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REVIEW

VASCULAR ACCESS

Hemodynamic considerations in arteriovenous vascular access modalities for hemodialysis

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ABSTRACT

Arteriovenous fistulas and arteriovenous grafts are the most commonly used vascular access for hemodialysis in patients with end-stage chronic kidney disease. However, both methods face significant challenges due to the hemodynamic disturbances induced by the arteriovenous anastomosis. This causes changes in vascular structure and blood flow velocity near the anastomosis site after the fistula/graft surgery, and introduces abnormal wall shear stress and cyclic stretch. This leads to endothelial cell dysfunction, vascular smooth muscle cell proliferation, and adverse remodeling. The resulting effects include low patency rates due to vascular stenosis caused by intimal hyperplasia and insufficient outward remodeling. Additionally, the high flow conduit has been linked to adverse cardiac remodeling. To address this, various strategies have been explored to correct these localized hemodynamic abnormalities, aiming to improve long-term patency rates. In this review, an overview is provided of the current surgical techniques, anastomosis types, anastomosis angles, external scaffolds, modified fistula designs, and types of grafts. It evaluates the impact of these approaches on local hemodynamics in the access conduit and their potential effects on patient outcomes.

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End-stage kidney disease (ESKD) patients often rely on hemodialysis as renal replacement therapy. The arteriovenous (AV) vascular access is the lifeline for these patients. Introduced in 1966, the radiocephalic arteriovenous fistula (AVF)[1] in the wrist provides a reliable means of vascular access for repeated cannulations for chronic hemodialysis. This innovation laid the groundwork for the widespread adoption of chronic hemodialysis as a viable long-term treatment option, transforming the prognosis for patients with renal failure. Vascular access outcomes and durability have improved over the decades with, advancements in surgical techniques, arteriovenous grafts (AVGs), and central venous catheter (CVC) technology.

The AV access remains the preferred vascular access for chronic hemodialysis, with the radiocephalic AVF the most commonly used type.[2] Despite considerable progress, the creation and maintenance of functional arteriovenous vascular access continue to present significant challenges.[3] One-year primary failures rates of AVFs are poor, at 40%.[4] The primary complications affecting the longevity and efficacy of AV access include stenosis induced by intimal hyperplasia (IH), thrombosis, infection, and aneurysm for-

mation.[5] This contributes to a high burden on the patient, healthcare systems and society.[6]

Although underlying mechanisms are not yet fully understood,[7] current knowledge suggests that local hemodynamic factors, introduced by the arteriovenous conduit, play a crucial role in the success and failure of AV access.[8] A key factor is the difference in pressure between the arterial and venous system, which enables the high flow through the arteriovenous conduit as the blood flows through the path of least resistance. An AV access is typically considered suitable for cannulation when the flow exceeds 500 mL/min,[9] but many fistulas have far higher flow rates, reaching up to 3000 mL/min.[10] This is especially the case in AVFs in the upper arm such as the brachiobasilic AVF, where vessel diameters are typically larger. Together with the pressure differential and anatomical bifurcation created, turbulence is introduced in the blood flow. These disturbed flow patterns and shear stress variations at the AV access drive IH, and often result in inward remodeling (*i.e*. a decline in the luminal diameter of the vessel), and eventually stenosis.[7]

In addition to local vascular complications, arteriovenous conduits for hemodialysis can have systemic effects on the cardiovascular system. The high flow introduced by the AV access results in increased cardiac output, and can cause changes to blood pressure, left and right ventricular hypertrophy and may contribute to a decline in cardiac function over time, including congestive heart failure and pulmonary hypertension.[10, 11] This can exacerbate pre-existing cardiovascular conditions and risks such as hypertension and chronic heart failure, commonly found in hemodialysis patients.[12] The hyperdynamic circulation induced by the AV access can also lead to higher incidences of sudden cardiac death,[13] underscoring the need for careful monitoring and management of these patients. Conversely, cardiac output and blood pressure also have a significant impact on the hemodynamic profile of the AV access.

As flow profiles are a significant factor in the outcomes of AV access,[14] it is crucial to understand the effects of different modalities on the local and systemic hemodynamics. The presented study aims to provide background information into the local and systemic hemodynamic factors of AV access, a review of arteriovenous access modalities in scientific literature, and determine their local and systemic hemodynamic effects. The focus will remain on types of surgical procedures and devices for AVFs, and types of AVGs. The ultimate goal of this review is to describe strategies to enhance design and management of AV access to improve the outcomes for hemodialysis patients.

Local hemodynamic factors and effects

The hemodynamic profile of AV access – laminar or disturbed – is dependent on geometry, flow velocity, density and viscosity. Laminar flow is present in most of the cardiovascular system, and is smooth and orderly. However, disturbed flow is chaotic and increases the risk of uneven and multidirectional flow patterns.[15] In the context of AV access, disturbed flow is common due to the abrupt changes in vessel geometry, blood flow velocity at the anastomosis, and potentially inflow from distal veins and arteries. Vascular endothelial cells (ECs) and smooth muscle cells (SMCs) in the intima and media layers of blood vessels are affected by mechanical forces resulting from this disturbed blood flow and the increase in flow rate. The most well-studied mechanical factors are wall shear stress (WSS), and circumferential cyclic stretch.[16-19]

WSS is the frictional force between blood flow and the vessel wall surface. Both the magnitude and direction of WSS affect EC function.[20, 21] In straight vessels under physiological conditions, unidirectional WSS with normal value maintains vascular homeostasis by downregulating proinflammatory and proliferative markers in ECs. However, at the site of the anastomosis, flow patterns become unstable, leading to disturbed flow characterized by low and multidirectional WSS on the inner wall of the vein.[22] The common hemodynamic parameters for describing disturbed flow are:

- time-averaged wall shear stress (TAWSS), the average value of WSS throughout one cardiac cycle, which is low in the disturbed flow region;[23]
- the oscillatory shear index (OSI), a parameter quantifying the degree of flow reversal along the main flow direction, and
- relative residence time (RRT) representing the residence time of blood near ECs, which is high in disturbed flow locations.[24, 25]

This disturbed flow is crucial in upregulating proinflammatory and proliferative markers in ECs, potentially promoting IH.[7, 26, 27] Notably, when blood flows through the anastomosis, it induces relatively high WSS on the outer wall of the vein. When the blood flow is particularly high, the extremely high WSS can lead to endothelial damage and vascular calcification,[28] which can stiffen arteries and impair normal blood flow.

CS refers to the periodic expansion and contraction of

the vessel wall caused by differences in systolic and diastolic blood pressure. Physiological cyclic stretch ranges from 10-15% and varies among vessel types, and is important for maintaining the contractile phenotype of VSMCs in the tunica media.[29] Abnormal cyclic stretch induces a switch in VSMCs from a contractile to a proliferative phenotype.[30, 31] The contractile phenotype is essential for vascular contraction and blood pressure regulation, inhibiting VSMC proliferation and excessive extracellular matrix (ECM) synthesis.[32, 33] Conversely, proliferative VSMCs increase ECM synthesis and vessel wall thickness, with some migrating from the media to the tunica intima, contributing to IH along with other inflammatory cells.[34, 35]

The unnatural vibrations with high-frequency pressure fluctuations, often occurring due to transitional flows found in anastomoses, can reach frequencies up to hundreds of Hertz.[36] More recent studies suggest that such vibrations in AVFs are linked to the hemodynamic and structural changes post-creation.[36, 37] They are predominantly found at the anastomotic heel and the inner curvature of the vein, areas prone to vascular remodeling and stenosis development. The vibrations are believed to stimulate mechanobiological processes within the vascular wall, contributing to adverse remodeling and stenosis.

These factors are modulated by the local hemodynamics of the AVF, and are critical in the outcome of the AVF. Before AVF surgery, blood flow in the cephalic vein is very low, resulting in low uniform WSS, cyclic stretch and vibration. After creating the anastomosis, blood flow velocity and pressure increase dramatically and instantaneously. The abnormal anastomosis angle exacerbates local disturbed flow. Although vessels adapt by outward remodeling and luminal expansion to reduce WSS to a reasonable range, the disturbed flow near the anastomosis and abnormal cyclic stretch continuously stimulate local ECs and VSMCs. Activated ECs and VSMCs with a proliferative phenotype are key factors in the development of IH. Finally, the locally modified hemodynamics have been linked to aneurysm formation in the venous outflow through modification of the vessel wall.[38] Therefore, improving hemodynamics in the juxta-anastomotic region could inhibit IH and increase AVF patency.

Systemic hemodynamic factors and effects

Chronic kidney disease is a significant risk factor for cardiovascular morbidity and mortality.[12] The creation of a high-flow arteriovenous vascular access site for hemodialysis further amplifies these risks by introducing substantial alterations in systemic hemodynamics. Immediately after AV access creation, cardiac output (CO) increases significantly due to reduced systemic vascular resistance, heightened sympathetic activity, and increased stroke volume and heart rate.[10, 39] This rise in CO is necessary to accommodate the increased blood flow through the AV access.

Persistent high flow through the AV access can lead to adverse cardiac remodelling.[40] The chronic volume overload from increased blood volume and CO promotes the development of eccentric left-ventricular hypertrophy (LVH), characterized by enlarged cardiac chambers and increased left ventricular mass.[11]

A major risk associated with AV access is high-output heart failure, defined by an elevated cardiac index and symptoms such as dyspnea and enema. Continuous volume overload and myocardial structural changes drive this condition.[13] The increased CO also elevates pulmonary arterial flow and pressure, potentially leading to pulmonary hypertension. Furthermore, the diversion of blood flow through the AV access can result in organ hypoperfusion. Vascular access-related hand ischemia, or steal syndrome, can occur in the distal limbs,[41] but is most often limited to the ipsilateral hand. The heart can suffer from coronary steal, which may lead to congestive heart failure with inadequate organ perfusion and pulmonary congestion.[42] Cerebral hypoperfusion may occur, exacerbating cognitive impairment, already common in hemodialysis patients.[43]

Blood pressure management is crucial in this scenario. AV access creation can cause significant fluctuations in systolic and diastolic blood pressure. Initially, blood pressure may rise due to the increased CO and volume overload. However, during hemodialysis sessions, hypotension is common due to ultrafiltration and the blood diversion through the AV access. These fluctuations can cause symptoms like dizziness and fatigue, and persistent variability increases the risk of ischemic events and further cardiovascular instability.[44]

Subclavian vein stenosis and arterial stenosis are also potential complications associated with AV access. Ipsilateral venous subclavian stenosis can result from the high flow rates and increased venous pressure similarly to local stenoses, leading to venous hypertension, arm swelling, and impaired access function.[45] Arterial subclavian stenosis, although less common, can cause significant reductions in arterial inflow, exacerbating distal ischemia and potentially compromising the viability of the AV access.[46] Both types of stenosis can further aggravate the cardiovascular burden on dialysis patients and complicate the management of AV access.

