The prognostic role of finger pressures and access flows in hemodialysis patients

THE PROGNOSTIC ROLE OF FINGER PRESSURES AND ACCESS FLOWS IN HEMODIALYSIS PATIENTS

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Publication of this thesis was financially supported by:
Máxima MC, Catharina Ziekenhuis, Maastricht University, Maatschap Heelkunde Máxima MC, Chipsoft, Elara Solutions B.V., Congress Care B.V., TravelXL Alfa Reizen, Transonic Europe BV.

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Colofon

ISBN:	978-94-6458-225-3
Author:	Reshabh Yadav
Cover design & Lay-out:	Publiss | www.publiss.nl
Print:	Ridderprint | www.ridderprint.nl

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PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van Rector Magnificus, prof. dr. Pamela Habibović
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op maandag 13 juni 2022 om 16.00 uur

door

Reshabh Yadav

geboren te New Delhi op 13 oktober 1996

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Voor mijn familie

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Chapter 1

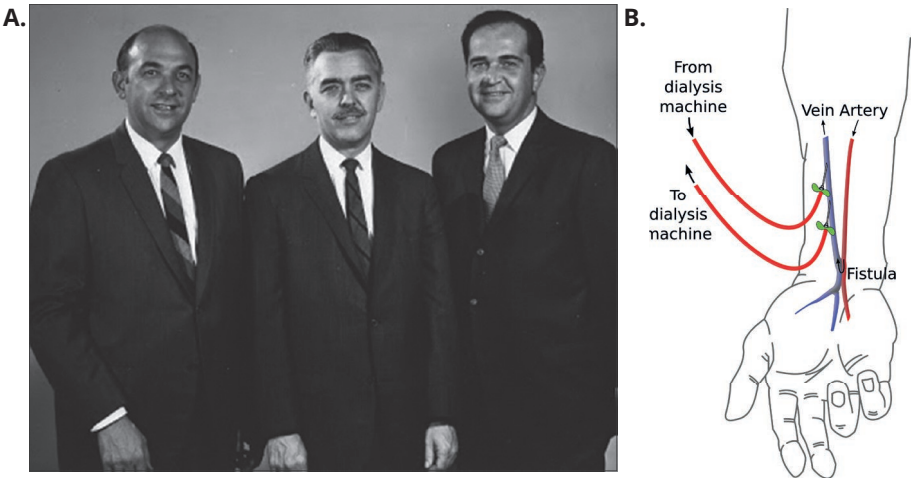
Introduction and outline

Introduction

Globally, more than 300.000 patients with end-stage renal disease (ESRD) rely on a hemodialysis (HD) access for renal replacement therapy (RRT) (1). At the end of 2019, over 5300 patients were registered in the Netherlands as being 'under treatment by means of HD' (2). Individuals harbouring a HD access require continuous attention as these fragile patients face a high risk of life threatening complications, hospitalization and early mortality (3,4).

If HD cannot be avoided, approximately 90% of the ESRD patients choose to receive a HD access compared to some 10% favoring peritoneal dialysis. Of all different HD access types, a native arteriovenous access (AVA) is preferred among nephrologists and vascular surgeons due to its relatively low frequency of complications and high patency rate as compared to central venous catheters (CVC) or arteriovenous grafts (AVG) (5,6). By far the most popular native AVA is the radiocephalic arteriovenous access (RC-AVA). This access was introduced in 1966 by the triumvirate Brescia, Cimino and Appel (7). Since then, the RC-AVA continues to be the method of choice as endorsed by international guidelines (1,5). If RRT is imminent and a patient prefers a AVA construction, it is investigated whether a RC-AVA at the wrist is possible and stands a fair chance of sufficient maturation.

Figure 1. A triumvirate of specialists who introduced the popular Cimino-Brescia AVA (radiocephalic RC-AVA) in 1966 (Brescia, Cimino & Appel (A). Schematic overview of a RC-AVA at the wrist in a side-to-side configuration (B).



The arm is inspected for vein visibility, radial artery pulsatility and hand circulation (1,5). Furthermore, epifascial venous diameters are measured using Duplex analysis, since an AVA that is constructed with a small diameter vein may mature insufficiently (8,9). Ultimately, these findings may guide the vascular surgeon in the preoperative phase in estimating whether creation of a RC-AVA is likely successful.

Current paradigm shift 'from distal to proximal'

The number of ESRD patients is steadily increasing (Figure 2). In the year of 2018, the incidence in the United States exceeded 130,000 for the first time ever (10). Rates of elderly patients developing ESRD have displayed the most rapid increase. For instance, in 2009 37% of patients receiving RRT were 65 years and older. By the end of 2019, this portion of elderly patients had increased to 45%, a percentage that is four times higher than thirty years ago in the Netherlands (2).

In most of these elderly patients, renal insufficiency is caused by hypertension, diabetes and/or arteriosclerosis (or a combination thereof) (10). As these patients frequently also have distal blood vessels of low quality, creation of a RC-AVA may not be possible. As a consequence, a more proximal AVA (BC-AVA) located at the elbow is gradually becoming the first choice AVA (11,12). Although a proximal AVA demonstrates a high chance of successful maturation, long term complications such as hemodialysis access-induced distal ischemia (HAIDI) and high flow (HFA, high flow access) are looming (13–15).

Potential roles of finger pressures (P_{dig}) in access workup of future HD patients?

A concise preoperative strategy for choosing the 'right AVA for the right patient' is essential. Intuitive is to identify a site at the arm having the most suitable arterial inflow and an optimal venous outflow. Finger plethysmography is a simple bedside modality that is utilized for determining blood pressure in the digits of the hand. When combined with a brachial pressure measurement, a digital brachial index (DBI) can be obtained (ratio between systolic P_{dig} divided by $P_{brach\ art}$). A DBI theoretically reflects the combined quality of all arteries along the arm-hand axis (and possibly also the quality of the overall circulation).

The potential prognostic value of a P_{dig} in the preoperative workup of a HD access is largely unknown. The European Society of Vascular Surgery (ESVS) as well as the latest Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines

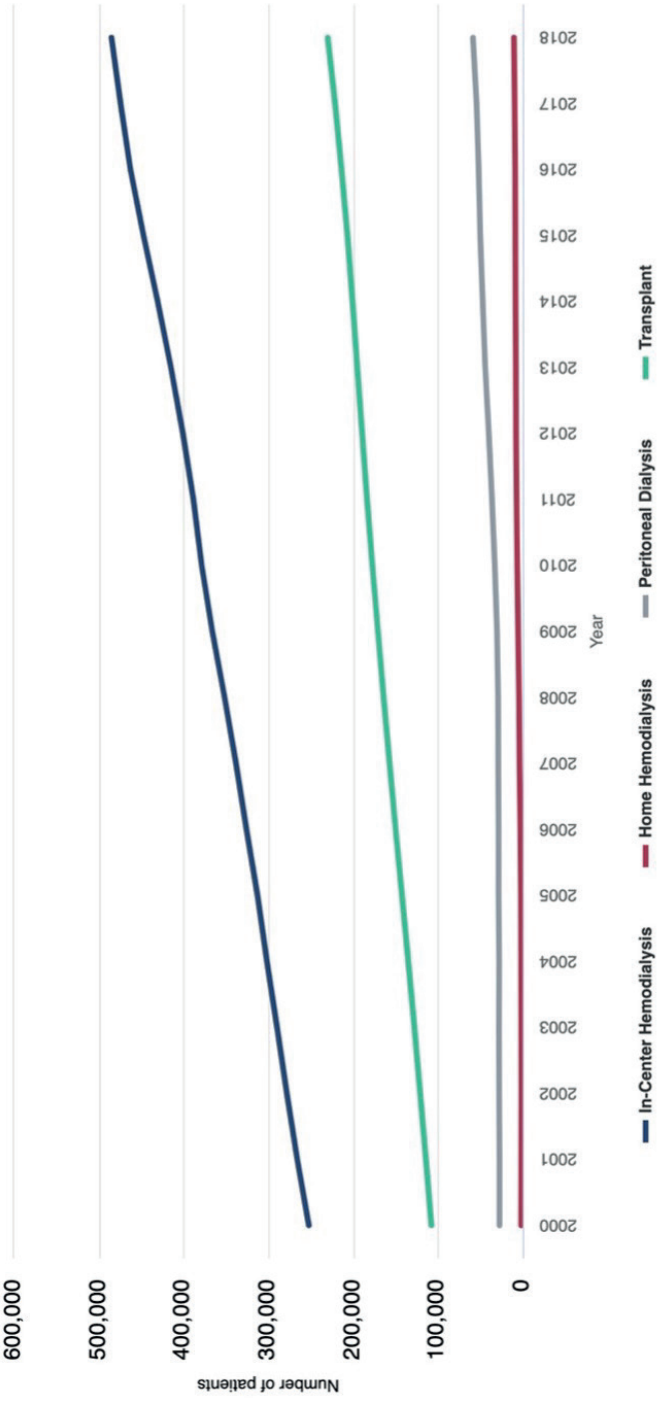


Figure 2. End-stage renal disease (ESRD) patients in the United States between 2000-2018 by modality (10).

only recommend non-invasive ultrasound as the modality optimizing HD access stratification, apart from a detailed patient history taking and physical examination (1,5). A measurement of a P_{dig} is not considered, also as the number of studies on its role regarding crucial outcomes measures such as patency, HAIDI and mortality is scarce. To date, a small body of access studies just focused on a relationship between P_{dig} and presence of HAIDI (16–18).

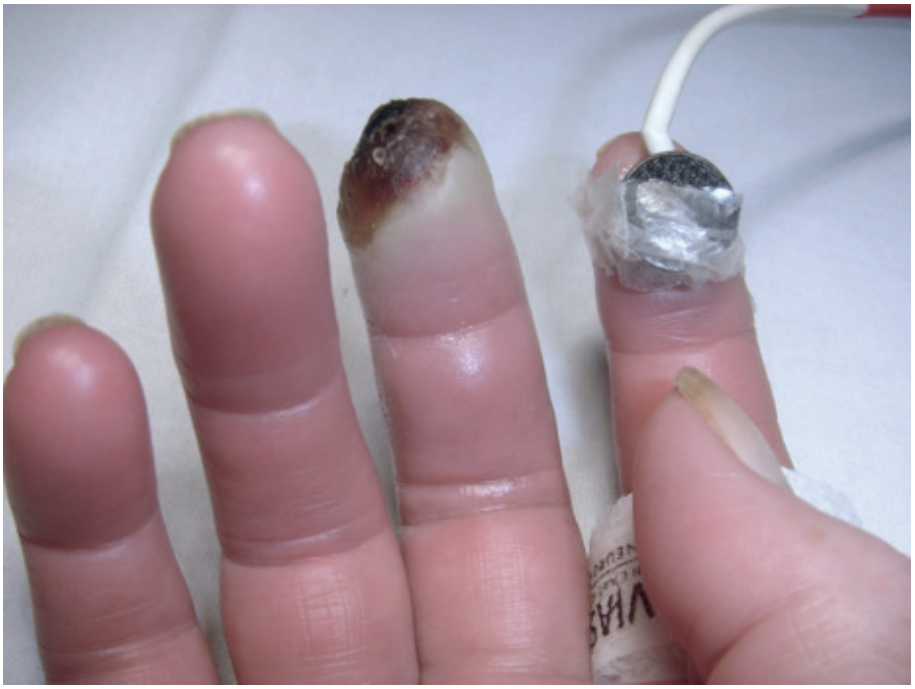
It is well known that cardiovascularly compromised HD patients with severely sclerotic arteries are prone to develop stenosis or thrombosis of their AVA. Previous studies in patients who were scheduled for access surgery found that the arterial wall calcifications in the lower arm vasculature were associated with lower primary as well as secondary access patency rates. However, a simple bedside tool evaluating degree of calcification is lacking (19–21). One might hypothesize that a P_{dig} (and DBI) possibly reflects the degree of arterial wall calcifications and may be associated with long-term AVA patency rates. However, the role of a P_{dig} measurement as a factor predicting access patency is unknown.

Can P_{dig} predict hand ischemia after access construction?

Some HD patients develop HAIDI (Figure 3). Symptoms initially include a cold and crampy hand of the dialysis arm. However, unbearable pain and even necrosis may occur at a later stage (13,22). HAIDI can affect up to 20% of the general HD population (13,23,24). The incidence of HAIDI is rising due to the current paradigm shift favoring a more proximal BC-AVA.

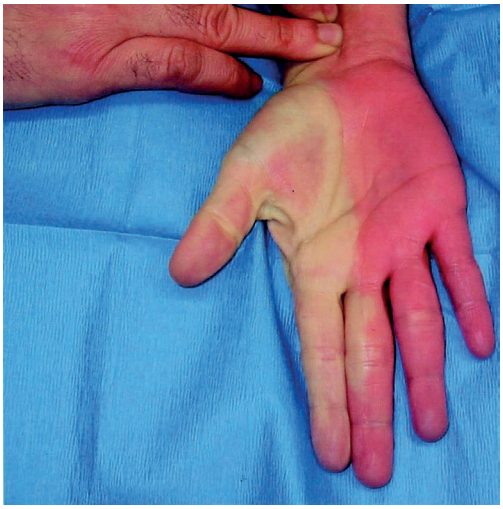
The pathophysiology of HAIDI is partly uncovered. Due to increased arm blood flow following HD access creation, augmented shear stress will lead to compensatory remodeling of the arm arteries aimed at maintaining an adequate perfusion pressure of the hand (25,26). However, individuals with severely sclerotic arteries (often in combination with diabetes) will likely have insufficient remodeling capacity thus failing to adapt to a changed hemodynamic environment (13). As a consequence, gradual loss of perfusion pressure towards the periphery (hand) may occur. When this drop in arm blood pressure is augmented due to turbulent flow at the AVA anastomotic site ('pressure sink'), distal hypoperfusion may further be intensified. In relatively healthy HD individuals, the hypoperfusion is compensated for by opening collateral arteries. However, collateral perfusion capacity in elderly diabetics may be insufficient leading to distal ischemia.

Figure 3. Type 4 HAIDI of middle finger in a patient with a BC-AVA.



In earlier days, the (modified) Allen Test (Figure 4) was suggested as a swift bedside technique for determining collateral perfusion of a hand. If hand pallor persisted after releasing of a compressed ulnar artery while digitally occluding the radial artery, collateral perfusion via the ulnar artery was deemed insufficient and an RC-AVA (compromising blood pressure in the radial artery) was not advised. However, several studies found that this Allen test, when performed prior to access creation, lacked prognostic accuracy in predicting HAIDI later on because of a high interobserver bias (27–29). One might hypothesize that an inadequate collateral perfusion as reflected by an increased P_{dig} *drop* during an Allen test may predict HAIDI. However, studies combining a measurement of P_{dig} and an Allen test in the preoperative workup of patients scheduled for an AVA were not performed.

Figure 4. Edgar Van Nuys Allen with his Test (A). Practical application of the Allen Test. Persistent blanching of the radial portion of the hand suggests insufficient collateralization via the ulnar system (B).



Possible associations between P_{dig}, HAIDI and cardiovascular mortality?

A general HD population displays a relatively high mortality rate (up to 20% per year), most often due to cardiovascular causes (2,10). An earlier meta-analysis of ESRD patients found that an ankle-brachial index (ABI; systolic blood pressure at ankle artery divided by systemic systolic blood pressure at arm) reflected long-term survival in an U-shaped manner (30). Similarly, it can be hypothesized that ESRD patients having an abnormal P_{dig} or increased P_{dig} drop after the Allen test also have an increased risk of cardiovascular death. Some think that presence of (distal) atherosclerosis and insufficient collateral perfusion can be considered as a surrogate marker of suboptimal cardiac health. In addition, it is unknown whether survival in patients with severe HAIDI is even more compromised compared to HD patients with a normal hand perfusion.

High Flow Access (HFA): Controversies in definition and management

A minimal 0.3-0.6 L/min access flow (Q_a) is required for effective HD (1,31). Occasionally, Q_a can increase inappropriately over time which may lead to systemic complications such as high-output cardiac failure (HOCF). An uncontrolled Q_a rise may be hazardous, especially in HD patients who often are already burdened with cardiovascular disease.

When an AVA develops Q_a of 1.0-1.5 L/min, or when the Q_a to cardiac output ratio >20%, a High Flow Access (HFA) is at hand according to international guidelines on vascular access management (1,5). However, literature studying the association between height of Q_a and cardiovascular complications is controversial. Some studies suggested that a HFA can have a significant effect on the cardiovascular system and a higher Q_a may lead to a greater risk of cardiac decompensation (15,33,34). In addition, cardiac output and Q_a are closely related (33). It is also known that people with HOCF of various etiologies have an approximately three times higher risk of death compared to people without (35). On the other hand, HD patients with a Q_a <1 L/min have a greater risk of both overall and cardiovascular death compared to patients with Q_a values between 1 and 2 L/min (36). Furthermore, no relationship was found between Q_a >2 L/min as measured during the very first haemodialysis session and mortality (37). All of these studies indicate that the clinical significance of Q_a in HD patients is ill-defined.

Joint Modelling Approach for analyzing Q_a

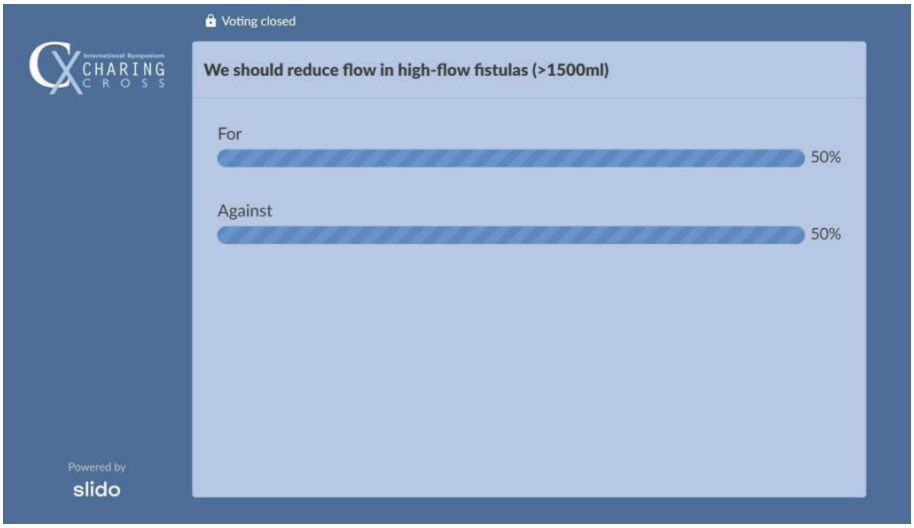
It is important to realize that Q_a in an individual patient can fluctuate substantially over time (38). Studies on the relationship between height of Q_a and HFA are generally limited to 'snapshots' of access flow (e.g. one or two consecutive Q_a measurements). However, cardiac reserve may possibly become exhausted due to *long-term exposure* to large Q_a quantities (and its fluctuations). In addition, all studies failed to consider the natural course of Q_a and possible measurement errors.

A recent study evaluating the response to drugs and risk of side effects found that the use of longitudinal survival models are promising for analyzing these complex associations (39). This 'Joint Modelling Approach' may prove worthwhile for studying potential relations between Q_a and adverse outcomes. Consequently, such novel dynamic statistical techniques might identify objective criteria defining a HFA requiring treatment. However, a Joint Modelling Approach was never utilized for studying *long term exposure to* Q_a and survival in a general HD population.

What is the most optimal treatment for HFA?

International guidelines currently fail to provide criteria for Q_a reducing interventions in HFA. A poll at the Charing Cross 2021 Meeting revealed that consensus regarding Q_a reduction of a HFA >1500 mL is lacking (Figure 5). In daily practice, diagnosing a HFA and timing of flow reduction surgery are based on clinical experience and best judgement. An evidence based Q_a monitoring scheme is yet to be validated. In addition, the Q_a reduction technique with the most promising long-term results is to be identified. An overview regarding the complete spectrum of surgical techniques for Q_a reduction might be a step contributing to such an optimal HFA treatment scheme.

Figure 5. Audience poll at Charing Cross 2021 questioning Q_a reduction in asymptomatic HFA.



Is a more proximal BC-AVA the best 'second choice'?

A RC-AVA at the wrist continues to be the access of choice because of its low rate of complications such as HAIDI and HFA. As mentioned earlier, a RC-AVA is not always feasible because of unsuitable distal vasculature, especially in an elderly, diabetic and cardiovascular burdened HD population. Three earlier studies

concluded that a more proximal BC-AVA in the elbow should become the access of first choice in octogenarians due to its better patency (40–42). Any clinician should judge the pros and cons of the spectrum of RRT's that best fits the individual patient. Nevertheless, survival is likely the most important parameter guiding such a paramount choice. Current literature consistently finds the lowest mortality rates in AVA's in comparison with AVG's or CVC's. Interestingly, it is unknown what impact AVA location (distal vs. proximal, or wrist vs elbow) has on long-term cardiovascular mortality.

Aims of the thesis

The general aim of this thesis is to study the prognostic roles of *finger pressures and AVA flows* in hemodialysis patients.

Specific aims regarding roles of finger pressures (Pdig)

1. To determine a possible association between a preoperative digital brachial index (DBI) and two-year AVA patency in HD patients.
2. To study whether a preoperative Allen Test combined with P_{dig} measurements may predict the onset of postoperative hand ischemia (HAIDI) in HD patients.
3. To determine if altered values of P_{dig} are associated with cardiovascular mortality in HD patients.
4. To evaluate whether a preoperative Allen Test can predict long-term mortality after AVA construction in HD patients.
5. To investigate whether patients with severe HAIDI have a limited survival compared to patient with normal hand perfusion.

Specific aims regarding role of AVA flow (Q_a)

6. To determine a possible association between Q_a and survival of HD patients.
7. To study whether AVA location influences mortality rates in HD patients.
8. To evaluate the spectrum of surgical techniques for Q_a reduction in HD patients with high flow AVA.

Thesis outline

Creating an optimal AVA is often a challenge whereas maintaining its patency is even more demanding. After two years, approximately half of all AVA's have failed. Unfortunately, a simple bedside method for predicting long-term patency before AVA creation is currently lacking. At present, a preoperative workup including an evaluation of the venous vasculature is standard procedure, but a P_{dig} (and its derivative, DBI, digital brachial index) possibly reflecting the overall arm circulation is not considered as a means of predicting access patency. In **chapter 2,** we discuss the potential role of a preoperative DBI measurement for determining 2-year AVA patency.

Hemodialysis access-induced distal ischemia (HAIDI) is a drastic complication following access construction that may occur in up to 20% of patients. It is characterized by pain and cramps in the dialysis hand. Amputation of fingers or hand is required in severe cases. The incidence of HAIDI is rising due to the contemporary shift favoring more proximally located AVA's. Previously, the Allen Test was utilized for evaluating the hand circulation prior to AVA creation. However, a high interobserver bias precluded the practical application of this test. We studied whether a combined Allen test-P_{dig} measurement was able to predict the onset of severe HAIDI (**chapter 3**).

Populations with ESRD requiring HD display high mortality rates due to concurrent cardiovascular disease. After four years, just half of a general HD population is still alive. However, individual variability is substantial. Therefore, recognizing factors that influence survival is crucial for adequately counselling prospective HD patients. Measurements of P_{dig} of the foot were found to predict mortality in patients with intermittent claudication due to atherosclerosis. A diminished peripheral collateral circulation might be an expression of comprised cardiovascular health. In **chapter 4**, we discuss the potential association between preoperative DBI values and cardiovascular mortality in a HD population.

Chapter 5 discusses if a preoperative Allen Test combined with P_{dig} was associated with mortality in HD patients.

Recent studies suggested that HAIDI patients have higher mortality rates compared to HD patients without, possibly due to the overall presence of generalized atherosclerosis. In **chapter 6,** we compare survival rates of HAIDI patients with controls.

At present, an evidence-based definition of a 'HFA requiring treatment' is lacking. Most of the pertaining studies base their advice on the absolute height of a single Q_a measurement. In **chapter 7**, we investigated potential associations

between various novel aspects of Q_a and survival in a HD population by utilizing a unique statistical 'Joint Modelling Approach'.

Studies on mortality rates of populations using different modes of HD (CVC, AVG, AVA) consistently find the highest survival rates in patients with a native AVA. However, it is unknown if location of AVA (wrist, elbow) is associated with survival. In **chapter 8**, we studied whether survival of patients with an wrist-based native AVA is different compared to patients having an elbow-based AVA.

Some HD patients have an AVA that continues to mature leading to an inappropriately high flow access. At present, guidelines advise to initially monitor a high Q_a access (HFA). If signs of cardiac overload occur, Q_a reduction may be considered. Hitherto, the most optimal surgical method for Q_a reduction is ill-defined. **Chapter 9** provides a scoping review on the spectrum of surgical techniques for Q_a reduction of a HFA.

A summarizing discussion, conclusions and future perspectives are provided in **chapter 10**. In **chapter 11**, we discuss the impact of the present dissertation. **Chapter 12** includes a Dutch summary. Finally, acknowledgements and curriculum vitae of the author are provided.

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PART I

The prognostic role of finger pressures (P_{dig})

Content

Chapter 2

Abnormal preoperative digital brachial index is associated with lower two-year arteriovenous fistula access patency

A potential novel modality for predicting access patency

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Published in *Journal of Vascular Surgery*
Volume 74, Issue 1, P237-245, July 01, 2021
Impact Factor: 4.4

Abstract

Objective

Aim of the present study was to assess whether a single measurement of a digital brachial index (DBI, ratio systolic finger pressure/systemic pressure) reflecting the arm's circulation was associated with access patency in severe chronic kidney disease (CKD) patients scheduled for arteriovenous fistula (AVF) surgery.

Methods

A bilateral DBI was obtained using digital plethysmography just prior to constructing the patient's first AVF between January 2009 and December 2017 in one center. A DBI between 80–99% was considered normal, whereas values <80% (low) or ≥100% (high) were termed abnormal. DBI values ipsilateral to the AVF were used for analysis. Primary and secondary access patency rates were calculated according to published standards and were compared using standard statistical techniques.

Results

Data sets of 163 patients were obtained (female, n= 69, age 71 ±12 years). Median follow-up was 40 weeks (range 0-104 weeks, follow-up index 99% ±1). Patients with abnormal preoperative DBI values had lower two-year primary patency rates (low DBI 25% ±11; high DBI 28% ±6; normal DBI 49% ±8; *p*=.018). Following correction for age, sex, hypertension, diabetes mellitus, cardiovascular disease, smoking status and history of an ipsilateral central venous catheter, an adjusted model demonstrated that abnormal DBI values conferred an increased risk for primary failure (Low DBI <80% HR 2.25 [1.13-4.48]; High DBI ≥100% HR 1.74 [1.06-2.85], both p<.030). Patients with a low preoperative DBI displayed a diminished secondary patency (HR 2.86 [1.08-7.59], p=.035). Conversely, diameters of outflow veins did not determine access patency.

Conclusion

Patients with abnormal DBI values prior to AVF construction for hemodialysis have lower two-year access patency rates compared to patients with a normal DBI. Plethysmographic finger measurements may have a role in the preoperative counselling of severe CKD patients requiring an AVF.

Keywords

Chronic hemodialysis; Digital brachial index; Patency; Vascular access

Introduction

Maintaining access patency is a major challenge for vascular surgeons involved in hemodialysis (HD) management. Following construction, autogenous arteriovenous fistulas (AVF) may initially fail to maturate or develop thrombosis or stenosis over time. After two years, just about half of AVFs were patent according to a recent review (1). A repetitively malfunctioning AVF is a burden for patients and caretakers (2,3). If untoward events are not timely recognized, an occluded access will lead to high morbidity rates and increased health care costs (4–6).

A number of factors determining patency following AVF construction were identified (7–10). Young age and absence of comorbidities such as diabetes contribute to high patency rates, but these parameters cannot be modified. The correct choice of an adequate diameter of the access' venous outflow tract is thought to contribute to the most optimal type of access, however its value for predicting a successful AVF is controversial (11). Nevertheless, several guidelines suggested the use of veins with a minimal 2.0-2.5 mm diameter for a radiocephalic AVF (RC-AVF) or a 3 mm diameter for a brachiocephalic AVF (BC-AVF) (8,9).

Whereas the importance of the venous vasculature in access surgery may seem limited, the role of the arterial vasculature in the preoperative strategy of AVF surgery is unclear. Some advised to evaluate the arterial condition using rates of calcification before choosing type of access (12,13). This approach may seem beneficial as the presence of arterial wall calcifications was found to reduce primary and secondary access patency rates (12–14). However, simple and convenient methods for identifying these calcifications have yet to be validated.

Finger plethysmography is a simple technique that is used to determine blood pressure in the digits of the hand (15,16). A digital-brachial index (DBI, systolic finger pressure divided by systolic brachial artery pressure) potentially reflects the quality of the arm circulation (17,18). Prior studies have shown that suboptimal digital pressures are associated with long-term cardiovascular mortality, suggesting that inferior arterial quality in the distal portions of the body might be a reflection of a suboptimal overall cardiovascular health (18–20). However, whether DBI could be utilized as a modality for the prognosis of long-term access patency is unknown. Therefore, the aim of the present study was to determine whether a value of DBI in patients with severe chronic kidney disease (CKD) prior to receiving their first AVF was related with two-year access patency.

Materials and Methods

General information and standard workup

CKD stage IV or V patients possibly requiring a HD access were referred to our vascular outpatient department by one of our nephrologists. A standardized preoperative workup entails history taking and examination of both arms and hands including radial and ulnar artery palpation. A plethysmographic finger pressure measurement was performed to determine the risk of post-operative hand ischemia. A bilateral Duplex ultrasound (DUS) determined diameters of both lower arm and upper arm veins. Based on these results, patients were counselled by one of four vascular surgeons on the pros and cons of access type and preferred location. Following informed consent, patients usually received the operation some 2-6 weeks later.

Adult patients who received their first AVF construction in the upper extremity in Máxima Medical Center (MMC, Veldhoven, the Netherlands) between January 2009 and December 2017 were eligible for this retrospective study. Patients with reliable values of digital plethysmography obtained within 6 months prior to access construction were included for analysis. Since plethysmography is considered a non-invasive stress-free modality which is standard care at our department, the Medical Research Involving Human Subjects Act (Dutch WMO) did not apply to the study and additional patient consent was not required as decided by the medical ethical committee of MMC.

Finger plethysmography and venous ultrasound

A vascular laboratory technician performed digital plethysmography (Nicolet Vasoguard 8 MHz, Scimet, Bristol, UK) to obtain systolic finger pressures (P_{dig}, mmHg) of both middle or index fingers. A photo plethysmographic sensor was placed on the distal phalanx and an inflatable cuff was wrapped around the proximal phalanx. Once a stable signal was obtained, the digital cuff was inflated until a maximum pressure of 200 mmHg was reached. The cuff was then gradually deflated until a pulsatile signal reappeared reflecting the systolic digital pressure. The DBI was calculated by dividing the highest systolic finger pressure by the systolic pressure obtained from one of both brachial arteries having the highest pressure.

Venous DUS (Aplio-XG Diagnostic Ultrasound System SSA-790A, Toshiba America Medical Systems, Inc, USA) was performed by a dedicated vascular

laboratory technician. Patients were positioned upright with the elbow at a 45 degree angle and the arm cushioned. Inner diameters of the median cubital vein, lower arm and upper arm basilic and cephalic vein were obtained of both arms.

Follow up

Following surgery, access flows were measured 4 to 6 weeks postoperatively (HD03, Transonic Systems IN, New York, USA) according to KDOQI guidelines (9). Weekly multidisciplinary meetings were held to discuss patients with complicated HD sessions including those exhibiting substantial changes in access flow or pressures (9). DUS was performed if a stenosis was suspected. If required, angioplasty was performed within 2-4 days.

Data collection

General patient characteristics, comorbidities, smoking status, use of anticoagulants and statins, results of finger plethysmography and venous arm DUS, timing and type of first vascular access construction and current HD status (yes/no) were retrieved from digital patient files (HiX 6.1, ChipSoft B.V., Amsterdam, The Netherlands; FinProDB 7.9, MedVision AG, Unna, Germany). Comorbidities were defined as follows: *diabetes mellitus* (diagnosis type 1 or 2 diabetes mellitus or currently using antihyperglycemic medication), *hypertension* (previous diagnosis of hypertension or use of antihypertensive medication), *cardiovascular disease* (prior diagnosis of angina pectoris, acute coronary syndrome, CABG, diagnostic imaging with signs of (prior) infarction or ischemia, ischemic stroke or transient ischemic attack, ≥70% stenosis of an arterial segment of the peripheral arteries or ≥50% stenosis in the coronary artery lumen, history of intermittent claudication, ischemic pain during rest, ischemic tissue loss, prior peripheral artery intervention or bypass, or demonstrated absolute toe pressure of <40 mmHg). The Dutch Nephrology guidelines, based on ICD-10 diagnoses, were used to classify causes of renal failure (21).

