressure (P_{dig}, **A**) and digital brachial index (DBI, **B**) with open access and clamped access and clamped minus open access in patients with mild (I-IIa), severe (IIb-IV) hemodialysis access-induced distal ischemia (HAIDI) and controls.

Mean HIQ-scores were over four times higher in HAIDI IIb-IV patients (191 ±17) compared with HAIDI I-IIa (47 ±8; P<.001) whereas controls displayed the lowest mean values (12 ±3). Group variation was considerable (Figure 2A). A linear inverse correlation was found between DBI with open access and HIQ-score (R^2=.39, P<.001; Figure 2B).

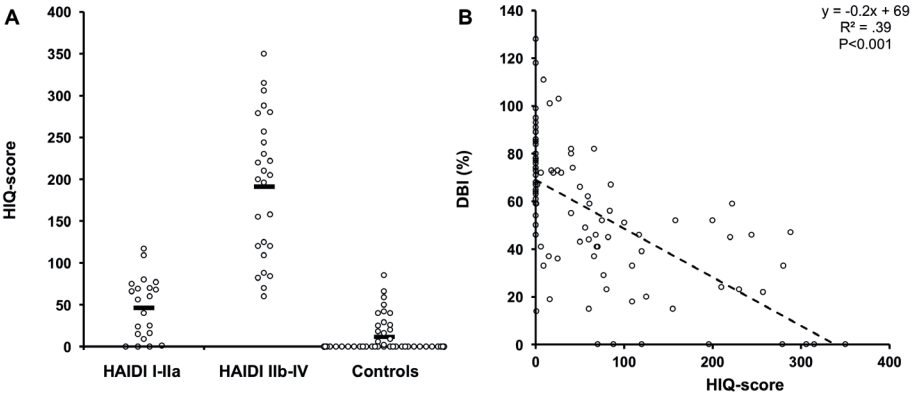

Figure 2. **(A)** Hand ischemic questionnaire (HIQ-) scores differ significantly between patients with mild (I-IIa), severe (IIb-IV) and absent hemodialysis access-induced distal ischemia (HAIDI). Horizontal bars indicate group mean values. **(B)** Digital brachial index (DBI) and HIQ-score are inversely correlated.

Survival

Mean follow-up was 27 months ±2 in HAIDI-patients and 37 months ±2 in controls (P=.004) with a FU-index of 97% ±2 and 100%, respectively (P=.193). Over the course of four years, 44 study patients died (44%; HAIDI I-IIa n=7; HAIDI IIb-IV n=16; Controls n=21), the majority (n=23, 52%) due to cardiovascular causes. Two and four-year overall survival in patients with HAIDI I-IIa (85% ±8 and 57% ±13, respectively) and controls (77% ±6 and 56% ±7, respectively) were similar (P=.818). In contrast, patients with HAIDI IIb-IV tended to display lower two- and four-year overall survival (62% ±10 and 34% ±10) compared with controls (P=.055). When combining HAIDI I-IIa with controls in post-hoc analysis, overall survival in HAIDI IIb-IV was significantly lower (P=.026; Figure 3A). Cardiovascular death-free survival did not differ among groups, neither in initial nor in post-hoc analysis (P=.32; Figure 3B).

Deceased patients with severe HAIDI were 8 years younger at time of death compared to deceased controls (HAIDI IIb-IV 71 years ±10 versus controls 79 years ±8; P=.013) while their age at the study start was lower as well (HAIDI IIb-IV 70 years ±8 versus controls 77 years ±8, P=.018).

Of the 28 patients with severe HAIDI, 22 underwent surgical revision (SBL, with or without additional banding n=9; basilic vein transposition n=5; DRIL, n=3; fistula ligation n=2; distal radial artery ligation, banding, RUDI, all n=1). Of these 22, 12 died during FU (cardiovascular death n=6). Four of the remaining six patients who did not undergo surgery received a PTA of an arterial inflow stenosis. Two of them died within FU, both due to cardiovascular causes. The last two patients did not receive any invasive treatment. Both died within 18 months following inclusion due to non-cardiovascular related causes.

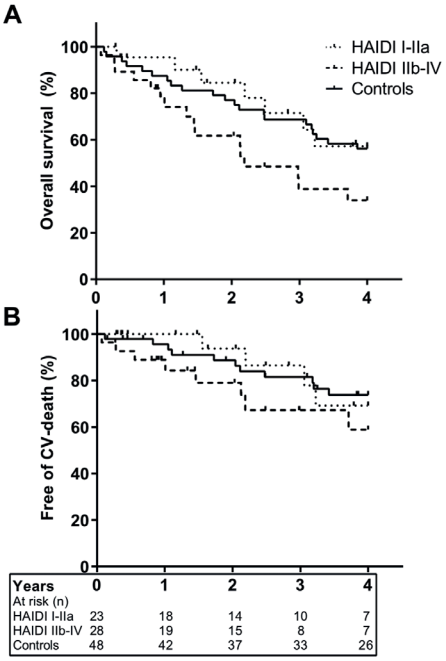

Figure 3. Cumulative Kaplan-Meier survival curves. **(A)** Overall survival of patients with mild (I-IIa) hemodialysis access-induced distal ischemia (HAIDI) and controls is similar whereas patients with severe HAIDI (IIb-IV) display poorer overall survival in post-hoc analysis (P=.026). **(B)** Cardiovascular (CV) death-free survival did not differ among groups (P=.319).

Overall and cardiovascular mortality

In univariate Cox regression analysis both P_{dig}-open (HR 0.991 [0.984 - 0.998], P=.017) and P_{dig}-clamped (HR 0.992 [0.985 - 0.999], P=.018) were associated with overall mortality. HAIDI IIb-IV (HR 1.93 [1.00 - 3.72], P=.050) and HIQ-scores (HR 1.003 [1.000 - 1.006], P=.043) displayed borderline significant associations with all-cause mortality. Interestingly, ∂P_{dig} and ∂DBI, but not P_{dig} and DBI in itself were associated with cardiovascular mortality (Table 2).

Table 2. Factors associated with overall (44 deaths) and cardiovascular mortality (23 deaths; univariate Cox regression analysis) in hemodialysis patients with and without hand ischemia.

		Overall mortality		Cardiovascular mortality	
		HR [95%-CI]	**P**	**HR [95%-CI]**	**P**
Age (years)		1.04 [1.01 - 1.07]	**.006**	1.02 [0.99 - 1.05]	.230
Gender (female = 1)		0.81 [0.44 - 1.47]	.481	0.51 [0.21 - 1.25]	.140
Diabetes Mellitus (present = 1)		2.22 [1.22 - 4.04]	**.009**	2.67 [1.16 - 6.13]	**.021**
Arterial occlusive disease (present = 1)		2.98 [1.62 - 5.51]	**<.001**	3.60 [1.51 - 8.55]	**.004**
Hypertension (present = 1)		1.72 [0.61 - 4.81]	.302	3.84 [0.52 - 28.54]	.188
Access	Wrist-based AVF (ref)				
	Elbow-based AVF	0.96 [0.48 - 1.91]	.902	1.20 [0.44 - 3.24]	.727
	PTFE-loop	0.41 [0.11 - 1.46]	.167	0.29 [0.34 - 2.52]	.264
P_{dig} (mmHg)	Open	0.991 [0.984 - 0.998]	**.017**	0.993 [0.983 - 1.004]	.194
	Clamped	0.992 [0.985 - 0.999]	**.018**	1.000 [0.988 - 1.012]	.993
∂P_{dig} (mmHg)		1.004 [0.995 - 1.013]	.409	1.014 [1.003 - 1.025]	**.016**
DBI (%)	Open	0.988 [0.978 - 0.999]	**.029**	0.989 [0.974 - 1.003]	.124
	Clamped	0.989 [0.980 - 1.000]	**.041**	0.998 [0.981 - 1.015]	.820
∂DBI (%)		1.007 [0.993 - 1.021]	.315	1.021 [1.004 - 1.039]	**.017**
HAIDI-grade	Control (ref)				
	I-IIa	0.89 [0.38 - 2.10]	.789	0.98 [0.31 - 3.09]	.976
	IIb-IV	1.93 [1.00 - 3.72]	**.050**	1.91 [0.76 - 4.79]	.166
Hand Ischemic Questionnaire (score)		1.003 [1.000 - 1.006]	**.043**	1.003 [0.998 - 1.007]	.226
Time on hemodialysis (months)		1.00 [0.99 - 1.01]	.595	1.00 [0.99 - 1.02]	.751
Access age (months)		1.00 [0.99 - 1.01]	.949	1.00 [0.98 - 1.02]	.980
Time on RRT (months)		1.00 [0.99 - 1.00]	.466	0.99 [0.98 - 1.01]	.261

HR, hazard ratio; CI, confidence interval; AVF, arteriovenous fistula; Ref, reference; PTFE, polytetrafluor-ethylene; RRT, renal replacement therapy.

Multivariate cox-regression analysis was performed with a maximum of four parameters per test. Following correction for age, presence of diabetes mellitus and presence of arterial occlusive disease, P_{dig}-open (HR 0.990 [0.983 - 0.998], P=.011) remained significantly associated with overall mortality, as did DBI-open (HR 0.989 [0.979 - 1.000], P=.046) in a separate analysis. Furthermore, P_{dig}-clamped (HR 0.993 [0.986 - 1.000, P=.051) but not DBI-clamped (HR 0.993 [0.983 - 1.004], P=.193) tended towards association with overall mortality following aforementioned correction. HIQ-score (HR 1.003 [1.000 - 1.006], P=.066) and HAIDI IIb-IV (HR 1.66 [0.83 - 3.31], P=.149) failed to attain a significant association with overall mortality in multivariate

Cox-regression analysis, although a trend was observed. Number of cardiovascular deaths was too small to perform a meaningful multivariate analysis.

Discussion

Anecdotal data suggest that HD-patients with an upper extremity vascular access have a poor survival once they have developed HAIDI. For example, two-year survival rates were between 36% and 60% in patients requiring surgery for HAIDI.[8,9,10] Three- and four-year survival rates were approximately 50% and 42% in two other samples having hand ischemia.[23,24] Survival rates of HD-patients with or without HAIDI were never compared in a single dialysis facility. The present single centre study hypothesized that patients with severe HAIDI (grade IIb-IV) had lower survival compared to HD-patients with mild (grade I-IIa), or no HAIDI. Grading of hand ischemia followed recent recommendations.[14] Our results indicate that patients with severe HAIDI have >20% lower survival after four years. Moreover, low digital pressures and DBIs are associated with higher overall mortality rates, even following correction for risk factors such as presence of arterial occlusive disease and diabetes mellitus, and increasing age.

Lower leg rest pain due to peripheral arterial occlusive disease (PAOD) and hand ischemia following HD-access creation (HAIDI) are much alike. Both result from blood pressure loss along the heart-extremity axis that is often due to progressive atherosclerosis. This is further aggravated by diabetes mellitus leading to insufficient blood supply.[2,5,25,26] The use of a similar grading system for both vascular syndromes as proposed in the 2016 Charing Cross meeting therefore seems justified. However, risk factors of PAOD and HAIDI may differ. For instance, the presence of an arteriovenous connection in HD-patients contributes to the loss of perfusion pressure, the subsequent fall in arterial flow and thus the development of HAIDI.[2] Furthermore, the heart-hand axis is considerably shorter than the heart-foot axis. Therefore, cut-off points associated with ischemia are different. HAIDI is defined when DBI values are <60%,[2,11,12,27] or even <40%.[14] In contrast, PAOD is deemed present when the ankle-brachial index is <90%,[26] whereas a 70% toe-brachial index threshold was proposed.[28] Despite these differences, increased mortality rates in both PAOD and HAIDI populations are at least partly due to a compromised vascular system with a high atherosclerotic burden.

