Chapter

Innovations in Hemodialysis Access

Nidharshan S. Anandasivam and Tessa K. Novick

Abstract

The established types of vascular access for hemodialysis are central venous catheters (CVCs), arteriovenous fistulas (AVFs), and arteriovenous grafts (AVGs). Innovations in CVC tip and coating design may improve patency and blood flow rates. AVFs are preferred over CVCs as they are less prone to clotting and infection, while providing reliable and adequate blood flow rates. However, AVF creation requires a surgical procedure with associated risks. Because of a paucity of surgeons available to create high-quality dialysis access, newer access creation techniques have been developed, including a percutaneous endovascular method that has the potential to revolutionize dialysis access. Innovations in AVGs include drug-eluting devices that may reduce neointimal hyperplasia and bioengineered blood vessels. To bypass vessel stenoses, a hybrid AVG/CVC device has been developed. Although many of these innovations have yet to become mainstream, they promise to improve dialysis access in the future.

Keywords: hemodialysis access, arteriovenous fistula, percutaneous arteriovenous fistula

1. Introduction

Hemodialysis is the most common modality of dialysis worldwide for patients with end-stage kidney disease (ESKD). In the US, approximately 786,000 patients have ESKD, and 71% of these patients are on dialysis, while 29% have received a kidney transplant [1]. Optimal vascular access is essential for hemodialysis to achieve adequate blood flow rates and maintain patency, while minimizing the risk of complications such as infection and thrombosis.

The most common options for vascular access for hemodialysis are central venous catheters (CVCs), arteriovenous fistulas (AVFs), and arteriovenous grafts (AVGs). AVFs are generally preferred over CVCs due to lower complications overall, reliable blood flow rates, and reduced need for corrective procedures. In those with tunneled CVCs, the likelihood of catheter-related bacteremia is 35% at 3 months and 48% at 6 months [2]. Patients with CVCs experience 4.6 catheter-related bacteremia episodes/1000 catheter-days [2]. Furthermore, up to 40% of catheter-related bloodstream infections lead to further complications such as osteomyelitis and endocarditis [3]. In a study of 865 dialysis patients, catheter dysfunction occurred at a rate of 10.58 episodes/1000 catheter-days and affected 56.65% of patients [4]. Other known risks of CVCs include catheter lumen thrombosis and central venous stenosis [2]. Compared to AVFs, CVCs have shown to have higher infection-related deaths

(RR = 2.30, $p < 0.05$), higher cardiac-related deaths (RR = 1.47, $p < 0.05$), and higher overall mortality risk (RR = 1.54, $p < 0.05$) [5]. Despite the plethora of evidence of AVFs demonstrating better outcomes compared to CVCs, certain vulnerable populations, like those receiving emergency-only hemodialysis (EOHD), are less likely to start their first dialysis with an AVF compared to standard hemodialysis patients [6]. This suggests that there are barriers to receiving timely optimal vascular access, and many would benefit from innovations in hemodialysis access.

The possibility of converting AVF creation from a mainstream surgical procedure to a mainstream interventional procedure holds promise for improving access for patients with CVCs in need of AVFs. This chapter will examine innovations in hemodialysis access as it pertains to CVCs, AVFs, and AVGs.

2. Central venous catheters

Central venous catheters are used widely for hemodialysis access. Non-tunneled catheters are used for emergent dialysis access and are common in the intensive care setting. Tunneled catheters are placed for hemodialysis access in urgent, but non-emergent, cases in hospitalized patients. Tunneled CVCs can be functional for over a year, but dysfunction and complications are not uncommon. Although CVCs have been associated with worse outcomes compared to AVFs and AVGs, they are still pervasive because they can be placed easily and utilized immediately. Furthermore, accessing CVCs avoids the needlesticks required for AVFs and AVGs. Despite this, it is generally recommended to use CVCs only as a bridge to AVFs because of the common complications of CVCs, or when individuals have limited life expectancy and the risks of AVF or AVG creation do not outweigh benefits. CVCs can be either non-tunneled (for emergent short-term use) or tunneled through subcutaneous tissue (for longer-term use on the order of months), and both are associated with higher morbidity and mortality compared to AVFs. Over the last several years, the design of CVCs has improved to maximize blood flow rate, minimize endothelial injury, improve catheter function and biocompatibility, and minimize infections [7].