Finally, the cardiovascular conditions introduced by the VA also significantly impact the fitness and well-being of dialysis patients. Kidney transplant patients with a prior AVF typically report a lower quality of life than a control group that received peritoneal dialysis before transplantation.[47] Moreover, proximal, high flow AVFs were associated with a lower quality of life than distal, low flow, AVFs.[47] These findings suggest that the AVF, and more specifically the high flow, are negatively associated with quality of life, although prospective trials need to be performed to confirm this potential causative relation. Managing these hemodynamic changes is essential for improving the long-term outcomes and well-being of dialysis patients.

Arteriovenous fistulas

The structure of AVFs significantly impacts hemodynamics, and surgical techniques directly influence this structure. Therefore, various surgical methods and configurations have been explored in attempts to optimize hemodynamic profiles and AVF patency.

Location

The location of the AVF in the arm has been found to affect local hemodynamic profiles significantly, with upper arm AVFs typically having higher flow rates corresponding to improved maturation rate and functional patency. However, secondary complications are also more prevalent as a result of the increased flow. Importantly, more proximal locations remain available for creating an AVF if distal fistulas fail, so guidelines recommend placing fistulas as distal as possible, provided sufficient vessel diameters.[22]

Since the inception of autogenous AVF surgery, anastomosis techniques include end-to-end (ETE), end-to-side (ETS), side-to-side (STS), and modified functional ETS anastomoses (Figure 1A-E, respectively). ETE involves anastomosing the cut ends of an artery and vein, while ETS connects a severed venous end to the side of an artery. STS involves creating sections in both vessels and anastomosing the edges of sections, whereby the distal vein functionality and inflow remains. Though the ETE AVF can avoid the bifurcation, computational fluid dynamics (CFD) simulations still showed disturbed flow occurs in the outflow tract where IH is common,[16] additionally, due to higher complication rates and the risk of distal limb ischemia, ETE is being replaced by ETS and STS.[48] Although the venous inflow remains in STS AVFs, CFD simulations find varying results on its effects on flow disturbances and multi-directionality of WSS,[49, 50] which is linked to an increase in IH. A meta-analysis found similar patency rates between ETS and STS anastomoses, but also a significantly increased occurrence of arterial steal syndrome with STS AVFs.[51] However, this may have been due to the more proximal placement of the STS AVF.

Modified functional ETS is a variation of STS where

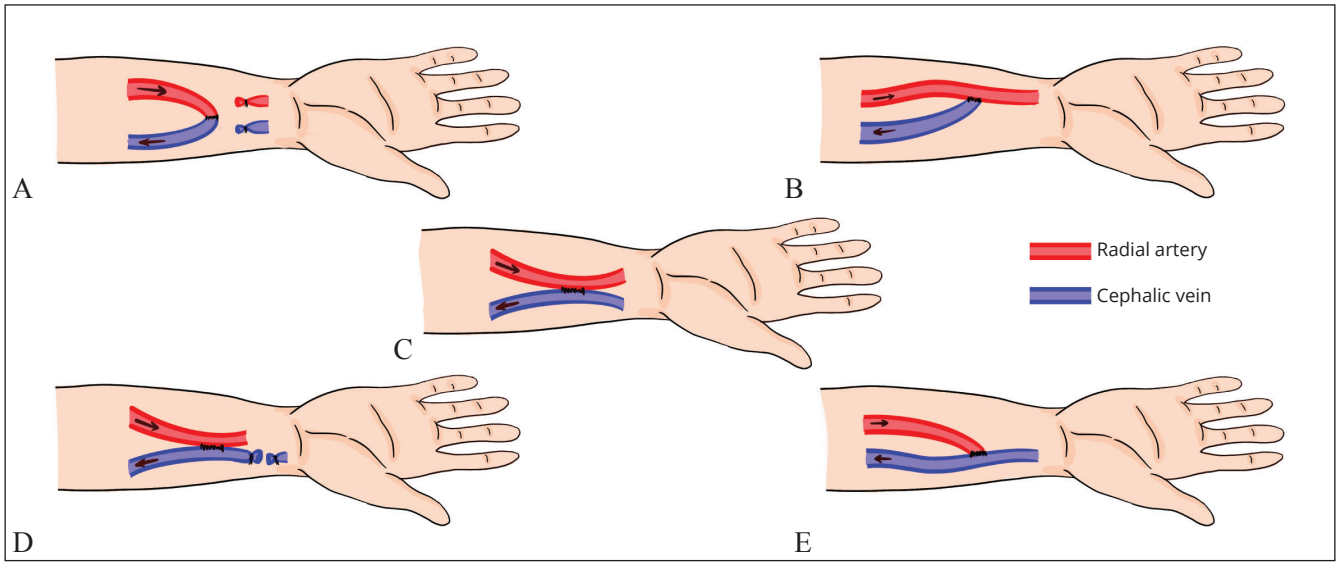

Figure 1.—Arteriovenous fistula configurations: A) end-to-end anastomosis; B) end-to-side anastomosis; C) side-to-side anastomosis; D) modified functional end-to-side anastomosis; E) radial artery deviation and reimplantation anastomosis.

the distal end of the vein is ligated when constructing the anastomosis. Post-anastomosis, arterial blood flows into the low-pressure venous system, significantly increasing venous blood flow to meet hemodialysis needs. A meta-analysis of 16 studies, including six RCTs, showed that traditional ETS had higher six-month patency rates than STS but lower 12-month rates than functional ETS.[52] Researchers utilized computational fluid dynamics (CFD) to compare hemodynamics in functional ETS and traditional ETS, finding that functional ETS provided higher venous blood flow and more uniform wall shear stress (WSS), potentially explaining its better outcomes.[49] Although more surgeons are opting for the functional ETS, there is currently no proof that improved hemodynamics have a direct impact on prognosis. More individualized hemodynamic studies are needed to confirm the clinical benefits of functional ETS.