The diagnostic relevance of an access compression test in HAIDI is underestimated. In an outpatient environment, compression of the venous outflow may indicate whether the hand ischemia is reversible and thus amendable to surgery.[19] In the vascular laboratory, increased P_{dig}(and DBIs) following clamping may confirm the reversibility of the hand ischemia.[2] The difference between P_{dig} with open and clamped access (∂P_{dig}, or ∂DBI) reflects the contribution of the pressure loss due to the arteriovenous connection. In the present study, ∂P_{dig} in both HAIDI-groups were twice as high compared with controls. However, absolute values of P_{dig} with compressed access were lower in HAIDI on group level. This is in line with the earlier suggestion that the arterial system in HAIDI-patients may be less compliant and stiffer, also likely due to atherosclerosis in the arterial system of the arm.[2,29] Measurements of arterial stiffness and vascular compliance (e.g., using radial applanation tonometry or brachial-ankle pulse wave velocity)[30] may therefore prove useful in predicting and monitoring hand ischemia. Furthermore, it seems that measurements of P_{dig} with open and clamped access are useful for assessing the arterial system's capacity to compensate for pressure loss due to a vascular access. Additionally, ∂P_{dig} (and ∂DBI) were shown to have some predictive value regarding cardiovascular mortality.

The present study may have several management consequences. Overall survival after four years was different as only one third of patients with severe HAIDI was still alive compared to over half of the control patients. One may suggest that surveillance of patients with severe HAIDI should be stricter. However, an anticipated association between presence of HAIDI IIb-IV and cardiovascular death was not readily observed. It is possible that numbers of cardiovascular deaths were too low while non-lethal cardiovascular events were not addressed. Several interventions may be considered to address mortality in patients with HAIDI. Mandatory use of statins may decrease overall mortality,[31] as well as use of blood pressure lowering agents.[32] Strict hypertension control with a 130 mmHg upper limit systolic pressure has been shown to lower mortality risk in patients with chronic kidney disease.[33] However, blood pressure targets in HD-patients remain uncertain due to a lack of trial data in this specific population. Stiffer arteries combined with relative hypotension may lead to organ hypoperfusion.[34] In this light, the effect of tight pressure control in the setting of HAIDI may prove counterproductive.[2] Intense glucose control, obligatory use of anticoagulants and an intensification of anti-tobacco

use policy may be worthwhile. Whether it is unethical to deny renal transplantation to patients with severe HAIDI having limited survival may not be concluded on the basis on our data.

As survival may be lower in severe HAIDI-patients, one might question whether interventions aimed at increasing digital pressure and blood flow towards the hand, thus diminishing hand ischemia, may influence life expectancy. As suggested earlier, invasive treatment is indicated in HAIDI IIb-IV.[5,14] In the current study, 26 of 28 HAIDI IIb-IV-patients indeed underwent invasive treatment including surgery whereas a conservative approach was followed in just two. In clinical practice, individualization of patient care should be considered. HAIDI is a local manifestation of systemic atherosclerosis and arterial stiffening[2] and effective treatment of the hand ischemia solely will not likely decrease the chances of dying. However, persisting HAIDI may be detrimental for the patient's quality of life and well-being.[35] Ongoing unbearable hand pain may contribute to a decision to terminate HD. Additionally, one may assume that some patients with HAIDI-IVb, having tissue loss and sepsis will benefit from surgery thus preventing (early) death. Future studies might elucidate whether presence of HAIDI and low digital pressures may represent 'modifiable parameters' which are key in mortality risk-scores.[36]

Increasing evidence indicates it may be worthwhile to use a HIQ in HD-patients. First, it is a tool that is able to evaluate the effect of remedial operations for HAIDI in terms of symptomatology (PROMS) as HIQ-scores drop drastically postoperatively.[17,18,19] Second, several studies indicated that a HIQ allows for differentiating between patients with and without hand ischemia.[15,16] A recent study demonstrated an inverse correlation between scores of DBI and HIQ in HAIDI-patients who received a basilic vein transposition.[19] In the current study, mean HIQ-scores were four times higher in patients with severe HAIDI compared with patients with mild ischemia. Additionally, none of the 28 patients having severe HAIDI scored <50 points on the 0-500 point scale. More intriguingly, HIQ-scores tended towards having an association with overall mortality, indicating that a subjective tool such as a symptomatology-score may be clinically relevant as was shown earlier with self-reported vitality measures.[37] Nevertheless, one should regard a HIQ as a screening tool rather than a diagnosticum for HAIDI. For instance, as patients without HAIDI may occasionally display values >50 (e.g., due to carpal tunnel syndrome or diabetic neuropathy),

one should not proceed to invasive interventions based on HIQ-scores alone. Future validation of the hand ischemic questionnaire is warranted.

This study has several limitations including a retrospective design possibly leading to incomplete data sets. The limited number of study patients may have led to low statistical power and relative conclusions. These small numbers possibly explain the absent association between presence of severe HAIDI and higher cardiovascular death rate while they precluded inclusion of additional parameters in multivariate analysis. However, this retrospective study should be considered as supporting a proof of concept that severe hand ischemia, as reflected by decreased finger pressures leading to insufficient blood flow, is associated with poorer survival. As the inclusion and follow-up periods were relatively long, loss to follow-up potentially induced bias. However, considering the study's >96% follow-up index, this risk was minimized. Patients on a waiting list for renal transplantation, often being healthier and younger, were included, also possibly introducing bias.[38] The institution's 60% DBI hand ischemia threshold is in line with recent recommendations.[27] However, some adhere to a threshold of 40% as was proposed by Schanzer et al.,[39] whereas others perform plethysmography only to differentiate between aetiologies without using a strict DBI cut off value. In either case, diagnosis and treatment of HAIDI should be tailored to the patient's individual circumstances.

In conclusion, severe but not mild hand ischemia in hemodialysis patients may be associated with poorer survival. Lower digital pressure is related to higher overall mortality, even following correction for known risk factors such as arterial occlusive disease, diabetes, and old age.

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Chapter 8

Systolic finger pressures during an Allen test before hemodialysis access construction predict severe postoperative hand ischemia

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Abstract

Objectives The Allen Test is a simple bedside method for determining hand perfusion. Earlier studies in hemodialysis (HD) patients found that an Allen Test before access construction did not predict hand ischemia later on. The study aimed to assess whether an Allen test combined with finger plethysmography before access surgery has a potential to predict the onset of severe hemodialysis access induced distal ischemia (HAIDI).

Methods Prior to the first access construction in chronic kidney disease (CKD) patients, systolic finger pressures (P_{dig}, mmHg) were obtained using plethysmography at rest and following serial compression of the radial and ulnar artery. A drop in P_{dig} (∂P_{dig}) was calculated as the difference between P_{dig}-rest and P_{dig}-compression. Severity of postoperative HAIDI was graded as suggested by a 2016 consensus meeting. Patients with a severe type of HAIDI (grade 2b-4, intolerable pain, invasive treatment required) were compared with controls not having HAIDI.

Results A total of 105 CKD patients (age 70 ±13, 65% males) receiving their first access between January 2009 and December 2018 in one centre fulfilled study criteria. Ten patients (10%) developed severe HAIDI 14 ±5 months after access construction. Prior to access creation, all HAIDI patients demonstrated a radial or ulnar dominant hand perfusion pattern compared to just 57% in controls (P=.010). Compression resulted in an almost two-fold greater ∂P_{dig} in patients with severe HAIDI (51 ±8 mmHg vs. 27 ±3 mmHg, P=.005). A 40 mmHg ∂P_{dig} cut-off value demonstrated optimal tests characteristics, (sensitivity 80%, specificity 77%, PPV 27%, NPV 97%) indicating a 10 times greater risk of developing severe HAIDI.

Conclusion Finger plethysmography quantifying ∂P_{dig} during an Allen test prior to access creation may identify patients who have a substantially increased risk of developing severe hand ischemia following hemodialysis access surgery.

Introduction

Adequate maturation of an autologous arteriovenous access (AVA) is a prerequisite for effective hemodialysis (HD).[1–4] In some HD patients, the presence of an AVA may lead to diminished perfusion of the ipsilateral hand.[5] Hemodialysis access-induced distal ischemia (HAIDI) may affect up to 20% of general HD populations.[6–8] Symptoms vary from a cold hand to rest pain, or even tissue loss (Figure 1).[6-10] A recent consensus meeting graded type of HAIDI as 'severe' if ischemic symptoms were intolerable and revascularization was required (Type 2b-4).[7] Incidence rates of HAIDI are nowadays rising due to aging diabetic populations with kidney failure having poor lower arm vessels.[5] In these patients, a brachial artery based AVA may be preferred but at the expense of a higher risk of developing HAIDI.[8]

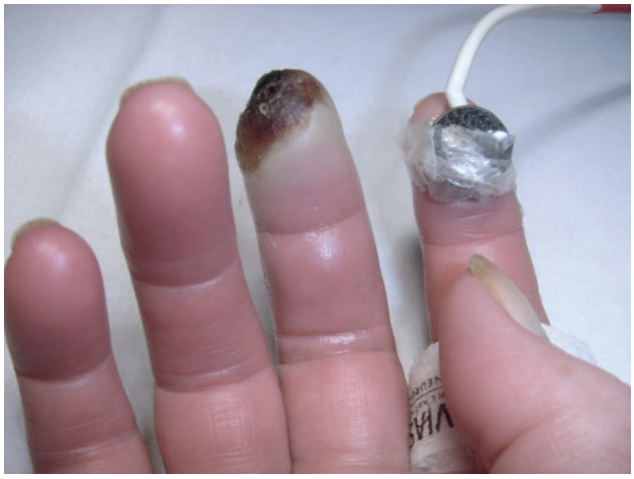

Figure 1. Finger plethysmography in type 4 HAIDI of middle finger.

Before HD access creation, an assessment of risk factors associated with HAIDI such as female sex and diabetes mellitus as well as a physical examination are performed. Although this workup may identify clues pointing towards an increased risk of hand ischemia, a predictive test is currently lacking. In earlier days, an Allen test was proposed as a bedside method determining perfusion reserve of the hand in patients who were planned for a radiocephalic (RC-) AVA.[11] If pallor persisted after releasing a compressed radial artery, collateral perfusion via the ulnar artery was deemed insufficient precluding the construction of an RC-AVA.[12] However, a high inter-observer bias prevented the general use of this preoperative test.[13,14]

Systolic finger pressures (P_{dig}), or its derivative DBI (digital brachial index, P_{dig}/Systolic brachial pressure) are found to objectively assess diminished digital perfusion once HAIDI has developed.[15-18] Patients who require hand revascularization for severe (type 2b-4) HAIDI exhibited DBI values well below 0.6 (normal >0.8).[6,15] Immediately after a successful operation, DBI values normalized.[19] It is unknown whether (changes in) P_{dig} during an Allen test reflect the arterial reserve capacity of a future dialysis hand.

Therefore, the aim of the present pilot study was to determine whether changes in P_{dig} during an Allen test prior to access construction predicted onset of severe postoperative HAIDI.

Material and Methods

General information and standard workup

This observational cohort study was conducted in one centre (Máxima MC, Veldhoven, the Netherlands), a Dutch hospital with a dialysis ward accommodating approximately 100 chronic HD patients. Patients with CKD who choose to undergo HD are referred by the nephrologist to our vascular outpatient department. During the preoperative counselling process, a patient history is obtained by one of four vascular surgeons followed by bilateral arm and hand inspection for signs of prior trauma or surgery, venous congestion or ischemia. Epifascial veins, radial and ulnar arteries are palpated. Arterial and venous vasculature of both arms are visualized with Duplex sonography (Nicolet Vasoguard, VIASYS Healthcare, USA). P_{dig} using plethysmography are obtained at the discretion of the vascular surgeons. Based on this information, the optimal arm and AVA location are discussed followed by HD access construction within 6 weeks.

Finger plethysmography and lower arm vessel dominance

P_{dig} of index and/or middle finger were assessed bilaterally by an experienced vascular technician using digital plethysmography (Nicolet Vasoguard 8 MHz, Scimet, Bristol, UK). On the palmar portion of the distal phalanx, a plethysmographic sensor was placed, while an inflatable cuff was wrapped around the proximal phalanx. The room temperature was maintained constant at 20 degrees Celsius. The cuff was inflated up to 200 mmHg and gradually deflated until a pulsatile signal reappeared reflecting systolic P_{dig} (in mmHg, Figure 1). A bilateral plethysmographic measurement during the Allen test takes approximately 15 minutes.

Plethysmographic measurements were performed in triplicate. A first P_{dig} was determined at rest approximately 30 seconds after application of the plethysmographic sensor. A second P_{dig} was obtained after 15 seconds of radial artery compression by the vascular technician's index finger. A third P_{dig} was repeated 15 seconds after release. After 30 seconds, measurements of P_{dig} were repeated following compression and release of the ulnar artery.