Catheter tip design has evolved from step tip to split tip to symmetric tip, with the goal of preventing thrombosis and recirculation of blood (**Figure 1**) [8]. The difference lies in the end of the catheter. The step tip catheter has its two ends offset by a distance, while the split tip catheter has a Y-shaped end with the two tips diverging. The symmetric tip catheter as the two ends of the catheter adjacent and mirroring each other. One study of 302 patients examined split tip and symmetric tip designs and found no difference in mean primary assisted patency [9]. One study found lower recirculation rates with the symmetric tip (0% for symmetric tip vs. 22.3–39.2% for split tip vs. 8.7–16.3% for step tip) [10]. A study comparing split tip and step tip catheters found that the step tip catheter delivered higher blood flow rates (433 mL/min vs. 414 mL/min), but both types were able to deliver blood flow rates that were well above that recommended by the Dialysis Outcomes Quality Initiative [11]. Overall, there have been mixed results, and it is inconclusive which design is optimal.

In theory, catheter coatings can be utilized externally and internally to prevent biofilm formation and activation of the coagulation cascade, which would prevent infection and thrombosis. Catheters can be coated with heparin to prevent thrombosis and antibiotics to prevent infection. However, a systematic review examining coatings have failed to show significant benefit [12].

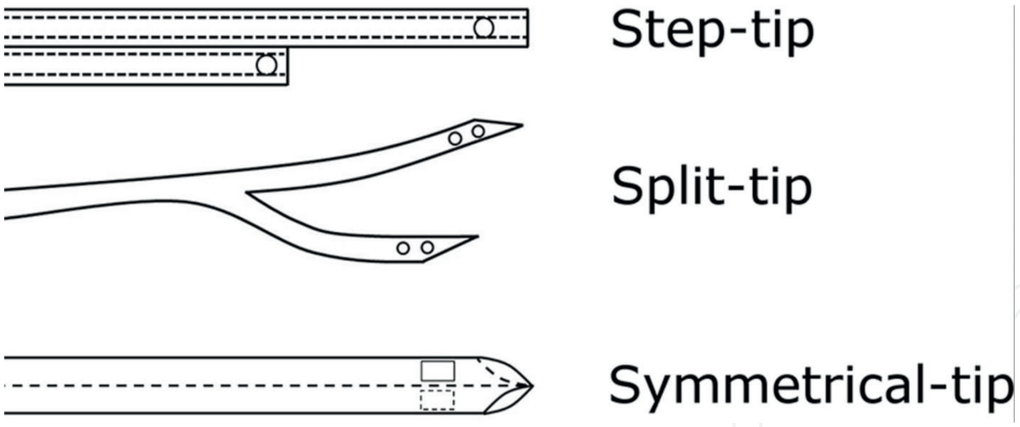

Figure 1.
Catheter designs. This illustrates three common types of catheter designs for hemodialysis access. The goal of the evolution from step tip to split tip to symmetric tip was to prevent thrombosis and blood recirculation. Although a few studies have demonstrated certain advantages for each, it is inconclusive which design is optimal overall. Reprinted from: [8] Copyright 2019, with permission from Elsevier. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/).

Although early catheters were made of silicone, newer polyurethane/polycarbonate polymers are used to increase luminal diameter (thin walls) while maintaining strength, flexibility, and rigidity to prevent luminal collapse at high negative pressures [13]. Large randomized controlled studies comparing catheter materials are lacking.

Catheter lock solutions have been used for the purposes of antisepsis (antimicrobials) and anticoagulation (heparin or citrate). There is weak positive evidence that antibacterial lock solutions decrease the incidence of catheter-related bloodstream infection [14]. To date, there has not been an ideal catheter lock solution that has reliably prevented infection or catheter dysfunction. It is controversial whether we should use antibiotic locks to treat catheter-related blood stream infections, as the evidence supporting this is minimal, and only includes small observational studies [15].

