The life cycle of the vascular access: from creation to ligation

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Chapter 8

Summary and discussion

Summary

A vascular access (VA) is required to accommodate chronic hemodialysis (HD) treatment. This thesis focused on the current outcomes of VAs, an attempt to improve arteriovenous fistula (AVF) maturation and the hemodynamic and cardiovascular downsides of AVFs.

Chapter 2 describes a retrospective cohort study in which we evaluated the maturation of radiocephalic AVFs (RCAVF) and upper arm AVFs, and compared it to the primary failure rate of arteriovenous grafts (AVG). We found that RCAVFs were most often the first access for an individual patient whereas upper arm AVFs were more commonly created in patients with a history of a failed VA. Even though, maturation failure was most common for RCAVFs at 24%, compared to 11% for upper arm AVFs. A significantly smaller proportion of AVGs was primarily not usable for HD, at less than 6%. We then attempted to create a model to predict nonmaturation of RCAVFs, which included a small vein diameter, female gender, peripheral vascular disease and cerebrovascular disease. With an area under the receiver-operator characteristic curve (ROC) of 0.6, this model lacked specificity to predict RCAVF maturation failure and thus was not clinically applicable to guide treatment decisions regarding the selection of AVF location for individual patients.

We then evaluated the patency outcomes of this cohort in **chapter 3**. We found that once a vascular access has successfully matured, the functional patency is very good, with a 3-year functional patency (censored for death and abandonment not related to the VA itself) of 83% for both RCAVFs and upper arm AVFs and 72% for AVGs. However, if all VAs are taken into account, and not only the matured VAs, the 3-year functional patency is worse for RCAVFs at 62% and better for upper arm AVFs at 74% and AVGs at 69%. Infections were more common in AVGs and AVGs required more maintenance procedures per year of patency, compared to AVFs.

It was previously shown that AVF maturation involves inflammation. In an animal model, prednisolone encapsuled in liposomes successfully inhibited this inflammatory response and resulted in an increased AVF lumen. **Chapter 4** presents the design of the LIPMAT study. In this double-blinded randomized controlled trial, we evaluated if liposomal prednisolone improves the maturation of RCAVFs in humans. Patients were treated twice with 150mg of liposomal prednisolone or placebo, at one day after surgery and two weeks thereafter. The study was powered to detect a 1.0 mm improvement of the juxta-anastomotic diameter at six weeks

after surgery. Secondary end-points of the LIPMAT study were cephalic vein downstream diameters and blood flow in the cephalic vein, radial artery and brachial artery. Adverse events and interventions were evaluated as safety end-points.

As described in **chapter 5**, 29 patients were treated in the LIPMAT study. The LIPMAT-study was the first to evaluate liposomal prednisolone for AVF maturation and was also the first study in which ESKD patients were treated with liposomal prednisolone. The juxta-anastomotic diameter at 6 weeks, the primary end point of the study, was 3.9 mm in the placebo group and 3.7 mm in the liposomal prednisolone group, a difference which was not statistically significant. At six weeks after surgery, the median AVF flow was 456 ml/min in the placebo group and 406 ml/min in the treatment group. The functional outcomes of RCAVFs in the LIPMAT study were comparable to those in literature, with 23% of RCAVFs in the placebo group failing due to nonmaturation, versus 13% in the treatment group.

Overall, liposomal prednisolone was tolerated well by this population. Although some infections were observed in the study, these were either minor, or well after the treatment effect of liposomal prednisolone had worn off. We therefore conclude that the LIPMAT study did not raise any safety concerns for liposomal prednisolone in ESKD patients and that these patients should not be excluded in any future studies evaluating the drug for other indications.