Patients were grouped into three categories of DBI values, that is *low* (<80%), *normal* (80-99%), or *high* (≥100%). These cut-off values were adapted from previous studies where groups were defined in analogy to studies focused on ankle-brachial index values (18,22–25). The lower limit is validated by the Dutch Guidelines on Vascular Access Management (25). DBI values of 100% and higher were considered contra-intuitive, since there is always a gradual loss of mean arterial pressure (MAP) towards peripheral portions of the arm (22).

DBI values and vein diameters of the access arm were used for analysis. Based on recent ESVS vascular access guidelines, veins were considered adequate when the following minimum diameter criteria were met: Cephalic vein ≥2.0 mm for RC-AVF and ≥3.0 mm for BC-AVF; median cubital vein ≥3.0 mm for Gracz-AVF; basilic vein ≥3.0 mm for brachiobasilic AVF (BB-AVF) (8).

A follow up index, the ratio between the investigated and potential follow-up period, was calculated as proposed (26). Date of AVF construction was used as the study's starting date. FU was terminated after two years or at December 31, 2017. Patients were considered "lost to follow up" if they had permanently moved to another dialysis facility during the observation period. For these patients, the date of last known alive was used.

Definitions of study outcomes

Primary as well as secondary patency were defined according to the Society for Vascular Surgery reporting standards (27). Primary patency was defined as the interval between AVF creation and the first re-intervention for dysfunction, the time of measurement of patency or the time of its abandonment. The definition of secondary patency was the time from AVF placement until access abandonment after one or more interventions, or the time of measurement of patency including achievement of a censored event (death, change of HD modality, loss to follow-up).

Statistical analysis

Statistical analyses were performed using SPSS version 25 (IBM SPSS Inc., Chicago, IL, USA). Cohort demographics were displayed as mean ± standard deviation (SD), or counts (percentages) if appropriate. Patient variables were tested for normality and expressed as mean ± standard error of the mean (SEM). DBI values were depicted as percentages. Variances between groups were analyzed with Fischer's exact test, Pearson's chi-square test or independent sample T-test as appropriate.

Time-to-event calculations for primary and secondary patency were analyzed with Kaplan Meier and survival analysis. Potential group differences were estimated using the Log-Mantel Cox test. Univariate Cox-Regression analysis was used to determine factors potentially influencing patency. Risk factors associated with patency were included in the multivariate analysis using Cox proportional

hazards models (7,8,28). In this multivariate model, missing values of venous diameters were included and labeled as "unknown' in order to prevent case dropping. Outcomes were displayed as Hazard ratio 95%-Confidence interval [HR 95%-CI]. *P*-values .050 were considered statistically significant.

Results

General

Between 2009 and 2017, a total of 268 patients received their first HD access in our institution. During this nine-year observation period, digital pressure measurements were performed in 179 patients of which 16 patients were excluded (technically failed study according to vascular technician n=9, arteriovenous graft n=3, finger pressure obtained >6 months n=3, leg access n=1). Therefore, a total of 163 patients fulfilled study criteria. Complete sets of vein diameters readings were present in 121 patients (74%).

A total of 80 patients (49%) received a wrist-based AVF (79 RC-AVF, 1 Basilico-ulnar AVF) whereas 83 (51%) had elbow-based AVF's (21 BC-AVF, 52 Gracz-AVF, 10 BB-AVF) (Table I). Patient demographics are presented in Table I. Patients in the low DBI group (<80%) were older, more often of female sex, displayed lower finger pressures, more frequently suffered from diabetes and had received more tunneled CVC's compared to patients in the normal (80-99%) and high (≥100%) DBI groups. Median follow-up was 40 weeks (range 0-104 weeks) with a follow-up index of 99% ±1.

In the first two postoperative years, 57 patients (35%) required invasive procedures for patency preservation. A total of 125 percutaneous transluminal angioplasties (PTA) were performed in 34 patients and 25 thrombectomies in 17 additional patients. Furthermore, 31 AVFs required surgical revision to facilitate maturation.

Patient characteristics in relation to DBI

Mean preoperative DBI was 98% ±18. Females had lower values compared to males (93% ±2 vs. 101% ±2, p=.003). Lower DBIs were also detected in diabetic patients (92% ±2 vs. 101% ±2, p=.002). However, values in patients with or without a history of CVD were similar (both 98% ±2). Hypertension did not influence DBI values (hypertension: 98% ±2 vs. normotension: 100% ±3, p=.554).

Table I. Characteristics of three DBI (digital brachial index) groups of CKD patients prior to primary hemodialysis access construction (n=163).

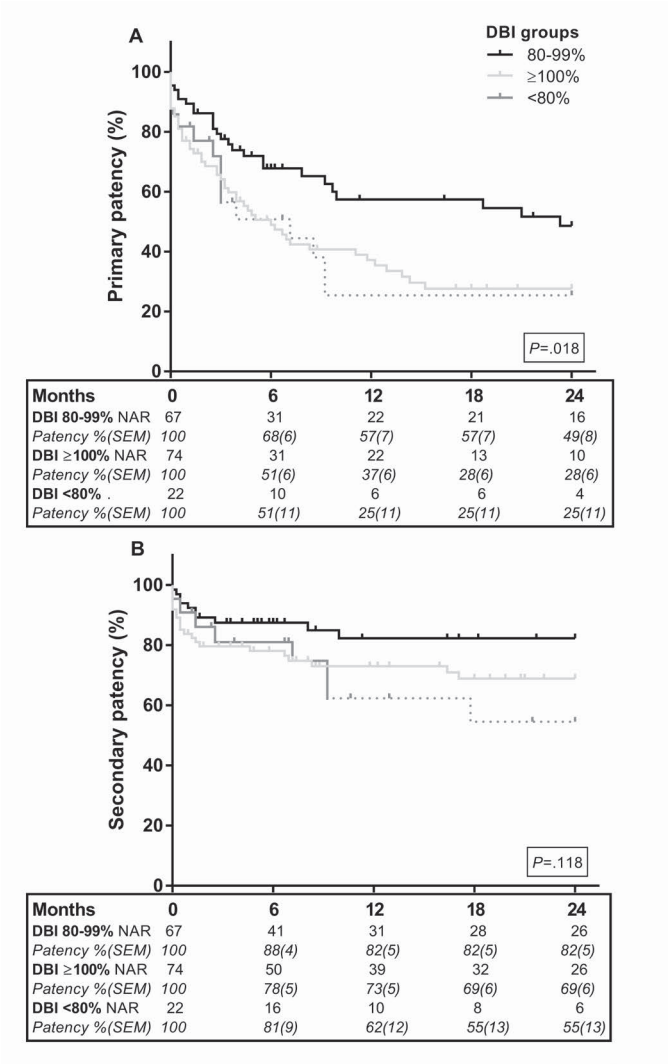
Characteristic	Total cohort N= 163	Normal DBI 80-99% N= 67	Low DBI <80% N= 22	High DBI ≥100% N= 74	*p*
Age (years, ±SD)	71 ±12	72 ±11	77 ±9	69 ±13	.016
Gender female (%)	69 (42)	35 (52)	12 (55)	22 (30)	.012
Diabetes Mellitus (%)	61 (37)	28 (42)	13 (59)	20 (27)	.015
Cardiovascular disease (%)	93 (57)	37 (55)	13 (59)	43 (58)	.992
Hypertension (%)	131 (80)	53 (79)	20 (91)	58 (78)	.406
Primary renal disease (%)					n/a
Glomerulonephritis/sclerosis	27 (17)	11 (16)	3 (14)	13 (18)	
Pyelonephritis	3 (2)	1 (2)	0	2 (3)	
Hypertension	19 (12)	5 (8)	2 (9)	12 (16)	
Renal vascular disease	19 (12)	11 (16)	0	8 (11)	
Diabetes	40 (25)	16 (24)	8 (36)	16 (21)	
Miscellaneous	48 (29)	19 (28)	8 (36)	21 (28)	
Unknown	7 (4)	4 (6)	1 (5)	2 (3)	
Statin use (%)	107 (66)	44 (66)	17 (77)	46 (62)	.424
Anticoagulant use (%)	104 (64)	40 (60)	14 (64)	50 (68)	.665
Prior tunneled CVC (%) Ipsilateral to AVF	34 (21) 3 (2)	17 (25) 0	6 (27) 2 (9)	11 (15) 1 (1)	.021
Smoking (%)	84 (52)	32 (48)	13 (59)	39 (52)	.808
Former	41 (25)	17 (25)	4 (18)	20 (27)	
Active	43 (26)	15 (22)	7 (31)	19 (26)	
AVF type (%)					n/a
Wrist-based	80 (49)	34 (51)	11 (50)	35 (47)	
Elbow-based	83 (51)	33 (49)	11 (50)	39 (53)	
Hemodialysis initiated (%)					.527
Yes	113 (74)	46 (69)	14 (64)	53 (72)	
No	40 (26)	21 (31)	8 (36)	21 (28)	
First post-operative Q_a (ml/min, ±SEM)	1101 ±69	1106 ±97	1032 ±148	1118 ±117	.920
Vein diameter (mm, ±SEM)					
Wrist-based AVF	2.4 ±0.1	2.4 ±0.1	2.8 ±0.2	2.2 ±0.1	.065
Elbow-based AVF	2.5 ±0.2	2.4 ±0.3	2.4 ±0.3	2.6 ±0.3	.828
Preoperative blood pressures (mmHg, ±SEM)					
Systolic brachial artery pressure	158 ±2	161 ±4	166 ±8	154 ±3	.130
Systolic digital pressure	154 ±3	147 ±4	116 ±8	172 ±3	<.001

SD, standard deviation; CVC, central venous catheter; AVF, Arteriovenous fistula; SEM, Standard error of the mean; n/a, not applicable. Q_a, Hemodialysis access blood flow.

Primary patency

Overall one- and two-year primary patency rates were 43% ±4 and 35% ±4, respectively. After two years, the groups with abnormal DBIs had the lowest primary patency (low DBI 25% ±11, high DBI 28% ±6, normal DBI 49% ±8; p=.018; Figure 1a).

Figure 1. Primary (A) and secondary (B) access patency in relation to preoperative DBI in CKD patients (n=163). NAR, number at risk; SEM, standard error of the mean. Dotted line represents SEM > 10%.



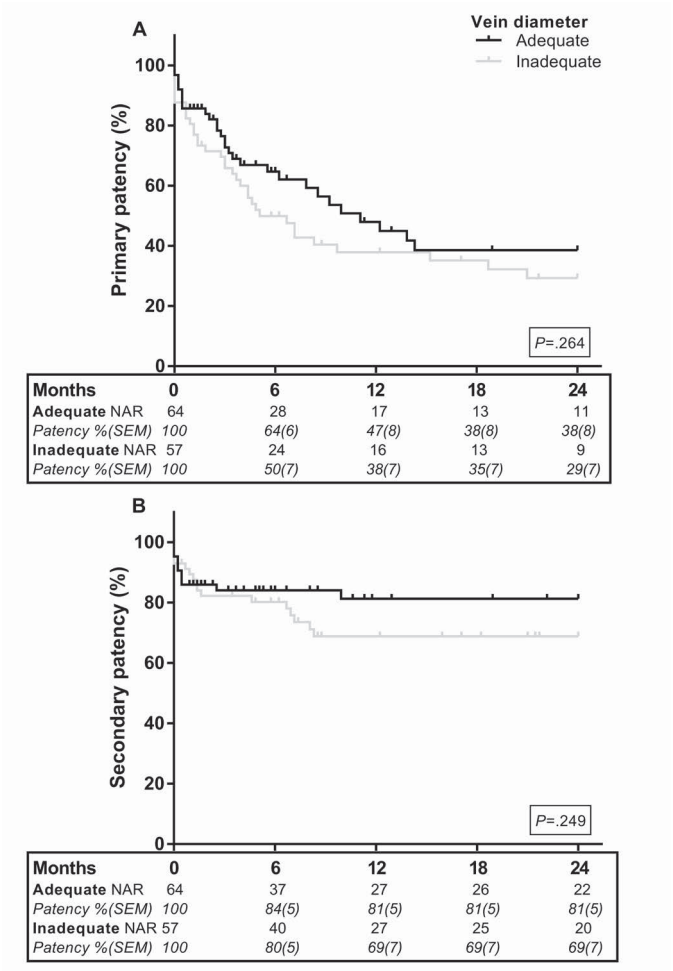
Secondary patency

After one and two years, secondary patency rates were 75% ±4 and 72% ±4, respectively. After two years, group differences were not statistically significant (p=.118; Figure 1b). However, a strong trend favoring a normal DBI was present (normal DBI 82% ±5 vs low DBI 55% ±13, p=.055; normal DBI vs. high DBI 69% ±6, p=.085; Figure 1b).

Preoperative vein diameters

A total of 47% patients had inadequate venous diameters (<2 mm and <3 mm cut-off points, respectively) whereas 53% had values above cut-off points (8). However, venous diameters did not determine outcome as the two-year primary patency was similar in both groups (above cutoff 38% ±8 vs. below cutoff 29% ±7, p=.264, Figure 2a). Secondary patency rates also did not differ between patients with adequate and inadequate minimal vein diameters (above cutoff 81% ±5 vs. below cutoff 69% ±7; p=.249; Figure 2b).

Figure 2. Primary (A) and secondary (B) patency in relation to preoperative vein diameters. NAR, number at risk; SEM, standard error of the mean.



Factors determining access patency

In univariate analysis, abnormal preoperative DBI values were associated with lower primary patency rates (Low DBI <80% HR 1.93 [1.01–3.70], p=.048; High DBI ≥100% HR 1.89 [1.17-3.05], p=.009, Table II). Following correction of generally accepted confounders such as age, sex, hypertension, diabetes mellitus, CVD, smoking status, RC-AVF, inadequate venous diameter and history of an ipsilateral CVC in a multivariate model, abnormal DBI values were the only independent predictors of primary patency (Low DBI <80% HR 2.25 [1.13-4.48], p=.022; High DBI ≥100% HR 1.74 [1.06-2.85], p=.029, Table II).

Table II. Factors determining primary access patency (Cox proportional hazards models).

		Univariate analysis			Multivariate analysis		
Variable		**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age		0.99	0.98-1.01	.402	1.00	0.98-1.02	.624
Female sex (vs. male)		1.417	0.92-2.19	.116	.78	0.48-1.27	.310
Hypertension		1.02	0.61-1.71	.940	1.07	0.61-1.87	.805
Diabetes Mellitus		0.77	0.49-1.20	.249	.815	0.49-1.35	.429
Cardiovascular disease		0.99	0.65-1.51	.967	1.12	0.69-1.83	.639
Smoking		0.79	0.52-1.20	.270	0.68	0.43-1.09	.108
Wrist-based AVF (vs. elbow-based AVF)		1.45	0.95-2.21	.085	1.42	0.84-2.37	.187
History of ipsilateral CVC		1.36	0.33-5.55	.667	0.93	0.21-4.14	.926
Inadequate vein diameter		1.32	0.81–2.14	.270	1.57	0.93-2.65	.090
DBI	<80%	1.93	1.01-3.70	.048*	2.25	1.13-4.48	.022*
	80-99% (Ref)						
	≥100%	1.89	1.17-3.05	.009*	1.74	1.06-2.85	.029*

AVF, arteriovenous fistula; CVC, central venous catheter; CI, confidence interval; HR, hazard ratio, DBI, Digital-brachial index.

Table III depicts an univariate analysis regarding factors influencing secondary patency rates. Following correction for the confounders mentioned earlier, a multivariate analysis found that a low DBI was associated with an increased risk of secondary failure (HR 2.86 [1.08-7.59], p=.035; Table III).

Table III. Cox proportional hazards model on secondary patency.

		Univariate analysis			Multivariate analysis		
Variable		**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age		0.99	0.97-1.02	.465	0.99	0.97-1.02	.690
Female sex (vs. male)		1.74	0.88-3.44	.109	0.54	0.26-1.15	.110
Hypertension		0.83	0.39-1.75	.625	0.97	0.44-2.14	.945
Diabetes Mellitus		1.04	0.55-1.98	.904	1.14	0.53-2.42	.741
Cardiovascular disease		0.82	0.44-1.54	.533	0.94	0.46-1.91	.867
Smoking		0.77	0.41-1.44	.407	0.68	0.34-1.35	.267
Wrist-based AVF (vs. elbow-based AVF)		1.83	0.97-3.47	.064	2.33	1.06-5.13	.035*
History of ipsilateral CVC		0.05	0.00-1409.94	.563	00	0.00-0.00	.981
Inadequate vein diameter		1.56	0.72–3.36	.257	2.14	0.96-4.78	.063
DBI	<80%	2.40	0.95-6.09	.064	2.86	1.08-7.59	.035*
	80-99% (Ref)						
	≥100%	1.90	0.89-4.03	.096	1.65	0.75-3.63	.214

AVF, arteriovenous fistula; CVC, central venous catheter; CI, confidence interval; HR, hazard ratio, DBI, Digital-brachial index.

Discussion

Earlier studies suggested a role of a digital brachial index (DBI) in the assessment of hand ischemia and in predicting mortality in severe CKD patients (15,16,18,22,29). The aim of the present study was to determine whether values of DBI that were obtained before creation of an arteriovenous fistula (AVF) for hemodialysis (HD) were related to patency. The results indicate that patients with either low DBI values (<80%) or abnormally elevated values (≥100%) had lower two-year primary patency rates compared to patients with a normal DBI. In contrast, preoperatively measured diameters of outflow veins did not predict access patency. The current results may suggest a potential role of a DBI using a simple plethysmographic measurement in the preoperative strategy of access surgery.

In the preoperative counselling process, arm vein diameter determination is advocated as an important step in choosing the optimal access type. However, the literature on the relationship between vein diameters and successful AVF maturation is controversial. Earlier studies indicated that preoperative vein mapping using duplex ultrasound (DUS) increased number of AVF's relative to grafts and reduced immediate failure rates (30,31). A recent study by Wilmink et al. demonstrated that vessel diameter criteria are of limited predictive value (11). One other study also did not find a relation with maturation or patency rates

(32). Conversely, Misskey et al. showed that venous outflow diameters <3.0 mm predicted low RC-AVF patency rates whereas a <3.4 mm venous outflow diameter was also related to lower BC-AVF secondary patency rates (33). The present study using venous DUS cut-off values as proposed by the 2018 ESVS guidelines did not find any correlation with access patency (8). Considering all of these studies suggest that venous diameters are not crucial in predicting short or long term AVF success.

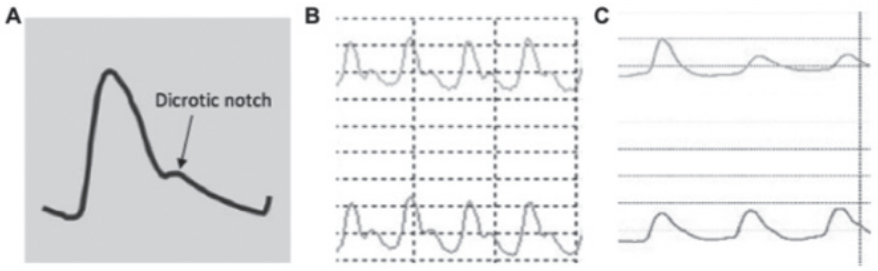
Studies on the quality of the arterial inflow tract in relation to access patency are scarce. One report evaluated the effect of radiographically visible radial artery calcifications in patients with Mönckeberg sclerosis receiving RC-AVF surgery. Individuals with calcified arterial walls had substantially lower two-year primary patency rates compared to those without (36% vs 72%) (14). A second study also found that a higher degree of vascular calcifications was associated with an increased risk of access failure (moderate calcifications: HR 3.82, severe calcifications: HR 4.65) (12). One study used microscopic examinations of preoperatively obtained arterial micro-calcifications (13). Patients who were positive for arterial micro-calcifications had a more than 20% higher rate of AVF failure. Although these studies may underscore the importance of a preoperative arterial quality assessment, the proposed methodologies are invasive, labor intensive, costly and patient unfriendly.

The potential role of a digital-brachial index in access surgery is ill-defined. Interestingly, normal values were never established. Therefore, the consequences of abnormally low values are unclear. Nevertheless, one may speculate that DBI values <100% reflect the presence of atherosclerosis along the brachial-to-digital artery tract. The role of abnormally elevated DBI values (≥100%) is even more puzzling. In analogy to elevated ankle-brachial indices, one might hypothesize that a DBI ≥100% indicates augmented vascular stiffness and decreased vascular compliance, possibly caused by persistent oxidative stress and chronic arterial wall inflammation (34,35). Physiological laws dictate that systolic blood pressures in distal portions of extremities in a normal situation are equal or somewhat lower compared to proximal pressures. Therefore, abnormally elevated DBI values are possibly a reflection of a poor systemic arterial vessel quality (18,22).

Arterial wall calcifications are not limited to distal arteries but likely represent atherosclerotic damage of the entire cardiovascular system. Abnormal DBI values possibly reflect an increased atherosclerotic burden and augmented

vascular stiffness or a combination thereof leading to increased cardiac workload and compromised coronary artery perfusion. Interestingly, cardiac changes in the blood volume with each heartbeat are mirrored in the shape of the photoplethysmography waveform. Photoplethysmographic (PPG) signal analysis has the ability to detect changes in systolic arterial blood pressure and vascular tone (36). In most cases of our study, patients with abnormal DBI values displayed a vasoconstrictive PPG waveform pattern (Figure 3). These abnormal waveforms have a lower PPG amplitude and a fused notch compared with a normal pattern, meaning that there is a decreased blood flow. These phenomena may suggest that DBI values are associated with cardiac pump function and potentially have the ability to reflect the overall cardiovascular health of an individual.

Figure 3. Characteristics of a normal PPG waveform (A & B) and an abnormal PPG waveform in a patient with a severely diminished DBI (C).



The literature on risk factors associated with hemodialysis access failure is diverse. One study found that old age, diabetes, smoking and presence of RC-AVF were associated with low six months primary patency rates (7). Conversely, a current guideline included a study reporting that only presence of CVD, time to access utilization and earlier CVC were factors determining patency rates (37). The present study analyzed all of these aforementioned parameters. Surprisingly, only abnormal DBI values were associated with a low primary patency rate, whereas presence of RC-AVF and low DBI values were independent risk factors of diminished secondary patency. However, it must be appreciated that access patency is a complex outcome parameter that is influenced by a wide range of factors.

The current study is the first to investigate the role of a preoperative DBI as a factor contributing to a successful access on the long-term. If the

results of the present study are confirmed in other populations, a bilateral DBI measurement may aid in selecting the optimal hemodialysis therapy in severe CKD patients. First, DBI measurements might help choosing the preferred arm. If DBI values are abnormal and vessel diameters are suboptimal in a non-dominant arm, a patient may be advised to receive an AVF construction in the dominant arm if these parameters are better. Secondly, abnormal DBI values may determine location of access construction in an arm. Whereas a distal AVF is normally chosen, a severely abnormal DBI might tip the balance towards a more proximal AVF since this type of access has superior long-term patency (28). However, it should be realized that an arm harboring a proximal AVF is more prone to develop hand ischemia, likely so if DBI values are low to begin with. In addition, DBI values may contribute to an optimal patient selection. High DBI values carry the highest risk of associated cardiovascular mortality. Therefore, fragile CKD patients with vascular polymorbidity presenting with a DBI of ≥100% possibly require a more thorough cardiovascular evaluation prior to access surgery. In patients with an unfavorable risk profile, a CVC may be preferred. However, it must be appreciated that selecting the most ideal treatment for future HD patients is always influenced by a complex interrelated set of risk factors. Therefore, management should always be tailored to an individual patient.

This study has several limitations including its retrospective design and restricted number of patients. Since DBI values were used to assess the risk of post-operative hand ischemia, access construction in the arm with a suboptimal DBI may have been avoided. Grouping DBI into three classes may seem arbitrarily as normal DBI values were never established. A previous study at our institute demonstrated that values of <80% or ≥100% were associated with lower survival rates. Furthermore, it was reasoned that DBI values ≥100% are abnormal since systolic pressures cannot increase along the arm-hand axis, whereas a 80% lower limit was proposed in earlier studies as well as in the Dutch guidelines on vascular access management (18,22–25). The present study did not include arterial DUS in the analysis, due to limited data. Current recommendations regarding arterial diameters are controversial (11,30,33,38). Prospective studies should determine whether arterial DUS is superior to digital plethysmography in predicting access patency.

In conclusion, severe CKD patients having abnormal DBI values prior to the first AVF construction sustain an increased risk of access failure within two years.

This effect may occur independent of the presence of generally accepted risk factors of access failure. Future prospective trials should determine the role of digital plethysmography as a bedside tool for access surgery.

Acknowledgements

We are grateful to the technicians of the vascular laboratory at the MMC for their contributions in obtaining the measurements.

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Chapter 3

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

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Published in *Journal of Vascular Surgery*
Volume 74, Issue 6, P2040-2046, December 01, 2021
Impact Factor: 4.4

Abstract

Objective

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 $P_{dig\text{-}rest}$ and $P_{dig\text{-}compression.}$ 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 center 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.

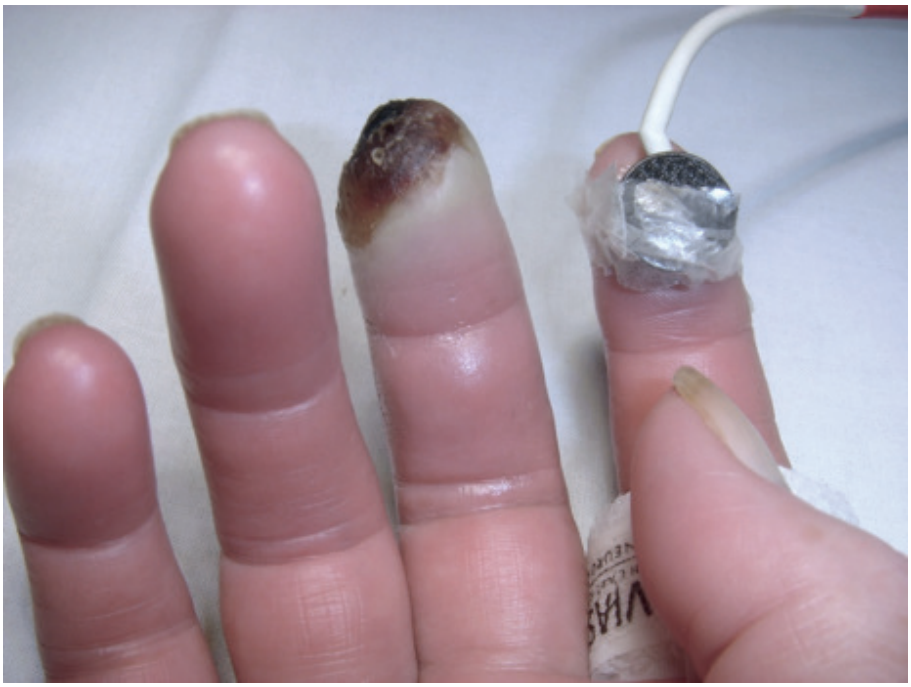
Keywords

Digital Brachial Index; vascular access; chronic hemodialysis; HAIDI; Hand ischemia

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). HD 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) (6,9,10). A recent consensus meeting graded type of HAIDI as 'severe' if ischemic symptoms were intolerable and revascularization was required (Type 2b-4, Inston et al.; 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 interobserver 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 center (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 Center 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 December 31, 2018. Patients transferred to a dialysis center 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 post-operative 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 I), 10 patients (10%) were diagnosed with severe (type 2b-4)

Table I. 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.

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 I).

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 II). 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 II. 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 III.

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

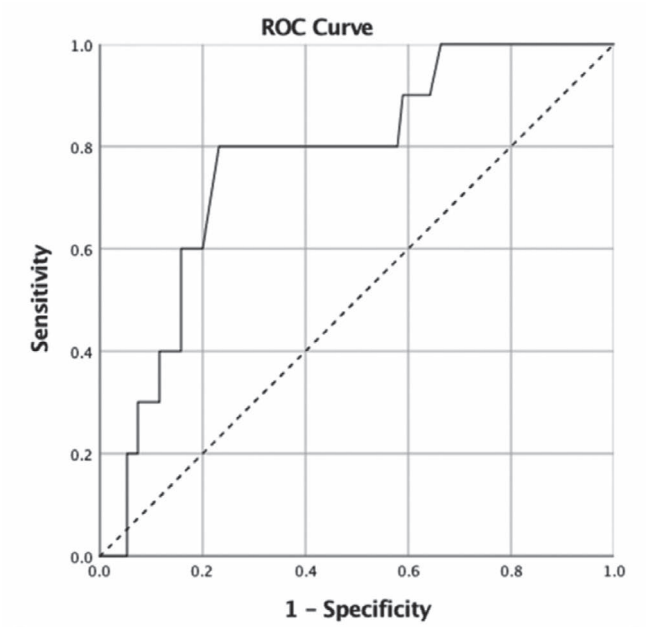
N.	P_{dig} preop	DBI (%)	∂P_{dig} preop	∂DBI preop	Dominance	First Access	P_{dig1} open	P_{dig1} Comp	HAIDI grade	Intervention
1	112	82	11	8%	Radial	RC-AVA	20	*	2b	Ligation
2	183	109	17	10%	Radial	RC-AVA	*	*	2b	RUDI
3	153	134	41	36%	Ulnar	RC-AVA	23	110	2b	PTA Subclavian artery
4	177	83	41	19%	Radial	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 was planned but patient died unexpectedly.

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.

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.

Acknowledgements

We thank all technicians of our vascular lab for their continuous effort, service and support.

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Chapter 3.1

Letter to the Editor

Avoiding hemodialysis access-induced distal ischemia

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Accepted in *Journal of Vascular Surgery, 2022*

To the Editor:

We applaud the recent article in the Journal of Vascular Surgery by *Yadav et al.* demonstrating a reliable method for predicting the emergence of HAIDI.[1] This well-designed study emphasized the identification of patients with arterial inflow to the hand limited to a single vessel, most often the radial artery. As the authors stated, hand ischemia following a vascular access procedure is not rare. Less severe symptoms, not resulting in specific treatment, can occur in up to 50% of patients.[2]

The clinical emergence of HAIDI may be multifactorial, requiring the surgeon to be familiar with a variety of procedural options for resolution of ischemia while maintaining a functional access. We focus preoperatively on identifying individuals at high risk for HAIDI and plan strategies for avoiding these complications.[3] When audible doppler flow in the palmar arch(s) disappears with compression of the radial artery (modified Allen's test), we often create a proximal ulnar artery inflow arteriovenous fistula in such patients where the radial artery is the only patent vessel to the hand.[4]

We hope the authors will comment on prevention of HAIDI in selected patients identified in their study by using such a strategy.

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Chapter 3.2

Invitational letter from the Editor

Reply to: Avoiding hemodialysis access-induced distal ischemia, by Jennings et al.

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Accepted in *Journal of Vascular Surgery, 2022*

To the Editor:

We thank Dr. Jennings and Dr. Mallios for their interest in our study dealing with prediction of hemodialysis access induced distal ischemia (HAIDI). Our pilot study suggests that patients who developed severe HAIDI (type 2b-4, invasive treatment required) after arteriovenous access (AVA) construction had compromised 'collateral reserve' as shown during the preoperative workup using modified Allen's test combined with digital plethysmography.[1]

We are delighted to further comment on the contention stating *'to prevent is better than to cure'*. To begin with, a decision on AVA type and location is, in part, guided by identification of modifiable and non-modifiable risk factors of HAIDI including earlier surgery, type of AVA, female gender, obesity, diabetes, cardiovascular disease and palmar arch anatomy. If construction of a wrist-based access is not feasible, *Jennings and Mallios* earlier reported that AVA construction with a proximal radial or ulnar artery inflow source shows promising long-term patency rates and is associated with a lower risk of HAIDI.[2] In addition, they advised to use the disappearance of an audible Doppler flow signal over the palmar arch following radial artery compression as a parameter of the hand's collateral capacity.[3] This elegant bedside method is also beneficial for determining palmar arch dominance, but may be subjective to a learning curve and observer bias in less experienced hands. Moreover, anatomy of palmar arches varies widely. Ideally, efficacy of this tool could increase once supplemented with simultaneous plethysmographic digital pressure measurements providing an objective parameter of altered finger perfusion.

If radial or ulnar artery occlusions are suspected, ultrasound (or angiography) along the entire length of forearm vessels may support a choice of optimal inflow artery.[4] In all cases if feasible, a wrist-based AVA remains the fistula of choice, not only because of the lowest risk on HAIDI, but also because of superior patient survival rates compared to more proximal access types.[5] Possibly, a wrist based-AVA may be constructed on the dominant arm. If not recommended, an AVA with proximal artery inflow is a reliable AVA type with promising long-term outcomes and low risk of post-operative HAIDI.