The difference between P_{dig} at rest and compression was termed ∂P_{dig}. If ∂P_{dig} values after radial (or after ulnar artery) compression were >10 mmHg different compared to resting values, a patient had radial artery dominance (or ulnar artery dominance).[20] If ∂P_{dig} values were <10 mmHg different, the patient had co-dominance. The highest ∂P_{dig} value ipsilateral to the future HD access location was used for analysis.

Study criteria

Eligible were CKD patients >18 years who were diagnosed with stage IV or V renal disease, who received their primary HD access between January 2009 and December 2018 in our institution and who had undergone P_{dig} measurements <6 months before access construction. Only patients undergoing an initial access procedure were considered eligible for study participation. Exclusion criteria were an incomplete set of plethysmography measurements, or when test results were considered erroneous by the vascular technician (e.g., in case of incompressible arteries).

Since digital plethysmography is considered a non-invasive stress-free test that is standard care at our vascular clinic, the medical ethical committee of Máxima Medical Centre judged that the rules of the Medical Involving Human Subjects Act (Dutch WMO) did not apply to our study protocol.

Diagnosis of severe HAIDI (Type 2b-4)

Follow up of access functioning is standardly performed as suggested by KDOQI.[4] Patients reporting symptoms suggestive of HAIDI are discussed in weekly meetings attended by a nephrologist, vascular surgeon, vascular technician, radiologist and vascular nurses. If HAIDI is likely on the basis of history (pain, cold hand, cramps, loss of strength, diminished sensibility) and physical examination (pallor, ulcers, weakened or absent radial pulsation), the patient undergoes digital plethysmography. HAIDI is diagnosed if history and physical examination are consistent with hand

ischemia in combination with abnormally low P_{dig} or DBI values.[3,4,15,21,22] HAIDI is graded as severe (type 2b-4) if pain is intolerable and invasive treatment is required as suggested by a 2016 consensus meeting.[7] Additional imaging with MR-angiography or Seldinger is performed in patients with HAIDI grade 2b or higher, unless a stenosis is considered improbable as judged in young patients. Success after intervention for HAIDI was arbitrarily defined as postoperative resolution of ischemic complaints, an increase in P_{dig} and freedom from additional interventions for HAIDI later on.

Data collection and definitions

Patient characteristics, comorbidities including diabetes mellitus, cardiovascular disease (CVD), hypertension, smoking status, statin and/or anticoagulants use, date and type of primary HD access construction, initiation of HD (yes, no) and P_{dig} values were obtained from electronic patient files (HiX 6.1, ChipSoft B.V., Amsterdam, The Netherlands; FinProDB 7.9, MedVision AG, Unna, Germany). The date of primary HD access construction served as the study starting date. To estimate the completeness of the study, a follow up index (FUI) was calculated as the ratio between the investigated and potential FU period.[23] FU was terminated after death or on December 31, 2018. Patients transferred to a dialysis centre other than MMC were deemed loss to FU. For this group, "date last known alive" was used.

Statistical analysis

Statistical analyses were performed using SPSS 25 (IBM SPSS Inc., Chicago, IL, USA). Baseline characteristics were shown as mean ±standard deviation (SD) or counts (percentages) when appropriate. Outcomes were tested for normality and displayed as mean ±standard error of the mean (SEM). Patients who did not develop HAIDI during the study period served as controls. Group differences were tested with the Fischer's exact test, independent sample T-test or Pearson's chi-square test when appropriate. A receiver operating characteristic curve was computed for determining optimum cut-off values for ∂P_{dig}. A relative risk (RR) on postoperative HAIDI was calculated with a 95%-confidence interval [RR 95%-CI]. P-values ≤ 0.05 were considered statistically significant.

Results

A total of 123 patients receiving a primary HD access between January 2009 and December 2018 underwent the plethysmographic tests panel in a single institution. As 18 of these were excluded due to incompressible digital arteries, a total of 105 patients fulfilled study criteria (age 70 ±13, 65% males; FUI 99% ±1). Of these 105 patients (Table 1), 10 patients (10%) were diagnosed with severe (type 2b-4) HAIDI, approximately 14 ±5 months after access construction. Not one of the 105 patients suffered from Raynaud's syndrome. HAIDI developed in 6 patients using their primary AVA, in 3 patients using a second AVA, and in one patient using a third AVA, all on the ipsilateral side. All HAIDI patients received invasive treatment as dictated by the consensus meeting.

A 100% success rate was attained after revision for HAIDI. All HAIDI patients experienced symptom relief whereas P_{dig} increased from 57 ±15 to 118 ±22 mmHg. Significant differences regarding demographics and history between HAIDI patients and controls were not observed (Table 1).

Table 1. Characteristics of cohorts developing HAIDI, or not.

Characteristic	HAIDI n=10	Controls n=95	Total cohort n=105	P
Age (years, ±SD)	74 ±13	69 ±13	70 ±13	.267
Sex, male (%)	5 (50)	64 (67)	69 (65)	.271
Diabetes Mellitus (%)	4 (40)	40 (42)	44 (42)	.898
Cardiovascular disease (%)	7 (70)	49 (52)	56 (53)	.267
Hypertension (%)	8 (80)	79 (83)	87 (83)	.801
Etiology of renal disease (%)				.396
Glomerulonephritis/sclerosis	- 3 (30)	- 14 (15)	- 17 (16)	
Pyelonephritis	- 1 (10)	- 2 (2)	- 3 (3)	
Hypertension	- 0 (0)	- 12 (13)	- 12 (11)	
Renal vascular disease	- 2 (20)	- 9 (10)	- 11 (11)	
Diabetes	- 3 (30)	- 25 (26)	- 28 (27)	
Polycystic	- 0 (0)	- 2 (2)	- 2 (2)	
Miscellaneous	- 1 (10)	- 27 (28)	- 28 (27)	
Unknown	- 0 (0)	- 4 (4)	- 4 (4)	
Statin use (%)	6 (60)	63 (66)	69 (66)	.655
Anticoagulant use (%)	7 (70)	53 (56)	60 (57)	.428
Smoking (%)	5 (50)	49 (52)	54 (51)	.759
Former	3 (30)	19 (25)	22 (21)	
Active	2 (20)	30 (32)	32 (30)	
Primary AVA type (%)				.586
RC-AVA*	-4 (40)	-56 (59)	-60 (57)	
BC-AVA	-6 (60)	-31 (33)	-37 (35)	
BB-AVA	-0	-3 (3)	-3 (3)	
UB-AVA	-0	-1 (1)	-1 (1)	
BT	-0	-1 (1)	-1 (1)	
AVG	-0	-3 (3)	-3 (3)	
HD initiated (%)	9 (90)	58 (63)	67 (63)	.082
Months on HD (mean ±SEM)	14 ±5	17 ±2	17 ±2	.571

AVA, arteriovenous access; RC, radio-cephalic; BC, brachio-cephalic; BB, brachio-basilic; UB, ulnar-basilic; BT, Basilic transposition; AVG, arteriovenous graft; * RC-AVF was standardly constructed at the wrist.

Prior to the patient's first access construction, serial radial and ulnar artery compression revealed that almost half (46%) of all 105 patients displayed radial artery dominance. In contrast, just 16% displayed ulnar artery dominance whereas 38% had a co-dominant hand perfusion pattern (Table 2). Interestingly, not a single patient developing severe HAIDI had co-dominance compared to 42% of controls (P=.010). HAIDI patients had an almost two-fold greater ∂P_{dig} (HAIDI: ∂P_{dig} 51 ±8 mmHg vs. Controls: ∂P_{dig} 27 ±3 mmHg, P=.005).

Table 2. Hand perfusion patterns and P_{dig} before access construction in patients who developed HAIDI compared to controls.

Characteristic	HAIDI n=10	Controls n=95	Total cohort n=105	P
Hand perfusion pattern (%)				**.010**
Radial dominance	9 (90)	39 (41)	48 (46)	
Ulnar dominance	1 (1)	16 (17)	17 (16)	
Co-dominance	0	40 (42)	40 (38)	
Systolic brachial artery pressure	161 ±10	162 ±3	162 ±3	.926
P_{dig}	171 ±8	153 ±3	155 ±3	.089
Digital brachial Index (DBI, %)	108 ±6	96 ±2	97 ±2	.078
∂P_{dig}	51 ±8	27 ±3	29 ±3	**.005**
∂DBI (%)	33 ±5	17 ±2	19 ±2	**.006**

∂P_{dig}, difference between P_{dig} at rest and during compression.

Furthermore, two of the 18 patients (11%) who displayed incompressible digital arteries prior to primary AVA construction developed HAIDI, a percentage that is comparable in patients having compressible arteries (10%). Preoperative plethysmographic characteristics of all 10 patients who developed severe HAIDI are depicted in Table 3.

Predictive accuracy of ∂P_{dig}

A ROC-analysis identified a 40 mmHg ∂P_{dig} cut-off value having optimal predictive characteristics (sensitivity 80%, specificity 77%, PPV 27%, NPV 97%) (Figure 2). The AUC was 0.77 ±0.07 [CI 0.63-0.91, P=.005]. These data indicate that CKD patients who demonstrate a ∂P_{dig} of >40 mmHg before access creation have a 10 times greater chance [RR 10.00, CI 2.25-44.39] of developing severe HAIDI after primary HD access construction.

Table 3. Preoperative plethysmographic data in patients who developed severe type 2b-4 HAIDI after HD access construction.

N	P_{dig} preop	DBI (%)	∂P_{dig} preop	∂DBI preop	Dominance	First Access	P_{dig} [1] open	P_{dig} [1] Comp	HAIDI grade	Intervention
1	112	82	11	8%	Radial	RC-AVA	20	*	2b	Ligation
2	183	109	17	10%	Radial	RC-AVA	*	*	2b	RUDI
3	153	134	41	36%	Ulnar	RC-AVA	23	110	2b	PTA Subclavian artery
4	177	83	41	19%	Radial	BC-AVA	*	152	2b	SBL
5	159	126	47	37%	Radial	RC-AVA	81	112	2b	RUDI
6	188	95	47	24%	Radial	BC-AVA	115	192	4a	SBL
7	188	104	67	37%	Radial	BC-AVA	54	115	3	BT[2]
8	195	112	76	44%	Radial	BC-AVA	*	*	2b	SBL
9	174	115	80	53%	Radial	BC-AVA	47	100	3	RUDI
10	179	122	84	57%	Radial	BC-AVA	*	124	2b	RUDI

P_{dig} presented in mmHg; Preop, preoperative; AVA, arteriovenous access; RC, radio-cephalic; BC, brachio-cephalic; Comp, compressed; RUDI, revision using distal inflow; PTA, percutaneous transluminal angioplasty; SBL, side branch ligation; *unreliable signal; [1] P_{dig} at the time of diagnosis HAIDI; [2] BT, basilic vein transposition was planned but patient died unexpectedly.

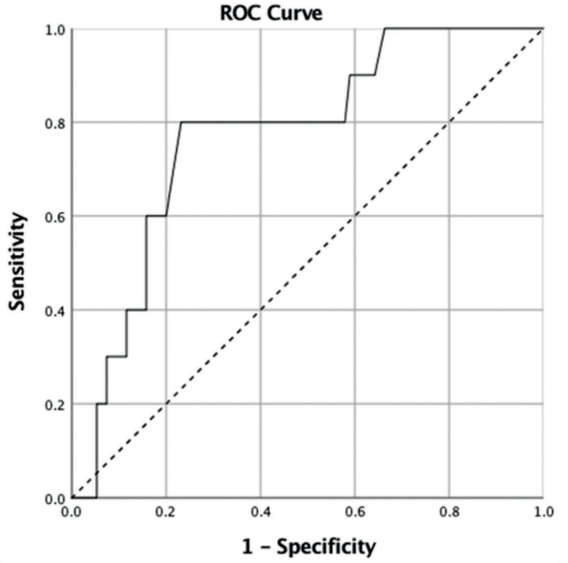

Figure 2. Receiver operating characteristic (ROC) curve illustrating that a 40 mmHg ∂P_{dig} cut-off value optimally predicts severe HAIDI (n=105 patients).

