

Studies on high flow and hand ischaemia associated with an upper extremity haemodialysis access

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Chapter 11

Impact section

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

Scientific impact

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

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

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

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

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

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

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

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

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

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

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

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

Social impact

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

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

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

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