Until **chapter 6**, we focused on making and maintaining a VA suitable for hemodialysis. Chapter 6 introduces a drawback of AVFs and AVGs, which increase cardiac output by their nature of a low-resistance circuit. In patients with a reduced diastolic or systolic left ventricular function, the heart may not be able to provide adequate cardiac output to accommodate both the AVF flow and organ perfusion. The resulting condition is known as high output heart failure, which may be underestimated since volume overload in HD patients is often attributed to other factors. High output heart failure may cause clinical symptoms, but also increases the left ventricular mass and pulmonary artery pressure, measures commonly recognized as risk factors for mortality. This chapter reviews observational studies on this topic, which demonstrate an improvement of left ventricular mass and pulmonary artery pressure after AVF closure.

At the time this research was performed, no randomized controlled trials were available which investigated the potentially beneficial effect of AVF closure on cardiovascular risk factors. We clinically experience that important differences exist among attitudes of healthcare providers towards keeping or abandoning an AVF after kidney transplantation. In **chapter 7**, we measured

physicians' attitudes towards this topic. A survey was sent out to members of eight societies, consisting of clinical case vignettes presenting patients with a functioning AVF after kidney transplantation. Age, AVF flow and left ventricular function were varied and respondents were asked if they would maintain or ligate the AVF. Five-hundred and eighty-five surveys were returned. A reduced left ventricular function and a higher AVF flow were recognized as factors which increased the tendency to ligate. Disagreement was however considerable, with over 20% of respondents electing to maintain an AVF even in a patient with a high AVF flow and a poor cardiac function.

Discussion and future perspectives

With the increasingly aging population and the rising rates of risk factors for end-stage kidney disease (ESKD) such as diabetes mellitus, the number of patients requiring renal replacement therapy is expected to keep rising and many of them will require HD. The VA remains the Achilles' heel of chronic HD treatment. As more patients will require HD, patients and the healthcare system will be increasingly burdened with the cost of VAs and their complications. Research aimed at improving VA success rates whilst limiting side effects is therefore important both to improve patients' quality of life and limit healthcare expenses.

Can we improve maturation?

In chapter 3 of the thesis, we demonstrated that the native AVF requires less maintenance procedures than the AVG, albeit at the cost of a high initial failure rate. This nonmaturation rate seems to be a multifactorial process involving pre-existing vascular pathology, a pro-inflammatory milieu and postoperative changes favoring the formation of neointimal hyperplasia [1]. Interventions to improve maturation have been disappointing so far. Several pharmacological strategies to improve maturation have been evaluated in human trials over the past years, yet none have demonstrated to improve maturation in a clinically relevant amount.

Targeting inflammation

The LIPMAT study failed to demonstrate a significant improvement of AVF maturation by liposomal prednisolone. Does this mean that inflammation is not an important target in AVF maturation? Preclinical studies may provide some insight into that. First, transgenic animal studies show that inflammatory molecules, such as MCP-1, CD44 and the TLR4 regulatory molecule RP105 were linked to AVF failure, whereas anti-inflammatory HO-1 and HO-2 were

described to be protective [2–6]. Also in humans, Stirbu and colleagues showed in a cohort of 258 patients that higher serum CRP levels at the time of AVF placement are independently associated with an increased risk of AVF patency loss [7]. Martinez et al quantified RNA transcription in human vein specimens obtained at AVF surgery and found that an inflammatory fingerprint was associated with nonmaturation [8]. Based on these studies, we conclude that inhibiting inflammation should not be abandoned as a therapeutic target.

So, how can we improve the efficacy of anti-inflammatory therapy? First, we need to make sure that the active drug actually reaches the vein in a sufficiently high concentration whilst limiting systemic exposure and side effects. In AVFs, typically three delivery vehicles are feasible for targeted drug delivery. As tested in the LIPMAT-study, liposomes may reach high local concentrations at sites of inflammation, but this has not been proven for AVFs in uremic patients, who may lose a significant portion of the drug to other tissues, including atherosclerotic arteries. Before using liposomes for future AVF research, local tissue delivery should be proven using, for example, imaging with a radioactive tracer. Another method of drug delivery in AVFs is using drug-coated balloons or stents. These are currently used for the treatment of stenoses that occur after the AVF has been created [9]. Finally, the surgery in which the AVF is created provides an ideal opportunity to apply a drug directly to the anastomosis. This method has been used for several drugs in the field of AVF research. Secondly, we need to select a drug with an effect which is likely to improve the physiology of maturation. Compelling drugs to attempt in this configuration are the mammalian target of rapamycin (mTOR) inhibitors, which inhibit T-cells but also directly inhibit vascular smooth muscle cell proliferation, limiting neointimal formation.