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Chapter 4

Abnormal digital brachial index prior to hemodialysis access construction is associated with increased cardiovascular mortality

An observational cohort study

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Published in *Hemodialysis International*
Volume 24, Issue 3, P335-343, May 14, 2020
Impact Factor: 1.8

Abstract

Objective

An abnormal ankle-brachial index indicating presence of peripheral arterial disease (PAD) is known to predict mortality in end-stage renal disease (ESRD). Hand ischemia, reflected by low finger pressures, is also a factor associated with increased mortality in patients undergoing hemodialysis (HD). Aim of the present study is to determine whether an abnormal digital brachial index in ESRD patients prior to HD access surgery is related to lower survival rates.

Methods

A digital brachial index (DBI, systolic finger pressure/systolic brachial arterial pressure) was obtained using digital plethysmography in ESRD patients before construction of a primary HD access between January 2009 and December 2018 in a single center. Patients were grouped based on categories of DBI (low <80%, normal 80-99%, high ≥100%). Overall and cardiovascular mortality were assessed with the ERA-EDTA classification system (ERA-EDTA codes 11, 14-16, 18, and 22-26, 29). Factors potentially influencing survival rates were analyzed using standard statistics.

Results

Follow-up was available in 199 patients (female n= 80; age 70 years ±12; follow-up index 99% ±1). Overall 2- and 4-year survival were similar among DBI groups Moreover, 2- and 4-year freedom from cardiovascular death were also not different (low DBI 80% ±8 and 58% ±11; normal DBI 86% ±4 and 75% ±6; high DBI 74% ±6 and 61% ±7). Following correction for age, diabetes mellitus, cardiovascular disease and smoking, a high DBI conferred a significantly increased risk of cardiovascular mortality (HR 2.09 [1.06 –4.13], p=0.03) and a trend towards higher overall mortality (HR 1.69 [0.98 – 2.93], p=0.06).

Conclusion

ESRD patients with an abnormally elevated DBI before HD access creation have an increased risk of cardiovascular mortality in the first four postoperative years.

Keywords

Digital pressure; ischemia; vascular access; chronic hemodialysis; survival analysis

Introduction

Hemodialysis (HD) in patients with end stage renal disease (ESRD) is associated with a poorer survival compared to ESRD patients not yet requiring HD. Cardiovascular disease (CVD) is considered the primary cause of death among HD patients (1). Despite an overall limited survival in a general dialysis population, individual variability is substantial (2). Therefore, recognizing factors predicting survival may aid in the approach of these fragile patients including the decision on type of HD access and further HD management (3,4).

Since mortality in HD is often determined by the patient's cardiovascular condition, it is worthwhile to identify factors associated with poor cardiovascular health (5,6). Values of ankle pressures and ankle-brachial indices (ABI) were related to cardiovascular and overall mortality in patients with chronic kidney disease in a U-shaped manner (7). Incidental data suggested that hand ischemia, as reflected by diminished finger pressures (or digital brachial index, DBI) was associated with a limited survival in a HD population (8,9). Based on these findings, the present study aimed to determine whether the presence of an abnormal DBI in ESRD patients *prior* to receiving a HD access was associated with increased mortality rates during the first years of dialysis. We hypothesized that, in analogy to ankle pressures, a similar U-shaped relationship between DBI and survival was present.

Material and Methods

This retrospective cohort study included patients who received a HD access between January 2009 and December 2018 in the Máxima Medical Center (MMC; Veldhoven, the Netherlands), a hospital in a semirural environment accommodating approximately 200.000 patients. At present, our dialysis facility harbors some 120 patients on chronic HD.

Patients who are referred to our vascular outpatient clinic by a nephrologist because of stage IV or V renal disease and who may wish to receive a HD access undergo a standard work-up protocol with a medical history and physical examination including inspection of the arm and hand and radial and ulnar artery palpation. Vein mapping of both arms using Duplex-sonography (Nicolet Vasoguard, VIASYS Healthcare, USA) is routinely performed and contributes to the decision for an appropriate type of access.

Finger pressures (P_{dig}, mmHg) of the middle and/or index finger of both hands are obtained using digital plethysmography (Vasoguard Nicolet 8 MHz, Scimet, Bristol, UK) by an experienced vascular laboratory technician. An inflatable cuff is placed around the proximal phalanx while a photo plethysmography sensor is attached to the distal phalanx. Once a stable signal is attained, the digital cuff is inflated up to a maximum pressure of 200 mmHg until the systolic arterial signal disappears. The cuff is then gradually deflated until a pulsatile signal reappears reflecting the systolic digital pressure. Patients were counselled on the pros and cons of various types of access. Following informed consent, they usually receive the operation within 6 weeks after the outpatient department evaluation.

Study inclusion criteria were adult patients (> 18 years), stage IV or V ESRD, construction of a primary HD access, and availability of finger pressures that were measured within 6 months prior to access construction.

The medical ethical committee of MMC decided that the rules laid down in the Medical Research Involving Human Subjects Act (Dutch WMO) did not apply to the study protocol as plethysmography is considered a stress-free non-invasive imaging modality which is currently standard of care in our institution.

Data collection and definitions

Patient demographics, comorbidities, smoking status, use of statin and/or anticoagulants, type and timing of primary access construction, HD status (yes, no) and finger pressures were collected retrospectively from electronic patient files (HiX 6.1, ChipSoft B.V., Amsterdam, The Netherlands; FinProDB 7.9, MedVision AG, Unna, Germany). Cause of renal failure was classified according to Dutch Nephrology guidelines based on ICD-10 diagnoses (5). A DBI was calculated as the systolic pressure of the index finger divided by the systemic pressure obtained from the arm with the highest pressure. The lowest DBI value of both hands was used for analysis. Patients were grouped into three categories of DBI as follows; low (<80%), normal (80-99%) or high (≥100%). The cut off values were based on earlier studies as well as on Dutch guidelines for vascular access management (10–13).

Causes of death during follow-up were obtained from the patient's file. A death was categorized cardiovascular as dictated by the ERA-EDTA classification (ERA-EDTA codes 11, 14-16, 18, 22-26, 29). Follow up index (FUI) was calculated in accordance to recent recommendations (14). Date of HD access construction

served as the starting date. FU was terminated four years after access surgery, following death or at December 31, 2018. Patients who had moved to another dialysis facility within the observation period were considered loss to FU and "date last known alive" was used.

Statistical analysis

Statistical analyses were performed using SPSS version 25 (IBM SPSS Inc., Chicago, IL, USA). Baseline characteristics were depicted as mean ± standard deviation (SD), or counts (percentages) when appropriate. Study parameters were tested for normality and expressed as mean ± standard error of the mean (SEM). DBIs were displayed as percentages. Possible differences between groups were compared using Pearson's chi-square test, Fischer's exact test or independent sample T-test when appropriate.

To determine whether a U-shaped relationship was present between DBI and mortality, cardiovascular and overall mortality rates over four years were plotted against DBI in 10% increments. Kaplan Meier analysis and Log-Mantel Cox testing were used to determine potential group differences. Univariate Cox-Regression tested which factors were associated with cardiovascular and overall mortality. A multivariate Cox-Regression model was generated with parameters displaying *P*-values <0.15 in the univariate analyses. Outcomes were displayed as Hazard ratio 95%-Confidence interval [HR 95%-CI]. Primary and secondary access patency rates were calculated as suggested (15). *P*-values 0.05 were considered statistically significant.

Results

During a 10-year period, 300 patients received a primary HD access in our facility. A total of 202 patients underwent finger pressure measurements within 6 months before access construction. As 3 patients received their access more than 6 months after the finger pressure assessment, a total of 199 patients fulfilled study criteria (female n=80, age 70 ±13 years). Characteristics are presented in Table 1. Characteristic of the 3 DBI groups are presented in Table 2. Rate of diabetes was higher in the <80% DBI group.

Table 1. Demographics of ESRD patients before hemodialysis access construction (n=199).

Characteristic	N=199
Age (years, ±SD)	70 ±12
Gender male/ female	119 / 80
Diabetes Mellitus (%)	78 (39)
Cardiovascular disease (%)	109 (55)
Hypertension (%)	157 (79)
Primary renal disease (%)	
Glomerulonephritis/sclerosis	34 (17)
Pyelonephritis	5 (3)
Hypertension	20 (10)
Renal vascular disease	20 (10)
Diabetes	48 (24)
Polycystic	2 (1)
Miscellaneous	61 (31)
Unknown	9 (5)
Statin use (%)	129 (65)
Anticoagulant use (%)	124 (63)
Smoking (%)	
Total	103 (52)
Former	60 (30)
Active	43 (22)
Type of constructed hemodialysis access (%)	
Wrist-based AVF	95 (48)
Elbow-based AVF	96 (48)
AVG	4 (2)
Other	4 (2)
Hemodialysis initiated (%)	
Yes	132 (66)
No	57 (29)
Unknown	10 (5)
Average time on hemodialysis (months ±SEM)	22 ±1.4

SD, Standard deviation; AVF, arteriovenous fistula; AVG, arteriovenous graft; SEM, standard error of the mean.

Table 2. Demographic characteristics according to digital brachial index (DBI).

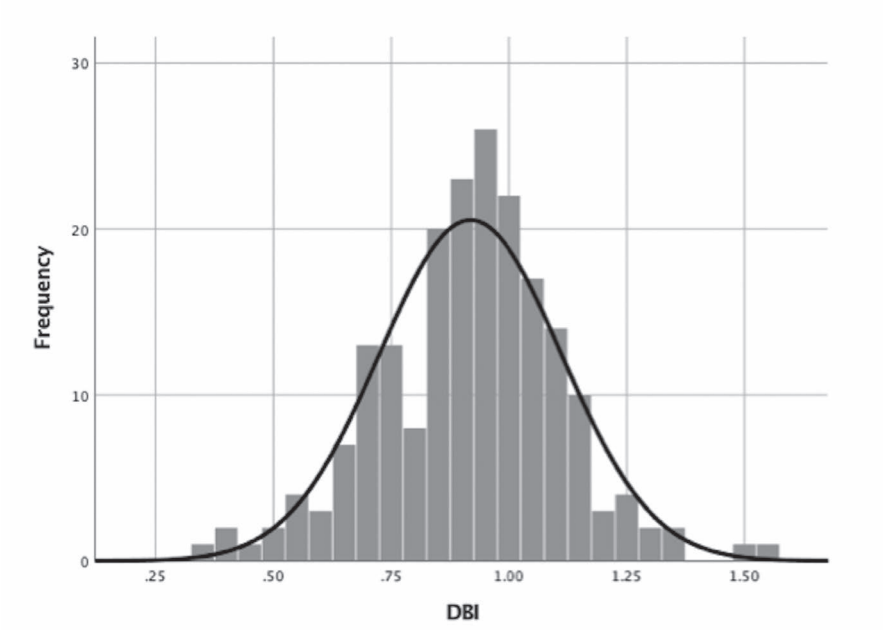
Characteristics	Normal DBI: 80-99% n= 81	Low DBI: <80% n= 48	High DBI: ≥100% n= 70	*p*
Age (years, ±SD)	71 ±12	73 ±12	68 ±13	.09
Gender female (%)	37(46)	22 (46)	21 (30)	.10
Diabetes Mellitus (%)	31 (38)	26 (54)	21 (30)	.03*
Cardiovascular disease (%)	43 (53)	26 (54)	40 (57)	.88
Hypertension (%)	61 (75)	40 (83)	56 (80)	.54
Primary renal disease (%)				n/a
Glomerulonephritis/sclerosis	15 (19)	9 (19)	10 (14)	
Pyelonephritis	1 (1)	2 (4)	2 (3)	
Hypertension	5 (6)	3 (6)	12 (17)	
Renal vascular disease	10 (12)	2 (4)	8 (11)	
Diabetes	18 (22)	13 (27)	17 (24)	
Polycystic	1 (1)	1 (2)	0 (0)	
Miscellaneous	24 (30)	17 (35)	20 (29)	
Unknown	7 (9)	1 (2)	1 (1)	
Statin use (%)	52 (65)	32 (67)	45 (64)	.96
Anticoagulant use (%)	46 (58)	29 (59)	50 (69)	.31
Smoking (%)	43 (53)	24 (50)	37 (53)	.81
Former	22 (27)	7 (15)	17 (24)	
Active	16 (20)	12 (25)	15 (21)	
Yes, but unknown	5 (6)	5 (10)	5 (7)	
Type of HD access (%)				n/a
Wrist-based AVF	40 (49)	21 (44)	34 (49)	
Elbow-based AVF	39 (48)	23 (48)	34 (50)	
AVG	1 (1)	2 (4)	1 (1)	
Other	1 (1)	2 (4)	1 (1)	
Hemodialysis received (%)				0.9
Yes	55 (68)	26 (54)	51(73)	
No	23 (28)	19 (40)	15 (21)	
Unknown	3 (6)	3 (6)	4 (6)	
Average time on hemodialysis (months ±SEM)	24 ±2	18 ±3	21 ±2	.27
Mean follow-up (years ±SEM)	2.3 ±0.2	1.8 ±0.2	2.4 ±0.2	.08

SD, standard deviation; AVF, Arteriovenous fistula; AVG, arteriovenous graft; SEM, Standard error of the mean; n/a, not applicable. Statistical significance was tested using a chi-square test for categorical variables and a t test for continuous variables.

Patient characteristics in relation to DBI and P_{dig}

DBI values before access construction were normally distributed (Figure 1), and mean DBI was 92% ±19. Males tended to have a higher DBI compared to females (94% ±2 vs 89% ±2, p=0.06). As expected, diabetics had a significantly lower DBI (diabetic: 86% ±2 vs non-diabetic: 95% ± 2, p≤0.01). In addition, P_{dig} of hypertensive patients was higher compared to patients with normotension (147mmHg ±3 vs 134 mmHg ±5, p=0.04) whereas DBIs were similar.

Figure 1. Distribution of DBI before access construction (n=199).



Preoperative P_{dig}, DBI, and mortality

Absolute values of P_{dig} were neither related to overall mortality (HR 1.00 [0.99 – 1.00], p=0.31) nor to cardiovascular mortality (HR 1.00 [0.99 – 1.01], p=0.88). In addition, absolute DBI was also not associated with any primary outcomes (Overall mortality: HR 1.27 [0.37 – 4.31], p=0.70; Cardiovascular mortality: HR 1.06 [0.24 – 4.64], p=0.93).

Survival and DBI

The follow-up index was 99% ±1, and mean follow-up was 2.2 years ±0.1. A total of 67 of the 199 patients died during the four years following access construction (34% death rate). Causes of death were cardiovascular (n=46; 69%), infection (n=11; 16%), HD discontinuation (n=4; 6%), cancer (n=3; 4%) or other causes (severe trauma, abdominal sepsis and pulmonary insufficiency, each n=1, 4%). Freedom from cardiovascular death was similar in the three groups of DBI (p=0.22; Figure 2). Moreover, overall survival in the three groups of DBI was also similar (p=0.30; Figure 3).

Figure 2. Freedom from cardiovascular death in relation to preoperative DBI in ESRD patients (n=199).

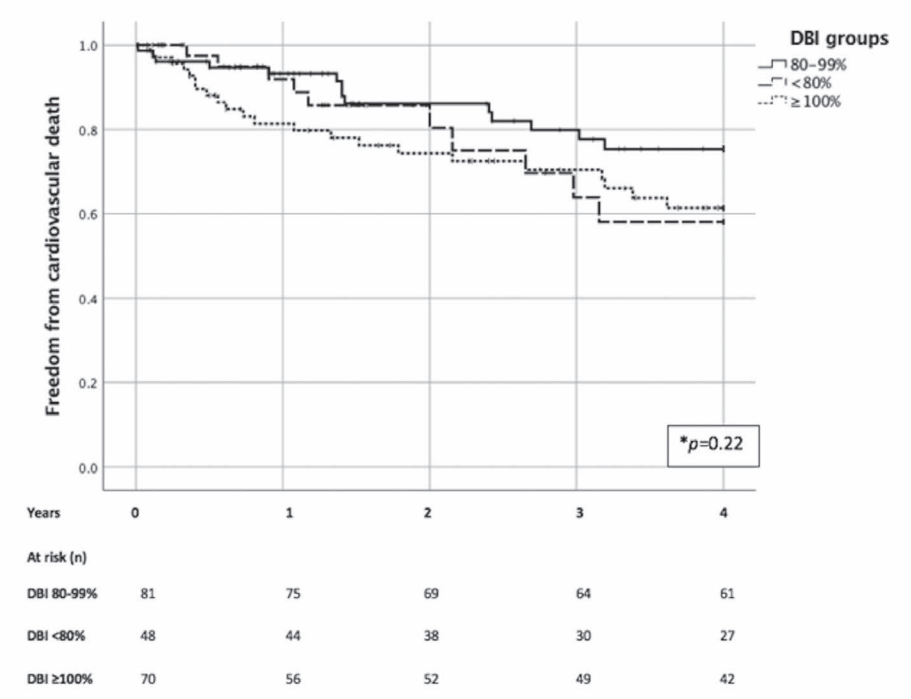
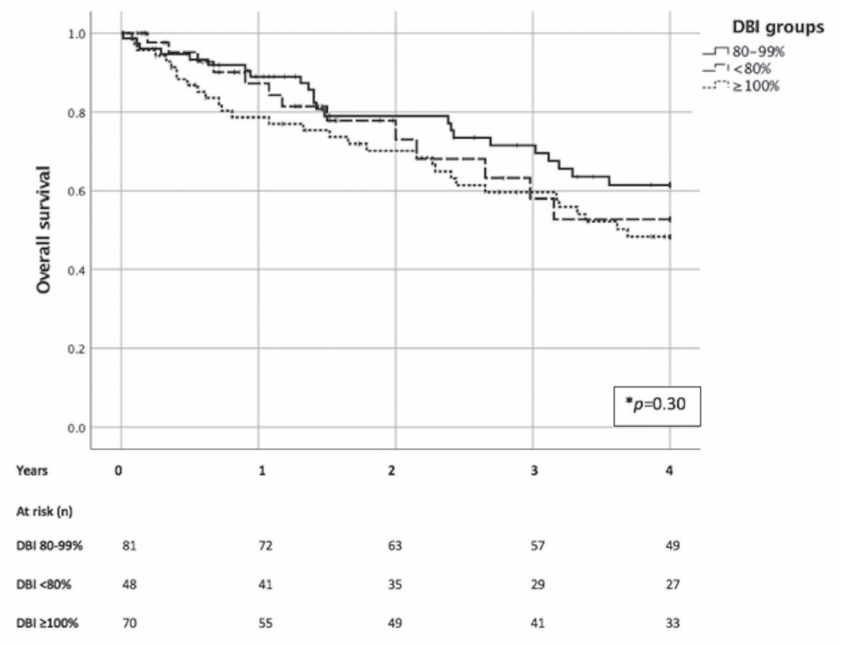


Figure 3. Overall survival in relation to preoperative DBI in ESRD patients scheduled for access construction (n=199).



According to univariate analysis, old age, presence of CVD and smoking were associated with increased overall and cardiovascular mortality. In contrast, the presence of diabetes mellitus was not (Table 3).

Table 3. Factors determining cardiovascular mortality and overall mortality in 199 HD patients (univariate analysis).

Cardiovascular mortality	HR (95%-CI)	*P*	Overall mortality	HR (95%-CI)	*P*
Age (years)	1.05 (1.02 - 1.08)	*<.01**		1.05 (1.02 - 1.08)	*<.001**
Sex (female)	1.13 (0.63 – 2.02)	*.68*		0.86 (0.52 – 1.40)	*.53*
Hypertension (yes)	1.28 (0.60 - 2.76)	*.52*		1.39 (0.73 – 2.65)	*.32*
Diabetes Mellitus (yes)	1.49 (0.83 - 2.66)	*.18**		1.21 (0.74 – 1.97)	*.45**
Cardiovascular disease (yes)	2.15 (1.15 – 4.03)	*.02**		2.80 (1.62 – 4.87)	*<.001**
Smoking (yes)	2.30 (1.22 – 4.31)	*.01**		1.94 (1.17 – 3.21)	*.01**
DBI <80%	1.54 (0.68 – 3.47)	*.30**		1.25 (0.63 – 2.46)	*.53**
80-99% (Ref)					
≥100%	1.79 (0.91 – 3.49)	*.09**		1.53 (0.89 – 2.62)	*.12**

HD = Hemodialysis; Ref = Reference; *included in multivariate analysis.

In a multivariate analysis following correction for age, diabetes mellitus, cardiovascular disease and smoking status, abnormally high DBIs conferred an increased risk of cardiovascular death, whereas an increase in overall mortality was also observed (Cardiovascular mortality: HR 2.09 [1.06 –4.13], p=0.03; Overall mortality: HR 1.69 [0.98 – 2.93], p=0.06; Table 4).

Table 4. Risk factors of cardiovascular mortality (A) and overall mortality (B) in patients following access construction.

A: Cardiovascular mortality			
Risk factors	HR	95% CI	*p*
Age (years)	1.05	1.02 – 1.09	*<.01**
Diabetes Mellitus (yes)	1.52	0.83 – 2.77	*.17*
Cardiovascular disease (yes)	1.39	0.73 – 2.66	*.32*
Smoking (yes)	2.22	1.17 – 4.21	*.02**
DBI values:			
<80%	1.28	0.56 – 2.92	*.56*
80-99% (Ref)			
≥100%	2.09	1.06 –4.13	*.03**

B: Overall mortality			
Risk factors	HR	95% CI	*p*
Age (years)	1.05	1.02 – 1.08	*<.001**
Diabetes Mellitus (yes)	1.20	0.72 – 1.99	*.48*
Cardiovascular disease (yes)	1.96	1.11 – 3.46	*.02**
Smoking (yes)	1.75	1.05 – 2.93	*.03**
DBI values:			
<80%	1.07	0.54 – 2.15	*.84*
80-99% (Ref)			
≥100%	1.69	0.98 – 2.93	*.06**

HR = hazard ratio; Ref = Reference ; CI = confidence interval. Associations were tested using Multivariate-Cox regression analysis. Factors were included with *P*-values 0.05 in univariate analysis. Diabetes was additionally included to the model.

Discussion

Previous research in chronic kidney disease patients has demonstrated that values of ankle-brachial indices (ABI) were related to cardiovascular and overall mortality in a U-shaped manner (16,17). The present study aimed to determine whether values of digital brachial index (DBI) in end-stage renal disease (ESRD) patients *prior* to receiving an access for hemodialysis (HD) were also associated with increased mortality rates during the first years after access creation. However, such a U-shaped relationship was not found. In contrast, ESRD patients who displayed an abnormally high DBI value (≥100%) sustained a twice as higher chance on a cardiovascular death in the first 4 years after access construction.

A convincing explanation for a potential relationship between abnormally elevated DBI and possibly increased mortality rates in ESRD patients is currently absent. In analogy to low toe pressures predicting mortality in PAD patients, generalized increased arterial stiffness and low vascular compliance may also play a role in ESRD patients (17–19). In both PAD and ESRD populations, a variety of pathogenic substances may result in ongoing oxidative stress and chronic inflammation of the arterial wall. Progressive stiffness of the arterial system is known to increase cardiac workload and to compromise coronary artery perfusion. This sequence of events may lead to cardiac ischemia and poorer survival (20,21). One study found that an aortic stiffness index indeed predicted death due to cardiovascular disease (22). Therefore, this phenomenon may also have occurred in our ESRD patients but these measures were not obtained in the present study population. Future studies using pulse wave velocity may shed a light on a possible relationship between arterial stiffness, abnormal DBI values and mortality in ESRD patients.

The current study hypothesized that, in analogy to PAD patients, a similar U-shaped relationship between DBI and survival was present in our ESRD population. In one PAD population, low as well as high values for ABI predicted mortality (23). Whereas mortality in patients with low ABI values is possibly related to an increased atherosclerotic load, mortality in patients with a high ABI values may primarily be due to an augmented vascular stiffness or a combination thereof defining the U-shaped relationship (23). Two other studies showed that high ABI values are frequently found in patients on HD or having chronic kidney disease, and that these patients had an increased risk on major adverse cardiovascular events (23, 24), similarly to our study population. In contrast, the present study

also found that the mortality rate was only higher in patients with an abnormally high DBI, but not with low values of DBI. Physiological principles dictate that systolic blood pressure (SBP) in the periphery of the upper extremity can never be higher compared to values in central portions of the arterial vasculature. As SBP usually diminishes along the heart-hand axis, an abnormally high DBI value (≥100%) likely reflects poor arterial vessel quality and diminished compressibility. Why lower survival was not found in our patients having low finger pressures is unclear but may be related to the limited statistical power. Prospective clinical trials are required to determine whether lower and upper limits for DBI values may be identified serving as prognostic markers for mortality in ESRD patients.

The role of diabetes mellitus in ESRD patients having abnormally elevated DBI values is not clear. Bevc et al. found the U-shaped association between DBI and cardiovascular mortality in a non-diabetic population (25). Based on the fact that diabetes is a generally accepted important risk factor promoting atherosclerosis, we added this risk factor into our multivariate analysis (26,27). Interestingly, the percentage of diabetics in the normal DBI as well as the abnormally elevated DBI group was similar. Therefore vascular stiffness in the upper extremity is not only determined by diabetes in end-stage renal disease patients based on our findings.

At this moment, DBI measurements using finger plethysmography are advocated for the detection of a variety of vascular diseases but also for evaluating the efficacy of surgery for hand ischemia (28–30). Results of the present study may suggest a novel role for DBI as these values have the potential to contribute to a decision whether a thorough evaluation of cardiovascular health is indicated before access surgery. However, evaluation of cardiovascular health should always be tailored to an individual patient as the ultimate goal is to optimize risk factor management. If an association between DBI values and cardiovascular mortality is prospectively confirmed, a simple non-invasive plethysmography analysis prior to access construction may aid in the decision regarding the execution of a long term program of cardiovascular risk reduction in these vulnerable ESRD patients. The present study should be seen as the progenitor for further research of the role of DBI measurement as a tool for risk evaluation in ESRD patients.

Several study limitations should be addressed including its retrospective character and the restricted number of patients. Our study design may have introduced immortal time bias as the start of follow up was later than the inclusion. However, as this 'immortal time' was relatively short (31 days ±3 SEM), it is unlikely

that this would have led to significant bias. Categorizing DBI values into three groups is arbitrarily as normal values of DBI were never established. However, it was reasoned that DBI values over 100% should be considered as pathological since perfusion pressures should diminish towards peripheral portions of the arm. The lower limit of 80% was earlier proposed and is in accordance with Dutch guidelines on vascular access management (10–13).

In conclusion, ESRD patients with an abnormally elevated DBI ≥100% confer an increased risk of cardiovascular mortality in the years after creation of a hemodialysis access. Prospective trials should confirm whether modalities of finger pressure measurements may prove useful for predicting poor survival in ESRD populations.

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Chapter 5

A preoperative modified Allen test result may be associated with long term mortality after hemodialysis access construction

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Published in *Journal of Vascular Access*
Volume 23, Issue 1, P109-116, Jan, 2022
Impact Factor: 2.3

Abstract

Objective

The modified Allen test (MAT) is a simple bedside method determining collateral hand circulation prior to hemodialysis (HD) access surgery. Hand ischemia as reflected by low systolic finger pressures (P_{dig}) is associated with high mortality rates in severe kidney disease (CKD) patients. Aim of the present study was to assess a possible relation between absolute finger pressure drop (∂P_{dig}) during a preoperative MAT and mortality after a first HD access construction.

Methods

P_{dig} (systolic pressure, mmHg) was measured using digital plethysmography following compression of radial and ulnar arteries in CKD patients just before access surgery between January 2009 and December 2018 in one center. The greatest ∂P_{dig} of both index fingers was used for analysis. Cardiovascular and overall mortality were assessed during the following 4 years using the ERA-EDTA classification system (codes 11, 14-16, 18, 22-26, 29). Cox regression analysis determined possible associations between ∂P_{dig} and mortality.

Results

Complete data sets were available in 108 patients (male n=71; age 70 years ±12; mean follow up (FU) 1.6 years ±0.1; FU index 99% ±1). Median ∂P_{dig} was 31 mmHg (range 0 – 167 mmHg). Patients having cardiovascular disease (CV+) demonstrated higher ∂P_{dig} values (CV+ 44 ±5 mmHg vs CV- 29 ±3 mmHg, p=.012). A total of 26 patients (24%) died during FU (CV+ death, n=16; 62%). For each 10 mmHg ∂P_{dig} increase, overall mortality increased by 10%, and CV+ mortality by 15% (Overall mortality: HR 1.10 [1.01 – 1.22], p=.048; CV+ mortality: 1.15 [1.03 – 1.29], p=.017). Following correction for age, ∂P_{dig} remained associated with CV+ mortality (HR 1.13 [1.00 – 1.26], p=.043).

Conclusion

A large drop in systolic finger pressure during a preoperative MAT is related to mortality after primary HD access surgery. The role of this potential novel risk parameter requires confirmation in a larger population.

Keywords

Digital pressure; ischemia; vascular access; chronic hemodialysis; survival analysis

Introduction

The Allen test is a simple bedside method that was used in the early years of hemodialysis (HD) access surgery for determining the risk of postoperative hand ischemia (1). This test is termed positive when hand palm pallor persists following release of a clamped radial artery while the ulnar artery is still compressed (or vice versa) (2). At present, a modified Allen test (MAT) is also used for identifying a deficit in hand circulation following radial artery cannulation or harvesting, and for predicting patency following HD access surgery in severe chronic kidney disease (CKD) patients (1,3,4).

Although a MAT may unveil insufficient hand perfusion, the test is not useful for quantifying grade of ischemia. If this is required, digital pressures (P_{dig}) using finger plethysmography may be measured (5). Earlier studies revealed that hand ischemia as reflected by low P_{dig} (and digital brachial indices, DBI) was associated with higher mortality rates in HD patients. This finding may reflect lack of compensatory capacity of the vascular system in some of these fragile patients (6–10).

Prior to choosing the optimal type of HD access in an CKD patient, stratification of risk factors is required. For instance, a patient having multiple risk factors and possibly a limited life expectancy may benefit from a permanent indwelling line rather than from an arteriovenous fistula or loop (5,11). Therefore, identification of potential novel predictors may be beneficial for preoperative management of this population. The present study aimed to determine a possible association between the magnitude of finger pressure drop (∂P_{dig}) during a MAT and mortality following access construction in severe CKD patients. It was hypothesized that a greater ∂P_{dig} was related to higher mortality rates. If so, this novel parameter may contribute to a decision on type of access surgery.

Material and methods

General information and standard workup

This retrospective observational cohort study included patients who received their first HD access between January 2009 and December 2018 in one center (Máxima MC, Veldhoven, the Netherlands), a Dutch hospital with a dialysis ward providing HD to approximately 110 patients.

Patients with stage IV or V renal disease were assessed by a nephrologist for possible risk factors leading to progression of CKD or kidney failure according to

recent guidelines (12,13). Based on this assessment, the nephrologist determined a need for HD and a timeline. Patients received a tailored life time access plan with emphasis on quality of life. In case HD was decide upon in a shared decision making environment, the patient was referred to the vascular outpatient clinic. A HD access was usually constructed within 6 weeks after a preoperative evaluation.

One of a team of 4 vascular surgeons performs a standardized work-up including inspection of both arms and hands for signs of earlier trauma, surgery, venous congestion or ischemia. In addition, palpation of epifascial veins as well as radial and ulnar arteries is performed. Each patient undergoes mapping of the venous vasculature of both arms using Duplex-sonography (Nicolet Vasoguard, VIASYS Healthcare, USA) allowing for selecting type and position of the most suitable HD access.

Study criteria

Patients were eligible for inclusion if they were >18 years and suffering from stage IV or V CKD, had received a primary HD access and had undergone P_{dig} measurements <6 months before access construction. Patients were excluded when digital plethysmography measurements were incomplete (e.g. missing compression tests), or when test results were considered erroneous due to incompressible arteries.

Since plethysmography is a non-invasive stress-free modality and is considered standard care in our clinic, the rules regarding the Medical Involving Human Subjects Act (Dutch WMO) did not apply to our study protocol as decided by the local medical ethical committee of the Máxima MC.

Finger plethysmography

A specialized vascular imaging technician performed the digital plethysmography (Nicolet Vasoguard 8 MHz, Scimet, Bristol, UK). Systolic finger pressures (P_{dig}, mmHg) of the index and/or middle finger of both hands were obtained. A plethysmography sensor is applied to the palmar portion of the distal phalanx, while the inflatable cuff is placed around the proximal phalanx. The cuff is then inflated up to a maximum pressure of 200 mmHg. Once a systolic arterial signal disappears, the cuff is gradually deflated until the pulsatile signal reappears, reflecting the systolic P_{dig}.