3. Arteriovenous fistulas

In 1966, Brescia et. al. created a connection between an artery and a vein and allowed it to mature giving rise to the AVF [16]. This was groundbreaking in delivering optimal blood flow for hemodialysis. Initial side-to-side anastomoses had issues with hand edema, so it was further refined to end-to-end anastomoses to prevent this. Even today, AVFs have lower infection rates and better patency than CVCs, as they remain the ideal option for dialysis access.

In the last decade, endovascular techniques have been devised to create AVFs, revolutionizing dialysis access creation with the power to improve patient access to high-quality AVFs. Two novel devices for endovascular interventions have been approved by the US Food and Drug Administration.

The first device, the everlinQ endoAVF system (TVA Medical, Austin, TX), was studied in the Novel Endovascular Access Trial (**Figure 2**) [17, 18]. This uses radiofrequency energy and catheter technology to create an AVF. Specifically in this procedure, the brachial vein is penetrated with a needle and guidewire, which is then passed into the ulnar vein. Separately, the brachial artery is punctured in an antegrade direction, and a guidewire is advanced to the ulnar artery. A venous magnetic catheter is introduced into the ulnar vein, while an arterial magnetic catheter is introduced

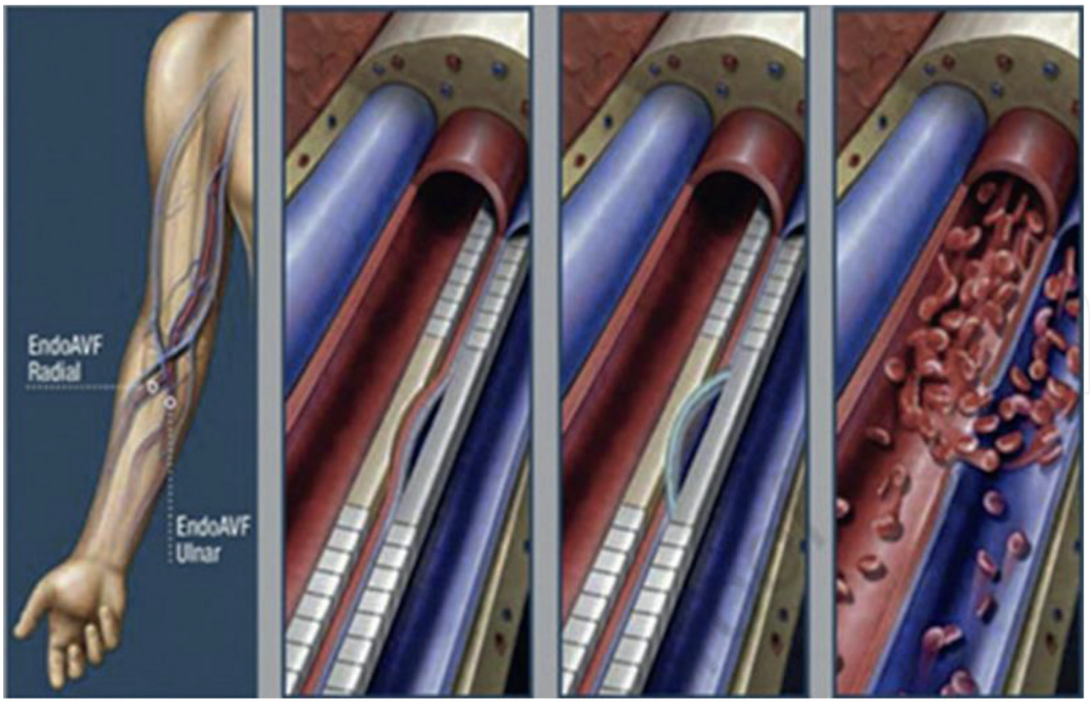

Figure 2.
EverlinQ EndoAVF system. This system allows for an endovascular approach to creation of an arteriovenous fistula (AVF). A venous magnetic catheter is introduced into the vein, while an arterial magnetic catheter is introduced into the artery. An anastomosis between the vein and artery is created as the magnetic catheters are aligned, allowing for activation of a radiofrequency electrode and creation of an AVF. Reprinted from: [17]. Copyright 2022, with permission from Elsevier. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/).

into the ulnar artery. An anastomosis is created between the ulnar artery and vein as the magnetic catheters are aligned, allowing for activation of a radiofrequency electrode. In the trial examining 59 AVFs created using this technique, the primary and cumulative patency at 12 months were 69 and 84%, respectively. Mean time for fistula maturation was 111 days [18].