Discussion

Incidence rates of hemodialysis access-induced distal ischemia (HAIDI) are nowadays increasing due to aging diabetic populations requiring an access that is constructed with lower arm vessels of limited quality.[4,24,25] Hitherto, an objective test predicting onset of HAIDI is lacking. Earlier studies revealed that low systolic finger pressures (P_{dig}) using finger plethysmography reflect insufficient digital perfusion in patients once HAIDI has developed.[15–18] The present study determined whether digital plethysmographic testing prior to the first access construction could predict severe HAIDI. The results indicate that all patients who developed severe HAIDI had a radial (or ulnar) artery dominant hand perfusion pattern. In addition, they had an almost two-fold greater ∂P_{dig} following compression. Consequently, a 40 mmHg ∂P_{dig} cut-off value conferred a 10 times higher risk on developing severe HAIDI. It is concluded that finger plethysmography with arterial compression tests prior to access creation may identify patients having an additional risk of developing severe hand ischemia.

Risk factors for chronic HAIDI are diabetes, earlier ipsilateral HD accesses, female sex, hypertension, central and peripheral arterial disease and smoking.[5,6,9,26] Moreover, a proximally located HD access may develop higher flows and consequent lower digital pressures.[6,8] HAIDI symptoms only arise once compensatory collateral flow fails to maintain adequate peripheral perfusion pressures.[6,27] In the present study, incidence of these known risk factors was similar in patients with HAIDI and controls suggesting a role of other causes.

Is hand perfusion pattern an unidentified factor contributing to the onset of HAIDI? The literature indicates that palmar arch inflow is more often dominated by the radial artery than the ulnar artery in most individuals.[28,29] For instance, a 55% radial dominance versus a 33% ulnar dominance was found.[20] A 41% radial dominance versus a 17% ulnar dominance rate was demonstrated in our 95 controls. Interestingly, all 10 patients developing severe HAIDI showed a single forearm artery dominance (radial or ulnar) pattern and displayed a two-fold greater ∂P_{dig} as compared to the control group. Conversely, not a single HAIDI patient had a co-dominant pattern indicating that collateral capacity may already be suboptimal before access creation, albeit asymptomatic. When the dominant artery is chosen for construction of the AVF, perfusion pressure distal to the arteriovenous

anastomosis may drop occasionally leading to hand ischemia if the non-dominant artery, possibly burdened with atherosclerosis, fails to provide sufficient collateral circulation. Selective forearm angiographic imaging may have identified atherosclerotic lower arm arteries but was not performed.

The present study may have clinical consequences. HAIDI is a dreadful complication occurring in up to 20% of brachial artery-based AVA's and in 2% of wrist-based AVA's (Figure 1).[5,6,8,9,30] When not timely recognized, tissue loss or even hand amputation may be required.[10] Therefore, weighing risk factors prior to access construction is a key factor in HAIDI management. This study suggests that patients who demonstrate a >40 mmHg ∂P_{dig} have a ten times higher risk of developing severe HAIDI after their first access creation. These findings must be discussed during the preoperative counselling process. Moreover, plethysmography during an Allen test may aid in selecting the most appropriate access arm. For instance, if both arms are equally suitable, the side with the lowest ∂P_{dig} and codominant arteries may be preferred. However, access management should always be tailored to the needs of an individual CKD patient.

The present study is limited due to its retrospective design, a small number of severe type 2b-4 HAIDI patients, data heterogeneity and inability to correct for potential confounders. As 2 of 4 vascular surgeons did not participate in the study because of a turnover in the team, just 123 patients (41%) of all 300 primary AVA's created during the study period were eventually included, possibly excluding potentially eligible patients. Each potential HAIDI patient is discussed in a weekly multidisciplinary meeting. There is no indication to suggest that HAIDI rates differ among the four surgeons who are involved in the standard care of these patients. In addition, digital pressures that were obtained prior to access construction were only used for study purposes and did not influence choice of access type or location. Since this is the first study investigating the association between ∂P_{dig} and HAIDI, it can be considered as a pilot concept for future prospective trials confirming the present findings. Furthermore, imaging of lower arm and hand vasculature was not performed. Normal values of $(\partial)P_{dig}$ were never established precluding comparison with other studies.

In conclusion, preoperative plethysmography during an Allen test may identify patients having an increased risk of developing severe HAIDI in the years after their first HD access construction. The role of this test modality requires confirmation in a larger population.

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Chapter 9

Summarizing discussion and conclusions

General

Wrist-based and elbow-based arteriovenous fistula (AVF) for haemodialysis (HD) were introduced the 1960's and 1970's, respectively.[1,2] Ever since, millions of people worldwide suffering from end-stage renal disease (ESRD) benefit from life-sustaining dialysis. While HD buys time, possibly in expectation of a renal transplant, this mode of renal replacement therapy (RRT) is not without long term sequelae. Apart from the fact that chronic intermittent HD is burdensome,[3] the arteriovenous access (AVA) itself may lead to long term complications limiting quality and duration of life. Two regularly occurring complications are development of a High Flow Access (HFA) and haemodialysis access-induced distal ischaemia (HAIDI). Earlier studies suggested that an elbow-based AVA imposes a greater risk of both of these complications as compared with wrist-based accesses.[4-6] As HD-population characteristics have changed over the last decades, with more people suffering from diabetes mellitus, peripheral arterial disease and hypertension while incident ESRD-patients are getting older, surgeons are forced to create more elbow-based instead of wrist-based accesses.[7] This trend is not without consequences with respect to HFA and HAIDI.

Part I: High Flow Access (HFA)

The first part of this thesis (**Chapter 2-5**) focuses on the treatment and possible impact of high flow (Qa) on haemodialysis (HD) patients. An AVA access Qa between 400 and 600 mL/min usually suffices for adequate exchange of waste products in the artificial kidney.[8] In some cases, ongoing maturation drives Qa above 1500 mL/min and beyond. It should be realised that cardiac output in most adults ranges between 4000 - 5000 mL/min. An AVA may thus impose an increased workload on the cardiovascular system. It was earlier suggested that this additional burden possibly leads to a higher risk of high-output cardiac failure (HOCF).[9] Indeed, a Qa >2000 mL/min proved to greatly affect the cardiovascular system.[10]

A variety of interventions is available in order to correct an access with an excessive Qa. Banding is by far the oldest and commonest technique, relying on increased outflow resistance and thus resulting in a decreased Qa. An earlier study of our department in patients with a HFA demonstrated that the short-term efficacy of banding with respect to Qa reduction was disappointingly low as over half of all banded patients developed recurrent HFA within one year.[11] On the other hand, a technique termed

RUDI (revision using distal inflow) appeared more promising as just 16% developed a recurrence within in one year.[12] In **Chapter two**, three-year efficacy in terms of recurrence and patency was studied in 21 patients undergoing RUDI using a saphenous vein interposition graft. Interestingly, 70% remained free from recurrent high Qa within one year. However, 50% of patients did develop recurrent high flow (> 2 L/min) within the 3-year study period. Strikingly, not one patient with a HFA and concomitant HAIDI developed a recurrence. Three-year patency rates were acceptable but interventions to maintain patency (e.g., thrombectomy or percutaneous transluminal angioplasty) were frequently required. It was concluded that RUDI possibly performs better than banding on the short term, but more effective ways of long-lasting flow reduction have yet to be discovered. Future studies comparing different Qa reductive techniques are required.

The short term efficacy of Qa reduction of RUDI has been established in several publications. However, changes in arm vessel flow and diameter patterns following this procedure were unknown. Studying these phenomena may aid in understanding vessel functioning and unveil factors contributing to recurrent high Qa. In **Chapter three**, Duplex measurements during the first postoperative year in 15 patients undergoing RUDI using a greater saphenous vein (GSV) are reported. Brachial artery and GSV diameters remained constant whereas the diameter of the (inflow) radial artery proximal to the new anastomosis doubled. This increase was less profound in patients with HFA and concomitant HAIDI (+80%) compared with HFA patients without HAIDI (+130%). Furthermore, ulnar artery flow increased significantly, likely as compensation for an imminent loss in hand perfusion after the pressure drop in the distal radial artery. HFA recurrence may be looming as (dilated) brachial artery diameters did not change over time.

Most studies on the effects of high Qa on (cardiovascular) mortality are based on one or a few Qa-measurements. However, one might argue that it takes time to exhaust cardiac reserves with lethal consequences. **Chapter four** shows the results of a statistical joint-modelling approach studying the relation between cardiovascular death and flow incorporating all available Qa measurements (n=5408) in a population of 165 HD-patients during a 9-year time period. A <900 mL/min 'initial' (very first measurement once HD has started) Qa following maturation of a primary AVA was associated with an increased cardiovascular mortality risk (HR 4.05

[1.94-8.43]). A low initial Qa possibly reflects a suboptimal condition of the host's cardiovascular system at the time of access maturation. Qa increases over 3-month intervals were also associated with increased risk of cardiovascular death (HR 4.48/100 mL/3 months [1.44-13.97]). It was hypothesized that these Qa-increases over time reflect a progressively failing homeostasis in already frail HD-patients. Randomly timed (high) Qa values were not predictive of cardiovascular mortality. These findings may be considered in monitoring programs.

There is an ongoing debate on definition and management of a HFA. Some surgeons only perform Qa reduction when cardiac and/or hand ischaemic complaints have developed in the presence of a high Qa. Others advise reduction when Qa exceeds a certain threshold (e.g., 1500 or 2000 mL/min), independent of the presence of complaints. As there is a lack of consensus, **Chapter five** provides an overview of definitions of HFA and Qa reducing techniques that were proposed over the last 40 years. A total of 66 publications comprising 940 patients were identified. Interestingly, diabetes mellitus was more commonly present in patients with HFA and concomitant HAIDI (58%) compared with patients with HFA without HAIDI (18%). In comparison, diabetes mellitus rates in an average HD population are between 30-40%. All studied techniques were found to decrease Qa but degrees varied. For example, following banding, Qa dropped about 1.1 L/min (no guidance by intraoperative flow tool) to 1.4 L/min (with guidance of an intraoperative flow tool). After revision using distal inflow (RUDI), the decrease approximated 1.7 L/min. A great diversity in work-up, indication for surgery, thresholds, definitions of HFA and recurrence, follow-up and methods of Qa reduction was found precluding firm conclusions. Furthermore, the majority of studies was retrospective with a limited number of patients. Factors possibly aiding in the decision to operate, for example extremely high Qa, presence of cardiovascular disease or HAIDI, should play a role in decision making. Moreover, factors possibly contributing to a wait-and-see approach, e.g., short life expectancy, a single high Qa measurement or a wish for access ligation following stable renal transplant, were discussed.

Part II: Haemodialysis access-induced distal ischaemia (HAIDI)

A brachial artery-based AVA usually offers an excellent mode for HD in terms of access patency and accessibility. In some patients however, the venous outflow segment may prove too short, too tortuous or too deep, precluding two needle dialysis. A basilic vein transposition (BVT), during which the basilic vein is rerouted more laterally along the biceps muscle, can help tackle this problem. It was observed that patients having symptoms of HAIDI prior to receiving a BVT reported a warmer and less painful hand following surgery. In **Chapter six**, results of a retrospective study in 10 patients with HAIDI undergoing BVT for an inadequate needle access segment were reported. Digital brachial indices (DBI, ratio of systolic finger pressure on systolic brachial-artery pressure; normal > 0.60) increased from 0.51 to 0.81 whereas scores of the hand ischaemic questionnaire dropped significantly from 220 to 9 (normal <50). Furthermore, a hypothesized inverse relation between DBI and questionnaire score was found. These findings indicated that BVT may effectively treat HAIDI-complaints. This effect is possibly explained by concurrent venous side branch ligation or construction of a smaller anastomosis thus attenuating the earlier 'pressure sink'.

In peripheral arterial occlusive disease (PAOD), presence of specific complaints and decreased toe pressures were found predictive of mortality.[13] In analogy to PAOD, HAIDI may in part also be considered a loco-regional expression of systemic vascular disease.[14] Intuitively, one may hypothesize that complaints and finger pressures in a patient with HAIDI are likely predictive of mortality. In **Chapter seven**, survival of 51 patients with different stages of HAIDI were compared with 48 peers without hand ischaemia. Patients with a severe type of HAIDI (e.g., unbearable pain during dialysis, rest pain, wounds; stage IIb to IV) were more likely to suffer from cardiovascular disease prior to the diagnosis HAIDI compared with patients with mild HAIDI (stage I to IIa) or no HAIDI at all. Intriguingly, low digital pressures -both with open as well as with compressed access-, high HAIDI complaint scores, and higher stages of HAIDI were related to increased mortality, even following correction for age and presence of cardiovascular disease and diabetes mellitus.