A variation of the MAT was used. A P_{dig} was first measured during a resting state, some 30 seconds following sensor application. A second measurement was performed after approximately 15 seconds of radial artery clamping (by applying pressure with the technician's index and middle fingers on the artery), and again some 15 seconds after declamping. This maneuver was repeated 30 seconds later with ulnar clamping and declamping. Measurements were obtained from both arms. The difference between a resting P_{dig} and a clamped P_{dig} was termed ∂P_{dig}. The largest drop in systolic pressure, irrespective of artery (ulnar or radial) or side (left or right), was used for analysis.

Data collection and definitions

Data regarding general demographics, comorbidities, smoking status, use of statin and/or anticoagulants, type and timing of primary access construction, HD initiation (yes/no), P_{dig} and cause of death were obtained from electronic patient files (HiX 6.1, ChipSoft B.V., Amsterdam, The Netherlands; FinProDB 7.9, MedVision AG, Unna, Germany).

Comorbidities were defined as follows: *diabetes mellitus* (having diagnosis type 1 or 2 diabetes mellitus, currently using antihyperglycemic medication), *hypertension* (diagnosed with hypertension, use of antihypertensive medication), or *cardiovascular disease* (previous diagnosis of acute coronary syndrome, angina pectoris, coronary artery bypass grafting, diagnostic imaging with presence of (prior) infarction or reversible ischemia, previous ischemic stroke, occlusive disease, transient ischemic attack, history of claudication, ischemic rest pain, ischemic tissue loss, prior peripheral artery intervention or bypass, or demonstrated absolute toe pressure of <40 mmHg).

Type of death was categorized as cardiovascular according to the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) classification system for causes of death (codes 11, 14-16, 18, 22-26, 29) (14). Patients were classified as radial dominant if the difference of ∂P_{dig} obtained from radial artery clamping was >10 mmHg compared to the ∂P_{dig} of the ulnar artery (and vice versa) (15). A patient was termed 'co-dominant' when ∂P_{dig} of radial artery and ulnar artery differed less than 10 mmHg. Date of HD access construction was considered as the study starting date. The follow up index (FUI) was calculated as recommended (16). FU was terminated four years after access surgery, following

death or at December 31, 2018. Patients moved to another dialysis clinic were considered loss to FU and “date last known alive” was used for this group.

Statistical analysis

The sample size was determined pragmatically by including all available patient records that were considered eligible for inclusion. For multivariable modeling as described below, the rule of at least 10 observations-per-variable (for linear regression) and 10 events-per-variable (for Cox proportional-hazards regression) was used to determine how many confounding variables were allowed in the model.

Statistical analyses were conducted using SPSS 25 (IBM SPSS Inc., Chicago, IL, USA). Baseline characteristics were displayed as mean ± standard deviation (SD) or counts (percentages) when appropriate. Study parameters were tested for normality and expressed as mean ± standard error of the mean (SEM). Pearson’s chi-square test, Fischer’s exact test or independent samples t-test were used when appropriate. Possible factors influencing ∂P_{dig} were analyzed using automatic linear modelling (ALM) (17).

Univariable Cox proportional- hazards regression was used to test whether ∂P_{dig} (as a continuous variable and in increments of 10 mmHg) was related to CV+ and overall mortality. Dependent on the outcome event-rate, a multivariable Cox regression was planned to correct for potential confounders that were selected based on previous research (18). Measures of association were displayed as hazard ratio with a 95%-confidence interval [HR 95%-CI]. Kaplan-Meier analysis was performed to display survival curves with 4 similar sized groups based on quartiles of the absolute ∂P_{dig} values. *P*-values 0.05 were considered statistically significant.

Results

A total of 300 patients received a primary HD access between January 2009 and December 2018, and complete data sets including MAT and ∂P_{dig} were available in 123 patients. As 15 cases were excluded due to incompressible arteries, 108 patients fulfilled study criteria and were analyzed (male, n= 71, age 70 years ±12, Table I). HD was successfully initiated in 69 patients (64%) within the observation period.

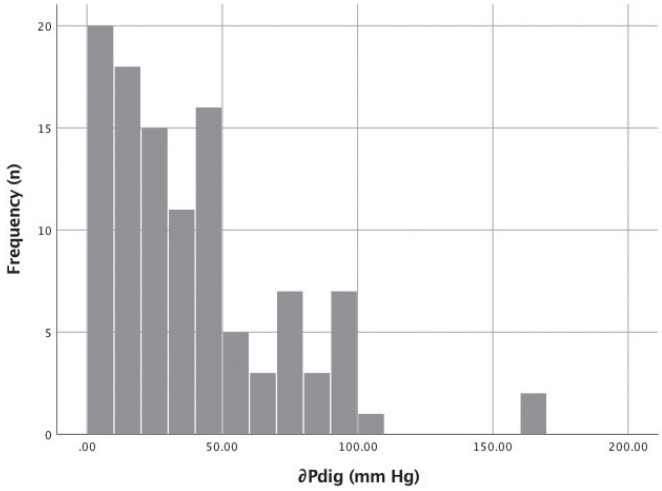
Table I. Patients data prior to HD access construction (n=108 patients).

Characteristic	
Age (years, ±SD)	70 ±12
Gender male/ female	71 / 37
Diabetes Mellitus (%)	46 (43)
Cardiovascular disease (%)	59 (55)
Hypertension (%)	91 (84)
Etiology of renal disease (%) - Glomerulonephritis/sclerosis - Pyelonephritis - Hypertension - Renal vascular disease - Diabetes - Polycystic - Miscellaneous - Unknown	 17 (16) 3 (3) 12 (11) 11 (10) 29 (27) 2 (2) 30 (28) 4 (4)
Statin use (%)	72 (67)
Anticoagulant use (%)	63 (58)
Smoking (%) - Former - Active	56 (52) 30 (28) 26 (24)
Hand perfusion pattern (%) - Radial dominant - Ulnar dominant - Co-dominant	 51 (47) 17 (16) 40 (37)
Type of constructed vascular access (%) - Wrist-based AVF - Elbow-based AVF - AVG - Other	 59 (55) 43 (40) 2 (2) 4 (4)
HD indeed initiated (%)	69 (64)
Months on HD (mean ±SEM)	15 ±2

AVF, arteriovenous fistula; AVG, arteriovenous graft.

Figure 1 shows a histogram of ∂P_{dig} values. Median ∂P_{dig} was 31 mmHg (range 0 – 167 mmHg). Almost half of the patients (47%, n=51) displayed radial artery dominance (Table I), 17 patients (16%) showed ulnar artery dominance whereas 40 (37%) were co-dominant.

Figure 1. ∂P_{dig} during MAT before HD access construction (n=108 patients).



Patient characteristics and ∂P_{dig} before access construction (n=108)

The presence of cardiovascular disease was associated with higher average ∂P_{dig} values (CV+ 44 ±5 mmHg vs CV- 29 ±3 mmHg, B 15.88 [3.61-28.16], p=.012) in univariate linear regression analysis (Table II). Using ∂P_{dig} as outcome variable, factors that fitted into the ALM-model were sex, diabetes mellitus, history of CVD, hypertension, anticoagulant use, statin use, history of smoking and age. In the ALM-model, only CVD was associated with ∂P_{dig} (p=.047).

Table II. ∂P_{dig} before access surgery and relation to patient parameters.

		Univariate analysis, ∂P_{dig}		
Variable	**B**	**95% CI**	β	***P value***
Age	0.48	-0.02-0.97	.18	.061
Female sex	-1.68	-14.95-11.59	-.02	.802
Hypertension	4.11	-13.17-21.39	.05	.638
Diabetes Mellitus	0.00	-12.74-12.74	.00	1.00
Cardiovascular disease	15.88	3.61-28.16	.24	.012*
Smoking	3.39	-10.76-17.54	.05	.635
Statin use	4.83	-8.68-18.34	.07	.480
Anticoagulant use	5.73	-7.29-18.75	.09	.385

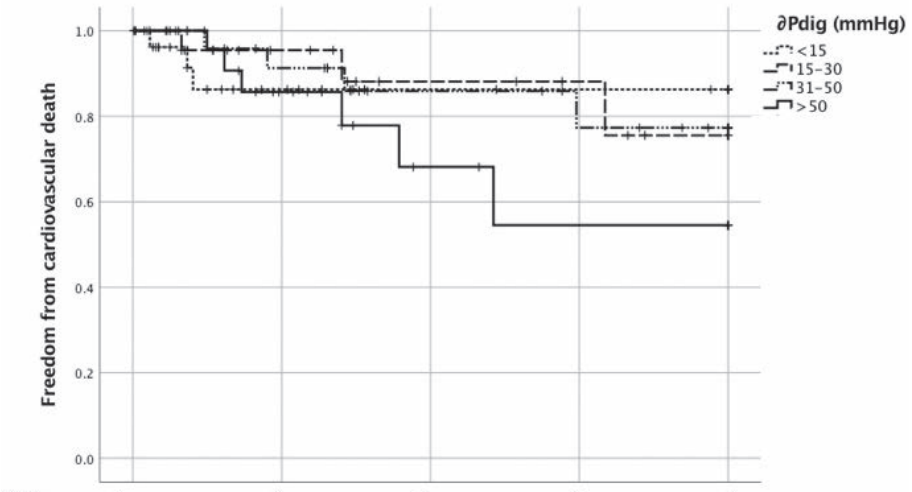
B, Unstandardized Beta; CI, Confidence interval; β, Standardized Coefficients Beta.

Preoperative ∂P_{dig} and mortality following HD access surgery

Mean follow-up after HD access construction was 1.6 years ±0.1 with a 99% ±1 FU index. In the four year observation period, 26 deaths were recorded. Mortality was caused by cardiovascular disease (n=16; 62%), infection (n=6; 23%), or HD discontinuation, cancer, severe trauma or pulmonary insufficiency (each n=1). Overall mortality as well as CV+ mortality rates in patients initiating HD or those remaining in predialysis were not different (Overall mortality: HD+ 24.6% vs. HD- 23.1%, p=.855; CV+ mortality: HD+ 14.5% vs. HD- 15.4%, p=.900).

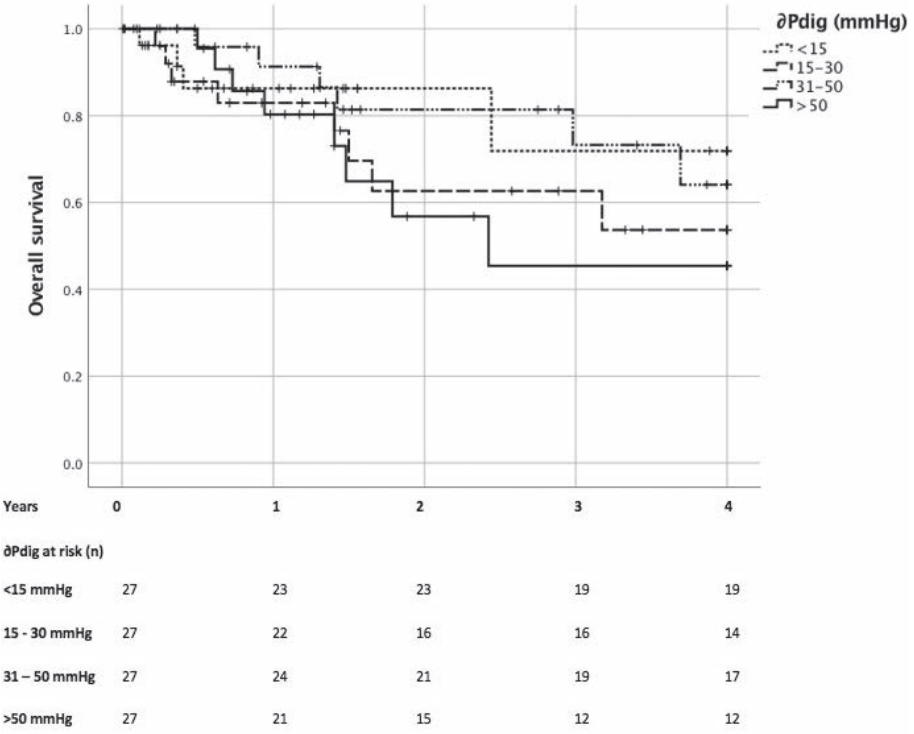
Freedom from cardiovascular death as well as overall patient survival were lowest in individuals with a ∂P_{dig} >50 mmHg (Figure 2 & 3).

Figure 2. Freedom from cardiovascular death following access surgery and ∂P_{dig} (n=108 patients).



∂Pdig at risk (n)					
<15 mmHg	27	23	23	23	23
15 - 30 mmHg	27	25	23	23	20
31 – 50 mmHg	27	24	23	20	20
>50 mmHg	27	23	18	14	14

Figure 3. Overall survival following access surgery in relation to preoperative ∂P_{dig} (n=108 patients).



Absolute values of ∂P_{dig} were also associated with CV+ mortality (HR 1.02 [1.00 – 1.03], p=0.012) and overall mortality (HR 1.01 [1.00 – 1.02], p=.046). For each 10 mmHg ∂P_{dig} increase, the overall mortality risk increased with 10% and for cardiovascular mortality with 15% (Overall mortality: HR 1.10 [1.01 – 1.22], p=.048; CV+ mortality: 1.15 [1.03 – 1.29], p=.017).

Following correction for old age (>80 years), an increase of ∂P_{dig} in increments of 10 mmHg remained associated with CV+ mortality (HR 1.13 [1.00 – 1.26], p=.043) but not with overall mortality (HR 1.08 [0.98 – 1.18], p=.125).

Discussion

The Modified Allen test (MAT) is advocated as a simple bedside tool for determining pattern of hand vascularization (19,20). A positive test result indicates that hand perfusion in a subject largely depends on just a single forearm vessel, either the radial or the ulnar artery (2,21). Apart from having diagnostic properties, a MAT was also useful in predicting onset of long term hemodialysis (HD) access-related complications such as hand ischemia (1,21,22). Several studies found that hand ischemia as reflected by a low systolic finger pressure (P_{dig}) was associated with increased mortality rates in HD populations (6–10). Based on these findings, we hypothesized an association between drop in P_{dig} (∂P_{dig}) during a MAT and mortality in CKD patients who were scheduled for access surgery. Interestingly, 52% of the individuals demonstrating a ∂P_{dig} >50 mmHg at the preoperative MAT had died after 4 years compared to just 15% with a ∂P_{dig} <15 mmHg. In addition, the risk of death due to cardiovascular cause increases with 15% for each 10 mmHg increase of ∂P_{dig}. This potential novel parameter may contribute to the preoperative counselling of CKD patients requiring renal replacement therapy but its validity requires confirmation in a larger population.

One needs to consider the arterial anatomy of the hand in order to appreciate the scope of a MAT. Vascular patterns of the hand are highly diverse but the superficial and deep palmar arches are the most important arterial structures. An incomplete superficial palmar arch (SPA) is a frequent variant as found in 21.5% of 650 autopsy samples (23). Malformations or absence of (portions of) the ulnar artery may also occasionally be found (24). Inflow of the palmar arch is most often dominated by the radial artery and sometimes by the ulnar artery (15,25). In one study, radial dominance was shown in 55% of the cases, whereas an ulnar dominance was present in 33% of their study population. The palmar arch in the current study was also more often dominated by the radial artery compared to the ulnar artery (47% vs 16%). During MAT, a fall in perfusion pressure of the digits as detected by plethysmography may in part be related to this interindividual variety in arterial vasculature (26). However, whether a lower perfusion pressure also subjectively leads to symptoms of ischemia is by large determined by the host's ability to recruit collaterals. For instance, a radiocephalic HD access may cause hand ischemia if the loss of perfusion pressure in the portion distal to the anastomosis is not compensated for by an increased flow in the ulnar (or the interosseous) artery. This situation may occur if these collateral vessels exhibit severe atherosclerosis due to peripheral arterial disease (PAD) or to diabetes mellitus.

In PAD, remodeling of small arteries in the affected limb may be inadequate or insufficient increasing the chance of arterial occlusions (27,28). A positive MAT may reflect this inability to adequately open collaterals aimed at maintaining tissue perfusion above the ischemic threshold. At a locoregional level, a debilitating finger or toe ischemia may occur but the host's overall integrity is not at risk. However, a failing capacity for mobilizing collaterals in the coronary arterial system may prove lethal as demonstrated by increased mortality rates (29,30). A properly functioning coronary collateral system will form alternative conduits for bridging severe stenoses or connecting vital epicardial arteries thus reducing fatal myocardial infarction rates (31). Data of the present study indicate that patients with a history of cardiovascular disease demonstrated a significantly greater ∂P_{dig} during MAT. Such a test result may suggest that the overall compensatory mechanism of the arterial system in such a patient is compromised due to a poor cardiovascular health. Interestingly, these events happened independent of presence of diabetes mellitus.

The clinical relevance of the present study is currently unclear. However, one may speculate that a large ∂P_{dig} during a simple plethysmographic MAT in a severe CKD patient with a negative cardiovascular history may contribute to a decision to yet undergo an objective evaluation of cardiovascular health status. Secondly, results of a plethysmographic MAT may play a role in the preoperative counselling process of a CKD patient destined to soon require renal replacement therapy. For instance, a positive test result in a frail patient with extensive comorbidities may tip the balance towards inserting a permanent indwelling line rather than executing arteriovenous access surgery (5, 13).

The current study has various limitations including its retrospective character, a limited sample size and the inability to correct for potential confounders possibly leading to data heterogeneity. Due to limited statistical capacity, CVD could not be included as a possible confounder for mortality. Since values of ∂P_{dig} are directly related to CVD, the MAT should be seen as a surrogate marker for the overall cardiovascular burden possibly leading to increased mortality rates. The study design may have introduced "immortal time bias" since the follow up started after inclusion. Mortality in this particular interval was therefore neglected. However, it is unlikely that this type of bias may have impacted outcome as this period of "immortal time" was relatively short (27 days ±2). In addition, visualization of the arterial anatomy using either angiography or Duplex was not performed so

information on anatomic variants and flow volumes is absent. A potential limitation also is the absence of published normal values of P_{dig}. One study claimed that a fall of ∂P_{dig} >40 mmHg in the thumb indicated an inadequate collateral ulnar arterial blood supply (20). Another study choose thresholds empirically (26). Since cut-off points for ∂P_{dig} are also lacking, it was arbitrarily decided to categorize ∂P_{dig} in quartiles.

Conclusion

A large drop in systolic finger pressure during a preoperative modified Allen test (MAT) was related to an increased mortality rate in the years after HD access surgery. The role of this potential novel risk parameter requires confirmation in a larger population.

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Chapter 6

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

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Published in *Journal of Vascular Access*
Volume 22, Issue 2, P194–202, June 26, 2020
Impact Factor: 2.3

Abstract

Objective

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-center 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 analyzed.

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).

Conclusion

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.

Keywords: Hand ischemia; survival; digital pressure; arteriovenous fistula; vascular access

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). Proportions developing HAIDI may rise in future populations as patients increasingly suffer from factors promoting blood pressure loss along the arterial tree including 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 a frustrated patient suffering from 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 were 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). Case series in HD-populations suggested that patients with hand ischemia had a poor survival (8-10). Aim of the present study was to determine whether survival was worse in HD-patients with severe HAIDI compared with patients with mild or no hand ischemia.

Material and 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} <50mmHg) (11-13). 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.

Statistical analysis

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 analyzed 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 FU was terminated in case of death, after 4 years of FU, at the end of December 2018, or when a patient was lost to FU ("date last known alive"). FU and FU index were calculated following recommendations (22) and p values 0.05 were considered significant.

Results

Between January 2006 and December 2018, 118 HD patients were analyzed for possible HAIDI by the senior author (MS): 67 patients did not meet the 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 and 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 the 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 with HAIDI IIb–IV patients (68%, p=.011). In contrast, access age and time on HD were higher in controls compared with HAIDI IIb– IV patients (both p<.01). Time on any RRT was similar among groups (Table 1).

Finger pressures and HIQ-scores

P_{DIG} with open access was higher in HAIDI I–IIa (57 ±5 mmHg) compared with HAIDI IIb–IV (35 ±6 mmHg; p =.009), while P_{DIG} in controls was highest (110 ±3 mmHg; p <.001). P_{DIG} with clamped access also differed (HAIDI I–IIa 115 ±8 mmHg; HAIDI IIb–IV 97 ±10 mmHg; controls 138 ±4 mmHg; <.001; Figure 1a). DBI showed similar differences (Figure 1b). Interestingly, ∂P_{DIG} was twice as high in both HAIDI groups (HAIDI I–IIa 59 ±7 mmHg; HAIDI IIb–IV 62 ±8 mmHg) compared with control patients (30 ±3 mmHg; p<.001) as was ∂DBI (Figure 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	0.585
Age (year, ± SD)	61 ±19	69 ±15	71 ±13	0.023
Diabetes mellitus (%)	35	43	38	0.827
Arterial occlusive disease (%)	30	68	38	0.011
Hypertension (%)	78	93	85	0.328
Wrist-based AVF / elbow-based AVF / PTFE-loop	1 / 20 / 2	1 / 26 / 1	18 / 21 / 9	<0.001
Access age (months, ± SD)	21 ±32	11 ±16	36 ±29	0.001
Time on hemodialysis (months, ± SD)	24 ±31	15 ±20	34 ±26	0.008
Time on RRT (months, ± SD)	40 ±60	35 ±79	42 ±36	0.877
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.

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 1. (a) Mean values with standard errors of absolute digital pressure (P_{DIG}) and (b) digital brachial index (DBI) 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.

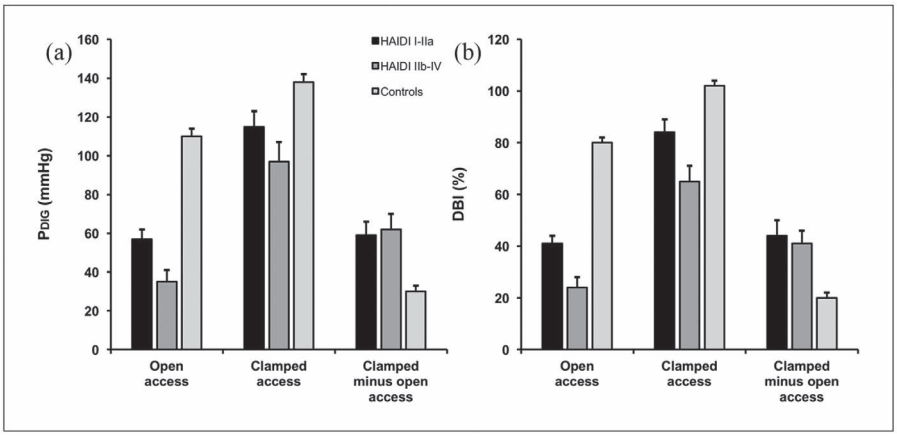
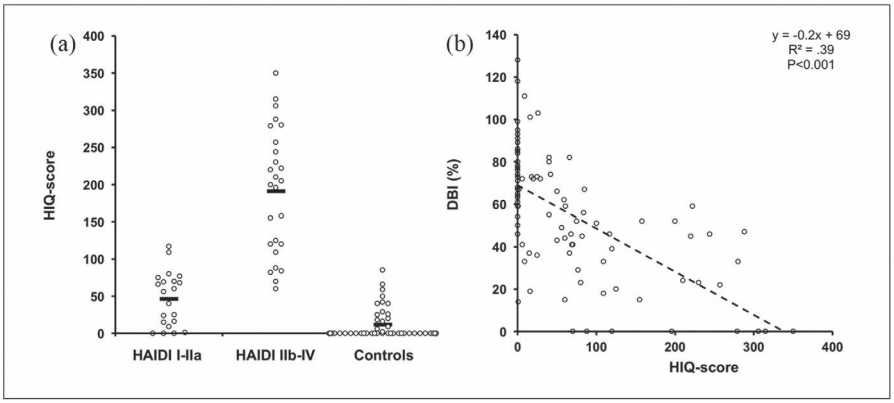


Figure 2. (a) Hand ischemic questionnaire (HIQ) scores differ significantly between patients with mild (I–IIa), severe (IIb–IV), and absent hemodialysis access-induced distal ischemia (HAIDI). Horizontal bars indicate group mean values. (b) Digital brachial index (DBI) and HIQ-score were inversely correlated.

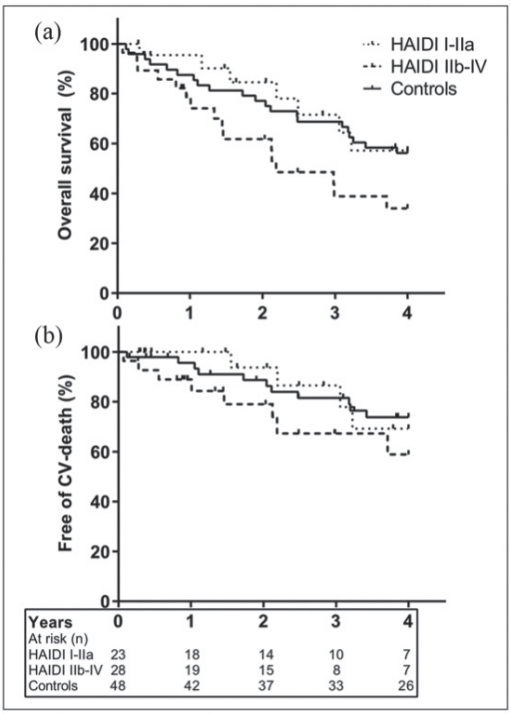


Survival

Mean FU was 27 ±2 months in HAIDI patients and 37 ±2 months in controls (*p* =.004) with an FU index of 97% ±2 and 100%, respectively (*p* =.193). Over the course of 4 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).

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).



Cardiovascular death-free survival did not differ among groups, neither in initial nor in post hoc analysis (p=.320; Figure 3b).

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

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*-value**	**HR [95%-CI]**	***P*-value**
Age (years)		1.04 [1.01 - 1.07]	**0.006**	1.02 [0.99 - 1.05]	0.230
Gender (female = 1)		0.81 [0.44 - 1.47]	0.481	0.51 [0.21 - 1.25]	0.140
Diabetes Mellitus (present = 1)		2.22 [1.22 - 4.04]	**0.009**	2.67 [1.16 - 6.13]	**0.021**
Arterial occlusive disease (present = 1)		2.98 [1.62 - 5.51]	**<0.001**	3.60 [1.51 - 8.55]	**0.004**
Hypertension (present = 1)		1.72 [0.61 - 4.81]	0.302	3.84 [0.52 - 28.54]	0.188
Access	Wrist-based AVF (ref)				
	Elbow-based AVF	0.96 [0.48 - 1.91]	0.902	1.20 [0.44 - 3.24]	0.727
	PTFE-loop	0.41 [0.11 - 1.46]	0.167	0.29 [0.34 - 2.52]	0.264
P_{DIG} (mmHg)	Open	0.991 [0.984 - 0.998]	**0.017**	0.993 [0.983 - 1.004]	0.194
	Clamped	0.992 [0.985 - 0.999]	**0.018**	1.000 [0.988 - 1.012]	0.993
∂P_{dig} (mmHg)		1.004 [0.995 - 1.013]	0.409	1.014 [1.003 - 1.025]	**0.016**
DBI (%)	Open	0.988 [0.978 - 0.999]	**0.029**	0.989 [0.974 - 1.003]	0.124
	Clamped	0.989 [0.980 - 1.000]	**0.041**	0.998 [0.981 - 1.015]	0.820
∂DBI (%)		1.007 [0.993 - 1.021]	0.315	1.021 [1.004 - 1.039]	**0.017**
HAIDI-grade	Control (ref)				
	I-IIa	0.89 [0.38 - 2.10]	0.789	0.98 [0.31 - 3.09]	0.976
	IIb-IV	1.93 [1.00 - 3.72]	**0.050**	1.91 [0.76 - 4.79]	0.166
Hand Ischemic Questionnaire (score)		1.003 [1.000 - 1.006]	**0.043**	1.003 [0.998 - 1.007]	0.226
Time on hemodialysis (months)		1.00 [0.99 - 1.01]	0.595	1.00 [0.99 - 1.02]	0.751
Access age (months)		1.00 [0.99 - 1.01]	0.949	1.00 [0.98 - 1.02]	0.980
Time on RRT (months)		1.00 [0.99 - 1.00]	0.466	0.99 [0.98 - 1.01]	0.261

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 (8-10) 3- and 4-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 center 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) may therefore prove useful in predicting and monitoring hand ischemia (30). 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 (17-19). 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.

Acknowledgements

We would like to acknowledge Ms. K. Wijns, vascular nurse practioner, for logistical and technical support.

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PART II

The prognostic role of access flows (Q_a)

Content

Chapter 7

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

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Published in *Nephrology Dialysis Transplantation*
Online ahead of print, August 12, 2021
Impact Factor: 6.0

Abstract

Objective

Aim of the study was to determine associations between characteristics of arteriovenous access (AVA) flow volume (Q_a, 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 analyzed. Initial Q_a was defined as the first Q_a value obtained in a well-functioning AVA by a two-needle dilution technique. Actual Q_a was defined as access flow at a random point of time. Changes in actual Q_a were expressed per 3-month periods. CVM was assessed according to the ERA-EDTA classification. The optimal cut-off point for initial Q_a was identified by a receiver operating characteristic curve. A joint modelling statistical technique determined longitudinal associations between Q_a characteristics and 4yr-CVM.

Results

A total of 5208 Q_a measurements (165 patients, male n=103; age 70±12 years, autologous AVA n=146, graft n=19) were analyzed. During follow-up (Dec 2010-Jan 2018, median 36 months), 79 patients (48%) died. An initial Q_a <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 Q_a <900 mL/min (53 ±7% vs. Q_a ≥900 mL/min: 87 ±4%, P <0.001). An association between increases in actual Q_a over 3-month periods and mortality was found (HR: 4.48 per 100mL/min, 95% CI [1.44-13.97], P =0.010) indicating that patients demonstrating increasing Q_a were more likely to die. By contrast, actual Q_a per se was not related to survival.

Conclusion

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

Keywords

Access flow; survival; end-stage renal disease; hemodialysis

Introduction

A minimum of 400-600 mL/min flow volume (Q_a) 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 Q_a ('actual' Q_a) may detect values >1500 mL/min occasionally leading to a high flow AVA (2). Persistent exposure to high Q_a may possibly overload the cardiovascular system and challenge cardiac function (3,4). Conversely, Q_a 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 Q_a 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 Q_a >1000 mL/min had a lower death rate compared to patients with a Q_a <1000 mL/min (8). Moreover, a possible relation between a first Q_a ever measured in a matured AVA ('initial' Q_a) and CVM is unknown. Therefore, associations between Q_a 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 Q_a surveillance (1). Most authors investigating possible associations with CVM used just one (or a limited number of) actual Q_a reading(s) (8,10). However, efforts towards identifying potential relationships between serial actual Q_a or additional Q_a 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 Q_a, actual Q_a 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 Q_a value was obtained.

Q_a definitions and measurements

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

All Q_a 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 Q_a >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, Q_a was set at 0 mL/min during this period. Q_a values were corrected for body surface area (BSA) that was calculated from length and weight (12).

Data collection

All Q_a 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 Q_a >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 Q_a 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 Q_a.

Associations between longitudinal measurements of Q_a and 4y-CVM were analyzed based on a joint modelling approach (15). This statistical approach considers possible associations of values of actual Q_a (and its changes) with CVM at any time during follow-up. Longitudinal changes in Q_a are first modeled 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 Q_a 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 Q_a (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 Q_a 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%).

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

Characteristic	Initial Q_a <900 mL/min N=67	Initial Q_a ≥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 (%) Glomerulonephritis/sclerosis Pyelonephritis Hypertension Renal vascular disease Diabetes Polycystic Miscellaneous Unknown	 15 (22) 1 (2) 6 (9) 5 (8) 22 (33) 0 (0) 16 (24) 2 (3)	 18 (18) 1 (1) 10 (10) 6 (6) 20 (20) 0 (0) 35 (36) 8 (8)	n/a
Smoking (%) Former Active	32 (48) 23 (34) 9 (13)	55 (56) 31 (32) 24 (24)	.282
Type of constructed vascular access (%) Wrist-based AVA Elbow-based AVA AVG Leg AVA	 25 (37) 35 (52) 6 (9) 1 (1)	 25 (26) 62 (63) 10 (10) 1 (1)	.198
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 Q_a (weeks)	31 ±4	32 ±4	.841
Initial Q_a (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.

Initial Q_a and cardiovascular mortality (CVM)

After four years, freedom from CVM was 34% lower in patients with an initial Q_a <900 mL/min (53 ±7%) vs Q_a ≥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 Q_a <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).