The second device used to create an AVF is the thermal resistance anastomosis device (TRAD) [19]. This uses thermal resistance energy to create an anastomosis between a vein and artery. In this procedure, a needle cannulates the vein (usually brachial or cubital) in a retrograde fashion using ultrasound, and then punctures into the proximal radial artery, allowing a guidewire to follow. Next, the TRAD advances into the vein-artery junction and creates a durable anastomosis. Angioplasty is done afterwards to augment flow into this anastomosis. In a study examining 107 percutaneous AVFs created using this Ellipsys Vascular Access System (Avenu Medical, San Juan Capistrano, CA), cumulative patency at 90, 180, and 360 days was 91.6, 89.3, and 86.7%, respectively [19].

These early results demonstrate that AVFs can be created through endovascular intervention, with reliable function afterwards. This can be accomplished by interventionalists without general anesthesia. If this were to become mainstream, patients needing dialysis access creation would have many more options rather than the necessity of waiting to see a vascular surgeon for AVF creation. Access to dialysis creation would be revolutionized.

Far infrared therapy has been studied for its effects in improving maturation and patency of newly created AVFs [20]. These are electromagnetic waves that may improve cutaneous blood flow. Many theorized mechanisms have been postulated

for how it may improve AVF function, including thermal effects, inflammation suppression, and decreased oxidative injury. In a randomized controlled study of 122 patients, 62 patients received 40 minutes of far infrared therapy 3 times weekly for a year. The intervention group had a higher blood flow rate, a lower occurrence of AVF malfunction (12% vs. 29%, p = 0.02), and more cumulative unassisted patency (87% vs. 70%, p = 0.01) within 12 months [20].

Neointimal hyperplasia presents a challenge to the patency of vascular access. Because of this, it is a therapeutic target. Vonapanitase (recombinant human elastase) has been studied in a randomized controlled trial to determine if it improved primary and secondary patency [21]. It is known to disrupt elastin and other peptides that may attract cell proliferation, and has potential benefit in improving AVF patency. When applied during radiocephalic AVF creation, vonapanitase reduced primary (HR = 0.37, p = 0.02) and secondary (HR = 0.24, p = 0.046) patency loss. It also was associated with fewer procedures to restore or maintain fistula patency. However, there was no significant difference in risk of primary patency loss with vonapanitase overall in this study. Further research is essential to evaluate the efficacy of vonapanitase in improving dialysis access patency.

4. Arteriovenous grafts

AVGs constitute about 12–13% of vascular accesses in Europe, Japan, Australia, and New Zealand, compared to 25% in the United States [22]. Although AVFs are much more common than AVGs, both are preferred over CVCs. AVGs may be preferable over AVFs when a patient has unsuitable veins for AVF or AVF maturation issues. A study examining mortality in maintenance hemodialysis patients showed that transitioning from a CVC to an AVG of AVF was associated with reduced mortality (hazard ratio [HR] = 0.69), and transitioning from AVG or AVF to a CVC was associated with higher mortality (HR = 2.12) [23].

In the past, AVG advances have focused on reducing vein stenosis and graft clotting, as well as altering flow dynamics. Recent advances in AVGs include early cannulation AVGs (eAVGs), anti-neointimal hyperplasia AVG therapy, hybrid AVGs, and bioengineered vessels as AVGs.

The eAVG is a graft that can be cannulated within 72 hours of placement for dialysis. It is designed to with materials to prevent back wall puncture, and with self-sealing properties to allow for immediate access [24]. One 2015 systematic review showed that eAVGs had similar complication and patency rates to standard AVGs made of expanded polytetrafluoroethylene (ePTFE) [25].

Another advance in AVG technology relies on surface modification. Heparin coatings have been created to lower the risk of thrombosis, although the evidence on whether it reduces thrombosis is controversial [26]. Other efforts have been made to make grafts more biocompatible through strategies such as outer wall modification using electrospinning, nanotopography, or lithography. To combat neointimal hyperplasia, which causes graft failure, sirolimus-eluting devices and paclitaxel coatings have been designed. Although a few studies have demonstrated successful use of these anti-proliferative agents, large comparative trials are lacking [27, 28].