Old age, female sex, earlier AVA surgery and presence of diabetes mellitus are well-established risk factors for the development of HAIDI.[4,15] However, there is a need for additional parameters optimizing the preoperative counselling process prior to access construction. Historically, the Allen

test was performed to subjectively assess perfusion patterns of the hand in patients who were to receive a radial artery catheterisation or a wrist access, but with little success.[16] In **Chapter eight**, we determined in 105 patients whether an Allen test supported with digital plethysmography before access construction could predict the onset of HAIDI later on. Strikingly, all 10 patients who developed severe HAIDI requiring invasive measures displayed a radial or ulnar arterial dominance prior to access construction compared with about 60% of patients without HAIDI (total control group, n=95). The drop in digital pressure during the Allen test in the HAIDI-group was almost twice as high compared with controls (51 mmHg versus 27 mmHg). In addition, patients with a pressure drop ≥40 mmHg during an Allen test had a ten-times higher risk of developing HAIDI after access construction compared with patients with a drop <40 mmHg. These data suggest that patients who develop HAIDI have a diminished collateral hand perfusion reserve even before access construction. If additional risk factors for HAIDI are also present in such a patient, one may consider to opt for an alternative access type that is associated with a smaller chance of hand ischemia.

Conclusions

1 Young age and high postoperative access flow (Qa) values following revision using distal inflow (RUDI) are predictive of high rates of recurrent HFA in hemodialysis (HD) patients.

2 HAIDI patients with a high flow access (HFA) have a smaller risk of recurrent high Qa following RUDI which is (partly) due to attenuated dilatation of the radial artery in this subgroup.

3 A low initial Qa as well as 3-months Qa-increases are predictive of a higher cardiovascular mortality risk, whereas single Qa values are of little relevance in HD patients.

4 Longitudinal Qa analyses are useful for predicting survival rates in HD populations.

5 Research on HFA and Qa reducing surgery for high Qa suffers from a lack of standardization in definition, indication for intervention and surgical techniques precluding definite conclusions on management.

6 Hand ischemia is abolished following a basilic vein transposition for an inadequate needle access segment.

7 Patients who developed severe HAIDI are at greater risk of untimely death compared to their counterparts with mild or no HAIDI.

8 Decreased finger pressures in HAIDI patients are predictive of overall mortality.

9 An Allen test complemented with finger plethysmography prior to construction of an arteriovenous access may identify patients who are at an increased risk of developing severe HAIDI later on.

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Chapter 10

Future perspectives

Future perspectives

In this chapter, food for thought on future research regarding haemodialysis care is provided. Covered topics are (1) ideas on the prevention of high flow (Qa) and hand ischaemia, (2) a brain wave regarding a remote controlled device regulating Qa precluding the need of invasive surgery in case of high Qa, (3) advice for future researchers on the planning of trials in asymptomatic HFA patients, (4) musings on the potential beneficial effect of preoperative training on distal perfusion and risk of HAIDI, and (5) a critical note on the role of systolic digital pressures.

1. Can high flow (Qa) and hand ischaemia be prevented?

A substantial portion of publications on high Qa focus on its treatment. Recurrences of high Qa are not uncommon and re-interventions are frequently required. However, preventing the development of high Qa is even more appealing as risks of surgery related complications, cardiac strain and HAIDI may be reduced whereas -possibly most importantly- a higher quality of life may be attained.

Most access guidelines advise to construct the first haemodialysis access as distally as possible. The radio-cephalic arteriovenous fistula (RC-AVF) thus is considered the first choice.[1,2] These distal fistulas pose the smallest risk of the development of both HFA and HAIDI. However, due to the contemporary changing patient characteristics (obesity, diabetes, PAD), distally located fistulae are at increased risk of failing maturating and thrombosis. As a consequence, surgeons are increasingly forced to construct more proximal accesses using the brachial artery as feeding vessel.[3] These brachial artery-based fistulae (BA-AVF) offer excellent patency and facilitate easy needling although they pose a greater risk of the development of a HFA and HAIDI.[4-6] Moreover, a recent study from our department reported worse survival in patients harbouring a BA-AVF compared with patients with a RC-AVF. Whether this effect was due to a common factor (suboptimal cardiovascular health) precluding construction of a RC-AVF or due to the presence of the access per se is unclear.[7] Interestingly, Jennings et al. have advocated the use of the proximal radial or ulnar artery rather than the brachial artery as feeding vessel for several years now. HFA and HAIDI occur less often with these proximal forearm fistulae (ProxRA-AVF) due to the smaller inflow vessel diameter. Patency and accessibility were excellent.[8] Practically, a

frequently used technique for flow reduction termed RUDI is based on the same principle.

If one was to propose a randomized controlled trial in this field, what would be the optimal aim? Comparing ProxRA-AVF with BA-AVF could help to determine whether increased (cardiovascular) mortality is -partly- determined by the presence of the access itself, or that patient factors are to blame. Other endpoints that should be considered in such a trial are access patency, surgical complications, both symptomatic and asymptomatic high Qa, HAIDI and quality of life. ProxRA-AVF could attain a more prominent role in the pecking order of access options. Whenever a ProxRA-AVF develops high Qa, a minimally invasive intervention, namely proximal radial artery ligation (PRAL), is likely sufficient to correct this problem.[9,10]

Although inventive surgical strategies may play a role in future management, strategies aimed at preventing end-stage renal disease in the first place are essential, thus minimizing a need for haemodialysis fistulae. A critical review of the current diabetogenic and obesogenic public space is needed. For example, try counting the number of fast food restaurants along the A2 or in city centres in the Netherlands. Or what to think of the daily salt intake? The Dutch ambition to obtain the first 'non-smoking generation' is a step in the right direction.

2. What to do in case of symptomatic high Qa?

As access surgery will remain necessary in the near future, some patients are bound to develop a high Qa. There is an urgent need for a uniform definition of HFA and of recurrent HFA in order to optimize care. Furthermore, in the search for the optimal durable standardized Qa reducing surgical technique, comparative trials are warranted. To date, banding is the most commonly used intervention for high Qa. However, types of banding techniques and outcome vary greatly and valid comparisons are not feasible. For example, Qa recurrence rates within one year were as high as 52% (26/50 patients) in a study from our department, despite the use of an intraoperative Qa tool guiding grade of banding.[11] A recent study found recurrence rates as low as 14% (52/398 interventions) a year after precision banding,[12] a percentage that is in line with the overall findings of the scoping review included in this thesis. Recently, Mallios et al. published results of a banding technique using a customizable stent in 10 patients

with high Qa. Qa values decreased by 50% and significant complications were absent.[13] Despite these promising results, additional interventions were still necessary in both studies.

Will it be possible to avoid such re-interventions? The immediate aim after fistula construction is the prevention of thrombosis so adequate maturation can ensue. Once haemodialysis is indeed required, Qa should be high enough for efficient exchange of waste products. However, in between haemodialysis sessions, a Qa that remains just above the access' thrombotic threshold suffices. Could a remote controlled technique have a role in 'navigating between Scylla and Charybdis'? For example, an annular device that is placed around the outflow vessel at the time of access creation could increase or decrease the access' diameter and thus Qa. In between sessions, the ring is constricted leading to a lower current Qa. Conversely, the ring is opened just prior to a dialysis session facilitating proper access flow. Using this approach, the risk of ongoing cardiac strain and hand ischaemia may be attenuated. Initially, it would suffice to alter the diameter based on Qa measurements at the hospital. Later on, Qa level is modified according to feedback Qa mechanisms in the device itself, if required. This idea was conceived in 2007 but was aborted due to technical limitations.[14] Efforts in this direction are currently made by the Leiden research group of professor J.I. Rotmans, MD PhD.

3. How to approach an asymptomatic HFA?

Despite the fact that type of surgical intervention as well as timing in symptomatic HFA patients are not specified yet, most authors agree that an intervention is mandatory. In asymptomatic patients however, consensus on whether or not to intervene is lacking. This is mainly due to the limited body of evidence of potential detrimental effects of high Qa as well as the effectiveness of preventive interventions in patients not reporting any symptoms. The lack of uniform definitions of symptoms also plays an important role in this matter. Trials comparing flow reductive surgery with a 'wait-and-see' approach in asymptomatic patients are therefore needed. Primary outcomes should include development of cardiac failure, (cardiac) mortality and quality of life. As the impact of a Qa of 2 L/min is intuitively greater in a woman of 160 cm weighing 50 kg compared with a man of 200 cm weighing 95 kg, indexing is probably important. The most informative method of indexing Qa (e.g., based on height, cardiac output or body surface area) has yet to be determined.

Furthermore, as single Qa measurements seemed to be of little relevance in the light of (cardiovascular) mortality, the use of a joint modelling approach including long term Qa data is advised. Such trials might help in tailoring management for individual patients: 'One size does not fit all'.

4. Can training influence a suboptimal modified Allen test?

In 2010, Kumar et al. reported brachial and radial arterial diameter increases as well as increased arm arterial flow velocities following weight training prior to construction of an AVF.[15] Whether or not this approach aids in access maturation remained unclear.[16] It would be interesting to assess whether simple weight training, or possibly even extensive prehabilitation prior to access surgery stimulates hand perfusion and helps prevent the development of HAIDI. Additionally, it would be interesting to see whether or not such a multimodal training could facilitate construction of more distally located accesses. A simple first step would be to investigate the effect of exercise on different perfusion characteristics including the modified Allen test (as published in this thesis), standard digital pressures and flow velocities. Hypothetically, pressure drops during an Allen test may be attenuated following training. As a consequence, the development of (severe) hand ischaemia within 6 months following access construction could decrease. Strikingly, the importance of (supervised) exercise therapy is well established in peripheral arterial occlusive disease (PAOD).[17] In (mild) HAIDI, evidence based exercise programs are lacking and possible beneficial effects have yet to be established. As HAIDI and PAOD share a similar pathophysiology, it might be worthwhile to initiate studies investigating the effects of training on fistula maturation and prevention and treatment of hand ischaemia.

5. How well do systolic digital pressures reflect (distal) perfusion?

Currently, literature on HAIDI often includes systolic digital pressures as proxy marker of hand perfusion. Low systolic digital pressures (<50 mmHg) or low digital brachial indices (DBI; <0.6; ratio digital pressure on systemic pressure) in the presence of characteristic complaints are suggestive of HAIDI.[18,19] Unfortunately, inter- and intra-observer reliability are not well established. Additionally, these values are susceptible to environmental influences (e.g., room temperature) and other factors (e.g., level of activity prior to the measurement). Moreover, a systolic value only comprises about 1/3rd of a heart cycle. Considering a unilaterally obtained systolic digital

pressure might lead to overestimation of the distal perfusion. A borderline low systolic pressure is likely accompanied by a low (or even unmeasurable) diastolic pressure leading to an insufficient mean arterial distal pressure. At present, the diagnosis HAIDI is mainly determined on the basis of clinical characteristics supported by these pressure measurements. However, determining intravascular mean pressures both in feeding arteries as well as in the outflow tract are likely more useful for assessing pressure loss and vessel resistance. Alternatively, measurements of arterial compliance or stiffness (e.g., brachial-ankle pulse wave velocity or radial arterial applanation tonometry) may also prove useful for evaluating vascular health.[20]

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Chapter 11

Impact section

General aim of this thesis was to study various aspects of pathophysiology, treatment and prognosis of high access flow (Qa) and haemodialysis access-induced distal ischaemia (HAIDI) in patients who dialyse via an upper extremity arteriovenous access.

Scientific impact

In part I, studies on high flow access (HFA) are reported. Assessment of the long-term efficacy of a technique termed Revision Using Distal Inflow (RUDI) was performed. Although earlier studies found acceptable short-term results in terms of stable access flows, half of them developed recurrent high Qa within 3 years after the operation. Moreover, re-interventions were frequently required to protect patency. RUDI, being a relatively complex intervention, may therefore not be the optimal Qa reducing technique (**Chapter 2**). As a consequence, the quest for a minimally invasive effective flow reducing surgical technique continues.