Targeting the extracellular matrix

Another target for AVF maturation may be the extracellular matrix, by wither inhibiting its formation or by promoting its degradation. Martinez et al investigated the relationship between pre- and post-operative venous fibrosis and maturation in vein samples obtained from 161 human two-stage AVFs [10]. It was hypothesized that fibrosis is associated with vascular stiffness and therefore adversely impacts maturation. In the pre-operative samples. extensive medial fibrosis was observed, however neither pre-operative fibrosis nor the intima/media ratio was associated with nonmaturation. The post-operative samples revealed that both medial fibrosis and the intima/media ratio significantly increase after AVF creation. Nonmaturation, defined in this study as a luminal diameter of less than 6 mm, was significantly associated with high medial

fibrosis and a high intima/media ratio. Next, the characteristics of fibrosis were investigated, revealing that alignment of collagen fibers circumferentially around the lumen was associated with less maturation. This study shows that the postoperative increase in fibrosis was indeed associated with nonmaturation. Can we then attempt to inhibit this fibrosis from forming? This was investigated by Hernandez et al who applied the collagen-crosslinking inhibiting substance β-aminopropionitrile locally around the venous segment in a rat AVF model [11]. Treated AVFs achieved a significantly larger lumen than controls. To our knowledge, no human trial with a drug derived from this research is yet in preparation.

Degradation of elastin fibers is another therapeutic target. This was evaluated by the investigators of the PATENCY-1 and PATENCY-2 trials [12]. In these studies, the drug vonapanitase, a recombinant elastase, was applied to the AVF anastomosis at the time of surgery. By disrupting elastin fibers, vonapanitase facilitates outward remodeling of the venous segment of the AVF. In the PATENCY-1 study, the drug did not improve primary patency but was associated with associated with better unassisted (39 versus 25%, p=0.035) and assisted (64 versus 44%) use for HD compared to placebo. The PATENCY-2 study failed to demonstrate superiority over placebo at the end points of AVF use for HD and secondary patency. The drug is no longer under active development for AVF maturation. Other unsuccessful interventions include antiplatelets, cholecalciferol, fish oil and nitrates [13–16].

Non-pharmacological means to improve maturation

Maybe, rather than attempting to improve maturation by pharmacological means, other approaches may be more successful. A randomized controlled trial in 2015 by Fontseré et al investigated the effect of postoperative muscle exercises and found a significant improvement of AVF use for HD [17]. A similar approach is currently under investigation in the PINCH trial, which investigates if pre-operative forearm exercise increases the pre-operative cephalic vein diameter, making creation of a more distally placed AVF possible [18]. An automatic pneumatic device which intermittently occludes the AVF vein during the maturation phase was also shown to improve the AVF diameters at one month after surgery [19]. A device which irradiates the AVF with far-infrared radiation improved maturation from 76% to 90% in a randomized controlled trial [20]. An implanted device which optimizes the arteriovenous anastomosis geometry was associated with an 88% maturation rate of RCAVFs in a retrospective study [21]. A randomized controlled trial is currently ongoing, with safety as its primary outcome and maturation, blood flow and patency as secondary outcomes [22].

Can we improve AVF maturation by selecting the right patients?