Endovascular AVFs

The endovascular AVF (endoAVF) allows the creation of a vascular conduit through catheterisation into the vessels, thus without necessitating surgery. The WavelinQ™ (Becton, Dickinson) and Ellipsys™ (Medtronic) are the most commonly used systems for endovascular AVF creation, using radiofrequency and a combination of heat and pressure, respectively, to create the anastomosis. The minimally invasive nature creates less vessel trauma which may lead to decreased maturation time and preferable EC activation. Both devices are used to create a STS in the deep mid-forearm vessels.

The hemodynamic profile in endoAVFs is dissimilar to that of standard STS AVFs due to the deepness of the site. The primary advantages result from the mid-forearm location, which is typically different compared to creation with standard surgical techniques. Flow rates in the mid-forearm are typically higher than in the wrist but lower than in more proximal locations,[2] and 6-month secondary patency was found to be 94%.[53] Therefore, low incidence of distal ischemia, aneurysm, and cardiac overload may be achieved even when wrist AVFs are not possible. However, interventions on endoAVFs are typically larger due to the deep location of the anastomotic site, and the effect of the learning curve of the devices cannot be excluded from results in literature.

Radial artery deviation and reimplantation (RADAR)

To address abnormal hemodynamics and reduce surgical injury at the anastomosis, the RADAR technique, where the artery is ligated and the end is anastomosed to the side of the vein, has shown promising clinical results[54] (Figure 1E). Short- and long-term follow-ups indicated higher primary (6 months: 93% *vs*. 53%; 12 months: 72.2% *vs*. 48.1%; 36 months: 62.1% *vs*. 37.6%) and secondary patency rates (6 months: 100% *vs*. 89%; 12 months: 98.4% *vs*. 72.1%; 36 months: 94.9% *vs*. 66.8%) and fewer reinterventions (6 months:10% *vs.* 74%) with RADAR compared to traditional methods.[55, 56] CFD and animal studies suggest RADAR reduces pressure and high WSS at the anastomosis rather than improve low and oscillatory WSS, potentially mitigating intimal hyperplasia. Hypertension, diabetes mellitus, and anemia are common combinations in ESKD patients, affecting blood flow velocity, vessel wall stiffness, and blood viscosity. Integrating these variables into CFD, other research found that RADAR reduced disturbed flow and flow velocity at the anastomosis as well as the extremely high WSS at the anastomosis toe, decreasing the risk of juxta anastomotic intimal hyperplasia.[57]

Although a higher incidence of distal ischemia (steal syndrome) may be expected due to the distal ligation of the artery, this does not appear to be an issue.[55] An explanation may lie in the presence of retrograde flow in conventional ETS AVFs in which distal hypoperfusion is exacerbated as the anastomotic site draws blood from the hand through the artery, whereas in RADAR the proximal inflow is merely diverted into the vein.

Finally, the RADAR AVF may pose additional challenges in patients suffering from diabetes mellitus and microangiopathy due to increased stiffness of the artery. However, due to the limited amount of literature on this technique, no evidence exists suggesting unsuitability of the RADAR technique for these patient populations.

Vessel diameter and anastomotic angle

Another aspect of the AVF structure is anastomosis angle which is also crucial in AVF hemodynamics. Researchers seek the optimal anastomosis angle to improve local hemodynamics and AVF outcomes (Figure 2). CFD analysis revealed that low and oscillatory WSS occurred primarily in the inner wall of juxta-anastomosis vein and the outflow tract vein, correlating with clinical stenosis locations, suggesting disturbed flow contributes to AVF intimal hyperplasia.[58, 59] Then, the distribution of low and oscillatory WSS were simulated in AVF models with anastomosis angles of 30, 45, 60, and 90 degrees, with 30 degrees showing the least abnormal WSS distribution at the juxta-anastomosis indicating the sharper angle may have a bet-

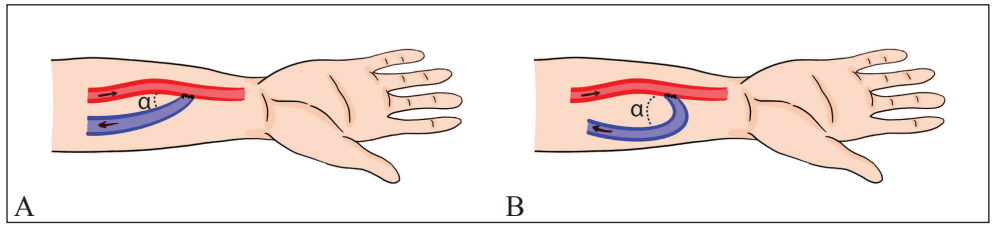

Figure 2.—Anastomotic angle "α" used for arteriovenous fistulas: A) sharp anastomotic angle; B) obtuse anastomotic angle.

ter AVF outcomes. Another study collected PTA data and AVF configuration from 27 patients with juxta anastomotic stenosis on their radiocephalic AVF, using patient-specific 3D vascular models and CFD found that the anastomosis angle was closely related to the blood flow velocity at the stenosis site, and ROC curve analysis suggested that patients with anastomosis angle greater than 46.5° had a significantly lower stenosis ratio and disturbed flow when compared to patients with an angle less than 46.5°.[60]