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

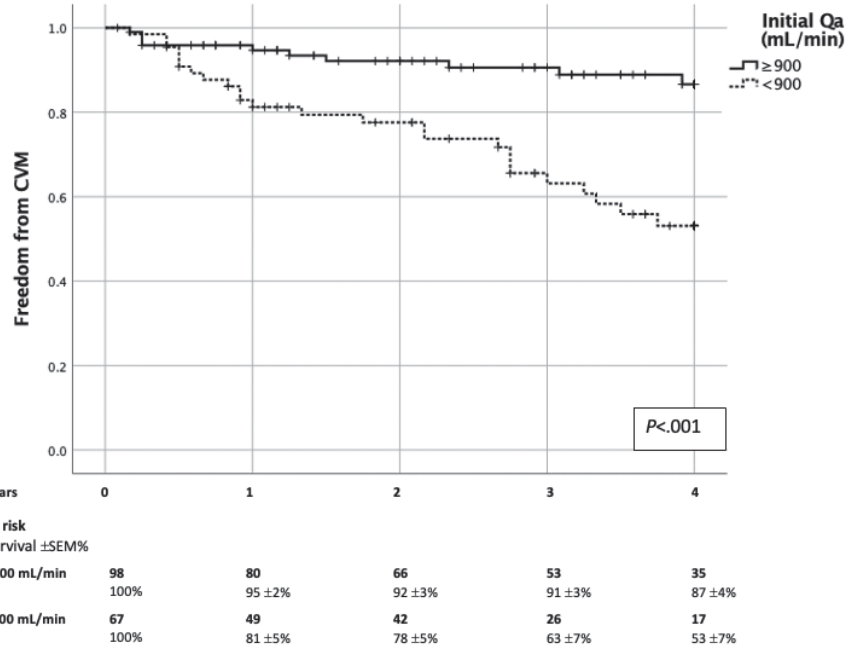


Table 2. Factors determining 4-yr CVM in HD patients undergoing initial Q_a analysis.

		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 Q_a	<900 mL/min	4.05	1.94-8.43	**<.001**	2.77	1.29-5.97	**.009**
	≥900 mL/min			Reference			Reference

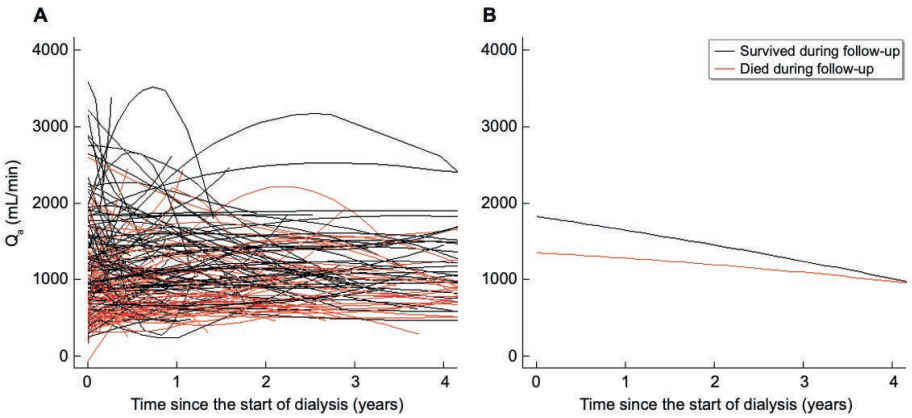
Cox proportional hazards model, CI, confidence interval; HR, hazard ratio; BSA, Body-surface area; Boldface *P*-value represents statistical significance.

Actual Q_a and cardiovascular mortality (CVM)

A total of 5208 Q_a measurements were available for longitudinal modelling (n=165 patients, median 23 values per patient). Substantial heterogeneity in Q_a trajectories was found (Figure 2A). Actual Q_a decreased slightly but significantly over the years after the initial Q_a (-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 Q_a increase over a 3-month period and increased risk of CVM was observed (HR: 4.48 per 100mL/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 100mL/min increase per 6 months, 95% CI: 1.20 to 3.73, *P* = 0.010). In contrast, single values of actual Q_a 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).

Figure 2. Q_a over time of individual patients (A) 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 Q_a 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 Q_a increase over a 12 ±4 months period since their initial Q_a. Following FRS, actual Q_a 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 Q_a increase over 3-months periods and 4yr-CVM (HR: 3.89 per 100mL/min increase per 3 months, 95% CI, 1.20 to 12.58, *P* =0.023).

Discussion

Incidence of HD patients with a high Q_a AVA is rising due to a contemporary trend favoring brachial artery based AVA over radial artery based AVA (17). A high Q_a 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 Q_a and survival are conflicting (8,9). We studied the role of actual Q_a but also focused on other characteristics of Q_a including initial Q_a, and periodical changes in actual Q_a. The results indicate that single values of actual Q_a were not associated with cardiovascular mortality (CVM). However, an increasing actual Q_a over 3-month periods conferred a higher CVM risk. In addition, HD patients having a <900 mL/min initial Q_a 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 $Q_a \geq$900 mL/min. It is concluded that studying these novel Q_a 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 Q_a of 1000-1500 mL/min, or when the Q_a 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*. (3) found that HOCF could occur with an AVA having an actual Q_a >2000 mL/min. Wu *et al*. (8) reported that survival was better in populations with an actual Q_a >1000 mL/min AVA. Similarly, Al-Ghonaim *et al*. (10) found that patients having an AVA with an actual Q_a ≥1000 mL/min did not have a higher mortality risk. However, these studies did not utilize ROC techniques for objectively determining the optimal cut-off value for initial Q_a. Guidelines and studies on HFA were hitherto based on the analysis of single actual Q_a values at random time points using standard statistical methods. The current study focuses on alternative qualities of Q_a using a sophisticated joint modelling technique.

The role of an initial value of Q_a with reference to long term survival is largely unclear. Immediately following AVA creation, a cascade of events will lead to a Q_a 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 remodeling characteristics are crucial factors determining successful AVA maturation. These findings suggest that a relatively high initial Q_a might be considered as a surrogate marker of better cardiovascular health (10,20,24–30). The present study found a direct relationship between initial Q_a and freedom from CVM. Moreover, a 34% difference in CVM after 4 years of HD sessions was found if a 900 mL/min initial Q_a threshold value was considered. The current analysis studied initial Q_a 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 Q_a over 3-month periods and a higher risk of CVM. A sound pathophysiological explanation is currently absent. Previous literature reported that a high Q_a may promote ventricular dilation and that exceptionally high Q_a levels may lead to HOCF over time (4, 18,31–34). Malik *et al.* (35) 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 unphysiologically hemodynamic adaptations (35). Our sensitivity analysis of 155 patients who did not receive flow reducing surgery (FRS) indicated that an

increase in Q_a 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 Q_a 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 cardiophysiological 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 Q_a following percutaneous transluminal angioplasty (PTA). Actual Q_a may temporarily be elevated after PTA but often do not attain previous values later on (40–43). For instance, Bacchini *et al.* (40) reported that AVA's with a baseline Q_a 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, Q_a 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 Q_a 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 Q_a 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 Q_a increase in the 12 months prior to the decision to undergo FRS. Surprisingly, all patients who underwent FRS demonstrated substantial lower actual Q_a 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 Q_a trajectories display considerable fluctuations over longer (than 3 month) periods, it was decided to adhere to Q_a change over a period of 3 months as one of our primary outcomes. Furthermore, a potential extra quantity of Q_a that is shunted via possible venous side branches was not incorporated in the standard Q_a-measurement. Only values of Q_a obtained by a dilutional method were included in the analysis. Q_a values that were measured by Duplex scanning before and after PTA were not studied. As the analysis was based on a Q_a-trajectory over time, rather than on a single Q_a-measurement, the effect of outliers and in between dialysis session Q_a variability is mitigated. Last, serial cardiac echography may have provided information on long term impact of Q_a but were not performed.

Conclusion

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

Acknowledgements

We thank Toon van Leeuwen and the dialysis unit team for their efforts in data extraction.

Supplemental Material

Table of Contents

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

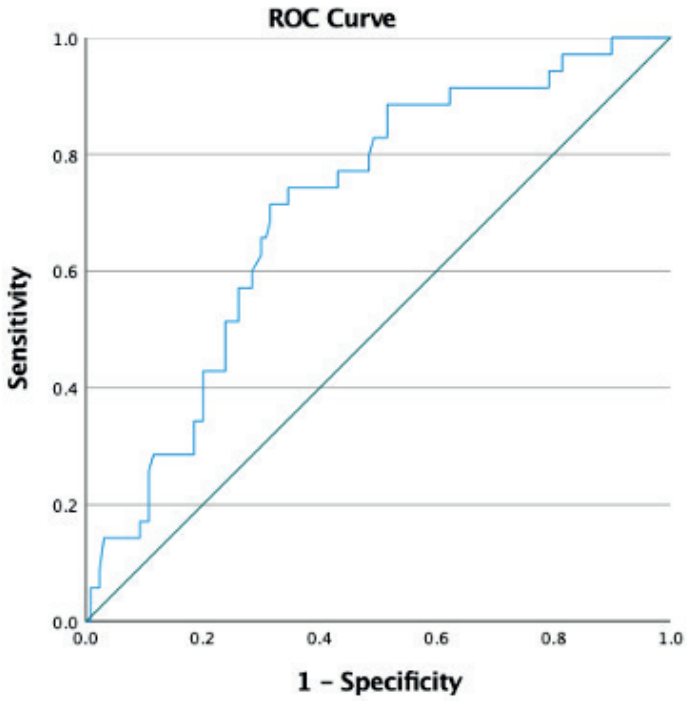
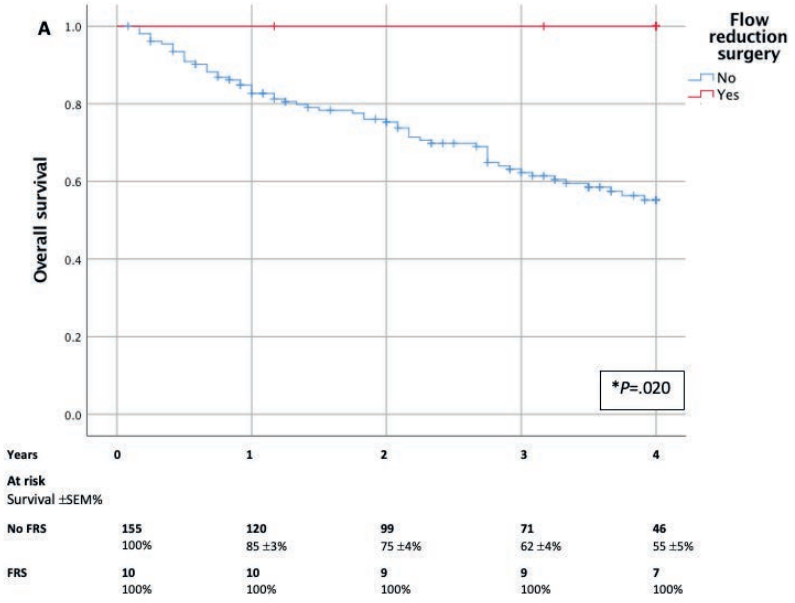
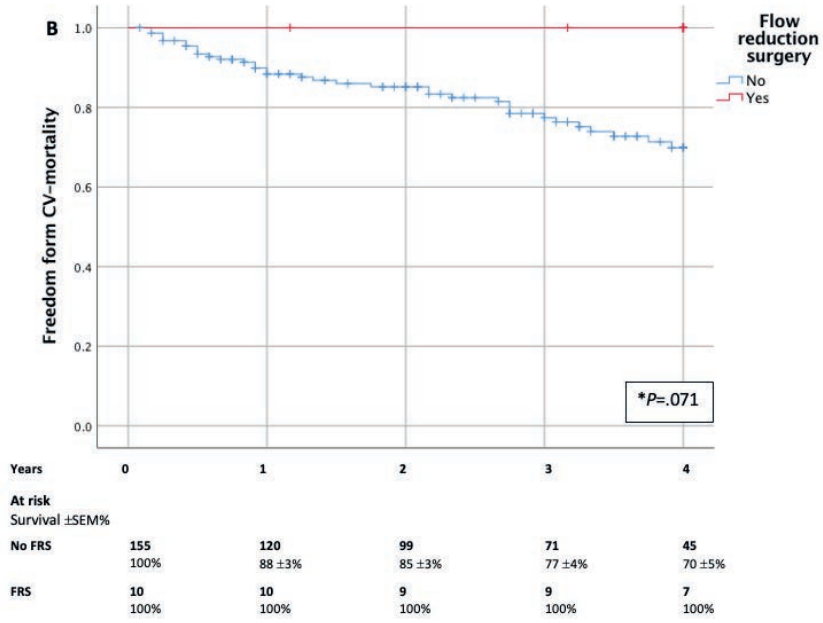


Figure S2. Four-year overall survival (A) and freedom from cardiovascular mortality (B) in patients undergoing FRS or not.





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Chapter 8

Lower cardiovascular mortality rates in hemodialysis patients with radial artery based fistulas

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Research Letter

Published in *European Journal of Vascular & Endovascular Surgery*
Volume 62, Issue 6, P1004-1005, December 01, 2021
Impact Factor 7.1

To the Editor:

Survival of patients undergoing chronic hemodialysis (HD) is limited, in part due to excessive cardiovascular mortality (CVM). Once HD is unavoidable, a radial artery based arteriovenous fistula (RA-AVF) is preferred in most cases. Because of aging populations, increasing rates of diabetes mellitus and cardiovascular disease (CVD), RA-AVF construction may not always be viable as the access of first choice. Therefore, alternatives such as a more proximal AVF or arteriovenous graft (AVG) need to be considered as recommended by ESVS guidelines (1). One study in a heterogenous group of HD patients with different types of AVF suggested inferior survival in brachial artery based AVF (BA-AVF) patients (2). Although such a BA-AVF is optional in patients presenting with an unsuitable distal vasculature, it is largely unknown what impact type of AVF has on CVM. The present study sought to determine whether AVF location was independently related to CVM rates in a homogenous HD population.

In this single center retrospective cohort study, patients who received a primary BA-AVF or a primary RA-AVF between January 2010 and December 2017 were included. All patients were on chronic (>3 months) and regular HD. The first access flow (Q_a) that was obtained from a matured AVF using a dilutional technique was termed *initial* Q_a. Stratification of initial Q_a values occurred according to a proposed 1000 mL/min threshold. Differences between groups with a BA-AVF or RA-AVF were analyzed using Cox proportional hazard models with a priori defined potential confounders and depicted as Kaplan-Meier curves. Study protocol approval was provided by our institutional research committee.

A total of 147 patients fulfilled study criteria (male n=97; age 71±12 year, BA-AVF n=97, RA-AVF n=50). During follow-up (median, 42 months), 55 patients died (37%), of which 60% due to cardiovascular causes (n=33). Demographics of the two AVF populations were similar regarding most parameters including age, rate of diabetes, history of cardiovascular disease or hypertension, although the RA-AVF group contained higher percentages of males and fewer smokers. The relation between AVF location and freedom from CVM is demonstrated in Figure 1 (upper panel). Four year freedom from CVM was 21% higher in RA-AVF patients (RA-AVF: 84 ±6% vs. BA-AVF: 63 ±6%, *P*=.016). If the 1000 mL/min threshold for initial Q_a was considered, differences were even more pronounced (Figure 1, lower panel). For instance, CVM after 4 years was 0 in patients with a RA-AVF having an initial $Q_a \geq 1000$ mL/min compared to a 57% in patients with a BA-AVF and an initial

Q_a <1000 mL/min. Multivariate analysis including predefined factors (age, sex, diabetes, cardiovascular disease, hypertension, smoking, initial Q_a <1000 mL/min and body-surface area) demonstrated that BA-AVF patients sustained an almost three times higher risk of dying from a cardiovascular cause when compared to RA-AVF (HR: 2.96, CI [1.16-7.59], *P*=.024).

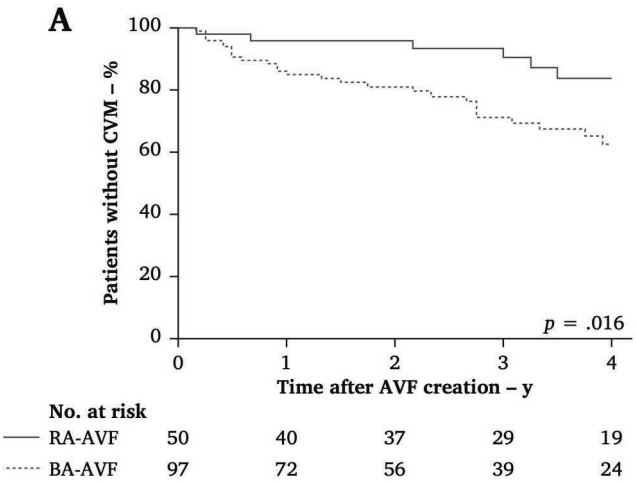
Studies investigating CVM in HD populations with various types of accesses (central venous catheter CVC, AVG, AVF) consistently found superior survival rates in AVF populations. Therefore, efforts should be directed towards having an AVF ready for use once HD is required, ideally without intervention of a temporary indwelling CVC. An AVF is more resistant to infections and sepsis compared to CVCs and AVGs. However, an AVF can become harmful in the long term by exhausting the cardiovascular system (3). Results of the present study indicate that RA-AVF patients demonstrate superior survival rates compared to BA-AVF patients, independent of other risk factors. In addition, survival is better with an initial Q_a ≥1000 mL/min, irrespective of distal or proximal AVF location.

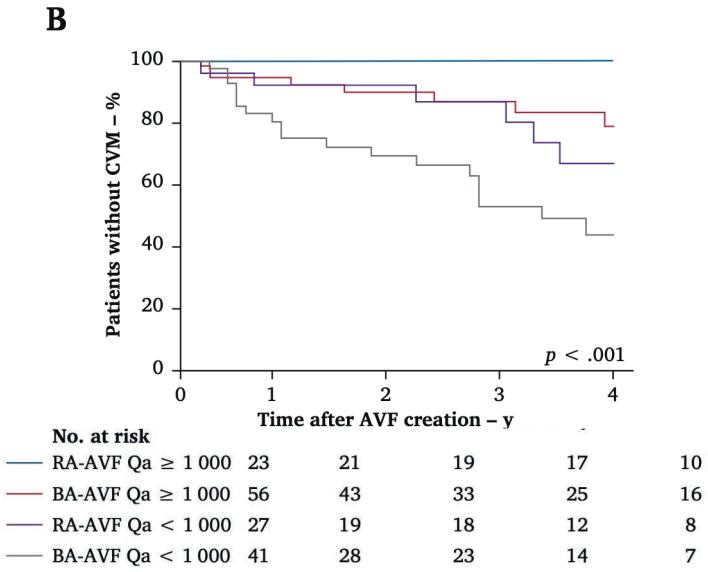
One may speculate on the nature of the beneficial effects of a distal AVF location and a high initial Q_a. A patient who qualifies for creation of a RA-AVF that matures well possibly has a healthier cardiovascular system with optimal remodeling qualities at the time of access construction compared to a patient requiring a BA-AVF. In addition, values of actual Q_a of a RA-AVF are usually lower compared to BA-AVF potentially limiting chronic systemic overload with detrimental sequelae in the long term (4). Furthermore, systemic endothelial function may be less compromised in a RA-AVF due to lower vascular shear stress in the AVF arm compared to BA-AVF (5).

Future guidelines should incorporate suggestions for increasing the likelihood of successful maturation of a distal AVF including advanced prediction models and avoiding catheterization via the non-dominant radial artery in patients with poor renal function. Moreover, one might suggest to exercise the forearms prior to access surgery to increase blood flow and vessel diameters facilitating more optimal RA-AVF construction and maturation (6).

Findings of this study confirm the role of a RA-AVF as a preferential first choice access because of the low cardiovascular mortality rate in addition to preservation of more proximal vessels. Location of AVF and initial Q_a may serve as additional prognostic markers in future prospective studies analyzing long term survival in HD populations.

Figure 1. Four-year freedom from CVM in relation to location of AVF (A) and to initial Q_a (B).





Acknowledgements

None.

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Chapter 9

Surgical reduction of high flow arteriovenous haemodialysis access

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Submitted to *Journal of Vascular Access*

Abstract

Access flow in some arteriovenous accesses may increase >1.5-2.0 L/min leading to a high flow access possibly overloading the cardiovascular system in the long term. Current management of high flow access is characterized by a lack of standardization in definition, criteria for flow reductive surgery and preferred techniques. Aim of this scoping review was to provide an overview of available evidence regarding the broad spectrum of surgical techniques for access Q_a reduction in haemodialysis patients with a high flow access (HFA).

PubMed and Embase were searched according to PRISMA guidelines. Studies reporting on invasive management of high flow access were selected. Inclusion required an English description of surgical technique in human high flow access including pre- and postoperative access flow-values. Definition of high flow access and indication for surgery were diverse.

Sixty-nine studies on 1016 patients (mean age 56 years [3-90 years], male 62%, diabetes mellitus 27%, brachial artery-based arteriovenous access 69%) fulfilled inclusion criteria. Performed techniques were banding (43%), aneurysm repair (17%), revision using distal inflow (11%), plication/ anastomoplasty (9%), proximalization of arterial inflow (5%), graft interposition (5%), proximal radial artery ligation (3%), or miscellaneous other techniques (7%). All techniques reduced access flow on the short term (mean drop 0.5-1.7 L/min). Secondary patency rates varied between 77 and 93% (mean follow-up, 15 [0-189] months). High flow access recurrence rates differed widely among publications (e.g. at 12 months, >50% following banding, 6% following revision using distal inflow) as did definitions of recurrence. Patient specific factors legitimizing invasive treatment are discussed.

It was concluded the current management of high flow access is suboptimal due to a lack of standardization in definition, indication for surgery as well as preferred techniques. Randomized trials comparing a wait-and-see approach versus different flow reducing techniques are warranted.

What this paper adds

Whether long term exposure to high flow is detrimental to a HD patient is controversial, as are definition, indication for surgery and establishment of the optimal technique. A literature review including 1016 HFA-patients identifies a variety of interventions but the overall level of evidence is low. A range of factors are discussed that may help to decide whether flow reduction is indicated for an

individual HFA-patient. Furthermore, this paper might provide a starting ground for future research on this complex problem.

Introduction

Arteriovenous accesses (AVA) may occasionally lead to locoregional and systemic complications such as haemodialysis access induced distal ischemia (HAIDI) or high flow.[1] Management of HAIDI is relatively straight forward.[2,3,4,5] In contrast, the approach of a high flow access (HFA) is a matter of debate.[6,7]

A minimal 300-400 mL/min (fistulas) or 600 mL/min (grafts) access volume flow (Q_a) is required for effective haemodialysis (HD).[8] However, Q_a may increase >1.5-2.0 L/min possibly increasing the risk of high-output cardiac failure.[9] Moreover, a HFA may promote cephalic arch stenosis and subsequent access failure in brachial-cephalic AVA.[10] Recent National Kidney Foundation (NKF) guidelines consider HFA as a separate entity. A Q_a of 1.0-1.5 L/min or 'a flow to cardiac output ratio >20%' are suggested as threshold values defining HFA but criteria mandating invasive treatment are not mentioned.[11]

In daily practice, management of HFA focusses on detecting clinical signs of cardiac overload, serial echocardiography and possibly prophylactic surgical Q_a-reduction. However, this approach is highly subjective and often based on a clinicians' best judgement. The European Society for Vascular Surgery (ESVS) access guidelines also advise regular monitoring of Q_a if >1.5 L/min, an echocardiography and identifying signs of congestive heart failure. Flow-reducing surgery is advised once subjective symptoms progress, when objective signs of heart failure emerge, or if Q_a continues to increase.[12]

Despite these guidelines, an evidence based HFA-monitoring scheme is lacking whereas the optimal operative method guaranteeing lower Q_a with uninterrupted HD has yet to be identified. Moreover, consensus on seemingly asymptomatic HFA is lacking. As a first step, aim of this scoping review is to provide an overview of available evidence regarding the variety of surgical techniques for Q_a-reduction.

Material & Methods

As the aim was to generate an overview of surgical techniques used in Q_a-reduction in HFA-patients rather than critically appraise data and synthesize an answer to a clinical question, a scoping review was deemed most feasible.[13] Both PubMed and EMBASE were searched according to PRISMA guidelines using terms comprising

hemodialysis, 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, hart 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 and if deemed pertinent, the publication was read in detail. Inclusion required a description of surgical technique and pre-and postoperative non-indexed Q_a-values. In case of overlapping patients, the article describing the largest cohort was included. Reviews, reports on AVA-ligation and animal studies were excluded. Data regarding patient characteristics, AVA-type, indication, Q_a-tool, pre- and postoperative Q_a, complications, follow-up, patency and HFA-recurrence were tabulated. When the exact performed surgical technique was 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), Q_a-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 termed asymptomatic or symptomatic in case of signs and/ or symptoms of cardiac origin and/ or distal ischemic origin. Q_a-thresholds were based on reported values but, if absent, on the patient with the lowest preoperative Q_a 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 Q_a >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.

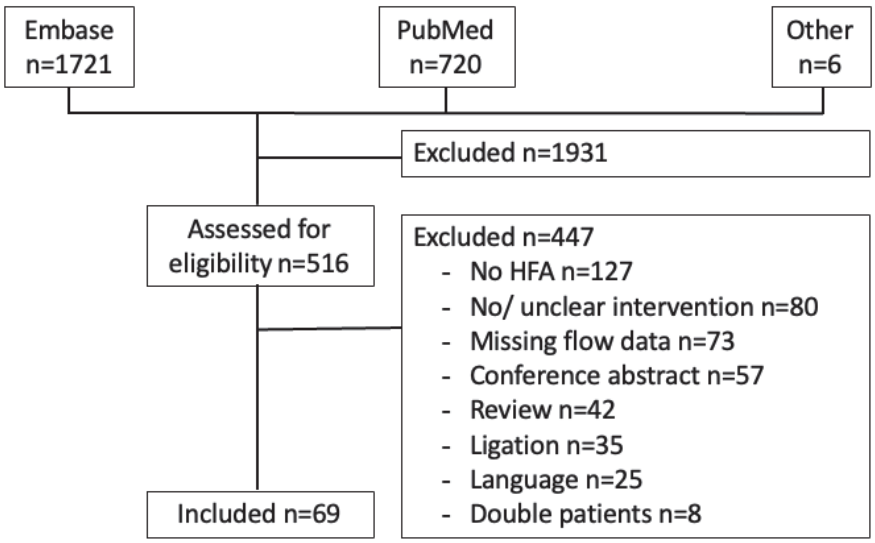
Results

The search strategy yielded 2447 studies between September 1973 and August 2021 (*figure 1*). Sixty-nine articles encompassing 1016 patients fulfilled study criteria (mean age 56 years [3-90], male 62%).[5,10,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81]

Five articles described two or more surgical techniques in different patients.[40,44,47,62,65] One article added data to a second included article without adding new patients.[15,16]

Diabetes mellitus (DM) was observed in 27% of patients and more commonly present in studies including HAIDI patients (60%) compared with studies in which HAIDI was absent (17%). The majority of patients (69%) harboured a brachial-artery based access. A total of 39 deaths occurred in 1005 observed patient years (one death per 26 observed patient years).

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



Definitions and surgical workup

Definitions of HFA and indication for Q_a-reducing surgery varied greatly. For example, reported cut-off values ranged from 0.6 L/min to 2.0 L/min.[21,61] Some authors ignored Q_a-thresholds and executed flow reduction when cardiac complaints or HAIDI were present. [40,59,73] One author stated that 'surgery was performed for high flow' but provided neither symptoms nor threshold values.[42]

Echocardiography supporting a decision of Q_a-reduction was used in 25 articles describing 413 patients (41%).[18,19,25,26,28,32,34,41,42,43,45,47,48,49,50,56,61,66,70,72,74,75,78,80] Echocardiographic parameters reflecting HOCF in the presence of a HFA were not stated although left ventricular mass index (LVMi) decreased following surgery.[25,70] 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 Q_a-reduction.[45]

Q_a-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 Q_a and higher finger pressures (figure 2c).[24] Several modifications were popularized. During Minimally Invasive Limited Ligation Endoluminal-assisted Revision (MILLER), an adjustable balloon is temporarily inserted into the venous outflow tract preventing 'over-banding' and consequent thrombosis.[10] T-banding includes wrapping of both venous outflow tract and feeding artery using a single T-formed band.[36] External Dilator-Assisted Banding (EDAB) uses a dilator-device that is temporarily placed at the exterior vessel wall. EDAB is used for both arterial and venous banding.[42]

Banding with intraoperative Q_a-tool

A total of 20 articles on banding with intraoperative Q_a-tools guiding surgery were included (n=336 patients, 60% male, mean age 56 [15-90]; table 1). One article completed available data of another article without adding new patients.[10,14,15,16,17,18,19,20, 21,22,23,24,25,26,27,28,29,30,31,32,33] Q_a-drop was 1.4 L/min (2.4 to 1 L/min). Complications were reported in 20 patients (6%) including access thrombosis/occlusion (n=13). Patency rate was 93% (mean follow-up 9 months, total 156

patient years). High Q_a recurred or persisted in 42 patients (13%). Definitions of recurrence varied greatly.

Banding without intraoperative Q_a-tool

Fourteen articles reported on banding without an intraoperative tool (n=105 patients, 64% male, mean age 61 [18-89]; table 2).[34,35,36,37,38,39,40,41,42,43,44,45,46,47] Q_a-drop was 1.1 L/min (2.1 to 1 L/min). Complications were reported in 20 patients (19%) including thrombosis/ occlusion (n=12). Patency rate was 89% (mean follow-up 8 months, total 29 patient years). High Q_a recurred or persisted in 20 patients (19%).

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 (%)	Q_a-method pre	$Q_{a\ pre}$ L/min mean (range)	$Q_{a\ post}$ L/min mean (range)	Q_a tool Intra	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
De Palma, '73 Banding14	C+/ H±/ As- ≥1.3	3	48 (21-62)	0	0	FA-AVA - Bovine (67) - GSV (33)	EM-probe	2.6 (1.3-4.0)	0.6 (0.6-0.7)	EM-probe	0	NR	NR	0	NR
Anderson,'75'76 Banding15,16 *	C+/ H-/ As- ≥1.4	3	48 (45-51)	67	0	RA-AVF (100)	EM-Probe	2.1 (1.4-2.9)	0.6 (0.5-0.7)	EM-probe	0	9 (8-10)	0	0	100
Fee, '76 Banding17	C+/ H-/ As- ≥1.6	4	41 (20-60)	25	25	FA-AVF - Bovine (75) - GSV (25)	Catheter	3.1 (1.6-4.9)	0.9 (0.2-2.2)	Catheter	Thrombosis (1)	5 (0.5-12)	1	1	75
Isoda, '94 Banding18	C+/ H-/ As- 3.7	1	52	100	0	RA-AVF (100)	Ultrasound	3.7	1.4	EM-probe	0	42	0	0	100
Murray, '04 Banding19	C-/ H-/ As+ 5.2	1	60	100	0	BA-AVF (100)	Dilution	5.2	3	Catheter	0	12	1	0	100
Thermann, '07 Banding20	C-/ H+/ As- ≥0.6	15	68 (46-84)	47	47	BA-AVF (87) BA-AVG (13)	Ultrasound	1.5 (0.6-2.8)	0.8 (0.3-1.5)	Dilution	0	18 (6-70)	1	3	91
Miller, '10 MILLER10	C+/ H±/ As- ≥1.5	69	56	62	33	BA-AVF (86) RA-AVF (9) BA-AVG (6)	Dilution	2.6	1.3	Dilution	Thrombosis (1)	11 (0-37)	4	2	89
Jennings, '12 MILLER21	C-/ H-/ As+ ≥0.9	22	43 (22-73)	59	32	NR	Ultrasound	1.6 (0.9-4.2)	0.8 (0.4-2.1)	Ultrasound	0	8 (3-24)	0	0	91
Nickel, '13 Banding22	C+/ H-/ As- ≥3.4	1	22	100	0	BA-AVF (100)	Ultrasound	3.4	1.7	EM-probe	0	1	0	0	100
Gkotsis, '15 Banding23	C+/ H-/ As- ≥1.1	12	42 (15-73)	75	NR	NR	Ultrasound	2.2 (1.1-3.3)	0.6 (0.5-0.9)	Ultrasound	0	12 (1-18)	0	0	100
Vaes, '15 Banding24	C±/ H-/ As+ ≥1	50	51 ±14	60	6	BA-AVF (96) RA-AVF (4)	Dilution	3.1 ±0.1	1.5 ±0.1	Ultrasound Transit time	Thrombosis (1) Infection (1)	6 (1-12)	26	3	100

Balamuthusamy, '16 Banding25	C+/ H-/ As- ≥2	12	65 ±14	NR	83	BA-AVF (100)	Ultrasound	3.7 ±0.8	1.1 ±0.4	Ultrasound	0	6	0	0	100
Teixeira, '17 Banding26	C+/ H-/ As->1.5	55	56 (21-87)	64	24	BA-AVF (95) RA-AVF (5)	Ultrasound	2.4 ±0.7	1.0 ±0.2	Ultrasound	Thrombosis (10) Rupture (3) False aneurysm (1)	NR	6	NR	91
	C-/ H+/ As- NR	64	66 (22-90)	58	56	BA-AVF (86) RA-AVF (8) BA-AVG (6)		1.7 ±0.7	0.7 ±0.2						
Baker, '17 Banding27	C-/ H+/ As- ≥2.4	1	34	0	100	BA-AVF (100)	Ultrasound	2.4	0.8	Ultrasound	0	12	0	0	100
Letachowicz, '18 EDAB28	C+/ H-/ As- ≥0.9	5	63 (40-77)	60	0	RA-AVF (100)	Ultrasound	1.4 (0.9-2.5)	0.5 (0.4-06.)	Ultrasound	0	0	0	0	NR
Mallios, '18 Banding29	C-/ H-/ As+ ≥2	1	75	100	0	BA-AVF (100)	Ultrasound	2.5	1.0	Ultrasound	Wall rupture & aneurysm (1)	2	1	0	100
Kahraman, '19 Banding30	C±/ H-/ As+ ≥1.2	10	48 ±11	40	30	NR	Ultrasound	1.3 ±0.1	0.6 ±0.1	Ultrasound	0	0	0	0	NR
Lee, '20 Dynamic band31	C±/ H-/ As± ≥2	5	60 (16-80)	NR	0	RA-AVF (40) RA-AVG (40) BA-AVF (20)	Ultrasound	3.0 (1.3-4.5)	1.1 (0.5-1.2)	Ultrasound	0	12 (12-12)	0	0	100
Turner, '20 Banding32	C+/ H-/ As- ≥5	1	53	100	0	BA-AVF (100)	Ultrasound	5.0	1.2	Ultrasound	0	24	1	0	100
Wan, '20 MILLER33	C+/ H-/ As- ≥1.5	1	65	100	0	RA-AVF (100)	Ultrasound	3.1	0.7	Ultrasound	0	6	0	0	100
Total N=20 publications		336	56 (15-90)	60	33	BA-AVF (73) RA-AVF (8) BA-AVF (2) RA-AVG (1) FA-GSV (1) FA-Bovine (1) NR (13)		2.4 (0.6-5.2)	1 (0.4-2.2)		Thrombosis (13) Rupture (4) (False) Aneurysm (2) Infection (1)	9 (1-70) Total 1873	42	5	93

C, Cardiac complaints; H, Hand ischaemic complaints; As, Asymptomatic; N, Number; DM, Diabetes Mellitus; Q_a, access flow; Pre, pre operative; Post, post operative; Intra, intra operative; FU, follow up; Re-HFA, recurrent or persistent high flow access; FA, femoral artery based; AVA, Arteriovenous acces; 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.