Another approach to improve maturation is to identify those patients in whom an AVF is likely to fail and to elect for a VA which is more likely to succeed in those patients. A scoring system was developed by Lok et al in 2006, in which demographic characteristics and comorbidities predicted nonmaturation and classified the risk of nonmaturation into four groups, ranging from low (24% risk) to high (69% risk) [23]. Farrington et al retrospectively studied 300 patients who received a new AVF whilst on HD with a central venous catheter [24]. Significant predictors for maturation were the preoperative arterial diameter, blood pressure and cardiac function. A prediction model based on these variables could predict maturation with fair accuracy, with an area under the ROC of 0.69.

The ARCH project developed a more patient-specific prediction of AVF flow based on pre-operative ultrasound measurements, which predicted postoperative flow accurately [25]. In a randomized controlled trial, this model was tested as a tool to aid the surgeon in choosing the most appropriate AVF configuration [26]. This did not result in an improved rate of maturation failure, which was 29% in the control group and 32% in the intervention group [27].

No single 'golden bullet' treatment for AVF maturation exists yet and that the future likely lies in combinations of novel pharmacologic interventions and surgical and supportive therapies. Even though computational models may stratify patients in low-to-high risk of nonmaturation groups, the clinical applicability of such models is limited. None of these models are able to identify those patients in whom an AVF will fail with near certainty. Only in those patients, not attempting to create an AVF may be a sensible approach, as such a strategy limits the options available for future AVF creation.

Can we select the right vascular access?

As we have shown, a well-functioning AVF is associated with a relatively low incidence of maintenance procedures, compared to AVGs. Does this mean that every HD patient should receive an AVF? Not necessarily.

A major disadvantage of the AVF is the time required for maturation. To allow for maturation and any procedures which may be required to assist maturation, an AVF is typically created pre-emptively: well before a patient needs to initiate HD. This introduces a problem: can we predict when a patient will actually need HD, and do we know if a patient will live long enough to reach ESKD? We cannot. Lee et al found in a large cohort of patients aged over 70 years, that two

years after VA creation, 67% had initiated HD, whilst 15% had died before starting HD and another 18% survived dialysis free [28]. In the subgroup of patients over 85 years of age, only 60% had initiated HD two years after VA creation. Catheter dependence at the start of HD was higher in the group receiving an AVF at 46%, compared to 29% in the group receiving an AVG. These results demonstrate that a significant proportion of elderly patients who receive a permanent VA pre-emptively will be exposed to the burden and complications of surgery and maintenance procedures, but will not benefit from the VA. For these patients, waiting until HD initiation is imminent and starting with a central venous catheter or an 'early stick' AVG may limit unnecessary procedures. Indeed, the last decade there has been a paradigm shift towards an individualized approach rather than a 'fistula first' strategy [29,30].

A final thought is that we are not fully aware which disadvantages commonly attributed to AVFs and AVGs are the result of confounding by indication due to different patient populations, rather than actual side effects of the VA itself. The Optimizing Access Surgery In Senior hemodialysis patients (OASIS) study which is currently ongoing may shed some light upon this. This randomized controlled trial will randomize elderly patients between a central venous catheter, AVF, or AVG and investigate interventions and complications, functional outcomes, quality of life and healthcare expenses.

Is closing AVFs after kidney transplantation a sensible strategy?

As described in chapter 6, observational studies suggest that cardiac parameters may improve after closure of an AVF. Obvious disadvantages of elective AVF ligation are the cost and burden of the procedure and the loss of a future VA option if the patient needs to resume HD. Elective ligation of AVFs is not common practice, with a recent study finding that in a cohort of 16.845 patients who received a kidney transplant with a functioning AVF or AVG, in only 779 cases (4.6%) that VA was ligated [31]. Most of these ligations were performed because of symptoms, most commonly steal syndrome (adjusted HR 41.0; 95% confidence interval 34.6-48.6).