It is largely unknown what the cause of this high recurrence rate is. A subsequent study found that dilated brachial arteries, the result of a chronic high flow state, did not decrease following RUDI. Conversely, they remained stable indicating a possible loss of remodelling capacity due to the previous longstanding high Qa. This phenomenon may possibly explain this high recurrence rate. If a loss of remodelling capacity is 'dose-dependent' and also holds true for other vessels (e.g., coronary vessels), earlier Qa reduction could be indicated as a means of protecting the host from cardiac overload. Following RUDI, proximal radial artery diameters did increase as hypothesized. Intriguingly, patients with concomitant HAIDI displayed less increase (+80%) compared with patients with HFA without HAIDI (+130%), likely explaining the absence of recurrent HFA in HFA-HAIDI patients following RUDI. Even though HAIDI partly developed due to the high Qa in this specific subpopulation, the arterial system in these patients is diseased due to atherosclerosis, ironically, protecting them from remodelling and recurrent HFA (**Chapter 3**).

Researchers have long questioned whether long term exposure to high Qa was detrimental for the host, or just beneficial as dialysis sessions are uncomplicated. It is intuitive to hypothesize a direct relation between high longitudinally acquired Qa values and cardiovascular mortality. One study in this thesis was designed to solve this issue. Using a sophisticated statistical technique termed joint-modelling, an association between

Qa increases per three months and higher cardiovascular mortality was established. Even more surprisingly, low initial Qa (<900 mL/min) was predictive of untimely death whereas randomly obtained Qa values were of little relevance. The clinical relevance of a single Qa measurement thus is questionable at best and should be reserved for detection of stenoses. However, its use for prediction of longevity of the host is questionable. Conversely, joining forces with statisticians allowing modelling will boost our understanding of possible relations between Qa, development of cardiac failure and mortality (**Chapter 4**).

Studies on high Qa are still in its infancy. For instance, literature on Qa reducing techniques is largely heterogeneous, definitions of high Qa and HFA lack uniformity and consensus on when and how exactly to intervene is absent. In order to ignite the discussion on these issues, a scoping review was conducted to further expose these knowledge gaps. The results indicate that fundamental questions remain on virtually all aspects of high Qa. High level trials are duly required to improve research and standardization. The ultimate goal is to improve care for this fragile patient population (**Chapter 5**).

Part II of this thesis focuses on various aspects of another severe long term complication of upper extremity based accesses termed hand ischemia (HAIDI). Some patients who have an upper arm cephalic vein that cannot be punctured by two needles required a conversion termed basilic vein transposition (BVT). Coincidentally, some HAIDI patients receiving such a BVT reported less hand pain and coldness following this operation. We studied a small group of patients and found that a BVT for an inadequate needle access segment indeed attenuates hand ischaemic complaints and may lead to increased digital pressures. BVT might be added to the armamentarium of vascular surgeons in treating HAIDI in a very specific subpopulation of patients (**Chapter 6**).

A further study investigated a possible association between low digital pressures, grade of HAIDI, HAIDI complaint scores and mortality. Such associations were a priori hypothesized and indeed established. The presence of HAIDI should be considered as an (severe) expression of the presence of cardiovascular disease. Stricter follow-up of these HAIDI patients is warranted. However, the exact form has yet to be established. The usefulness of the hand ischaemic questionnaire (HIQ) was further confirmed. As also reported in earlier studies, this tool may play a role in

grading and establishing the presence of HAIDI, in evaluating the effect of interventions and in identifying haemodialysis patients at increased risk for mortality (**Chapter 7**).

An Allen test was previously advocated as a test to assess hand perfusion patterns. However, suboptimal test characteristics precluded a widespread use of this simple bedside method. We hypothesized that an Allen test complemented with systolic digital pressure measurements may be more accurate in determining hand perfusion as in HAIDI. We hoped that this combined test was predictive of the development of HAIDI following access construction. Strikingly, all patients developing severe HAIDI displayed a dominant perfusion pattern, which means that the hand is fully dependent on one of the two arteries for its perfusion, prior to access construction compared with just over half of patients not developing HAIDI. Moreover, greater pressure drops during an Allen test prior to access creation predicted the development of HAIDI later on. Whether or not it is possible to improve hand perfusion, for example through pre-operative weight training, has yet to be established. Our published technique is relatively simple. So, to speak, it could be implemented in hospitals with a vascular diagnostic department 'tomorrow' in order to gain experience with this novel promising parameter (**Chapter 8**).

The smaller studies in this thesis (**Chapter 2, 3 and 6**) have added to the knowledge on how (not to) approach high Qa and HAIDI. They raised new questions on drivers of high Qa recurrence, on importance of vascular quality and on tailoring management of HAIDI in subcategories of patients. The larger studies (**Chapter 4, 7 and 8**) changed our views on haemodialysis care. The use of single Qa measurements in haemodialysis research focusing on mortality proves outdated and should be replaced by longitudinal data. The presence of severe HAIDI reflects poor vascular quality and should be considered as an alternative marker of cardiovascular disease. Additionally, systolic digital pressures during an Allen test might provide inside in the vascular system of a patient and deserve further studying. Finally, the scoping review in **Chapter 5** sheds a light on the paucity in knowledge on Qa, serving as a roadmap for clinicians and future researchers alike.

The contents of this thesis have been published in a variety of international vascular surgical and nephrological journals. Data were also presented internationally, both in Europa as well as in the United States, on a wide

variety of high level conferences such as the Annual Meeting of the European Society for Vascular Surgery and at Kidney Week of the American Society of Nephrology. These data will surely stimulate future researchers to perform follow-up studies on longitudinal Qa measurements, digital pressures prior to access construction and HAIDI. Besides scientific implications, our data can easily be translated to daily surgical practice. It provides practical considerations on when to intervene in HFA patients, on a technique both countering an inadequate needle access segment and HAIDI in one go, and possibly in counselling individual patients on type of haemodialysis access construction.

Social impact

Chronic kidney disease (CKD) plays a major role in public health with significant effects on morbidity and mortality. Health care costs for treatment of CKD are higher than ever and still increasing, partly due the longer survival of patients with end stage renal disease (ESRD), but also as a result of more effective strategies to replace the renal function. Just to illustrate, at the end of 2021 over 18 thousand people in the Netherlands received some form of renal replacement therapy (RRT) conferring a 1.5 time increase since 2006. Worldwide, it is estimated that about 5 million people are to suffer from CKD by the end of 2030. Causes are diverse, but comorbidities such as diabetes mellitus, hypertension and cardiovascular disease are labelled as most influential.

Excluding patients that received a kidney transplantation (almost 12.000 donor kidney bearers at the end of 2021), haemodialysis is the most prevalent form of RRT. Moreover, most patients requiring RRT receive haemodialysis while waiting for a donor kidney. Numbers of prevalent haemodialysis patients in the Netherlands have been well above 5.000 for more than a decade now. Although patients might benefit from dialysis in terms of prolonged survival, access-related complications are plentiful. Published rates of HFA development are about 4%. HAIDI is thought to develop in up to 20% of the patients, although higher percentages have been reported. As surgeons are increasingly forced to construct accesses more proximally due to high failure rates or a low a priori chance of maturation of distal accesses, rates of HFA and HAIDI rates are prone to increase. For patients, associated complaints may lead to minor discomfort but often also to major constraints in daily functioning reducing quality of life. Re-

interventions bear additional risk of surgical complications, and time spent on the surgeons table cannot be used for life fulfilling activities.

The potential social impact from this thesis for haemodialysis patients is twofold. The data add to a growing body of evidence regarding HFA and HAIDI development and treatment. Surgeons might use this thesis to improve decision making and counselling of patients considering pre-operative planning and treatment of complications. Furthermore, vivid discussion in order to come to uniform definitions and standardized evidence based treatment of HFA and HAIDI alike are bound to improve patient care in the long run.

Chapter 12

Nederlandse samenvatting (Dutch summary)

Nederlandse samenvatting (Dutch summary)

De nieren verwijderen afvalstoffen uit het bloed via de urine. Bij sommige mensen verliezen de nieren deze capaciteit en ontstaat (eindstadium) nierfalen. Zonder behandeling stapelen afvalstoffen zich op in het lichaam. Dit kan uiteindelijk leiden tot de dood. Kunstmatige bloedspoeling (hemodialyse) via een kunstnier kan bij deze patiënten het leven verlengen. Voor adequate bloedspoeling is het noodzakelijk een oppervlakkig bloedvat (ader) met een stroomminuutvolume (Qa) van 400-600 ml per minuut aan te kunnen prikken, het liefst met twee naalden. In het menselijk lichaam bestaat een dergelijk bloedvat niet. In de jaren '60 van de afgelopen eeuw werd hiervoor de arterioveneuze fistel (AVF) geïntroduceerd. Een AVF is niet veel meer of minder dan een kunstmatige directe verbinding tussen een slagader (arterie) en een ader (vene), bijvoorbeeld aangelegd in de arm van de patiënt. Het slagaderlijk systeem wordt gekenmerkt door een hoge bloeddruk terwijl het aderlijk systeem lage drukken kent. Door de genoemde verbinding tussen de twee systemen gaan er grote hoeveelheden bloed direct vanuit het hart door de slagader via de ader terug naar het hart. Een dergelijke AVF zorgt ervoor dat patiënten adequaat hemodialyse kunnen ondergaan.

Buiten het gegeven dat het ondergaan van hemodialyse zwaar is (soms wordt het vergeleken met het telkens rennen van een marathon, drie keer per week), kan de AVF zelf ook nog leiden tot vervelende complicaties die de kwaliteit van leven beperken. Twee van deze complicaties zijn het ontwikkelen van een te hoge Qa ('high flow access', HFA), en het ontwikkelen van onvoldoende bloedtoevoer naar de hand ('haemodialysis access-induced distal ischaemia', HAIDI). Als de AVF wordt aangelegd ter hoogte van de pols, is het risico op deze twee complicaties kleiner dan wanneer deze wordt aangelegd ter hoogte van de elleboog. Echter, door de tegenwoordige veranderde patiëntkenmerken die leiden tot verslechterde vaatkwaliteit (meer suikerziekte, meer vaatziekte, oudere patiënten), moeten chirurgen helaas steeds vaker uitwijken naar elleboogfistels. Deze trend leidt tot het heden ten dage vaker vóórkomen van zowel HFA als HAIDI.

Deel I: High Flow Access (HFA)

Het eerste deel (**Hoofdstuk twee tot en met vijf**) van deze thesis richt zich op de behandeling en de mogelijke invloed van een hoge Qa op hemodialysepatiënten. Zoals gesteld is een Qa van 400-600 ml/min voldoende voor adequate afgifte van afvalstoffen aan de kunstnier. Soms blijft een AVF steeds verder 'groeien' en kan de Qa hoger worden dan 1.5 of zelfs 2 liter per minuut! Houd hierbij in het achterhoofd dat het hart normaalgesproken 4-5 liter per minuut pompt om het hele lichaam van voldoende bloed te voorzien. De AVF kan dus voor een toegenomen werklast voor het hart zorgen. Eerder onderzoek suggereerde dat deze bijkomende werklast grote effecten op het hart- en vaatstelsel zou kunnen hebben. Hartfalen leek bijvoorbeeld vaker voor te komen bij mensen met een Qa groter dan 2 liter per minuut, vergeleken met patiënten met een veel lagere Qa.

Over de jaren zijn er verschillende ingrepen bedacht om een hoge Qa te verminderen. De oudste, meest intuïtieve en bekendste techniek heet 'banding'. Tijdens deze ingreep wordt een (kunststof) bandje rondom het aderlijk deel van de AVF aangelegd. De doorsnede van het afvoerende traject neemt zo af, de weerstand over de AVF wordt groter, en de Qa neemt af. Een eerdere studie uit Máxima Medisch Centrum (MMC) toonde aan dat meer dan de helft van de patiënten die 'banding' ondergingen binnen een jaar wederom een te hoge (>2 l/min) Qa had. Een andere en technisch meer complexe techniek is 'revision using distal inflow' (RUDI). Bij deze ingreep wordt de originele aansluiting tussen de slagader en ader in de elleboog gesloten. Met behulp van een buisje (lichaamseigen bloedvaatje ofwel kunststof) wordt er een nieuwe verbinding op de onderarm gemaakt, bijvoorbeeld net onder de elleboog of zelfs bij de pols. De fistel wordt zo van bloed voorzien vanuit een bloedvat met een veel lager volume. Een eerdere studie vanuit MMC toonde dat 16% van de patiënten die een RUDI ondergingen opnieuw een te hoog Qa hadden binnen een jaar na de ingreep. In **Hoofdstuk twee** worden de langetermijnresultaten beschreven in 21 patiënten. Meer dan 2/3^{e} van de patiënten bleef vrij van een hoge Qa binnen een jaar na de ingreep. Echter, na drie jaar had de helft toch weer een te hoge Qa (>2 l/min) ontwikkeld. Interessant genoeg ontwikkelde geen van de patiënten die tegelijkertijd HFA en HAIDI hadden opnieuw een te hoge Qa. Gedurende de bestudeerde drie jaar waren er regelmatig ingrepen nodig om de doorgankelijkheid van de AVF te waarborgen. Soms

ging dit via een dotterprocedure, soms was een chirurgische ingreep noodzakelijk waarbij een stolsel werd verwijderd. Geconcludeerd werd dat RUDI mogelijk betere resultaten biedt dan banding op de korte termijn maar ook dat de ideale Qa-verlagende techniek voor de langere termijn nog niet gevonden is. Studies die verschillende technieken onderling vergelijken zijn nodig.