Significant correlations have been established between anastomotic angle and vessel diameter, and the distribution of disturbed hemodynamics in AVFs. CFD studies suggested that the blood flow velocity and WSS at the anastomosis site increased when the venous diameter was smaller than the arterial diameter, leading to a larger area of disturbed flow and a higher risk of thrombosis. In this scenario, the anastomosis angle had little effect on local hemodynamics. Conversely, when the venous diameter was larger than the arterial diameter, increasing the anastomosis angle reduced the area of disturbed flow and normalized WSS.[61] To further investigate the impact of larger anastomosis angles on AVF hemodynamics, the concept of obtuse angle anastomosis has been proposed. CFD studies indicated that the obtuse angle ETS AVFs significantly reduced disturbed flow and lowered abnormally high WSS compared to traditional anastomosis techniques. However, clinical studies did not show that obtuse anastomosis angle could improve primary, assisted primary, or secondary patency compared to sharp angle anastomosis.[62, 63]

In summary, functional ETS and RADAR show potential advantages over traditional methods, though direct evidence linking improved hemodynamics by functional ETS and RADAR to better clinical outcomes is lacking. Reducing low and oscillatory WSS may protect endothelial function and prevent intimal hyperplasia, while addressing high WSS could also lower stenosis rates.

External vessel support devices

The VasQ™ (Laminate Medical Technologies) external vessel support device is designed to enhance the performance and longevity of AVFs (Figure 3A). It has two distinct features: it provides rigid support to the venous wall to reduce tension, and it fixes the anastomotic angle at 38° and tapers outwards in the outflow vein to beneficiate flow conditions in the juxta-anastomotic region.

Although sample sizes were small, a longitudinal study using high-fidelity CFD simulations based on 3D patient-specific models showed that the device helps stabilize blood flow velocity and reduce disturbed flow and shear stress metrics over time.[64] The largest difference in flow patterns and remodeling between the group receiving the

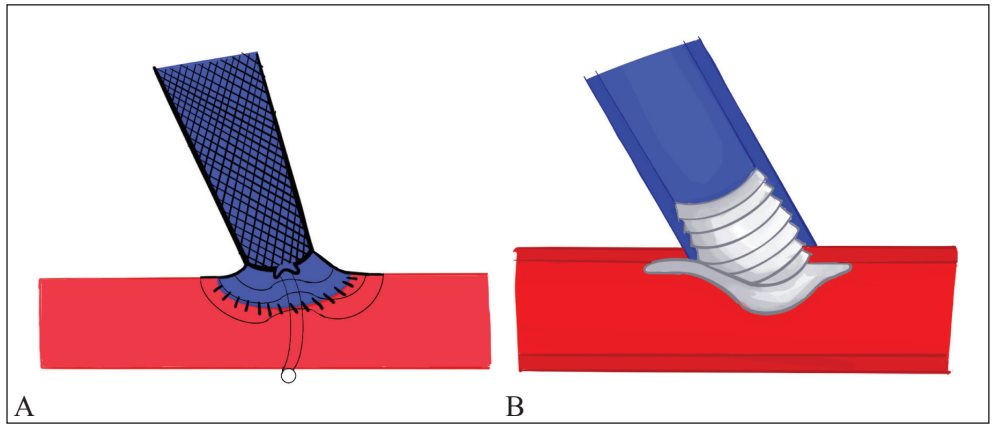

Figure 3.—External and internal devices used to standardize and lock the anastomotic angle of an arteriovenous fistula: A) VasQ™ external vessel support; B) OptiFlow™ internal vessel support.

external support device and the control group appeared to be at the intermediate timepoint at 3 weeks, at which the study group showed far less remodeling, more laminar flow patterns and low WSS. Moreover, the velocity profile in the control groups was more indicative of high frequency vibrations. The morphological changes, flow patterns and WSS appeared more similar between the groups at 1 year after the surgery with statistically significant differences between the groups diminishing.

Multiple clinical studies have been conducted with the VasQ™, which typically report high maturation, and primary and secondary patency rates with the device. Lower primary failure (29.4% *vs*. 6%, P=0.0251) and higher 6-month primary patency rates (79% *vs*. 53%, P=0.04) were found compared to a control group in a single center study.[65] Moreover, a decreased brachial artery flow rate (0.71 L/min intervention group *vs*. 0.81 L/min control, P=0.05) and cardiac output were found (4.5 L/min intervention group *vs*. 5.6 L/min control, P=0.05) at 6 months,[66] although other studies found a higher, but non-significant increase in venous flow with the VasQ™.[67] High patency rates, exceeding 70%, are also reported at 18 months[68] and 36 months.[69] This may in part be attributed to the improved hemodynamic profile induced by fixating the anastomotic angle, decreasing WSS, and offering venous support which may reduce excessive outward remodeling and wall vibrations. However, the long-term studies offer no valid control. Only one RCT (20 *vs*. 20 patients) has been conducted with the VasQ™ in literature. Although patency rates were higher, this did not always translate to a statistically significant difference due to underpowering. Such an improvement was only noted in functional patency at 6 months (P=0.01).[67]

The longitudinal flow study[64] suggests turbulence is not fully addressed, and WSS, cyclic stretch and resulting remodeling are decreased, but not mitigated. The negative consequences of these hemodynamic factors are thereby most likely merely delayed. Consequently, the device appears to primarily aid in AVF maturation and could be particularly advantageous for patients with an imminent start to dialysis. This underscores the necessity for longer-term randomized controlled trials to better establish any long-term clinical benefits of the VasQ™ device.