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 (%)	Q_a-method pre	$Q_{a\ pre}$ L/min mean (range)	$Q_{a\ post}$ L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
Tzanakis, '99 Banding34	C+/ H-/ As- ≥1	1	48	100	0	RA-AVF (100)	Ultrasound	1.6	0.6	0	6	0	0	100
Malik, '03 Banding35	C-/ H+/ As- ≥1.5	2	NR	NR	0	NR	Ultrasound	1.7 (1.7-1.7)	0.8 (0.8-0.8)	0	6 (6-6)	0	0	100
Schneider, '06 T-Banding36	C+/ H-/ As- ≥1	22	63 (45-81)	73	0	BA-AVF (91) RA-AVF (9)	Ultrasound	2.0 (1.3-3.2)	1.0 (0.6-1.4)	Hematoma (2) Thrombosis (2)	2 (1-3)	5	0	100
Lombi, '10 Banding37	C+/ H-/ As- ≥2	1	61	0	0	RA-AVF (100)	Ultrasound	7	3	0	NR	1	0	NR
Ladenheim, '15 MILLER38	C-/ H+/ As- ≥1.3	1	63	0	0	BA-AVF (100)	Ultrasound	1.3	0.7	Pseudo aneurysm & band migration (1)	2	1	0	100
Shintaku, '15 MILLER39	C±/ H-/ As± ≥1.4	7	54	86	0	RA-AVF (100)	Ultrasound	2.0 (1.4-2.6)	1.2 (0.9-2.0)	Thrombosis (1)	12	1	0	83
Kanno, '15 Banding40	C+/ H-/ As- ≥0.6	37	64 (38-83)	62	19	BA-AVF (54) RA-AVF (46)	Ultrasound	1.3 (0.6-4.6)	0.5 (0.2-1.3)	Thrombosis (9) Infection (2)	NR	7	NR	75
Imran, '15 Banding41	C+/ H-/ As- ≥5	1	65	100	0	RA-AVF (100)	Ultrasound	5.0	1.8	0	1	0	0	100
Letachowicz, '16 EDAB42 - Art. (9) - Ven. (3)	C+/ H-/ As- ≥1.5	12	54 (30-77)	42	NR	RA-AVF (75) BA-AVF (25)	Ultrasound	3.7 ±0.8	1.5 ±0.3	0	5 (1-10)	0	0	100
Ragupathi, '16 Banding43	C+/ H-/ As- ≥2	1	54	100	0	BA-AVF (100)	Ultrasound	8	4.3	0	2	1	0	100
Nojima, '18 Banding44	C±/ H±/ As± ≥1.4	4	67 (50-89)	50	25	RA-AVF (75) BA-AVF (25)	Ultrasound	2.1 (1.8-3.0)	0.6 (0.4-0.7)	0	26 (4-60)	0	2	75
Warja, '20 MILLER45	C+/ H-/ As- ≥2.8	1	18	NR	100	BA-AVF (100)	Ultrasound	2.8	3.0	0	1	1	0	100

Cerqueira, ‘21 MILLER46	C±/ H+/ As- ≥1	6	61 (47-80)	33	50	BA-AVF (100)	Ultrasound	2.1 (1.6-30)	1.5 (1.2-1.8)	Infection (1) Aneurysm (1)	12	0	0	100
Malik, ‘21 Banding47	C+/ H-/ As- ≥1.5	9	57 (27-73)	78	0	RA-AVF (56) BA-AVF (44)	Ultrasound	2.3 (1.3-3.9)	1.5 (0.7-2.5)	0	1.5	4	0	100
Total N=14 publications		105	61 (18-89)	64	16	BA-AVF (61) RA-AVF (39)		2.1 (0.6-8)	1 (0.2-4.3)	Thrombosis (12) Infection (3) Haematoma (2) (Pseudo) aneurysm (2) Band migration (1)	8 (1-60) Total 350	20	2	89

C, Cardiac complaints; H, Hand ischaemic complaints; As, Asymptomatic; N, Number; DM, Diabetes Mellitus; Q_a, access flow; Pre, pre-operative; Post, post-operative; 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.

Venous aneurysm repair

As a result of increased Q_a through an AVA, veins may grossly dilate leading to venous aneurysms. Various options and techniques are based on the assumption that reducing the aneurysm diameter results in an increased AVA outflow resistance and reduced Q_a.

Six articles reporting on various types of venous aneurysm repair fulfilled inclusion criteria (n=177 patients, 68% male, mean age 51 [20-89]; table 3).[48,49,50,51,52,53] Q_a-drop was 1.6 L/min (2.7 to 1.1 L/min). Complications were reported in 13 patients (7%) including thrombosis (n=4). Patency rate was 82% (mean follow-up 16 months, total 243 patient years). High Q_a-recurred or persisted in 11 patients (6%).

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). Q_a-reduction occurs as the access inflow is now provided by a smaller caliber artery.[58] RUDI is also advocated for HAIDI.[59] 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 transected and mobilized outflow vein and the proximal radial artery thus avoiding an interposition graft.[60]

Ten articles reported on RUDI (n=110 patients, 62% male, mean age 57 [28-78]; table 3).[47,54,55,56,57,58,59,60,61,62] Q_a-drop was 1.7 L/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 Q_a recurred or persisted in 23 patients (21%). RUDI using a basilic vein graft (n=4) was ineffective.[58]

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.[84]

Eight articles on plication/anastomoplasty were included (n=91 patients, 60% male, mean age 57 [9-86]; table 3).[40,44,63,64,65,66,67,68] 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 flow recurred or persisted in 3 patients (3%).

Table 3. Publications on aneurysm repair, RUDI and plication for flow reduction of a high flow access.

Author, year Aneurysm Repair	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Q_a-method pre	$Q_{a\ pre}$ L/min mean (range)	$Q_{a\ post}$ L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
Rokosny, '1448	C-/ H-/ As+ NR	62	60 (28-81)	63	16	RA-AVF (65) BA-AVF (35)	Ultrasound	4 ±1.9	1.7 ±0.8	Bleeding (3) Infection (3) Thrombosis (1)	15 ±15	3	8	80
Wohlfart '1649	C-/ H-/ As+ ≥1.5	30	52 ±12	73	7	BA-AVF (53) RA-AVF (40) AVG (7)	Ultrasound	3.3 (1.5-5)	1.8	0	12	0	0	NR
Shah, '1850	C+/ H-/ As- ≥1.5	1	36	0	0	BA-AVF (100)	Ultrasound	5.2	1.2	0	9	0	0	100
Marumatsu, '1851	C-/ H-/ As+ ≥1.3	1	52	0	0	BA-AVF (100)	Ultrasound	1.3	0.9	0	2	0	0	100
Wan, '1952	C-/ H-/ As+ ≥1	41	37 (18-60)	71	10	RA-AVF (95) BA-AVF (5)	Ultrasound	1.6 ±0.3	0.8 ±0.1	0	27 (12-43)	0	1	NR
Matoussevitch, '2153	C±/ H±/ As± ≥1.5	42	49 (20-89)	72	5	RA-AVF (50) BA-AVF (50)	Ultrasound	2.6 (1.5-6)	0.7 (0.3-1.3)	Bleeding (3) Thrombosis (1)	12 ±3	8	3	85
Total N=6 publications		177	51 (20-89)	68	10	RA-AVF (63) BA-AVF (36) AVG (1)		2.7 (0.3-6)		Bleeding (6) Thrombosis (4) Infection (3)	16 (2-43) Total 2912	11	12	82

Author, year RUDI	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Q_a-method pre	$Q_{a\ pre}$ L/min mean (range)	$Q_{a\ post}$ L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
Andrade, '04 PTFE54	C±/ H+/ As- ≥1	2	39 (29-48)	100	50	BA-AVF (100)	Ultrasound	1.2 (1.1-1.2)	0.6 (0.5-0.7)	0	6 (6-6)	0	1	100
Chemla, '07 PTFE55	C+/ H-/ As- ≥1.6	17	54 (31-76)	59	NR	BA-AVF (88) BA-AVG (12)	Dilution	3.1 (1.9-4)	1 (0.4-2.6)	Thrombosis (5)	16 (7-39)	1	0	77
Parmar, '09 GSV56	C+/ H-/ As- ≥10	1	50	100	0	BA-AVF (100)	Ultrasound	10.4	3.6	0	7	1	0	100
Beecher, '10 Vein57	C-/ H+/ As- ≥2	2	60 (56-64)	100	100	BA-AVF (100)	Ultrasound	2.5	1.1	0	24 (24-24)	0	0	100
Vaes, '15 Basilic vein58	C+/ H±/ As± ≥1.5	4	53 (38-64)	75	0	BA-AVF (100)	Dilution	3.2 (2.9-3.4)	1.8 (0.9-3.2)	0	8 (3-12)	3	0	100
Misskey, '16 PTFE(15) GSV(3)59	C-/ H+/ As- NR	20	64 ±15	55	85	BA-AVF (100)	Dilution	1.9 ±0.5	0.9 ±0.2	Wound complication(1)	24 (0-48)	0	1	78
Loh, '16 Direct(17) Vein(1)60	C±/ H±/ As± ≥1.5	28	55 ±3	43	69	BA-AVF (96) BA-AVG (4)	Ultrasound	2.2 ±0.2	1 ±0.1	0	15 +2	4	0	87
Gerrickens, '18 GSV61	C±/ H±/ As± ≥1.5	21	54 (28-75)	67	10	BA-AVF (100)	Dilution	3.1 (1.5-4)	1.2 (0.6-1.9)	Thrombosis (3) Haematoma (2) Pseudo aneursym (1)	28 (0-36)	9	2	84
Leskovar, '19 Cormatrix62	C-/ H-/ As+ ≥2	1	53	0	0	BA-AVF (100)	Ultrasound	2.3	0.8	0	12	0	0	100
Malik, '21 NR47	C+/ H-/ As- ≥1.5	14	62 (43-78)	71	0	BA-AVF (79) RA-AVF (21)	Ultrasound	3.5 (1.7-7.5)	1.3 (0.6-2.0)	Thrombosis (1)	1.5	5	0	100
Total N=10 publications		110	57 (28-78)	62	44	BA-AVF (94) RA-AVF (3) BA-AVG (3)		2.8 (1.1-10.4)	1.1 (0.4-3.2)	Thrombosis (9) Bleeding (2) Pseudo aneurysm (1) Wound complication (1)	17 (0-48) Total 1892	23	4	86

Author, year Plication	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Q_a-method pre	$Q_{a\ pre}$ L/min mean (range)	$Q_{a\ post}$ L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
Shemesh, '9963	C-/ H+/ As-	1	65	0	0	BA-AVG (100)	Ultrasound	1.2	0.9	0	28	0	0	100
Schenk, '0164	C-/ H-/ As±	1	28	100	0	BA-AVF (100)	Ultrasound	5.8	1.9	0	1	0	0	100
Aschwanden, '0365	C-/ H+/ As-	2	72 (60-78)	100	0	BA-AVF (100)	Ultrasound	1.5 (1.4-1.6)	0.5 (0.4-0.6)	0	8 (3-12)	0	0	100
Tellioglu, '08 66	C±/ H±/ As-	30	48 (9-57)	53	0	AVF (83) AVG (17)	Ultrasound	2.7 (1.9-3.6)	0.6 (0.5-1)	0	12 (12-12)	0	0	97
Patel, '15 67	C-/ H+/ As-	26	58 ±15	58	62	BA-AVF (100)	NR	2 ±0.8	0.6 ±0.5	0	12	NR	0	92
Kanno, '1540	C+/ H-/ As-	25	64 (29-86)	68	20	RA-AVF (72) BA-AVF (28)	Ultrasound	1.3 (0.6-2.4)	0.6 (0.3-1.1)	Thrombosis (1)	NR	1	0	96
Ferrante, '16 68	C-/ H+/ As-	1	86	100	0	RA-AVF (100)	Ultrasound	2.1	1.1	0	2	0	0	100
Nojima, '1844	C±/ H±/ As±	5	72 (61-79)	60	40	BA-AVG (60) RA-AVF (40)	Ultrasound	1.4 (1.4-1.7)	0.5 (0.3-0.9)	0	19 (5-34)	2	1	60
Total N=8 publications		91	57 (9-86)	60	39	BA-AVF (40) AVF (27) RA-AVF (23) AVG (5) BA-AVG (4)		2 (0.6-5.8)	0.6 (0.3-1.9)	Thrombosis (1)	12 (1-34) Total 814	3	1	93

C, Cardiac complaints; H, Hand ischaemic complaints; As, Asymptomatic; N, Number; DM, Diabetes Mellitus; Q_a, access flow; Pre, pre-operative; Post, post-operative; 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, poly tetra fluor ethylene; GSV, greater saphenous vein; Vein, venous graft; Direct, direct anastomosis without graft.

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 when a graft is incorporated into the outflow vein.[44] Data on both techniques were combined in this review. GIT is performed in both radial artery- 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).[44,62,65,69,70,71,72] Q_a-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 flow 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.[75] 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).[73,75,74] Q_a-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 flow 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% Q_a-reduction.[85]

Proximalization of arterial inflow (PAI)

During PAI, a piece of PTFE-graft or vein is positioned between the axillary artery and the disconnected venous outflow tract. The original anastomosis is oversewn (figure 2h). This technique was promoted for HAIDI patients as an axillary anastomosis is not associated with a marked loss of perfusion pressure.[86] PAI may also result in a lower Q_a.

Two articles were included (n=46 patients, 61% male, mean age 69 [45-86]; table 4).[76,77] Q_a-drop in brachial artery-based AVA was 0.5 L/min (1.5 to 1.0 L/min)

while Q_a in prior radial artery-based AVA remained unchanged (0.8 L/min). Postoperative complications were absent. Patency rate was 77% (mean follow-up 23 months, total 90 patients years). High flow recurred in 1 patient (2%).

Miscellaneous techniques

Radial artery transposition (RAT) uses a transposed radial artery as the new inflow artery for a brachial artery-based AVA resulting in a Q_a-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 0.8 L/min mean drop in Q_a (1.4 to 0.6 L/min).[40]

Transposition of the basilic vein (BVT) reduced mean Q_a with 0.6 L/min (1.8 to 1.2 L/min) in ten 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. Q_a 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 Q_a-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. Q_a was reduced by 1.4 L/min (2.2 to 0.8 L/min).[81]

Table 4. Publications on the graft interposition technique (GIT), proximal radial artery ligation (PRAL), proximalisation of arterial inflow (PAI) 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 (%)	Q_a-method pre	$Q_{a\ pre}$ L/min mean (range)	$Q_{a\ post}$ L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
Rosental, '8069	C-/ H+/ As- ≥1.6	1	28	NR	100	Bovine (100)	EM-Probe	1.6	0.9	0	NR	0	0	100
Aschwanden, '0365	C-/ H+/ As- ≥1.4	1	67	100	0	BA-AVF (100)	Ultrasound	2.8	0.9	0	29	0	0	100
Lubas, '1370	C+/ H-/ As- ≥2	1	48	100	0	BA-AVF (100)	Ultrasound	2.5	1.4	0	5	1	0	100
Kaneko, '1871	C+/ H-/ As- ≥2	1	55	0	0	RA-AVF (100)	Ultrasound	2.2	0.9	0	12	0	0	100
Nojima, '1844	C±/ H±/ As± ≥1.4	16	62 (37-83)	75	25	RA-AVF (69) BA-AVF (31)	Ultrasound	2.3 (1.4-3.6)	0.9 (0.6-1.2)	0	34 (1-68)	0	1	88
Leskovar, '1962	C-/ H-/ As+ ≥2	1	52	100	0	BA-AVF (100)	Ultrasound	3.5	1.8	Thrombosis (1)	4	0	0	0
Hashimoto, '2072	C+/ H-/ As- ≥1.5	25	61 ±13	56	20	RA-AVF (64) BA-AVF (36)	Ultrasound	3.4 (1.8-6)	1.5 (0.5-2.2)	Thrombosis (5) Infection (1)	47 (1-112)	0	2	72
Total N=7 Publications		46	60 (28-89)	64	22	RA-AVF (62) BA-AVF (37) Bovine (2)		2.9 (1.4-6)	1.3 (0.6-2.2)	Thrombosis (6) Infection (1)	39 (1-112) Total 1769	1	3	78

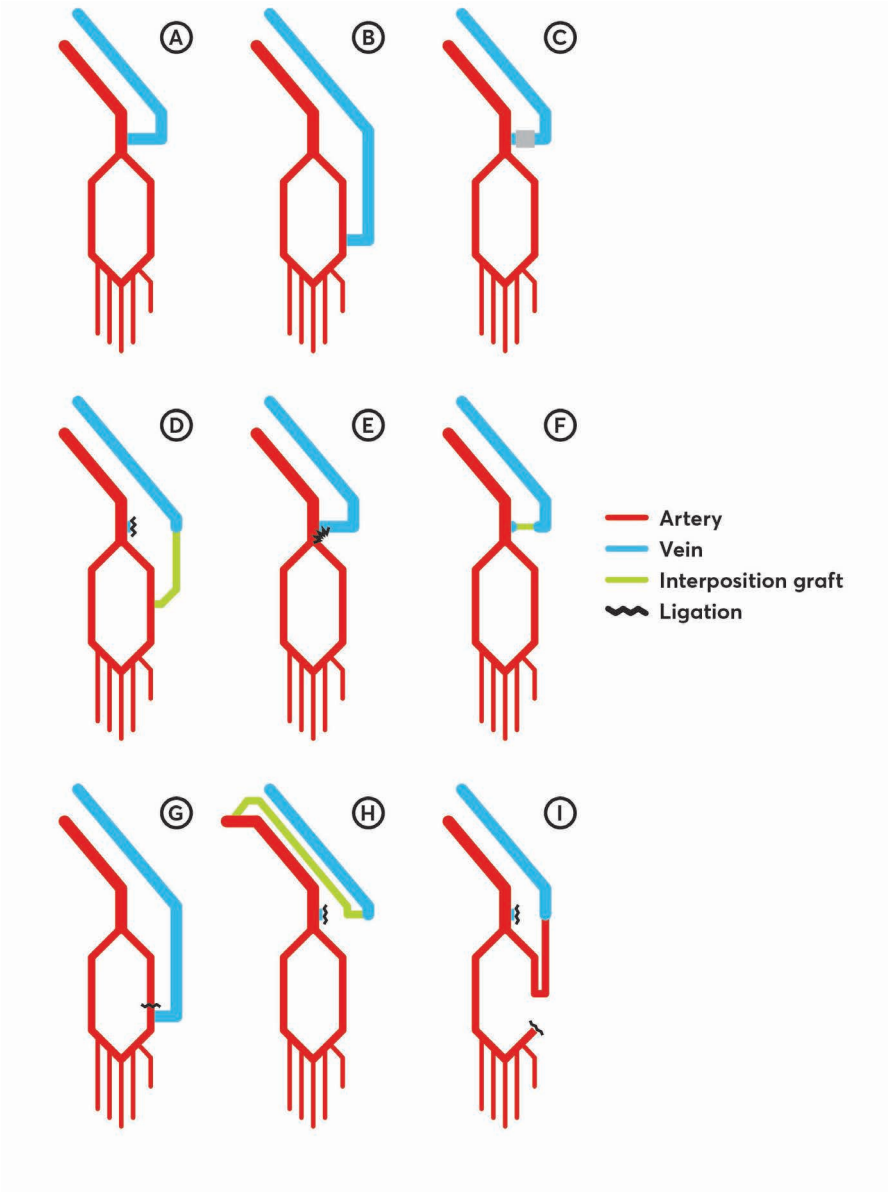
Author, year PRAL	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Q_a-method pre	$Q_{a\ pre}$ L/min mean (range)	$Q_{a\ post}$ L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
Smith, '0873	C+/ H-/ As- ≥1	1	32	0	0	RA-AVF (100)	Dilution	3	1.2	0	6	0	0	100
Oe, '0974	C+/ H-/ As- ≥2	1	68	0	0	RA-AVF (100)	Ultrasound	4.1	1.9	0	1	0	0	100
Bourquelot, '1075	C±/ H±/ As± ≥1	29	45 (16-82)	59	0	RA-AVF (100)	Ultrasound	1.7 (1-3)	0.8 (0.5-1.6)	Thrombosis (1) Aneurysm (1)	20 (0-89)	2	0	78
Total N=3 Publications		31	45 (16-82)	55	0	RA-AVF (100)		1.8 (1-4.1)		Thrombosis (1) Aneurysm (1)	19 (0-89) Total 587	2	0	81

Author, year PAI	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Q_a-method pre	$Q_{a\ pre}$ L/min mean (range)	$Q_{a\ post}$ L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
Thermann, '1076 PTFE	C-/ H+/ As- NR	38	70 (54-86)	58	71	BA-AVF (87) RA-AVF (13)	Ultrasound	1.4 (0.6-2.6) 0.8 (0.4-1.5)	1.0 (0.6-1.8) 0.8 (0.4-1.5)	0	19 (6-40)	0	1	75
Matoussevitch, '1477 Basilic vein	C-/ H+/ As- NR	8	62 (45-82)	75	63	BA-AVF (100)	Ultrasound	1.8 (0.9-4.5)	0.8 (0.5-1)	0	44 (0-52)	1	2	88
Total N=2 Publications		46	69 (45-86)	61	70	BA-AVF (89) RA-AVF (11)		1.5 (0.9-4.5) 0.8 (0.4-1.5)	1.0 (0.4-1.5) 0.8 (0.4-1.5)	0	23 (0-52) Total 1074	1	3	77

Author, year, technique Miscellaneous	Indication C/H/As Threshold L/min	N	Age, years mean (range)	Male (%)	DM (%)	Access-type (%)	Q_a-method pre	$Q_{a\ pre}$ L/min mean (range)	$Q_{a\ post}$ L/min mean (range)	Complications (one month)	FU, months mean (range)	Re-HFA	Death	Patency at FU end (%)
Bourquelot, '0978 RAT	C±/H±/As± ≥0.8	47	44 (3-82)	53	11	BA-AVF (100)	Ultrasound	1.7 (0.8-3.0)	0.6 (0.2-1.9)	0	20 (0-189)	0	5	70
Kanno, '1540 Art. Band &ligation	C+/ H-/ As- ≥0.6	12	72 (39-86)	50	8	RA-AVF (100)	Ultrasound	1.4 (0.7-2.5)	0.6 (0.3-0.8)	Infection (1)	NR	1	0	100
Gerrickens, '185 BVT	C±/ H±/ As- ≥0.8	10	61 (54-75)	80	40	BA-AVF (100)	Dilation	1.8 (0.8-2.1)	1.2 (0.7-1.9)	Pseudoaneurysm (1)	2 (2-2)	0	0	100
Hong, '2079 Stent graft	C-/ H-/ As+ ≥1.5	3	62	NR	NR	BA-AVF (100)	Ultrasound	1.7 (1.5-1.9)	1 (0.9-1.1)	0	8 (6-12)	0	0	100
Katsui, '2080 RAHT	C+/ H-/ As- ≥1.5	1	73	0	0	RA-AVF (100)	Ultrasound	2.3	0.6	0	2	0	0	100
Mallios, '2081 Endo-RUDI	C-/ H-/ As+ ≥2	1	60	100	0	BA-AVG (100)	Ultrasound	2.2	0.8	0	6	0	0	100
Total N=6 Publications		74	62 (3-86)	56	14	BA-AVF (81) RA-AVF (18) BA-AVG (1)		NA	NA	Infection (1) Pseudo aneurysm (1)	15 (0-189) Total 792	1	5	NA

GIT, graft interposition technique; C, Cardiac complaints; H, Hand ischaemic complaints; As, Asymptomatic; N, Number; DM, Diabetes Mellitus; Q_a, access flow; Pre, pre-operative; Post, post-operative; 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; PAI, proximalisation of arterial inflow; PTFE, poly tetra fluor ethylene; RAT, radial artery transposition; Art. Band & ligation, arterial banding and ligation; BVT, basilic vein transposition; RAHT, reimplantation of an artery with a hairpin turn; Endo-RUDI, endovascular revision using distal inflow; AVG, arteriovenous graft; NA, not applicable.

Figure 2. Schematic overview of different access flow (Q_a) 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); I) Radial artery transposition (RAT).



Discussion

Aim of this scoping review was to discuss surgical options in patients with HFA. HFA-incidence may be up to 4% of a general HD-population.[7] A range of surgical techniques was introduced in recent years. However, most experience is gained with banding which was introduced in the 1970's.[87] Although efficacy and patency rates are acceptable, long term freedom from recurrent HFA is disappointingly low following banding. One study in 50 banded patients found that HFA (>2.0 L/min) recurred in 52% during a 1-year observation period. Young age and immediate post-banding Q_a >1.0 L/min were risk factors for recurrent high Q_a.[24] The present review found that the use of an intraoperative tool guiding grade of banding did not improve success. RUDI, PRAL and PAI were recently promoted for HFA-reduction but long term data are scarce.[61,75,76] A 1-year follow-up study indicated that recurrence happened just once after RUDI (6%).[58] After three years however, HFA had recurred in 50%.[61] Due to limited numbers, relatively short follow-up periods per technique and the lack of comparative trials, the level of evidence is low. Therefore, choice of technique is merely a matter of the surgeon's preference.

One of the factors delaying the initiation of high level evidence trials is the lack of a universally accepted HFA-definition. Recent dialysis guidelines proposed a 1.0 to 1.5 L/min Q_a-cut-off value.[11,12] However, indexing Q_a is intuitively more appealing.[6] For instance, a man standing two-meter-tall likely suffers less from the cardiovascular effects of a Q_a >2.0 L/min compared to a woman weighing 45kg. 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 flows were excluded from this review.

The role of patient history and physical examination in HFA management are unclear. Dyspnea, tachypnea, peripheral edema, systolic bruits and a gallop rhythm may reflect a symptomatic HFA.[7] A validated heart failure questionnaire (e.g. the Minnesota questionnaire) may identify progressive cardiac overload contributing to a decision to intervene.[90] The current review underscores the diversity in HFA-work-up and criteria for Q_a-reduction. The role of echocardiography should be studied, appreciating that 75% of ESRD-patients already demonstrate left ventricular hypertrophy prior to HD initiation.[91,92] Left ventricular mass significantly increased at one, three and twelve months after access creation, even in the absence of high Q_a.[82,93] The present review found that approximately 41% of operated HFA-patients received a preoperative echocardiographic evaluation.

Biomarkers such as BNP or ANP in maturing AVA before and after Q_a-reduction deserve further study.[82,83]

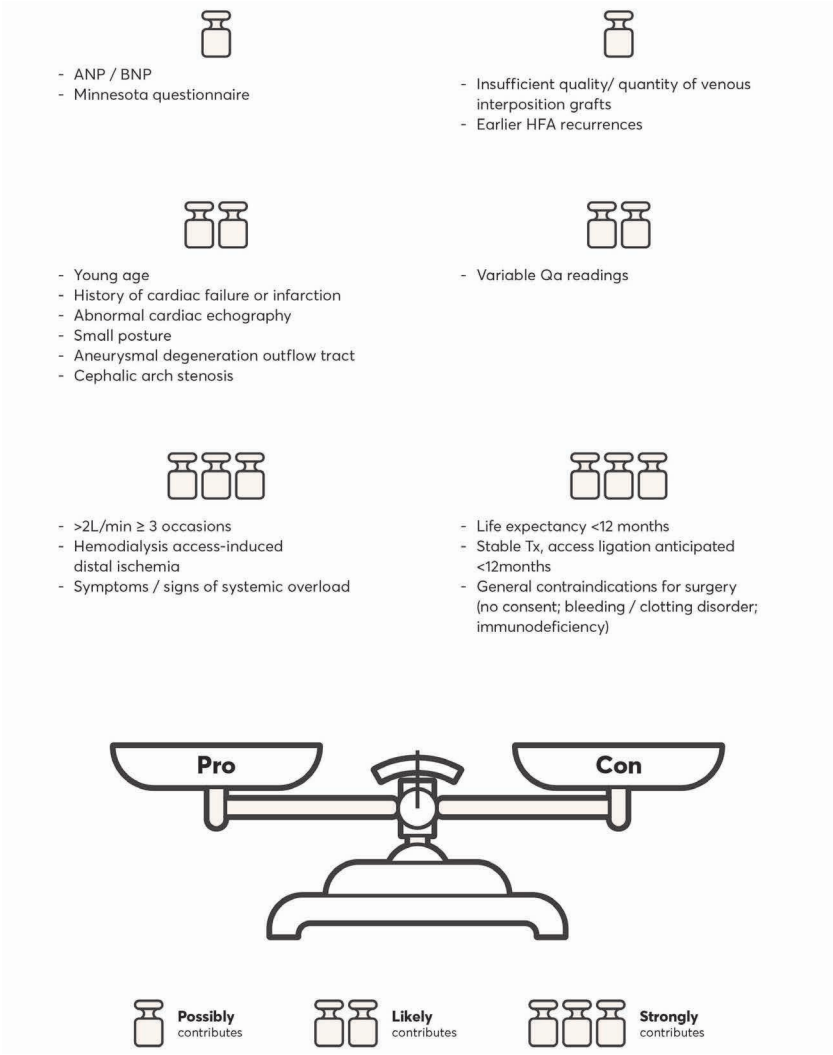
Management of seemingly asymptomatic HFA-patients remains controversial. The presence of concomitant HAIDI may tip the balance towards surgery.[7,61] It is reasonable to hypothesize that long lasting exposure to high Q_a may progressively exhaust cardiac reserve. An association between Q_a >2.0 L/min and onset of HOCF was suggested earlier.[9] It may be worthwhile to serially monitor these asymptomatic HFA-patients. Interestingly, a recent retrospective study showed that an *initial* flow <0.9 L/min was associated with increased risk of cardiovascular mortality. In contrast, *current* or *actual* Q_a was of little relevance with respect to (cardiovascular) survival. In addition, Q_a-increases over 3 month-periods as calculated using a joint-modelling technique did show a significant association with cardiovascular mortality. It is largely unclear whether AVA reduction in HFA patients leads to a decrease in (cardiovascular) mortality. Interestingly however, 4-year survival in 10 patients undergoing Q_a-reductive surgery was 100% compared to 55% in patients who did not.[94]

Is there other circumstantial evidence supporting surgery in (a)symptomatic HFA? Interestingly, the present review identified just 39 deaths during 1005 observed patient years (1:26). In contrast, a recent publication on the natural history of a general HD-ward reported 21 deaths during 148 observed patient years (1:7).[95] However, mean age was substantially higher and diabetes more common.[95] In one other study, patients with Q_a <1.0 L/min had poorer survival compared with patients with Q_a >1.0 L/min. Interestingly, Q_a >2.0 L/min was not related to excess mortality.[96] It is concluded that the slim body of evidence favouring Q_a-reduction and its effect on mortality, both in symptomatic and asymptomatic HFA-patients, does not allow for firm conclusions.