Zoals benoemd is het gunstige korte termijneffect van RUDI voor HFA aangetoond. Echter, eventuele veranderingen in de bloedstroom en vaatdiameters in de armvaten na deze ingreep zijn niet eerder beschreven. Het bestuderen van deze veranderingen kan mogelijk leiden tot een beter begrip van factoren die bijdragen aan het opnieuw ontwikkelen van een te hoge Qa (recidief) na RUDI. Met behulp van een specifieke op het Dopplereffect gebaseerde echografische techniek, Duplex genaamd, kunnen stroomsnelheden en vaatdiameters gemeten worden. Vijftien patiënten uit twee ziekenhuizen werden gedurende een jaar na RUDI, uitgevoerd met een lichaamseigen beenader (vena saphena magna, VSM), op gezette tijden middels Duplex onderzocht. De resultaten van dit onderzoek zijn te lezen in **Hoofdstuk drie**. De wijdte van de grote bovenarmslagader (arteria brachialis) was, zoals verwacht, vergroot in alle deelnemende patiënten voorafgaand aan RUDI. Ondanks de verlaging van de Qa, die in alle patiënten na RUDI optrad, nam de diameter van deze slagader niet af. De diameter van de gebruikte VSM bleef eveneens gelijk. De gevonden groei van het eerste deel van de onderarmslagader (arteria radialis) was meer uitgesproken in de 9 patiënten met een te hoge Qa zonder klachten van HAIDI voorafgaand aan RUDI (+130%) in vergelijking met de 6 patiënten die een te hoge Qa en HAIDI hadden voorafgaand aan RUDI (+80%). De stroomsnelheid in de andere onderarmslagader (arteria ulnaris) steeg aanzienlijk, waarschijnlijk om voor het verlies van doorstroom in de arteria radialis achter de AVF te compenseren. Het feit dat de arteria brachialis na RUDI niet afneemt in diameter zorgt mogelijk al voor een vergroot risico op het krijgen van een recidief verhoogde Qa.

Het is goed te weten dat bij hemodialysepatiënten ongeveer eens per 6-8 weken een Qa meting wordt verricht op de dialyseafdeling om eventuele problemen zoals vernauwingen in de AVF tijdig op te kunnen sporen. De meeste studies die het effect van een (hoge) Qa op sterfte aan hart- en vaatziekten onderzochten, zijn gebaseerd op een of enkele Qa-metingen. Men zou echter kunnen denken dat het tijd kost voor een fistel met een

hoge Qa om de reservecapaciteit van het hart uit te putten. 'Joint-modelling', een complexe statistische techniek, stelt ons in staat álle over diverse jaren uitgevoerde Qa metingen van een patiënt te onderzoeken in een statistisch model. In **Hoofdstuk vier** wordt deze techniek toegepast om de relatie te zoeken tussen sterfte aan hart- en vaatproblematiek en alle beschikbare Qa metingen (totaal 5408 in 9 jaar) in een groep van 165 patiënten. Interessant genoeg wees een relatief lage 'eerste Qa' (de allereerste Qa meting na het uitrijpen van de AVF) van <900 ml/min op een vier keer verhoogd risico op sterfte vergeleken met patiënten met een hogere 'eerste Qa'. Mogelijk wijst een lage 'eerste Qa' op relatief slechte kwaliteit van het hart- en vaatstelsel wat voorspellend is voor sterfte. Het systeem is als het ware niet uitgerust om, naast de normale behoeften, zo'n extra aanbod te generen. Verder bleek dat stijgingen van Qa (100 ml/3 maanden) ook geassocieerd waren met een verhoogd risico op sterfte. In theorie wijzen deze stijgingen op het toenemend falen van het lichaam om zichzelf in balans te houden. Daarentegen, willekeurig afgenomen (hoge) Qa metingen waren op geen enkele manier voorspellend voor sterfte. Deze kennis kan van invloed zijn op toekomstige monitoringsprogramma's.

In het werkveld is er een discussie gaande omtrent definitie en juiste behandeling van een HFA. Sommige vaatchirurgen grijpen enkel in wanneer er sprake is van klachten (bijvoorbeeld van het hart of van de hand) in aanwezigheid van een hoge Qa. Andere adviseren een ingreep wanneer de Qa boven een bepaalde drempelwaarde ligt (bijvoorbeeld 2 l/min), ongeacht of er klachten zijn of niet. Gezien dit gebrek aan overeenstemming biedt **Hoofdstuk vijf** een overzicht van definities van HFA en gebruikte behandelingstechnieken in de afgelopen 40 jaar. In totaal werden er 66 publicaties gevonden die gezamenlijk 940 patiënten beschreven. Patiënten met een hoge Qa en HAIDI leden vaker aan suikerziekte (58%) vergeleken met patiënten zonder HAIDI (18%). Ter vergelijking, in gemiddelde dialysepopulaties ligt het percentage rond de 40%. Alle bestudeerde technieken verlaagden Qa. De mate waarin dit gebeurde verschilde echter. Bijvoorbeeld, Qa daalde na 'banding' met 1.1 l/min wanneer er tijdens de operatie geen Qa metingen werden verricht, en met 1.4 l/min wanneer dit wel werd gedaan. Na RUDI daalde de Qa met 1.7 l/min. Een enorme variatie in preoperatieve onderzoeken, operatie-indicatie, drempelwaarden, definities van HFA en recidief HFA, postoperatieve opvolging en methoden van Qa vermindering werd gevonden. Daarbij was de dataverzameling in de meeste artikelen gebaseerd op informatie die was opgehaald uit het

verleden (retrospectief onderzoek), en waren de patiëntaantallen veelal klein. Dit alles maakt het onmogelijk ferme conclusies te trekken. Factoren die een rol moeten hebben bij de beslissing (operatief) in te grijpen bij een hoge Qa zijn onder andere extreem hoge waarden, aanwezige hart- en vaatziekten, en HAIDI. Factoren die mogelijk bijdragen te kiezen voor een afwachtend beleid zijn bijvoorbeeld een toch al korte levensverwachting, een enkele hoge Qa meting, of de wens tot opheffen van de AVF na een succesvolle niertransplantatie.

Deel II: Haemodialysis access-induced distal ischaemia (HAIDI)

Het tweede deel van de thesis (**Hoofdstuk zes tot en met acht**) richt zich op verschillende facetten van HAIDI. In het begrijpen van de oorzaak en diagnostiek van HAIDI is de rol van de bloeddruk (bovendruk, systolische druk) in de vinger en van de vinger-arm-index ('digital brachial index', DBI, normaal >0.6) van groot belang. Deze DBI wordt berekend door de gemeten systolische vingerdruk te delen door de gemeten systolische bloeddruk in de arm. Verder wordt in MMC voor de diagnose HAIDI reeds jaren gebruik gemaakt van de 'hand ischaemic questionnaire' (HIQ, score van 0 tot 500, normaal <50) waarin een patiënt de vijf typerende klachten van hand ischemie (koude, pijn, tintelingen, krachtverlies, krampen) scoort in ernst en frequentie.

Normaalgesproken biedt een elleboogfistel van de arteria brachialis een prima toegang voor hemodialyse. Soms is het aderlijk deel van de AVF echter te kort, te kronkelig of ligt het te diep om het traject met twee naalden aan te kunnen prikken. Zo is dialyse minder effectief uit te voeren. Verplaatsing van een specifieke bovenarmader (de vena basilica) middels een techniek genaamd vena basilica transpositie ('basilic vein transpostion', BVT) kan hierbij helpen. Tijdens deze ingreep wordt deze ader, die normaal gesproken relatief diep in de arm ligt, oppervlakkiger over de bicepsspier gelegd. Bij toeval bleek dat sommige patiënten na een BVT minder last hadden van pijn en koude in de hand. **Hoofdstuk zes** omvat een kleine retrospectieve studie van tien patiënten met HAIDI die een BVT ondergingen wegens een niet adequaat aanpriktraject. De DBI steeg van gemiddeld 0.51 naar 0.81. HIQ-scores zakten van 220 naar 9. Verder werd een verband gevonden tussen de hoogte van de HIQ-score en DBI. De bevindingen van dit onderzoek tonen aan dat BVT mogelijk effectief is tegen HAIDI in geselecteerde patiënten. Dit effect kan ofwel worden

toegeschreven aan het afbinden van zijtakken van de vena basilica ofwel door het aanleggen van een nieuwe kleinere verbinding tussen de slagader en de ader.

Bij perifeer arterieel vaatlijden (PAD), in de volksmond 'etalagebenen', bleek de aanwezigheid van specifieke klachten en verminderde teendrukken voorspellend voor sterfte. PAD en HAIDI vertonen gelijkenissen. Beide aandoeningen kunnen worden gezien als een plaatselijke uiting van algeheel verslechterde vaatkwaliteit. We veronderstelden dat de aanwezigheid van HAIDI-klachten en verlaagde vingerdrukken mogelijk ook voorspellend konden zijn voor sterfte in een dialysepopulatie. Vierjaarsoverleving van 51 patiënten met verschillende gradaties van HAIDI werd vergeleken met die van 48 dialysepatiënten zonder HAIDI in **Hoofdstuk zeven**. Patiënten met ernstige HAIDI (graad IIb-IV; klachten van ondraaglijke pijn in rust of tijdens dialysesessies ofwel het ontstaan van wonden) leden vaker aan hart- en vaatziekten dan patiënten met milde (graad I-II) of zonder HAIDI. Lage vingerdrukken, hoge HIQ-scores en hogere gradaties van HAIDI waren allen gerelateerd aan sterfte, ook na correctie voor leeftijd en aanwezigheid van hart- en vaatziekten en suikerziekte.

Eerder vastgestelde risicofactoren voor het ontwikkelen van HAIDI zijn hoge leeftijd, vrouwelijk geslacht, eerdere toegangschirurgie, en de aanwezigheid van suikerziekte. Om de preoperatieve informatievoorziening van patiënten die een AVF moeten gaan krijgen te verbeteren en het risico op HAIDI beter in te kunnen schatten zijn aanvullende parameters nodig. In het verleden werd de Allen test voorafgaand aan een dotterprocedure of de aanleg van een AVF gebruikt om de bloedtoevoer naar de hand te beoordelen. Deze test ziet er in het kort als volgt uit. De patiënt maakt enkele keren een vuist en knijpt stevig door. Vervolgens laat de patiënt de vuist weer los. Tijdens de tweede en derde keer drukt de chirurg afwisselend de arteria radialis of ulnaris ter hoogte van de pols dicht. Tijdens het loslaten van de vuist beoordeelt de chirurg de terugkeer van de doorbloeding in de handpalm door naar de kleurverandering te kijken: van bleek naar rode/ roze. Op deze manier zou de chirurg kunnen beoordelen of de beide onderarmslagaders even belangrijk zijn voor een goede doorbloeding, of dat een van beide slagaders de doorbloeding grotendeels bepaalt ('dominant'). Deze test was in het verleden weinig succesvol bij dialyse patiënten door een te grote subjectiviteit. Door deze Allen test aan te vullen met vingerdrukmetingen zou deze methode misschien wel kunnen worden gebruikt. De hoogte van

het eventueel gemeten drukverval zou mogelijk iets kunnen zeggen over de mogelijkheid tot compensatie van het vaatstelsel. Ook kan met maat en getal in potentie worden bepaald of, en zo ja, welke slagader 'dominant' is.