Internal vessel support devices

An alternative method to fixating the anastomotic angle is the Optiflow™ (Bioconnect Systems), which is a cylindrical silicone insert placed inside the ligated outflow vein with a flange that is placed into the artery to create an ETS AVF with a predetermined angle of 60°[70] (Figure 3B). Due to the insert there is no contact between the blood and the vessel walls at the arteriovenous bifurcation. Some support to the vessels is provided by the insert, although less than in the VasQ™ due to reduced stiffness of silicone compared to the metal in the external support device.

The first-in-human study in 10 patients noted a sufficient increase in venous diameter in all patients at 6 weeks with no adverse effects.[70] The only prospective and controlled study, including 41 patients receiving the insert, reported unassisted maturation rates of 76%, 72%, and 68% at 2, 6, and 13 weeks, respectively, with no statistically significant differences to the control group.[71] Flow rates also did not differ significantly. The larger diameter Optiflow™ had a higher maturation rate at both 6 and 13 weeks (P=0.04 and P=0.01, respectively), which is typically expected with larger vessel diameters.

In a case report a patient is described with multiple occurrences of significant stenotic lesions just distal to the device at the transition from the silicone to the native wall, thought to be the result of IH induced by flow dynamics.[72]

Limited data exists to support the benefits in maturation and decreased stenosis using the Optiflow™. Although the endothelium at the anastomotic bifurcation is not exposed to flow, downstream IH still occurs. The case report may be a sign that the transition from the device material to the native vessel even induces more local flow disturbances as overall maturation and patency shows no improvement. This transition zone might also be susceptible to kinking, which can further increase IH risks. The device is currently no longer marketed, as funding constraints caused termination of development.[73]

Suturing techniques

The piggyback Straight Line Onlay Technique (pSLOT) is a surgical method designed to prevent IH and enhance AVF maturation by eliminating torsional stress in the outflow vein and reducing hemodynamic stresses resulting from the torsion.[74] Torsional stress can create local flow disturbances, which may disrupt EC functionality, promote EC activation, and thereby contribute to stenosis formation.[75] In pSLOT, the cephalic vein is dissected to ensure a straight-line outflow, minimizing torsional stress. An anastomosis is created by placing the ligated vein in a "piggyback" position over a deep artery and suturing it in place, ensuring proper alignment and avoiding twisting.

The first clinical study found a significantly decreased

rate of venous stenotic lesions with a 36-month follow-up in pSLOT compared to an ETS control (29% *vs.* 11%, P=0.04), with no significant differences in flow rate between the groups.[75] Further long-term outcomes from an observational study showed that AVFs created using pSLOT achieved high functional patency rates at 12, 24, and 60 months, with primary patency at 42.8%, 31.6%, and 20.8%, and secondary patency at 81.8%, 77.6%, and 71.7%, respectively.[76] Another study confirmed that the pSLOT technique decreases the incidence of early stenotic problems and maturation failure, supporting its potential to improve long-term outcomes for AVF patients.[74]

Similarly, the diamond-shaped anastomosis technique is another method for creating AVFs, aimed at ensuring long-term patency and functionality. This technique involves a geometrically precise creation of a diamond-shaped arteriotomy, which is matched with a corresponding venotomy.[77, 78] The diamond shape facilitates a more uniform distribution of stresses in the vessel wall and reduces turbulence, which is critical for maintaining fistula patency. Although clinical data is very scarce, one study has shown that the diamond-shaped anastomosis technique results in high early-stage patency rates, reporting an 89% patency rate at six months post-surgery.[79]

This low IH found throughout the studies suggests that either or both WSS and EC activation are decreased as a result of reducing wall stress in the outflow vein. However, the limited amount of data does not allow a distinction to be made between contributions of these effects to the improved outcomes.

Arteriovenous grafts

Arteriovenous grafts (AVGs) use synthetic or biological materials to connect arteries and veins, providing an alternative site for needle insertion during hemodialysis when native arteriovenous fistulas (AVFs) are deemed unsuitable (Figure 4A, B). Although native AVFs are the preferred type of access for most patients, AVGs are considered predominantly in patients with poor vascular conditions and a high risk of non-maturation.[80, 81] Notably, the early cannulation AVG allows incident hemodialysis patients to be cannulated within 48-72 h, reducing the need for CVCs and are therefore gaining popularity.[82] The KDOQI guidelines now suggest that the choice between AVF and AVG should be individualized, considering patient and physician circumstances as both options offer similar primary and secondary patency rates.[2] Despite these advantages, AVGs are more prone to stenosis near the venous anastomosis compared to AVFs, often requiring more frequent interventions.[2, 83] The primary cause of stenosis is IH induced by disturbed flow and the compliance mismatch between the graft material and vessel. Since the grafts must first be manufactured, either synthetically or biologically, their design can be modified to improve hemodynamics. Synthetic materials, most often expanded tetrafluoroethylene (ePTFE), have been used for decades. However, more recently tissue-engineered blood vessels have gained attention, as they require less or no foreign material to be implanted.[84, 85] Hemodynamically, the primary differences lie in the frictional coefficient of the graft which may marginally effect flow velocities in the graft and outflow vein.