Our survey in chapter 7 also demonstrated considerable disagreement amongst physicians on how to approach these VAs. Patients also seem to have different opinions. A recent survey in 301 kidney transplantation recipients by Bardowska et al showed that 23% of respondents considered AVF ligation, while 39% do not want to have their AVFs ligated [32]. These findings demonstrate that the evidence available is at best not considered convincing, or conflicting at worst.

Recently, results from the first randomized controlled trial on this topic were published. Rao et al randomized 54 kidney transplantation recipients to AVF ligation or no ligation and performed cardiac magnetic resonance imaging at baseline and 6 months [33]. A significant improvement of -22 grams of left ventricular mass was observed in the treatment group, with no significant change in the control group. Improvements in other cardiac parameters were also observed.

These studies demonstrate that the AVF indeed has a detrimental effect on cardiac parameters and that ligation may reverse these changes, although evidence with benefit on hard clinical end points is not yet available.

Future perspectives

In recent years, VA research has seen several innovations and some have found their way into the clinic already. One novelty is the endovascular AVF (endoAVF), which is performed by placing catheters into the ulnar artery and vein, which attract each other using magnets and then create the anastomosis using a radiofrequency electrode. This method induces less surgical trauma to the vessels and may limit the formation of intimal hyperplasia. Its use is limited to a selected group of patients with anatomy suitable to create an endoAVF and the anastomosis is created at the proximal forearm, reducing length available for cannulation compared to RCAVFs. In patients enrolled in the NEAT study, 87% of endoAVFs were physiologically suitable for HD within 3 months [34]. Compared to matched patients who received a surgical AVF, the 70% of endoAVF patients did not need additional interventions in the first year, compared to 18% for surgical AVFs [35].

Another way to prevent catheter- or AVG-related complications is tissue engineering: to create a new blood vessel which is constructed of the patients' own tissue, but does not suffer from nonmaturation like AVFs do.

Human acellular vessels are created in the laboratory using patient- or donor-derived fibroblasts and smooth muscle cells which are placed on a biodegradable scaffold [36]. These cells then produce an extracellular matrix resembling an arterial wall. After decellularization, these grafts can be implanted as a VA, which over time gets populated with the recipients' own cells. Two single-arm studies with these grafts demonstrated a primary patency of 28% but a good 89% secondary patency at one year after surgery. The incidence of infections was very low, with one event per 89 patient-years [37].

Another approach is in-vivo tissue engineering, in which the patient grows his or her own blood vessel. A rod-shaped implant is placed into the subcutaneous tissue, which elicits a foreign-body response which starts off as an inflammatory process and results in the attraction of myofibroblasts which produce a collagen capsule around the implant. After the implant is removed, the capsule remains as a hollow tube. This tube can then be connected to an artery and vein, forming a VA [38]. This method has been tested in a preclinical model, in which endothelialization of the tissue capsule was observed, showing that these capsules indeed form true blood vessels. A safe margin of bursting pressure was demonstrated [39]. In a highly thrombogenic animal model, the patency of these tissue-engineered grafts was comparable to AVGs. A human trial which investigates the performance of these tissue-engineered blood vessels will commence soon.

Conclusion

For long, the AVF was considered the best VA and a 'fistula first' strategy was advocated. This belief also found its way into legislation, with the fraction of patients starting HD with an AVF currently used as a quality indicator in the Netherlands. The choice of VA remains however a trade-off between advantages and disadvantages, weighing the risks of not reaching ESKD, nonmaturation, starting HD with a catheter, cardiovascular complications and long-term VA related complications. No 'one size fits all' treatment exists and every decision should be individualized, weighing these advantages and disadvantages and taking the patients' preferences into account. This was recognized in the most recent update of the KDOQI guidelines, published in 2020 [40]. Rather than focusing on a 'fistula first' target, an individualized Life-Plan should be made, of which the choice of VA is an important part.

It is clear that the perfect VA does not exist, but that the demands placed on them will only increase in the future with advances such as the wearable kidney and the shift towards home hemodialysis, making this field of research of vital importance for the future success of treatment of patients.

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