This review suffers from shortcomings that are inherent to limited volume 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 patency rates. Conference abstracts were excluded, possibly leading to exclusion of newer or yet less-accepted methods of Q_a-reduction. However, it must be appreciated that this scoping review on the current state of Q_a-reducing surgery, using both EMBASE and PubMed databases, provides an overview supporting tailored management for each individual HFA-patient. Factors such as extremely high Q_a, the presence of cardiac or hand ischemic complaints or a history of myocardial infarction might support a decision towards surgery. In contrast, a short life expectancy, a single measurement of high Q_a or stable

renal transplant function and a wish for access ligation may aid in the decision not to intervene. 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; Q_a, access flow; Tx, renal transplantation.



Are there any future directions in HFA-management? The present review identified controversies that must be considered prior to advising flow correction in both symptomatic and asymptomatic HFA-patients. An important step is a randomized controlled trial comparing 'watchful waiting' with 'Q_a-correction' in (a)symptomatic HFA, ideally taking into account multiple Q_a-measurements using a joint modelling technique. Suggested outcome parameters are cardiac events and mortality. Secondary outcomes may be resolution of concomitant HAIDI and cardiac complaints, echocardiographic parameters and biomarkers.

In conclusion, the present scoping review evaluates the experience dealing with the invasive treatment of high flow arteriovenous haemodialysis accesses. The optimal sequence of management steps is unknown due to a lack of standardization of definitions, diagnostic work-up and surgical technique. There is an urgent need for RCTs to determine if - and if so, which - HFA-patients benefit from flow reduction.

Supplementary material

Supplement 1. Search

(((hemodialysis) OR (haemodialysis) OR (renal replacement therapy) OR (RRT) OR (dialysis) OR (dialysis[MeSH Terms]) OR (renal replacement therapies[MeSH Terms)) AND ((hemodialysis access) OR (vascular access) OR (arteriovenous fistula) OR (arteriovenous graft) OR (AVF) OR (high flow access) OR (HFA) OR (arteriovenous fistula[MeSH Terms]) OR (anastomose, arteriovenous[MeSH Terms])) AND ((Q_a) OR (flow) OR (access flow)) AND ((Symptomatic) OR (asymptomatic) OR (cardiac overload) OR (cardiac failure) OR (high-output cardiac failure) OR (HOCF) OR (Nicoladoni-Branham sign) OR (Echocardiography) OR (cardiac failure[MeSH Terms]) OR (Aneurysm) OR (Aneurysmatic degeneration) OR (AVAIS) OR (Arteriovenous access-induced steal) OR (Steal) OR (Steal syndrome) OR (dialysis access steal syndrome) OR (DASS) OR (hand ischemia) OR (Ischemia) OR (finger) OR (HAIDI) OR (Hemodialysis access-induced distal ischemia) OR (cephalic arch stenosis) OR (CAS)) AND ((Surgery) OR (Operation) OR (Surgical intervention) OR (revision) OR (Aneurysm repair) OR (Aneurysmorrhaphy) OR (proximalization of arterial inflow) OR (PAI) OR (flow reduction) OR (distal revascularization interval ligation) OR (DRIL) OR (endovascular technique) OR (endovascular) OR (percutaneous) OR (endoluminal) OR (banding) OR (Minimally invasive limited ligation endoluminal-assisted revision) OR (MILLER) OR (revision using distal inflow) OR (RUDI) OR (radial artery transposition) OR (RAT) OR (Plication) OR (Anastoplasty) OR (Distalisation) OR (distalization) OR (proximal radial artery ligation) OR (PRAL) OR (clip) OR (clipping) OR (graft interposition) OR (graft inclusion) OR (GIT) OR (surgery[MeSH Terms]) OR (treatment[MeSH Terms]) OR (endovascular procedure[MeSH Terms]) OR (minimally invasive surgical procedures[MeSH Terms])))

Embase search

(((hemodialysis) OR (haemodialysis) OR (renal replacement therapy) OR (RRT) OR (dialysis) OR ('hemodialysis') OR ('renal replacement therapies')) AND ((hemodialysis access) OR (vascular access) OR (arteriovenous fistula) OR (arteriovenous graft) OR (AVF) OR (high flow access) OR (HFA) OR ('arteriovenous fistula') OR ('anastomosis') OR ('blood vessel shunt')) AND ((Q_a) OR (flow) OR (access flow)) AND ((Symptomatic) OR (asymptomatic) OR (cardiac overload) OR (cardiac failure) OR (high-output cardiac failure) OR (HOCF) OR (Nicoladoni-Branham sign) OR (Echocardiography) OR ('heart failure') OR (Aneurysm) OR (Aneurysmatic degeneration) OR (AVAIS) OR (Arteriovenous access induced steal) OR (Steal) OR (Steal syndrome) OR (dialysis access steal syndrome) OR (DASS) OR (hand ischemia) OR (Ischemia) OR (finger) OR (HAIDI) OR (Hemodialysis access induced distal ischemia) OR (cephalic arch stenosis) OR (CAS)) AND ((Surgery) OR (Operation) OR (Surgical intervention) OR (revision) OR (Aneurysm repair) OR (Aneurysmorrhaphy) OR (proximalization of arterial inflow) OR (PAI) OR (flow reduction) OR (distal revascularization interval ligation) OR (DRIL) OR (endovascular technique) OR (endovascular) OR (percutaneous) OR (endoluminal) OR (banding) OR (Minimally invasive limited ligation endoluminal-assisted revision) OR (MILLER) OR (revision using distal inflow) OR (RUDI) OR (radial artery transposition) OR (RAT) OR (Plication) OR (Anastoplasty) OR (Distalisation) OR (distalization) OR (proximal radial artery ligation) OR (PRAL) OR (clip) OR (clipping) OR (graft interposition) OR (graft inclusion) OR (GIT) OR ('surgery') OR ('therapy') OR ('endovascular surgery') OR ('vascular surgery')))

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PART III

Content

Chapter 10

Summarizing discussion, conclusions and future perspectives

Summarizing discussion

The number of patients with end-stage renal disease (ESRD) requiring a hemodialysis (HD) arteriovenous access (AVA) is increasing worldwide. In some elderly ESRD patients having poor arm vessel quality due to diabetes or arteriosclerosis, construction of the most popular native radiocephalic AVA (RC-AVA) is not advised. As a consequence, a more proximal brachiocephalic AVA (BC-AVA) located at the elbow may be required. Although such a 'proximal' AVA often matures successfully, a long term complication such as hemodialysis access-induced distal ischemia (HAIDI) occurs more frequently. Moreover, there are ample data indicating that a BC-AVA may occasionally lead to a 'high flow access' (HFA, high flow access) possibly leading to an earlier (cardiovascular) death when compared to a RC-AVA. At present, a number of *unmodifiable* risk factors of HAIDI and HFA such as age and gender are identified. However, there is a need to unveil other risk factors, or possibly even *modifiable* factors *prior* to AVA construction that may aid caretakers in counselling patients regarding the onset of these long term complications.

The first part of this thesis (**Chapter 2-6**) investigated whether finger pressures (P_{dig}) *in general* may have a prognostic role in the standard workup of patients scheduled for arteriovenous access (AVA) surgery. Finger plethysmography is a simple bedside modality that is utilized for determining blood pressure in the digits of the hand. When combined with a brachial artery pressure measurement, a digital brachial index (DBI) can be calculated (ratio between systolic P_{dig} divided by $P_{brach\ art}$). It may be hypothesized that a DBI theoretically reflects the combined quality of the arterial arm-hand axis and may possibly also be associated with the overall quality of the systemic circulation.

In **Chapter 2**, we determined the association between a DBI and 2-year AVA patency in ESRD patients scheduled for their first access creation. An abnormal preoperative DBI (low DBI <80%, high DBI >100%) value was associated with an almost two times lower primary patency rate compared with patients having normal DBI (80-100%) values (normal DBI: 49%, low DBI: 25%, high DBI: 28%). Moreover, 2-year secondary patency rates were the lowest in the abnormal DBI groups (normal DBI 82%, low DBI: 55%, high DBI 69%). Multivariate analysis demonstrated that abnormal DBI values were independently related to an approximately two times higher risk of primary access failure (low DBI HR: 2.25; high DBI HR: 1.74). Surprisingly, diameters of outflow veins, considered by most clinicians and current

guidelines as the most important predictor of successful AVA maturation, did not predict long-term patency. Findings of this study suggest a potential role of finger plethysmography in determining the optimal preoperative choice for a native AVA.

In earlier days, an Allen test was proposed as a simple bedside modality for predicting HAIDI, but often with little success. However, the role of an Allen test combined with finger plethysmography was never investigated. Can late-onset HAIDI be predicted on the basis of a preoperative combined measurement of Allen test-P_{dig}? In **Chapter 3**, a pilot study in 105 ESRD patients aimed to determine whether changes in P_{dig} during an Allen test prior to the first AVA construction predicted the onset of severe postoperative HAIDI. The results indicated that all patients who developed HAIDI later on displayed a radial or ulnar dominant perfusion pattern prior to AVA construction compared to half of the patients without HAIDI. If P_{dig} dropped by more than 40 mmHg during the Allen test, a patient sustained a 10 times greater risk of developing severe HAIDI. Digital plethysmography during an Allen test during may aid in identifying patients with an increased risk of developing HAIDI later on.

Previous studies have suggested correlations between a low ankle-brachial index (ABI) and high cardiovascular mortality (CVM) rates in HD populations. Analogously, it may be hypothesized that abnormal digital brachial index (DBI) values prior to the first AVA construction are also associated with increased CVM rates. In **Chapter 4**, a single-center retrospective 10 year cohort study encompassing 199 ESRD patients investigated this possible association. Patients were categorized as having an abnormal DBI (<80% or ≥100%) or with normal DBI values (80-99%). All-cause mortality rates as well as CVM rates were similar two and four years after AVA construction. However, a multivariate analysis correcting for potential confounders demonstrated that a high DBI prior to AVA construction conferred a two times higher risk of dying from a cardiovascular cause (HR 2.09, P=0.03). Finger plethysmography may play a role in selecting the most optimal renal replacement treatment stratagem in particular for polymorbid and frail ESRD patients.

The study reported in chapter 3 demonstrated that the Allen Test combined with finger plethysmography is a useful tool reflecting collateral perfusion capacity of the hand and associated risk of developing hand ischemia after AVA surgery. To go one step further, one may also hypothesize that an insufficient hand collateral perfusion is a reflection of a poor overall compensatory capacity

of the cardiovascular system. In **Chapter 5**, we discuss the role of a combined preoperative Allen test/P_{dig} measurement for assessing the risk of cardiovascular mortality (CVM) after the first AVA creation. P_{dig} was measured in ESRD patients following compression of radial and ulnar arteries as part of a standard preoperative AVA surgery work-up between January 2009 and December 2018 in our center. Patients (n=108) having cardiovascular disease prior to AVA construction displayed a greater drop in P_{dig} (∂P_{dig}) values (CV: 44 ±5 mmHg vs. without-CV: 29 ±3 mmHg, P=0.012). For each 10 mmHg ∂P_{dig} drop, overall mortality increased by 10%, and cardiovascular mortality by 15%. Finger plethysmographic measurements may therefore possibly be used to a-priori predict an increased cardiovascular mortality risk following AVA construction but this novel parameter requires confirmation in larger trial.

Earlier data suggested that survival is lower in HD patients developing HAIDI after AVA construction. However, whether patient survival is related to grade of HAIDI is unknown. In **Chapter 6** we performed an observational study analyzing survival rates of patients with mild HAIDI (Grade I-IIa), severe HAIDI (Grade IIb-IV), and without HAIDI (control group). Overall 4-year cardiovascular mortality rates were similar in patients with mild HAIDI and controls. In contrast, 4-year survival in patients with severe HAIDI was just 34% compared to 57% in mild HAIDI. These results indicate that patients developing severe HAIDI likely require a more rigorous surveillance of their cardiovascular health.

The second part of this thesis (**Chapter 7-9**) discusses the role of AVA flow (Q_a) and AVA location as predictors of survival in HD populations. A minimum 400-600 mL/min Q_a is needed for effective HD. Compared to RC-AVA patients, individuals with a BC-AVA have an increased risk of developing Q_a above 1500 mL/min, a condition termed high flow access (HFA) as proposed by international guidelines. Management of a HFA is largely based on six weeks measurements of Q_a ('actual') as suggested by DOQI, but these values often vary substantially. Efforts to assess the overall effect of height of Q_a over longer time periods were hitherto not performed.

In **Chapter 7**, we analyzed 5208 Q_a measurements in 165 patients over a 9-year period to determine a possible relationship between Q_a and survival by utilizing a sophisticated statistical method termed 'Joint Modelling Approach'. If the very first Q_a value obtained from a matured AVA ('initial Q_a') was below 900 mL/min, a patient sustained a four times higher 4-year cardiovascular death risk

(HR: 4.05) when compared to patients with a ≥900 mL/min initial Q_a. When analyzing fluctuations of Q_a over time, an association between a 3-month Q_a increase and mortality was found (HR 4.48 per 100 mL/min increase). In contrast, height of actual Q_a values per se were not related to survival. These novel parameters may contribute to an optimized surveillance of HD patients demonstrating sudden increases of Q_a values.

A vast number of studies investigating CVM rates consistently found better survival rates in patients with a native AVA as compared to patients who dialyze via a central venous catheter or arteriovenous graft. Considering the ongoing paradigm shift favoring a native brachial artery based (BA)-AVA, it is essential to know if AVA type has any impact on long-term survival. In **Chapter 8**, a retrospective cohort study aimed to determine potential survival differences in RA-AVA and BA-AVA populations. Four year freedom from CVM in RA-AVA was 84% compared to 63% in BA-AVA. If stratified for a 1000 mL/min initial Q_a threshold, CVM after four years was zero in patients with a RA-AVA and an initial Q_a 1000 mL/min. In contrast, patients with a BA-AVA and an initial Q_a <1000 mL/min displayed a dismal 57% CVM rate. Multivariate analysis considering predefined factors concluded that patients with a BA-AVA sustained an almost three times higher risk of CVM after four years compared with patients having a RA-AVA. Findings of this pilot study confirm the status of a RA-AVA as the first choice native access. In addition, AVA location and initial Q_a may serve as additional prognostic markers in future survival models.

In daily practice, management of HFA consists of detecting signs of cardiac overload, serial echocardiography and, when decided upon, a surgical Q_a reduction. An evidence-based algorithm is lacking. The approach towards Q_a reduction is highly subjective and is based on a clinician's best judgement according to the most recent ESVS guideline. In **Chapter 9**, a scoping review critically discusses the spectrum of surgical options for Q_a-reduction in HFA patients. 69 studies encompassing 1016 patients were included. Banding was the most popular treatment option (53%) followed by revision using distal inflow (RUDI, 15%), plication/anastomoplasty (8%), proximalization of arterial inflow (PAI, 6%), graft interposition (6%), proximal radial artery ligation (PRAL, 4%), or miscellaneous other techniques (8%). All of these therapies were effective in the short term (500-1600 mL/min mean drop in Q_a). However, access patency as well as HFA recurrence rates varied widely and were substantial. The current state of HFA management is far from evidence-based. Randomized trials comparing a wait-and-see approach with Q_a reduction are needed for establishing a standardized treatment regimen for HFA.

Conclusions

1. An abnormal digital brachial index (DBI) before a vascular access construction is associated with a lower 2-year arteriovenous access (AVA) patency.

2. Finger plethysmography combined with an Allen test prior to AVA construction in end stage renal disease (ESRD) patients may identify an increased risk of developing HAIDI.

3. Abnormal DBI values are associated with a higher cardiovascular mortality in ESRD patients who are on chronic haemodialysis (HD).

4. Finger plethysmography combined with an Allen test may predict mortality after AVA construction.

5. Patients with severe HAIDI have a limited survival compared to patients with a normal hand perfusion.

6. Longitudinal analyses of Q_a are useful for predicting survival rates in HD populations.

7. Patients with a brachial artery based AVA or low Q_a initial values display higher cardiovascular mortality rates compared to patients with a radial artery based AVA or high Q_a initial values.

Future perspectives

1. A prominent role for plethysmography in counselling on risk of hand ischemia

Previously, the role of digital plethysmography in end-stage renal disease (ESRD) populations was limited due to the lack of clinical studies. It was scarcely used in hemodialysis (HD) patients with an AVA for supporting a possible diagnosis of hemodialysis access-induced distal ischemia (HAIDI). The Allen Test also is a rather old-fashioned bedside method that is occasionally used for assessing the collateral circulation of the hand in cardiological patients requiring a radial artery catheterization. Nephrologists and surgeons earlier suggested to apply this Allen test prior to arteriovenous access (AVA) surgery to predict the onset of HAIDI later on, but a large observer bias precluded its clinical use for this purpose.

The present thesis suggests a potential role of digital plethysmography (combined with a modified Allen test) in ESRD patients who are counselled on the pros and cons of various types of renal replacement therapy. If an ESRD patient considers to start HD via an AVA, the risk of developing hand ischemia may be estimated on the basis of results of digital plethysmography. This finding has clinical consequences. It can be advised to explore alternative methods of HD such as an indwelling line in particular frail and polymorbid female patients displaying low values of P_{dig}. However, it must also be appreciated that the current method of performing digital plethysmography is limited to a determination of a systolic finger pressure. Future studies may explore whether additional characteristics such as mean finger pressure or arterial signal analysis may exert any diagnostic value. A necessary step is to establish normal values of P_{dig} and digital brachial indices (DBI) during rest and during a modified Allen test in healthy volunteers.

2. Finger plethysmography, access patency and patient survival

Studies of the present thesis also suggest potential other roles for digital plethysmography in ESRD patients who are counselled on the pros and cons of the different types of renal replacement therapy. Access patency is one of the most crucial outcome measures of AVA surgery. International guidelines advise duplex sonography of the arm vessels in the workup as the one and foremost modality determining AVA patency. Our study focusing on the role of a normal P_{dig} found

that not vein diameter but P_{dig} is crucial for patency. Future trials prospectively incorporating a range of other data including 3-dimensional vessel models and affiliated characteristics are necessary to confirm the dominant role of a preoperative P_{dig} in the list of modifiable and unmodifiable risk factors predicting AVA patency.

Mortality rates in an average HD population are notoriously high, with a 5-year survival rate of approximately 50%. Currently, clinicians involved in HD care use standard patient characteristics for estimating survival rates. However, such approximations are quite subjective as individual variability is substantial. Stratification of ESRD patients sustaining a higher risk of cardiovascular death on the basis of objective measures will aid in optimizing a HD treatment strategy. The present thesis also identified a value of a preoperative P_{dig} as a novel risk factor of death. As a consequence, having an abnormal P_{dig} supports a strict regimen of CVRM including the prescription of statins and stimulating an active nonsmoking life style in ESRD populations.

3. An extended Q_a surveillance program in future HD populations?

In the vast majority of HD centers, access flow (Q_a) measurements occur every six weeks as suggested by DOQI and current guidelines. Results are essentially only used to predict or monitor a developing stenosis of the venous outflow tract. In some institutions, multiple values of Q_a above the 1500-2000 mL/min cut-off threshold contribute to the diagnosis high flow access (HFA). If so, a combination of sensitive clues in patient history, physical examination and imaging may support a decision to perform Q_a reducing surgery aimed at attenuating the ongoing systemic vascular overload. However, it is long known that values of Q_a may vary substantially from time to time in most HD patients. As a consequence, nephrologists and access surgeons have previously relied on a limited number of consecutive six week values of Q_a for diagnosis and management of HFA.

Studies of the current thesis introduced a set of novel characteristics of Q_a such as *actual* Q_a (value at a certain point in time, often a six week one), *initial* Q_a (first Q_a ever obtained from a functioning AVA), and 3-month-*changes* in Q_a. The role of these Q_a characteristics regarding cardiovascular mortality were explored in a large homogenous HD population by utilizing advanced statistics. Contrary to

earlier studies reporting on the essential role of consecutive high actual Q_a values, only 3-month-*increases* in Q_a determined risk of CVM and long-term survival. This phenomenon is possibly explained by a progressively failing homeostatic environment. First, these findings require validation in future studies, preferably on a national scale. If confirmed, HD patients demonstrating considerable swift asymptomatic increases of Q_a should undergo a program of functional tests and imaging of cardiovascular status followed by an invasive program of secondary prevention.

4. Does location of native access determine survival of HD patient?

The demographic profile of contemporary HD patients has changed over the previous decades. At present, they start HD at a higher age and they are more frequently diagnosed with diabetes mellitus, hypertension and cardiovascular disease. These changes have caused a paradigm shift favoring a brachial artery based AVA as the first choice HD option in septuagenarians and octogenarians. However, it was largely unknown whether this shift conferred any consequences regarding patient survival. One study in this thesis was aimed at comparing survival rates in patients having a native wrist AVA or having an elbow AVA. Interestingly, patients with a distal AVA demonstrating an over 1 L/min initial Q_a were all alive after 4 years of observation. Conversely, patient survival rate with a proximal AVA and a <1 L/min initial Q_a was just 43%. A statistical analysis considering 7 other risk factors identified AVA location as the most dominant one. This important finding urgently calls for an RCT comparing survival in patient who qualify for both a RC-AVA or BC-AVA. Stratification for age is needed. Results of such a trial will replace the current 'one size fits all' regimen that is largely based on insufficient factors such as vessel diameter.

5. The role of 'big data' and 'artificial intelligence' in HD care

Currently, international access guidelines propose a rather generalized patient approach. However, each ESRD patient is unique in his or her way mandating a tailored treatment. Previous recommendations are largely derived from studies utilizing traditional statistical models. Advanced diagnostic and prognostic models

using machine learning and artificial intelligence (AI) will become valuable tools supporting patient-specific approaches. AI has found its way in various specialties. AI aids ophthalmologists in detecting retinopathy, cardiologists in identifying atrial fibrillation, radiologists in diagnosing pneumonia and oncologists in predicting patient survival (1–4). Nationwide efforts are required for collecting and analyzing large scale data. In the nephrological arena, the RENINE & MONDO registry may serve for this purpose. At present however, this database lacks crucial information including access patency and complication rates as well as additional important specifications such as type of AVA (5,6).

The horizon

Studies of the present thesis contributed to unveiling important roles of digital plethysmography, access location and access flow characteristics in relation to onset of complications and survival of hemodialysis patients. Several hurdles must be taken prior to safely incorporating these novel findings in standard patient care. Intensive collaboration with various stakeholders facilitating large scale qualitative studies confirming these findings is required.

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Chapter 11

Impact

Scientific contribution

Aim of the present thesis was to study the potential of both finger pressures using plethysmography as well as the role of access flow (Q_a) regarding a number of crucial outcome parameters in hemodialysis (HD) patients. At the start of this thesis, we hypothesized that plethysmography could play an important role as a prognostic tool. Plethysmography is a simple, cost-friendly and non-invasive bedside modality for determining blood pressure of the digits of the hand. We were convinced that, by using digital plethysmography prior to AVA construction, we would be able to detect any possible (latent) loss of blood pressure along the arm-hand axis potentially reflecting degree of atherosclerosis. We hypothesized that a lowered blood pressure at the hand has important prognostic modalities determining, in part, the onset of hand ischemia after AVA construction (hemodialysis access induced distal ischemia, HAIDI). Moreover, it was anticipated that plethysmography of the digits could predict access patency, and possibly even patient survival.

In **chapters 2, 3, 4, 5 and 6**, scientific evidence is provided confirming the prognostic value of finger pressures regarding these issues. Our results were published in 4 highly rated peer-reviewed journals and presented at several (inter) national conferences. The study unveiling the association between an abnormal digital brachial index and diminished access patency was selected in the top 5% global abstracts at the 2020 European Society of Vascular Surgery (ESVS) Annual conference.

The exact role of access flow volume (Q_a) measurements in the management of HD patients is also ill-defined. Although an association between Q_a and high-output cardiac failure and cardiac death was previously suggested, international guidelines are still struggling with an evidence-based role of a measurement of Q_a with respect to cardiovascular survival. Although it is long known that an elbow-based AVA generates higher Q_a levels compared to a wrist-based AVA, any possible impact on mortality rates of different types of AVA's was unknown. **Chapter 7** indicates that advanced statistical methods are very valuable for analyzing the complex associations between Q_a and long-term survival of a HD population. Since single "actual" Q_a may fluctuate substantially over the course of a year, these values were not found to have any prognostic value. However, it is essential to consider 3-month-trends in Q_a as a factor predicting survival. **Chapter 8** reported that patients having an elbow-based AVA sustain a 3 times higher risk

of cardiovascular death compared to patients with a wrist-based AVA. The studies reported in **chapter 7 and 8** were published in two high impact factor journals (Nephrology Dialysis & Transplantation, impact factor 6.0; European Journal of Vascular & Endovascular Surgery, no. 1 journal in Vascular Surgery, impact factor 7.1) and were also presented at (inter)national conferences.

Studies of the present thesis have changed our view on the role of these novel risk factors in the long term management of HD patients. This thesis will certainly stimulate follow-up studies confirming the prognostic value of finger pressures and longitudinal analysis of Q_a in the management of HD patients.

Social impact for the hemodialysis population

Chronic kidney disease (CKD) is an important contributor to public health problems and has a significant impact on mortality and morbidity of patient populations. Costs for treatment of CKD have increased drastically since the 1960s following introduction of a wide range of live-saving therapies for patients with end-stage renal disease (ESRD). At present, the prevalence of patients receiving renal replacement therapy (RRT) worldwide is approximately 2.5 million, whereas this number is expected to have doubled by the end of 2030. Several national screening programs have shown that more than 10% of the 'healthy' adults display markers reflecting CKD with even higher percentages in octogenarian populations. Causes for CKD are diverse, but cardiovascular disease, diabetes and hypertension are labelled as the most important causes.

Hemodialysis (HD) is the most prevalent type of RRT, and a native arteriovenous access (AVA) is univocally the preferred type of HD access. Although ESRD patients may benefit from HD in terms of prolonged long-term survival, complications associated with the presence of the AVA are numerous. In addition, incidence rates of adverse outcomes are rising due to growing numbers of frail and elderly patients requiring HD. The primary patency rate of an AVA two years after construction is just 51%, whereas the secondary patency rate is 64%. These data indicate that the course after AVA construction in seldomly uncomplicated. Besides poor patency rates, survival rates of the average HD population are even lower compared to populations of patients suffering from several different types of solid-organ cancers. For instance, approximately half of all HD patients are dead after 5 years, mostly due to cardiovascular disease. Therefore, identifying risk factors, both modifiable as well as unmodifiable, are crucial for quality of life and survival of HD patients.

Our studies have shown that patients with abnormal digital brachial index (DBI) values have a primary access patency rate as low as 25%, whereas patients with normal DBI values display a two times higher rates (49%). Patients presenting with abnormal DBI values conferred a two times higher risk of cardiovascular mortality as compared to patients with normal DBI values. A preoperative DBI obtained by digital plethysmography may therefore identify high-risk patients possibly burdened with cardiovascular disease. These conclusions highlight the necessity of developing screening and intervention programs to improve AVA outcomes, ideally incorporating digital plethysmography following validation in future studies.

Hand ischemia in the presence of an AVA (hemodialysis access-induced distal ischemia, HAIDI) is a dreadful complication with a serious impact on quality of life. Previous studies reported percentages up to 20%, whereas up to 80% of seemingly asymptomatic patients reported one or more symptoms associated with hand ischemia (coldness, pain, cramps etc.). Around 5% of all HD patients require invasive treatment for hand ischemia at one point in their life. A tool that accurately predicts HAIDI was never identified. Our studies are the first to show that an Allen Test under plethysmographic control, prior to AVA construction, has a potential to accurately predict the onset of HAIDI. With this information, vascular surgeons can counsel their patients on risk of HAIDI once a certain type of AVA is preferred. Conversely, alternative types of HD treatment with a lower or negligible risk of complications including HAIDI may be advised if this newly identified risk factor is present.

When the condition of distal arm arteries is too poor for a wrist-AVA, an elbow-AVA is often preferred. However, possible hemodynamic consequences are often not considered. In the long term however, patients survival has more priority than AVA patency. Based on our study results demonstrating that a wrist-AVA is associated with a superior survival, it may seem prudent to initiate a preoperative program focusing on improving circumstances for successful wrist AVA construction including lower arm training and radial artery preservation, next to forearm vein preservation. Furthermore, strict surveillance of trends rather than actual Q_a deserves careful consideration in future HD management.

In conclusion, studies of this thesis may aid professionals in optimizing a tailored management of patients who are scheduled to undergo renal replacement therapy, especially regarding the prediction of morbidity and mortality associated with the presence of their life-saving vascular access.

Chapter 12

Nederlandse samenvatting (Dutch Summary)

Nederlandse samenvatting (Dutch summary)

Dit proefschrift omvat studies naar de rol van vingerdrukken (P_{dig}) en shuntflows (Q_a) bij hemodialysepatiënten.

Deel I: De rol van vingerdrukken bij hemodialysepatiënten

Het eerste deel van dit proefschrift (**Hoofdstuk 2-6**) onderzocht of vingerdrukken (P_{dig}), die vóór het aanleggen van een arterioveneuze toegang (AVA) voor hemodialyse (HD) worden bepaald, iets zouden kunnen zeggen over zowel het toekomstig AVA functioneren als ook de patiënten overleving. Vingerplethysmografie is een eenvoudige methode voor het meten van de bloeddruk in de vingers. In combinatie met een standaard bloeddrukmeting aan de bovenarm kan een digitale brachiale index (DBI) worden berekend (ratio vingerdruk / brachialisdruk). In theorie zou deze DBI de kwaliteit van de arteriële vaatvoorziening van de arm kunnen weerspiegelen, of misschien zelfs iets kunnen zeggen over de kwaliteit van het gehele lichaamsvaatstelsel.

In **hoofdstuk 2** hebben we onderzocht of DBI waarden, gemeten bij eindstadium nierfalenpatiënten vlak voor aanleg van hun eerste AVA, gerelateerd waren aan het openblijven van de AVA ('patency'). Een abnormale DBI-waarde (te lage DBI, <80%; te hoge DBI, >100%) bleek twee jaar later geassocieerd te zijn met een bijna twee keer lagere 'primaire' AVA patency (= open blijven zonder enige aanvullende ingreep) in vergelijking met patiënten met normale DBI-waarden (80-100%) (2-jaar primaire patency: normale DBI: 49%, lage DBI: 25%, hoge DBI: 28%). Bovendien was de 'secundaire' patency (= open blijven met aanvullende ingrepen) na twee jaar het laagst in de groepen met abnormale DBI waarden (2-jaar secundaire patency: normale DBI 82%, lage DBI: 55%, hoge DBI 69%). Verrassend genoeg waren veneuze diameters, door de meeste clinici en de huidige richtlijnen beschouwd als dé voorspeller van een succesvolle AVA, niet geassocieerd met langetermijn patency. Deze bevindingen suggereren een potentiële rol voor vingerplethysmografie bij het informeren van patiënten aangaande de keuze van het meest optimale type AVA.

Ongeveer 20% van de patiënten ontwikkelt na AVA constructie een doorbloedingsstoornis van de dialysehand (HAIDI, hemodialysis access induced distal ischemia). Vroeger is gepoogd om een doorbloedingsstoornis van de hand te voorspellen met behulp van de 'Allen-test'. Bij deze test wordt tijdens

afwisselend afdrukken van een van de twee slagaders bij de pols naar verandering in handpalmkleur gekeken. Als de hand deels wit blijft bij een afgedrukte slagader, zou dit iets zeggen over de conditie van de handdoorbloeding en compenserend collateraal vermogen, en mogelijk ook het fenomeen handpijn na aanleggen van een AVA kunnen voorspellen. De Allen-test is echter vanwege onnauwkeurigheid tegenwoordig goeddeels verlaten. Echter, de rol van een Allen-test in combinatie met vingerplethysmografie is nooit eerder onderzocht. In **Hoofdstuk 3** wordt een studie bij 105 eindstadium nierfalen patiënten beschreven, waarbij gekeken wordt of veranderingen in P_{dig} tijdens een Allen-test bij patiënten voorafgaand aan de eerste AVA-constructie, later ernstige HAIDI kan voorspellen. Bij alle 10 patiënten die later HAIDI ontwikkelden bleek de handdoorbloeding al voor AVA-aanleg volledig afhankelijk van een van de twee slagaders ('radiaal ofwel ulnair dominant'). Bij controlepatiënten zonder HAIDI was dit slechts in de helft van de gevallen zo. Wanneer de P_{dig} tijdens de Allen-test met meer dan 40 mmHg daalde, bleek de patiënt een 10 keer hoger risico op het ontwikkelen van ernstige HAIDI te hebben. Een vingerdrukmeting tijdens een Allen-test draagt dus bij aan het identificeren van patiënten met een verhoogd risico op HAIDI.