Hoofdstuk acht beschrijft de voorspellende waarde van deze aangepaste Allen test voorafgaand aan de aanleg van een AVF voor het ontwikkelen van HAIDI in 105 patiënten. Tien patiënten ontwikkelden later ernstige HAIDI. Opvallend genoeg hadden alle tien deze patiënten een dominant doorbloedingspatroon. Van de overige 95 patiënten, die geen HAIDI ontwikkelden, had slechts 57% een dominant doorbloedingspatroon. In de patiënten die later HAIDI zouden ontwikkelen daalde de vingerdruk tijdens de Allen test bijna twee keer meer dan in de andere patiënten (51 mmHg versus 27 mmHg). Wanneer de daling in vingerdruk voorafgaand aan de aanleg van de AVF groter was dan 40 mmHg wees dat op een tien keer verhoogd risico op het ontwikkelen van HAIDI vergeleken met patiënten waarbij dit drukverval kleiner dan 40 mmHg was. Deze data wijzen erop dat de handdoorbloeding al voorafgaand aan de aanleg van de AVF verstoord was bij de patiënten die later HAIDI zouden ontwikkelen. Het is verstandig hiermee rekening te houden wanneer zowel een groot drukverval als andere risicofactoren voor HAIDI aanwezig zijn voorafgaand aan de aanleg van de AVF.

Appendices

List of publications

Gerrickens MWM, Yadav R, Vaes RHD, Scheltinga MRM. A scoping review on surgical reduction of high flow arteriovenous haemodialysis access. *Journal of Vascular Access*. 2022 Nov 25. Online ahead of print.

Gerrickens MWM*, Yadav R*, van Kuijk SMJ, Vaes RHD, Snoeijs MGJ, Scheltinga MRM. Access flow volume (Qa) and survival in a hemodialysis population: An analysis of 5208 Qa measurements over a 9-year period. *Nephrology Dialysis Transplantation. 2022 Aug; 37(9):1751-1757.*

Yadav R, **Gerrickens MWM,** van Kuijk SMJ, Teijink JAW, Scheltinga MRM. A preoperative modified Allen test may be associated with long term mortality after hemodialysis access construction. Journal of Vascular Access. 2022 Jan; 23(1):109-116.

Yadav R, **Gerrickens MWM,** Vaes RHD, Scheltinga MRM. Lower cardiovascular mortality rates in hemodialysis patients with radial artery based fistulas. European Journal of Vascular and Endovascular Surgery. 2021 Dec; 62(6):1004-1005.

Yadav R, **Gerrickens MWM**, Teijink JAW, Scheltinga MRM. Systolic finger pressures during an Allen test before hemodialysis access construction predict severe postoperative hand ischemia. Journal of Vascular Surgery. 2021 Dec; 74(6):2040-2046.

Yadav R, **Gerrickens MWM**, Teijink JAW, Scheltinga MRM. Abnormal preoperative digital brachial index is associated with lower 2-year arteriovenous fistula access patency. Journal of Vascular Surgery. 2021 Jul; 74(1):237-245.

Gerrickens MWM, Yadav R, Wouda R, Beerenhout CH, Scheltinga MRM. Severe hemodialysis access-induced distal ischemia may be associated with poor survival. Journal of Vascular Access. 2021 Mar; 22(2):194-202.

Yadav R, **Gerrickens MWM**, Teijink JAW, Scheltinga MRM. Abnormal digital brachial index prior to hemodialysis access construction and cardiovascular mortality. Hemodialysis International. 2020 Jul; 24(3):335-343.

Gerrickens MWM, Vaes RHD, Wiersma V, van Kuijk SMJ, Snoeijs MGJ, Govaert B, Scheltinga MRM. Revision using distal inflow for high flow hemodialysis access alters arterial flow characteristics in the dialysis arm. Journal of Vascular Surgery. 2020 Mar; 71(3):920-928.

Gerrickens MWM, Vaes RHD, Govaert B, Teijink JAW, Scheltinga MRM. Basilic vein transposition for unsuitable upper arm hemodialysis needle access segment may attenuate concurrent hand ischemia. Hemodialysis International. 2018 Jul; 22(3):335-341.

Gerrickens MWM, Vaes RHD, Govaert B, van Loon M, Tordoir JHM, van Hoek F, Teijink JAW, Scheltinga MRM. Three-year patency and recurrence rates of revision using distal inflow with a venous interponate for high flow brachial artery-based arteriovenous fistula. European Journal of Vascular and Endovascular Surgery. 2018 Jun; 55(6):874-881.

List of presentations

2022	
June	**Gerrickens MWM,** Yadav R, van Kuijk SMJ, Vaes RHD, Snoeijs MGJ, Scheltinga MRM. Arteriovenous access flow and cardiovascular mortality: An analysis of 5208 flow measurements in a hemodialysis population. Poster presentation, 22e Nederlandse Nefrologiedagen. Veldhoven, Nederland.

2019	
December	**Gerrickens MWM**, Yadav R, Wouda R, Beerenhout CH, Scheltinga MRM. Ernstige, maar niet milde handischemie is geassocieerd met verminderde overleving van hemodialysepatiënten. Poster presentation, Symposium Experimenteel Onderzoek Heelkundige Specialismen. Amsterdam, Nederland.
November	**Gerrickens MWM**, Yadav R, Wouda R, Beerenhout CH, Scheltinga MRM. Ernstige, maar niet milde handischemie is geassocieerd met verminderde overleving van hemodialysepatiënten. Oral presentation, Najaarsdag van de Nederlandse Vereniging voor Heelkunde. Ede, Nederland.
	Gerrickens, MWM, Vaes RHD, Wiersma V, van Kuijk SMJ, Snoeijs MGJ, Govaert B, Scheltinga MRM. Excessively high fistula flows in hemodialysis patients possibly result in an irreversible loss of arterial remodelling capacity. Poster presentation, American Society of Nephrology's Kidney Week. Washington DC, Verenigde Staten.

Gerrickens MWM, Yadav R, Wouda R, Scheltinga MRM.
Severe but not mild hand ischemia is associated with poorer survival in hemodialysis patients. Poster presentation, American Society of Nephrology's Kidney Week. Washington DC, Verenigde Staten.
American Society of Nephrology Kidney STAR Program - travel grant.

September **Gerrickens MWM**, Vaes RHD, Wiersma V, van Kuijk SMJ, Snoeijs MGJ, Govaert B, Scheltinga MRM.

Revision using distal inflow for high flow elbow-based hemodialysis access alters flow characteristics in the dialysis arm without diminishing brachial artery diameters. Oral presentation, 33rd annual meeting of the 'European Society for Vascular Surgery'. Hamburg, Duitsland.

May **Gerrickens MWM**, Vaes RHD, Wiersma V, van Kuijk SMJ, Snoeijs MGJ, Govaert B, Scheltinga MRM.
Overmatig hoge fistelflows in hemodialysepatiënten leiden mogelijk tot irreversibel verlies van arterieel remodelleren. Oral presentation, Nederlandse Vereniging voor Heelkunde Chirurgendagen. Veldhoven, Nederland.

March **Gerrickens MWM**, Vaes RHD, Wiersma V, van Kuijk SMJ, Snoeijs MGJ, Govaert B, Scheltinga MRM.
Revision using distal inflow for high flow hemodialysis access alters arterial flow characteristics in the dialysis arm. Poster presentation, 19e Nederlandse Nefrologiedagen. Veldhoven, Nederland.

Gerrickens MWM, Vaes RHD, Wiersma V, van Kuijk SMJ, Snoeijs MGJ, Govaert B, Scheltinga MRM.
Overmatig hoge fistelflows in hemodialysepatiënten leiden mogelijk tot irreversibel verlies van arterieel remodelleren. Oral presentation, 22e vaatdagen. Noordwijkerhout, Nederland.

2018

September	**Gerrickens MWM**, Wouda R, Vaes RHD, Govaert B, Teijink JAW, Scheltinga MRM. Do characteristics in patient history predict digital pressures in hemodialysis patients harbouring an upper extremity arteriovenous access? A cross-sectional study. Poster presentation, 32nd annual meeting of the 'European Society for Vascular Surgery'. Valencia, Spanje.
April	**Gerrickens MWM**, Vaes RHD, Govaert B, van Loon M, Tordoir JHM, van Hoek F, Teijink JAW, Scheltinga MRM. Langetermijnresultaten van 'revision using distal inflow' voor hoge flow elleboogs-hemodialysefistels met en zonder hand ischemie. Oral presentation, 21e vaatdagen. Noordwijkerhout, Nederland.
March	**Gerrickens MWM**, Vaes RHD, Govaert B, van Loon M, Tordoir JHM, van Hoek F, Teijink JAW, Scheltinga MRM. Three-year patency and recurrence rates of revision using distal inflow with a venous interponate for high flow brachial artery-based arteriovenous fistula. Poster presentation, 18e Nederlandse Nefrologiedagen. Veldhoven, Nederland.

2017

September	**Gerrickens MWM**, Vaes RHD, Govaert B, van Loon M, Tordoir JHM, van Hoek F, Teijink JAW, Scheltinga MRM. Patency and recurrence rates of the revision using distal inflow technique for high flow brachial artery based arteriovenous fistula. Plenary oral presentation, 31st annual meeting of the 'European Society for Vascular Surgery'. Lyon, Frankrijk.

Gerrickens MWM, Vaes RHD, Govaert B, van Loon M, Tordoir JHM, van Hoek F, Teijink JAW, Scheltinga MRM.

Patency and recurrence rates of the revision using distal inflow technique for high flow brachial artery based arteriovenous fistula. Fast-track oral presentatie, 31st annual meeting of the 'European Society for Vascular Surgery'. Lyon, Frankrijk.

Koninklijke Nederlandse Akademie van Wetenschappen van Walree - travel grant.

June **Gerrickens MWM**, Govaert B, Teijink JAW, Scheltinga MRM.

Basilic vein transposition for inadequate upper arm needle access segment may reduce concurrent hand ischaemia. Oral presentation, 52nd annual meeting of the 'European Society for Surgical Research'. Amsterdam, Nederland.

April **Gerrickens MWM**, Govaert B, Teijink JAW, Scheltinga MRM.

Vena basilica transpositie wegens een inadequaat dialyse aanpriktraject vermindert mogelijk co existente handischemie. Oral presentation, 20e Vaatdagen. Noordwijkerhout, Nederland.

March **Gerrickens MWM**, Govaert B, Teijink JAW, Scheltinga MRM.

Vena basilica transpositie wegens inadequaat dialyse aanpriktraject vermindert mogelijk co existente handischemie. Poster presentation, 17e Nederlandse Nefrologiedagen. Veldhoven, Nederland.

Het schrijven van een proefschrift is geen one man show, dit werk is daarop geen uitzondering. Het einde van mijn promotietraject -en daarmee mijn activiteiten in de (vaat)chirurgische wereld- nadert met rasse schreden. Nu rest mij niets dan een woord van dank aan eenieder die, direct of indirect, bijgedragen heeft aan deze thesis.

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Michael Wilhelmus Marcus Gerrickens, given name Michel, was born on April 26th, 1992 in Heerlen, the Netherlands as number four in a family that was to exist of six children. From 2004 to 2010, he attended pre-university education (Voortgezet Wetenschappelijk Onderwijs, VWO) at College Rolduc -in 2010 renamed to Charlemagne College- in Kerkrade. From 2010 to 2011, Michel completed a propaedeutic year in Health Sciences at Maastricht University. After this, he started the pursuit of his medical career by studying Medicine in Maastricht. He graduated with distinction from the master of Medicine in 2017. During his last internship at the department of surgery at Máxima Medical Centre Veldhoven he laid the foundation of his dissertation on high flow and hand ischaemia in haemodialysis patients under supervision of co-promotor Marc Scheltinga, vascular surgeon. Following graduation, Michel worked as a resident not-in-training (ANIOS) of surgery and at the emergency room at Máxima Medical Centre until 2019. Somewhat later that year, he started a residency of psychiatry as ANIOS at GGZ Oost Brabant, Helmond. Subsequently, Michel began as psychiatric resident in-training (AIOS) in 2020 at the High Intensive Care unit, GGZ Oost Brabant, Helmond. Despite this shift in specialization, he continued his research on vascular access surgery throughout the subsequent years. He expects to finish his training and become a board certified psychiatrist in 2025.

Michel lives together with his girlfriend Isabel Nguyen in Utrecht. In his free time, he enjoys playing (bass) guitar and percussion.