Helical flow graft

Helical flow, a physiological pattern that resists atherosclerosis, is characterized by axial and circumferential components induced by the curved and non-planar geometry of the vascular structure.[86] Helical flow reduces vortex and recirculation, lowers endothelial cell exposure to low and oscillatory wall shear stress (WSS), and decreases monocyte and platelet adhesion.[87-91] Researchers have explored altering AVG designs to induce helical flow at the anastomosis, potentially mitigating intimal hyperplasia. Swirling and spiral grafts are two such designs. Swirling grafts feature non-planar geometry (Figure 4C), while spiral grafts have an internal spiral ridge (Figure 4D). By adjusting the helical pitch, curvature radius, and ridge shape, these designs can enhance helical flow.[92-96] Although CFD-based designs suggest improved outcomes, there are few animal or human trials. In a porcine model, researchers found that spiral ePTFE grafts induced helical flow but did not reduce intimal hyperplasia compared to standard grafts after 14 days implantation.[97] Another study implanted swirling grafts in 20 CKD patients, reporting six-month primary, assisted primary, and secondary patency rates of 57.9%, 84.4%, and 100%, respectively, indicating potential improvements in assisted primary and secondary patency rates, but larger clinical trials are needed.[98]

Tapered grafts

Tapered grafts, designed with a smaller arterial end and larger venous end, were initially developed to reduce distal limb ischemia by decreasing inflow with a small diameter and reducing flow velocity and the outflow with the increased diameter[99] (Figure 4E). Further research showed that tapered grafts also affect hemodynamic conditions

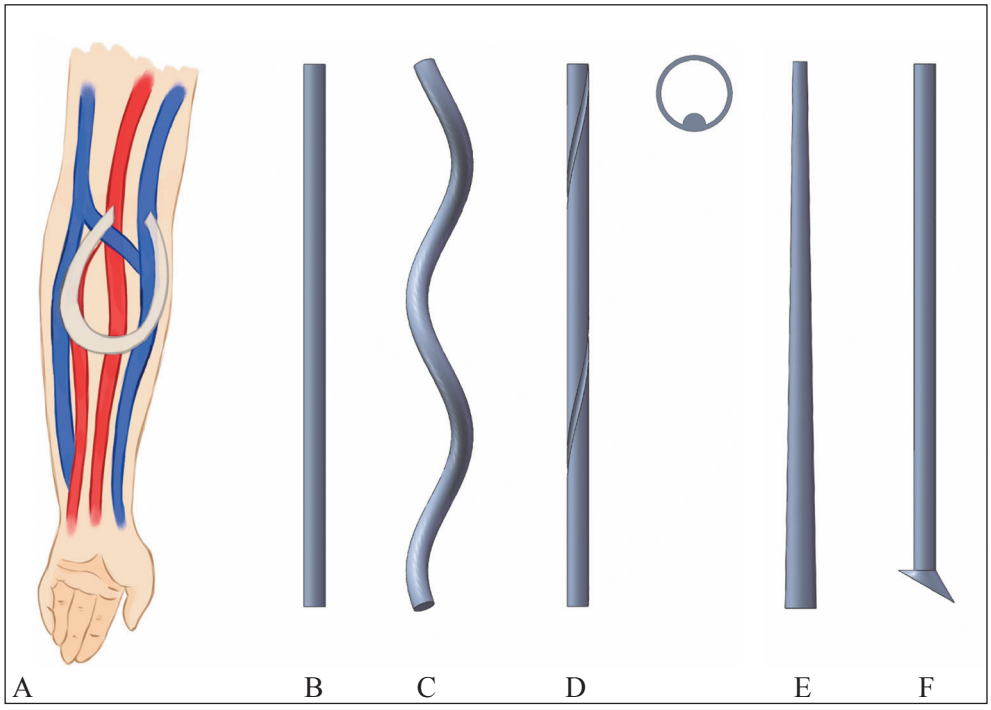

Figure 4.—Different types of AVG used to modify hemodynamics: A) AVG in the arm; B) standard graft; C) swirling graft; D) spiral graft and its cross section; E) tapered graft, with an increased diameter on the venous side; F) cuffed/patched graft.

at the venous anastomosis, reducing disturbed flow and high WSS downstream, thus potentially lowering IH and thrombosis.[100] However, a meta-analysis of five studies including >4000 patients found that tapered grafts did not significantly reduce the risk of steal syndrome or infection and had comparable primary and secondary patency rates to standard grafts.[101] An explanation may lie in the venous diameter dictating the venous flow conditions, and therefore effects such as WSS and cyclic stretch in the venous outflow.

Cuffed and patched grafts

Cuffed and patched grafts are other designs aimed at improving local hemodynamics at the venous end. CFD simulations suggest that cuffed grafts lower indicators of disturbed flow such as wall shear stress gradient, wall shear stress angle gradient, and radial pressure gradient at the anastomosis toe,[102-104] reduce abnormally high WSS in the host artery,[105] while enhancing helical flow in the distal outflow tract[102, 106] (Figure 4F). Patched grafts also improve local disturbed flow patterns but have a smaller impact on distal helical flow compared to cuffed grafts.[102] Clinical studies comparing these grafts are limited. A meta-analysis of eight studies (six cuffed and two patched) involving 414 patients indicated that cuffed grafts improved one-year primary and secondary patency rates and reduced stenosis rates, whereas patched grafts did not offer these benefits.[107]

In conclusion, various modified types of AVGs have been designed to improve hemodynamics and reduce complications. While some designs show promise hemodynamics in CFD models but small-scale studies show benefits in reality, larger clinical trials are necessary to confirm their efficacy and long-term benefits.