Voorgaande studies in patiënten met etalagebenen en dialysepopulaties hebben een verband aangetoond tussen een lage enkel-armindex en toegenomen cardiovasculaire mortaliteit (CVM). Zo kan ook worden verondersteld dat een abnormale DBI-waarde vóór constructie van de eerste AVA mogelijk ook geassocieerd is met verhoogde CVM. **Hoofdstuk 4** beschrijft een cohortstudie in 199 eindstadium nierfalen patiënten waarbij er gekeken wordt of dit verband er werkelijk is. Patiënten werden ingedeeld op basis van een 'abnormale DBI' ($<$80%, of $\geq$100%) of een 'normale DBI' (80-99%). 2- en 4-jaar na constructie van de AVA aanleg bleken de CVM percentages in alle DBI groepen gelijk. Echter, na statistische analyse waarbij werd gecorrigeerd voor bepaalde factoren bleek, dat een hoge DBI vóór aanleg van de AVA later een twee keer hoger risico op CVM gaf. Vingerplethysmografie kan dus ook een rol spelen bij het voorspellen van latere overleving. Dit kan van belang zijn bij de keuze van de meest optimale dialysebehandeling voor de juiste patiënt.

De studie van hoofdstuk 3 toonde aan dat de Allen-test in combinatie met vingerplethysmografie een nuttig hulpmiddel is om de 'doorbloedings-reserve' van de hand in te schatten. Om nog een stap verder te gaan, veronderstelden we dat een ontoereikende doorbloedings-reserve van de hand misschien wel een uiting

is van een suboptimaal 'compenserend vermogen' van het *gehele* cardiovasculaire systeem. In **Hoofdstuk 5** bespreken we de rol van een gecombineerde Allen-test/ P_{dig}-meting voor het bepalen van het risico op cardiovasculaire mortaliteit (CVM) na AVA constructie. P_{dig} werd gemeten tijdens een Allen-test als onderdeel van de standaard AVA work-up bij eindstadium nierfalen patiënten. Patiënten die tussen januari 2009 en december 2018 een shunt hadden ontvangen werden bestudeerd (n=108). Patiënten met eerdere cardiovasculaire aandoeningen (CV+) voorafgaand aan AVA-constructie vertoonden bij de Allen-test een grotere daling in P_{dig} waarden (CV: -44 ±5 mmHg vs. zonder-CV: -29 ±3 mmHg, P=0.012). Voor elke ∂P_{dig}-daling van 10 mmHg nam het risico op algehele mortaliteit toe met 10%, en voor wat betreft CVM zelfs met 15%. Vingerplethysmografische metingen kunnen daarom mogelijk worden gebruikt om bij voorbaat een verhoogd cardiovasculair sterfterisico na AVA-constructie te voorspellen, maar deze nieuwe parameter vereist wel bevestiging in grotere onderzoeken.

Eerder onderzoek suggereerde dat overlevingspercentages lager zijn bij HD patiënten die later HAIDI ontwikkelden. Het is echter niet bekend of overleving ook gerelateerd is aan de *ernst* van HAIDI. In **Hoofdstuk 6** wordt een observationele studie gerapporteerd waarin de overlevingspercentages van patiënten met milde HAIDI (graad I-IIa) en ernstige HAIDI (graad IIb-IV) worden vergeleken met een controlegroep zonder HAIDI. De 4-jaars cardiovasculaire mortaliteit bleek vergelijkbaar bij patiënten met milde HAIDI en controles. Daarentegen was de 4-jaarsoverleving bij patiënten met ernstige HAIDI slechts 34% vergeleken met 57% in milde HAIDI. Deze resultaten geven aan dat patiënten met ernstige HAIDI een strengere controle op hun cardiovasculaire conditie nodig hebben.

Deel II: De prognostische rol van AVA-flow (Q_a) bij hemodialysepatiënten

Het tweede deel van dit proefschrift (**Hoofdstuk 7-9**) bespreekt de rol van AVA-flow (Q_a) en AVA-locatie in de arm als voorspellers van overleving in dialysepopulaties. Een minimale Q_a van 400-600 mL/min is vereist voor effectieve hemodialyse (HD). In vergelijking met patiënten met een polsshunt (RC-AVA), lopen personen met een elleboogshunt (BC-AVA) een veel hoger risico op het ontwikkelen van Q_a boven 1500-2000 mL/min, door internationale richtlijnen ook wel aangeduid als een high flow access (HFA). HFA surveillance is hedentendage gebaseerd op *enkelvoudige* metingen van Q_a ('actuele Q_a'), meestal in het kader van het voorspellen van zich ontwikkelende vernauwingen in de shunt. Echter, deze 6-wekelijkse Q_a metingen kunnen per keer aanzienlijk variëren. Pogingen om de rol van seriële (te hoge) Q_a waarden over langere tijdsperioden te beoordelen in relatie tot belangrijke uitkomstmaten zoals (cardiovasculaire) mortaliteit, zijn tot op heden niet verricht.

In **Hoofdstuk 7** analyseerden we 5208 'actuele' Q_a-metingen (n=165 patiënten, periode van 9 jaar) om een mogelijke relatie tussen hoogte van Q_a en overleving te bepalen. Hiertoe gebruikten we een geavanceerde statistische methode genaamd *'Joint Modeling Approach'*. Wanneer de allereerste Q_a-waarde gemeten in een gerijpte en functionele AVA ('initiële Q_a') < 900 mL/min was, bleek de patiënt een vier keer hoger risico op 4-jaars CVM te hebben (HR 4.05) in vergelijking met patiënten met een initiële Q_a >900 ml/min. Bij analyse van Q_a-fluctuaties over meerdere maanden werd een duidelijk verband gevonden tussen Q_a-stijgingen over 3 maanden en CVM (HR 4.48 per 100 mL/min verhoging). Daarentegen bleek de hoogte van *enkelvoudige* actuele Q_a-waarden niet gerelateerd aan overleving. Deze nieuwe parameters kunnen bijdragen aan een verbeterde (cardiovasculaire) surveillance van HD-patiënten die plotselinge verhogingen van Q_a-waarden vertonen.

Een groot aantal onderzoeken naar CVM-percentages in HD populaties vond consequent betere overlevingspercentages bij patiënten met een AVA van eigen lichaamsmateriaal in vergelijking met patiënten die dialyseerden via katheters of kunstaders. Gezien de huidige toegenomen voorkeur voor het aanleggen van een BC-AVA, is het essentieel om te weten of AVA-type (pols- of elleboog-) invloed heeft op de overleving. In **Hoofdstuk 8** rapporteert een retrospectieve cohortstudie over de mogelijke overlevingsverschillen tussen patiënten met een RC-AVA- en BC-AVA. Vier jaar 'vrijheid van CVM' bleek een stuk hoger in RC-AVA (84%) dan

bij een BC-AVA (63%). Wanneer 1000 mL/min als afkappunt van initiële Q_a werd gebruikt, was de overleving van patiënten met een RC-AVA en een initiële $Q_a \geq 1000$ mL/min 100%. Daarentegen vertoonden patiënten met een BC-AVA en een initiële Q_a <1000 mL/min een overleving van slechts 43%. Een multivariate analyse, rekening houdend met vooraf gedefinieerde factoren, gaf aan dat patiënten met een BC-AVA na vier jaar een bijna drie keer hoger risico op CVM hadden in vergelijking met patiënten met een RC-AVA. De bevindingen van deze pilotstudie bevestigen dat RC-AVA altijd als eerste keus AVA overwogen dient te worden. Bovendien kunnen AVA-locatie en initiële Q_a dienen als aanvullende prognostische markers in toekomstige overlevingsmodellen.

In de dagelijkse praktijk bestaat het diagnostisch traject van een mogelijke HFA uit het identificeren van tekenen van cardiale overbelasting en seriële echocardiografie. Indien verdacht voor HFA, kan behandeling middels een chirurgische Q_a-reductie overwogen worden. Echter, een *evidence-based* algoritme ontbreekt nog steeds. De beslissing tot Q_a-reductie is subjectief en is volgens de meest recente ESVS-richtlijn 'gebaseerd op het beste oordeel van de arts'. In **Hoofdstuk 9** bespreken we de chirurgische opties voor Q_a-reductie bij HFA-patiënten. In totaal werden 69 studies met 1016 patiënten bestudeerd. Banding was de meest populaire behandelingsoptie (53%) gevolgd door revision using distal inflow (RUDI, 15%), plicatie/anastomoplastie (8%), proximalisatie van arteriële instroom (PAI, 6%), transplantaat-interpositie (6%), proximale radiale arterie onderbinding (PRAL, 4%), en nog diverse andere technieken (8%). Al deze therapieën waren effectief op korte termijn (500-1600 mL/min gemiddelde Q_a daling). AVA patency en HFA-recidief percentages varieerden echter sterk en waren aanzienlijk. De huidige staat van HFA-management is verre van evidence-based. Gerandomiseerde studies die een afwachtende beleid vergelijken met Q_a-reductie zijn nodig voor het opzetten van een gestandaardiseerd behandelingsregime voor HFA.

Appendices

List of publications

1. **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.

2. 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.

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

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

5. **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 Jul 26. 2021 Dec;74(6):2040-2046.

6. **Yadav R**, Scheltinga MRM. Invitational reply to: Avoiding hemodialysis access-induced distal ischemia. Accepted in Journal of Vascular Surgery.

7. **Yadav R**, Gerrickens MWM, van Kuijk SMJ, Vaes RHD, Snoeijs MGJ, Scheltinga MRM. Access flow volume (Q_a) and survival in a hemodialysis population: An analysis of 5208 Q_a measurements over a 9-year period. Nephrology Dialysis Transplantation. 2021 Aug 12. Online ahead of print.

8. Gerrickens MWM, **Yadav R**, Vaes RHD, Scheltinga MRM. Surgical intervention for high flow arteriovenous haemodialysis access: A scoping review on spectrum of techniques. Submitted to Journal of Vascular Access.

9. **Yadav R**, Gerrickens MWM, Vaes RHD, Scheltinga MRM. Different patient survival with hemodialysis fistulas of brachial artery or radial artery European Journal of Vascular & Endovascular Surgery. 2021 Dec;62(6):1004-1005

Wi-2/ other publications

10. **Yadav R**, Gerrickens MWM, Vaes RHD, Govaert B,van Loon M, Tordoir JHM, van Hoek F, Teijink JAW, Scheltinga MRM. Revision using distal inflow' voor high flow dialysefistels, een wat mager succesverhaal? MMC Medisch Journaal; Jaargang 48 – nummer 1- 2019.

11. JC Diggele van, J Sjatskig, F Akca, S Verstraeten, C de Roest, K de Kort, **R Yadav**, NJ Verberkmoes. Incidence of stroke after anatomical pulmonary resection and the role of the remaining left atrium stump. Dutch Society of Thoracic Surgery, Book of Abstracts. 2018 May 25.

12. **Yadav R**, Gerrickens MWM, Teijink JAW, Scheltinga MRM. Daling in systolische vingerdruk door een Allen Test voorspelt ernstige handischemie bij hemodialysepatienten. Accepted in MMC Medisch Journaal.

13. **Yadav R**, Gerrickens MWM, Scheltinga MR. Abnormal Finger Pressures Prior to Primary Hemodialysis Access Construction Predict Overall Mortality and Cardiovascular Mortality in End-Stage Renal Disease Patients. European Journal of Vascular & Endovascular Surgery. 2019 Dec 1;58(6):e691.

14. **Yadav R**, Gerrickens MWM, Scheltinga MRM. An Abnormal Pre-Operative Digital Brachial Index is Associated With a Lower Two Year Access Patency. European Journal of Vascular & Endovascular Surgery. 2021 Dec;62(6): E85.

15. **Yadav R**, Gerrickens MWM, van Kuijk SMJ, Vaes RHD, Snoeijs MGJ, Scheltinga MRM. Erratum to: Access flow volume (Q_a) and survival in a haemodialysis population: an analysis of 5208 Q_a measurements over a 9-year period. Nephrol Dial Transplant. 2022 Feb 15. Online ahead of print.

16. **Yadav R**, Vaes RHD, Scheltinga MRM. Survival in Haemodialysis Patients is Related to Location of Arteriovenous Fistula. EJVES Vascular Forum. 2022 Jan; 54(9).

List of conference presentations

1. **Yadav R,** Gerrickens MWM, Teijink JAW, Scheltinga MRM. Een abnormale vinger-arm index voor het aanleggen van een hemodialyse shunt is geassocieerd met lagere 2-jaars patency. Chirurgendagen 2022. Oral presentation.

2. **Yadav R,** Vaes RHD, Scheltinga MRM. Overleving van hemodialysepatiënten is gerelateerd aan locatie van arterioveneuze fistel. Chirurgendagen 2022. Oral presentation.

3. **Yadav R,** Gerrickens MWM, van Kuijk SMJ, Vaes RHD, Snoeijs MGJ, Scheltinga MRM. Flow volume (Qa) in hemodialyseshunts en overleving: Een 9-jaar analyse van 5208 Qa-metingen in een hemodialysepopulatie. Chirurgendagen 2022. Oral presentation.

4. **Yadav R,** Gerrickens MWM, Teijink JAW, Scheltinga MRM. Vingerdruk tijdens een Allen Test vóór aanleg van een hemodialyseshunt kan latere handischemie voorspellen. Chirurgendagen 2022. Oral presentation.

5. **Yadav R**, Gerrickens MWM, Teijink JAW, Scheltinga MRM. Systolische vingerdruk tijdens een Allen Test vóór aanleg van een hemodialyseshunt kunnen latere handischemie voorspellen. Vaatdagen 2022. Oral presentation.

6. **Yadav R**, Vaes RHD, Scheltinga MRM. Overleving van hemodialysepatiënten is gerelateerd aan de locatie van de arterioveneuze fistel. Máxima MC Wetenschapsweek 2022. Oral presentation.

7. **Yadav R**, Gerrickens MWM, van Kuijk SMJ, Vaes RHD, Snoeijs MGJ, Scheltinga MRM. Flow volume in hemodialysefistels in relatie tot overleving van een hemodialysepopulatie: Een 9-jaar analyse van 5208 flow-metingen. Máxima MC Wetenschapsweek 2022. Poster presentation.

8. **Yadav R**, Gerrickens MWM, Teijink JAW, Scheltinga MRM. Een abnormale vinger-arm index voor aanleggen van een hemodialyse fistel is geassocieerd met lagere 2-jaars doorgankelijkheid. Máxima MC Wetenschapsweek 2022. Oral presentation.

9. **Yadav R**, Gerrickens MWM, van Kuijk SMJ, Vaes RHD, Snoeijs MGJ, Scheltinga MRM. Vascular access flow volume (Q_a) and survival in a dialysis population: An analysis of 5208 Q_a measurements over a 9-year period. 35th ESVS Annual Meeting, Rotterdam, 2021. Oral presentation.

10. **Yadav R**, Gerrickens MWM, Teijink JAW, Scheltinga MRM. Systolic finger pressures during an Allen test before vascular access construction predict severe postoperative hand ischemia. 35th ESVS Annual Meeting, Rotterdam, 2021. Poster presentation.

11. **Yadav R**, Vaes RHD, Scheltinga MRM. Survival in hemodialysis patients is related to location of arteriovenous fistula. 35th ESVS Annual Meeting, Rotterdam, 2021. Poster presentation.

12. **Yadav R**, Gerrickens MWM, Teijink JAW, Scheltinga MRM. Een abnormale vinger-arm index voor het aanleggen van een hemodialyse shunt is geassocieerd met lagere 2-jaars doorgankelijkheid. Vaatdagen 2021, Virtueel. Oral presentation.

13. **Yadav R**, Gerrickens MWM, Teijink JAW, Scheltinga MRM. Systolische vingerdrukken tijdens Allen Test hebben een rol bij het voorspellen van ernstige handischemie na aanleg van een hemodialyse shunt. Vaatdagen 2021, Virtueel. Poster presentation.

14. **Yadav R**, Gerrickens MWM, van Kuijk SMJ, Vaes RHD, Snoeijs MGJ, Scheltinga MRM. Flow volume (Q_a) in hemodialyseshunts in relatie tot overleving in een hemodialysepopulatie: Een 9-jaar analyse van 5208 Q_a metingen. Vaatdagen 2021, Virtueel. Poster presentation.

15. **Yadav R**, Gerrickens MWM, Teijink JAW, Scheltinga MRM. Abnormale vinger-arm index is geassocieerd met verminderde 2-jaar patency van een hemodialyse toegang. MMC Wetenschapsdag 2021. Poster presentation.

16. **Yadav R**, Gerrickens MWM, Teijink JAW, Scheltinga MRM. Abnormaal verhoogde vinger-arm index voorafgaand aan constructie van hemodialysetoegang is geassocieerd met toegenomen cardiovasculaire mortaliteit. MMC Wetenschapsdag 2021. Oral presentation.

17. **Yadav R**, Gerrickens MWM, Scheltinga MRM. Daling in vingerdruk na radiale of ulnaire arteriële compressie voorafgaand aan aanleg hemodialyseshunt is geassocieerd met toegenomen lange termijn mortaliteit. MMC Wetenschapsdag 2021. Poster presentation.

18. **Yadav R**, Gerrickens MWM, Teijink JAW, Scheltinga MRM. Systolische vingerdrukken voorafgaand aan de Allen Test voorspellen ernstige handischemie na aanleg van een hemodialyse toegang. MMC Wetenschapsdag, 2021. Oral presentation.

19. **Yadav R**, Gerrickens MWM, Teijink JAW, Scheltinga MRM. Een abnormale vinger-arm index voor het aanleggen van een hemodialyse shunt is geassocieerd met lagere 2-jaars doorgankelijkheid. NVvH Chirurgendag, cancelled due to COVID, 2021. Accepted for oral presentation.

20. **Yadav R**, Gerrickens MWM, Scheltinga MRM. An abnormal digital brachial index prior hemodialysis fistula construction is associated with 2 year access patency. 34rd ESVS Annual Meeting, Virtual, 2020. Oral presentation.

21. **Yadav R**, Gerrickens MWM, Scheltinga MRM . Daling in vingerdruk na radiale of ulnaire arteriële compressie voorafgaand aan aanleg hemodialyseshunt is geassocieerd met toegenomen lange termijn mortaliteit. NVvH Chirurgendagen, cancelled due to COVID, 2020. Accepted for oral presentation.

22. **Yadav R**, Gerrickens MWM, Scheltinga MRM. Abnormal finger pressures prior to primary hemodialysis access construction predict overall mortality and cardiovascular mortality in end-stage renal disease patients. 33rd ESVS Annual Meeting, Hamburg, 2019. Oral presentation.

23. Groos P, Kromhout J, Scheepers M, Skrabanja T, Smeets K, Slegers R, Winkel K, **Yadav R**. Towards a representative NAFLD liver model. Bytemal Conference, Maastricht, 2018. Poster presentation.

24. Groos P, Kromhout J, Scheepers M, Skrabanja T, Smeets K, Slegers R, Winkel K, **Yadav R**. Advanced in-vitro model of human primary hepatocytes on optimal surface topography. Bytemal Conference, Maastricht, 2018. Poster presentation.

25. Groos P, Kromhout J, Scheepers M, Skrabanja T, Smeets K, Slegers R, Winkel K, **Yadav R**. Towards a representative NAFLD liver model. European Fatty Liver Conference, Maastricht, 2018. Poster presentation.

Awards & Grants

- **2022: MMC Wetenschapsdag:** 2 invitations for final rounds, top 6 abstracts of hospital
- **2021 Vaatdag:** Invited for final rounds, top 5% of all abstracts
- **2021: MMC Wetenschapsdag:** 2 invitations for final rounds, top 4 abstracts of hospital
- **2020 34rd ESVS Annual Meeting:** invited for final rounds, selected as top 5% of all abstracts
- **2019 Van Walree Grant** funded by the Koninklijke Nederlandse Akademie van Wetenschappen (KNAW)
- **2018 SWOL grant** funded by The University Fund Limburg

Dankwoord

De eindstreep van dit proefschrift is bereikt. Mijn voorkeur gaat uit naar daden over woorden betreft het bedanken van een ieder. Uiteraard verdient dit ook een schriftelijke vermelding.

Het team waarmee ik de afgelopen jaren heb samengewerkt kent bekendheid op dit deelgebied binnen de vaatchirurgie, waarbij ik van geluk mag spreken dat het lot ons bij elkaar heeft gebracht. De toewijding van iedereen om dit proefschrift tot een succes te maken is simpelweg niet in woorden uit te drukken.

Beste Prof. dr. Teijink, Beste Joep,

Uw energie, kennis en daadkracht is onuitputtelijk. In de meeste letterlijke zin bent u 24 uur per dag, 7 dagen per week, 365 dagen per jaar bereid om de beste kwaliteit van zorg en onderzoek te leveren, ongeacht wat het kost. Terwijl veel personen ten tijde van de COVID periode geen werk meer konden verrichten, heeft u Claudicationet getransformeerd naar Chronisch Zorgnet met een landelijke dekking op 3500 locaties om chronische aandoeningen te verhelpen.

Als ik langer dan een uur geen reactie op mijn bericht had, begon ik me al zorgen te maken over u. Uw energie is beslist aanstekelijk en gaf me telkens de motivatie om grenzeloos door te zetten. Ik kijk vol vreugde uit om onze samenwerking voort te zetten bij de verbetering van de diagnostiek en behandeling van TOS-patiënten.

Beste Dr. Scheltinga, Beste Marc,

Vanaf dag 1 wisten we meteen dat ons een prachtige tijd te wachten stond. Uw verhaal van de stoel met de losse leuning is me altijd bij gebleven, en toont aan dat alles werkelijk mogelijk is zolang je er zelf in gelooft. Als er meerdere personen gelijkwaardige toewijding als u hadden, was de zorg mogelijk 10-20 jaar verder geweest.

Gepromoveerd op studies verricht aan Harvard Medical School onder de befaamde Douglas Wilmore, 230+ publicaties in gerenommeerde bladen, talloze promoties. Men kan denken dat dit ten koste gaat van de patiëntenzorg, maar er staat toch echt een 10/10 gewaardeerd op Zorgkaart.

U heeft me afgelopen jaren 24/7, 365 dagen per week bijgestaan, ongeacht vakanties, ongeacht feestdagen. Een manuscript kon ik 23:00 sturen en het was de volgende dag nauwkeurig nagekeken. Het was een synergetische samenwerking wat tot deze interessante resultaten heeft geleid. U heeft meer energie en daadkracht dan de gemiddelde arts-assistent heelkunde, ik hoop daarom dat u nog een langere periode door blijft gaan met uw activiteiten. Ik zal u altijd waar mogelijk bijstaan en hopelijk kunnen we samen nog meer mooie primeurs behalen binnen de dialysechirurgie!

Dankuwel voor de leerzame tijd.

Beste leden van de beoordelingscommissie, ik ben u allen hartelijk dankbaar voor de tijd die u allen heeft geïnvesteerd in het nauwkeurig beoordelen van dit proefschrift. Ik mag van geluk spreken met een beoordelingscommissie van dergelijk niveau en uw suggesties zullen voor toekomstig onderzoek beslist waardevol zijn.

Beste medeauteurs, hartelijk dank voor jullie waardevolle bijdrage aan het tot stand brengen van de manuscripten.

Beste Michel Gerrickens, mijn vragen, suggesties en commentaar kon ik bij jou altijd kwijt. Jij hebt mij in de juiste startblokken gezet waarmee dit proefschrift als een sneltrein de eindbestemming op tijd en met kwaliteit heeft bereikt. Ook jouw adviezen om altijd open-minded te zijn heb ik altijd waardevol gevonden en hebben invloed gehad op mijn keuzes. Hoewel jouw hart niet bij de chirurgie ligt, ben ik ervan overtuigd dat jij een goede beschouwend specialist zal worden.

Beste Dr. Vaes, beste Roel, het grootste deel van dit proefschrift heb ik je helaas moeten missen aangezien jij en je gezin zich letterlijk aan de andere kant van de wereld bevonden. Jouw timing van terugkomst had niet beter gekund, jouw adviezen bij de Flow-Survival studie waren van onschatbare waarde. O.a. dankzij jou hebben we deze primeur behaald. Ik hoop in de toekomst dat jij ook door zult blijven gaan met onderzoek, je kennis zal de dialysezorg naar een hoger niveau tillen!

Beste Dr. van Kuijk, beste Sander, wat jij geprogrammeerd hebt voor de Flow-Survival studie is daadwerkelijk ongelofelijk. De betreffende statistische technieken zijn vooruitstrevend en van ongekend niveau. De resultaten hebben directe invloed op ons kijk op huidige flow-data. Binnen een jaar 60+ publicaties, het zal niet lang meer duren tot je oratie :) !!!

Beste Chirurgen van het Máxima MC, hartelijk dank voor alle mogelijkheden en interessante, leuke feedback voor mijn diverse onderzoeken. De sfeer alhier bij de heelkunde is onderscheidend!

Beste Dr. Papen-Botterhuis en Dr. Govaert, beste Nicole en Bastiaan, bij u vond eigenlijk het eerste gesprek plaats, waartoe dit allemaal heeft geleid. Ik dank u beiden hartelijk voor het vertrouwen.

Beste Dr. Janssen, beste Loes. Wij zijn ongeveer tegelijk begonnen en je hebt me altijd direct bij gestaan voor hulp vanuit allerlei hoeken. Van statistiek tot logistiek, van coschappen tot werkplek. Dank voor alle hulp.

Beste Dr. Verhofstad, beste Nicole, jij kwam later in beeld, maar desondanks heb je me perfect geleid in het proces tot en met de promotie. Hartelijk dank voor de hulp en hopelijk zien we elkaar vaker in het Catharina Ziekenhuis.

Beste Jos Peters, hartelijk bedankt voor je hulp, advies en vertrouwen. Als raadslid ben je onmisbaar voor Valkenswaard.

Beste Toon van Leeuwen, hartelijk dank voor het ophalen van de cruciale data van de Flow-Survival studie. Je bent een ware technicus op dit gebied.

Beste Kim Wijns, jij bent een cruciaal persoon voor de dialyseonderzoekslijn. Ik dank je hartelijk voor alle inzet en hulp.

Beste Dr. Dieleman, beste Jeanne, hartelijk dank voor alle tips en tricks vanuit epidemiologisch perspectief.

Beste Vaatlaboranten, jullie zijn het hart van het vaatlaboratorium. Dank voor het uitvoeren van de 100'en metingen en de service. De invloed van jullie werk vormt de basis van dit onderzoek.

Beste mede-promovendi, binnen het MMC zijn wij absoluut het zaligste clubje! Jammer genoeg konden we elkaar niet vaak zien, mede dankzij COVID en andere activiteiten o.a. van mijzelf. Gelukkig zijn we altijd in de buurt. Succes met jullie promoties en het bemachtigen van een opleidingsplek Heelkunde!

Beste Sabine, dank voor alle wijze lessen, adviezen, balans en steun. Jij hebt invloed gehad op de richting van het schip!

Beste Joep, Konrad, Jilles, Luc, Remco, Jens, Thom, Pim en Bas. Prachtig, na 10 jaar nog steeds een hecht clubje. Ondanks dat initieel iedereen verspreid was, zijn we gelukkig allemaal weer bijeen in het vreugdevolle Brabant. De mooie avonturen die we met zijn allen hebben meegemaakt zijn onvergetelijk. Hoewel de lama vaak kwijtgespeeld wordt, geldt dat gelukkig niet voor onze onbreekbare vriendschap. Onze tradities zijn officieel met de complete club begonnen op Mallorca en zullen zich beslist tientallen jaren voortzetten op wekelijkse basis alsmede met onze jaarlijkse reis. More adventures have yet to come!!!

Beste Maassquad, Beste Bob, Ignace, Konrad, Toju, Joep, Ephrahim en Luuk. Vanaf jaar 1 al beste vrienden. Van mooie feesten in Maastricht tot reizen naar Alicante, we hebben altijd en overal een leuke tijd beleefd. Bob zorgde altijd voor de balans, Ignace voor de Belgische ambience, Konrad voor zijn droge humor, Toju voor de wijze lessen, Joep met zijn taferelen, Ephrahim voor de management en Luuk voor de goede sfeer. Ieder heeft een unieke waarde, wat zich ook zal uiten in jullie carrières. Het schip is richting het Noorden gevaren, ik hoop dat uiteindelijk iedereen van ons deze richting op gaat en blijft.

Beste Ralf, jouw ken ik al sinds 2005 en niks is. De tweede prijs staat niet in jouw woordenboek. Vroeger keken we samen hoe we 4-0 konden scoren, nu kijken we hoe we het data landschap in NL naar een hoger niveau kunnen tillen.

Beste vrienden en vriendinnen van het Sondervick, beste Anouk, Bas, Dominique, Feline, Jens, Jilles, Joep, Konrad, Noortje, Quirien, Sterre, Kim, Sophie, Avyola, Fleur, Ilse en Karlijne. Jullie vormden het hart het van de tijd die wij beleefd hebben op het Sondervick. Onvergetelijke vreugde. We hebben elkaar allemaal zien opgroeien vanaf dat we jonkies met beugels waren. De wekelijkse partijen, de pauzes, de vakanties, deze zijn werkelijk onvergetelijk. Helaas zijn we letterlijk alle windrichtingen opgegaan, maar niet uit het hart!

Beste IFMSA vrienden, beste Luc, Anouk, Demi, Eva, Jens, Joep en Konrad. Dit clubje is op grappige wijze en toevalligheden ontstaan wat tot onvergetelijke momenten heeft geleid gedurende de bachelor fase. Huize Scharnerweg was het hoofdkwartier voor plezier. Gedurende de coschappen waren onze contacten helaas minder door de activiteiten, echter zullen we dit weer op korte termijn oppakken.

Beste Peter en Annemieke, contacten sinds vorig millennium. Jullie hebben een hart waar menig mens voorbeeld aan kan nemen. Dank voor jullie hulp.

Beste Joep, Jens en Konrad. Voor de oplettende kijker zal het vast opgevallen zijn dat jullie wel vaak terugkomen in het dankwoord. Toeval? :) De meeste vriendschappen zijn vanuit deze kern in principe ontstaan. We kennen elkaar al bijna 15 jaar. Samen opgegroeid, samen geneeskunde gaan studeren en een prachtig huis in Maastricht weten te bemachtigen in de bachelor jaren. Allen

nominaal afgestuurd als arts. En dit is nog maar het begin van een jarenlange voortzetting. Op naar mooie tijden!

Beste Mama en Papa, jullie hebben letterlijk altijd voor mij klaar gestaan. Jullie hebben er alles aan gedaan om ervoor te zorgen dat wij de top kunnen halen. Nog vandaag de dag vraag ik jullie om adviezen welke mij als persoon daadwerkelijk naar een hoger niveau tillen. Jullie zorgen ervoor dat alles gefaciliteerd wordt en dat ik plezier heb in het behalen van mijn doelen. Dit proefschrift is het bewijs van jullie doorzettingsvermogen en kennis.

Beste Monique, we weten allebei door wie eigenlijk dit proefschrift is ontstaan, evenals mijn co-promotor. Ik ben blij dat jij een mooie vervolg carrière in Utrecht hebt gezet, waarbij een prachtig toekomst nabij bevestigd is.

Curriculum Vitae Auctoris

Reshabh Yadav was born on October 13th, 1996 in New Delhi. In 2015 he graduated successfully from high school (Sondervick College) with a TTO VWO gymnasium degree. Thereafter, he was directly admitted to Medical School of the University of Maastricht. His keen interest for medical research already developed in the second year of Medical School. In 2016 he was selected for the Honours Program of Maastricht University (top 5% of class), where he was elected as chairman of the Live4liver research team taking the lead of 10 researchers. Simultaneously in his second year he already started doing research in Catharina Hospital, supporting clinical activities for the multicenter SANICS II trial. In his third year, he joined the Young Investigators Team (YIT) at the department of cardiothoracic surgery.

With good luck Reshabh Yadav met Dr. Marc R.M. Scheltinga, a well-known surgeon in the Maxima Medical Center. This introduction led to a full PhD-track where Prof. Dr. Joep A.W. Teijink joined as his promotor. Reshabh Yadav received his Doctor of Medicine degree in September 2021 and few months after he will defend his PhD on June 13th 2022.

In his free time, Reshabh Yadav is a keen golfer playing HCP 8.1.

Reshabh Yadav has already been contacted by notable management consulting firms. For now, Reshabh Yadav has chosen to continue his medical career which includes residency combined with postdoctoral research in vascular surgery and (interventional) radiology.