Stents

Bare metal stents can be used as internal vessel support to treat aneurysms and stenoses in VA outflow and cephalic arch. The deployment of these stents is intended to provide a sustained mechanical force to keep the vessel lumen open and resist inward remodelling.[108] Often these stents include a membrane on the inner side – covered stents – to prevent thromboses forming on the stent material, because the stent's structure can create areas of altered shear stress, which may influence EC behavior and vessel wall remodeling. The membrane also provide a more uniform surface which would limit the occurrence of flow disturbances.

Covered stents are primarily used in treating stenoses. A meta-analysis including 8 RCTs found that a higher patency could be maintained by using covered stents in

AVG patients compared to using percutaneous transluminal angioplasty alone.[109] Although good patency could be achieved in AVF patients,[110] no significant results were found, possibly due to the relatively small number of patients. Similarly cephalic arch stenosis treated with covered stents also show positive outcomes compared to other treatments in a meta-analysis with 19 clinical studies, with a 73% patency rate at 12 months.[111]

Although direct effects on anastomotic and systemic flow are limited in the application of stents and covered stents, these findings do suggest that membrane stents typically perform better than the bare metal variety. An explanation may lie in the exposure of the bare metal to blood, which could induce thrombus formation. However, the flow disturbances resulting from the non-uniform surface of the stent could promote IH formation. Finally, the clinical benefit of freedom from target lesion reintervention may be questionable, especially when including the increase in cost from placing a device, for which studies are necessary.

Discussion

Despite its many sub-optimal clinical outcomes, AV access remains the access of choice for hemodialysis patients. Although it is difficult to deny that the altered hemodynamics introduced by creating a permanent arteriovenous connection play a significant role in these negative outcomes, modalities aimed at improving hemodynamics most often show only limited benefit over the traditional radiocephalic AVF introduced 60 years ago.

Computer modelling and simulations, such as CFD, have gained interest in recent years, with the quality of the studies improving. Through CFD studies on arteriovenous access conduits, our understanding of the local hemodynamics has advanced. Moreover, techniques that can model the AV access in vivo and examine hemodynamic conditions exist, such as ultrasound vector volume flow and 4D flow quantification MRI. This allows monitoring and modelling of the AV access hemodynamics *in vivo* by creating a digital 3D model of the anastomosis and applying CFD. However, these imaging modalities are currently most often limited to use for research purposes, and less often in clinical care. Unfortunately, these techniques have not yet resulted in modalities that improve the outcomes, despite hemodynamic conditions undergoing some improvement. This underscores the complexity of the VA, and the multitude of factors that influence it and the outcomes. Cellular response can be difficult to predict and directly relate to hemodynamic factors, and challenging to analyze and determine in vivo. Combining in vitro testing with CFD and complex flow disturbance to monitor both hemodynamic and cellular effects may therefore be a powerful tool in further unravelling the complexity of AV access. Such models are currently under development.[112]

Hemodynamic conditions and clinical outcomes are not the only considerations in the choice of AV access. While certain modalities discussed may show statistically significant improved patency, decreased failure, or lower intervention rates, the cost of including such modalities is often not taken into account. As AV access and maintenance is often paid for by, *e.g*., governments or health insurers, a cost benefit is usually critical in the adaptation of such modalities. For example, endoAVFs may result in higher patency rates compared to radiocephalic AVFs, but this financial benefit could be mitigated by the increased cost of the more complex angioplasty or coiling procedures due to the deepness of the anastomosis. To properly assess efficacy of AV access modalities, cost analyses are of critical importance.

Current guidelines state that a minimum blood flow of 500 mL/min[9] is required to be considered suitable for cannulation and adequate hemodialysis, which is still orders of magnitude higher than physiological venous flow. The presence of a constant supraphysiological venous flow with an arterial pressure will inevitably result in non-physiological conditions in the venous system, which the vessel will try to normalise.[7] Apart from central venous catheters, which have their own significant drawbacks, no AV access solutions are currently available that mitigate this supraphysiological flow, which only needs to be present during the typical 12 hours of dialysis per week. Our research group is currently working on an implantable device that closes the AV access outside of dialysis sessions to normalize the flow, so that the supraphysiological conditions are only present during these 12 hours per week.[113]

The modalities in this overview were selected based on the authors' expertise in peripheral AV access and a critical review of available literature. However, no formal systematic review was conducted, so some modalities or studies may have been unintentionally excluded, introducing potential bias. Additionally, many of the included modalities are not widely used, and the supporting literature is often limited or lacks RCTs, so conclusions should be interpreted with caution.

Finally, pharmacological modalities, such as vasodilators or hypotensive medication, are at times administered to patients peri-operatively. As these can affect, *e.g*. the

blood pressure, indirect effects on AV access hemodynamics can also be expected. Although they may result in improved clinical outcomes, due to their non-direct effect on hemodynamics, they lay outside the scope of this review.

Conclusions

In conclusion, while arteriovenous VA remains the preferred modality for hemodialysis, its inherent hemodynamic alterations continue to pose significant clinical challenges. Despite various attempts to optimize hemodynamics through alternative AV access modalities and advanced modelling techniques, the outcomes have seen only modest improvements over the traditional radiocephalic AVF. The complexity of AV access hemodynamics, influenced by multifactorial interactions between flow dynamics and cellular responses, underscores the difficulty in achieving consistent clinical benefits. The current standard of maintaining supraphysiological venous flow, while essential for dialysis, perpetuates non-physiological conditions in the venous system, with no viable alternatives to mitigate these effects yet available.

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Conflicts of interest

Nicholas A. White, Koen E. van der Bogt and Joris I. Rotmans hold shares in XS Innovations, a company that develops vascular access devices. All other authors have no conflicts of interest.

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Authors' contributions

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