Hybrid AVG systems have allowed navigation through central vein stenosis. The Hemodialysis Reliable Outflow device (HeRO, Merit Medical Systems, South Jordan, UT), uses a combination of a tunneled CVC and AVG to provide hemodialysis access while bypassing a venous stenosis or occlusion (**Figure 3**) [29]. Although expensive,

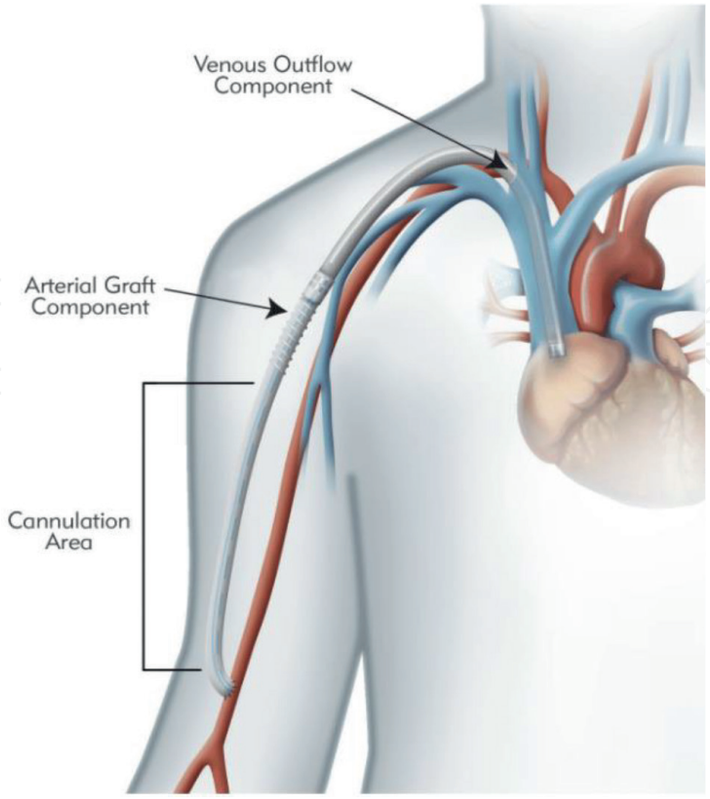

Figure 3.
Hemodialysis reliable outflow (HeRO) Graft. This illustrates the HeRO Graft, which utilizes an expanded polytetrafluoroethylene (ePTFE) component to bypass venous stenoses and occlusions. The graft is anastomosed to an artery on one end and is inserted into a central vein on the other end, bypassing the stenosis/occlusion in between. Reprinted from: HeRO Graft [Internet]. Merit Medical; 2022. Available from: https://www.merit.com/peripheral-intervention/access/renal-therapies-accessories/merit-hero-graft/. Copyright 2022, from Merit Medical.

this device may save cost due to lower complications compared to a tunneled CVC alone [30].

Over the last few decades, tissue bioengineered vessels have been created to replace prosthetic grafts. Blood vessels may be chemically treated to decrease immunogenicity. Human vascular cells may be grown on biodegradable scaffolds. One study in the US and Poland investigating human acellular vessels found that after a year, primary patency was 28% and secondary patency was 89% [31]. Overall, these bioengineered vessels have demonstrated better patency than standard AVGs in a few studies, but evidence of clinical benefit over standard AVGs is lacking.

5. Conclusion

Innovations in CVCs, AVFs, and AVGs over the last several decades have revolutionized care for patients needing long-term dialysis. The main challenges in assuring adequate hemodialysis access include timing and logistics of obtaining an AVF, preventing access stenosis and thrombosis, and preventing infection. The abovementioned innovations are cornerstones in improving quality of care in patients undergoing long-term hemodialysis. Overall, more research into the efficacy of these innovations, as well as larger comparative trials, are needed to gain the public's trust and bring these innovations into the mainstream. However, the wealth of literature

on these hemodialysis access improvements suggests that the future will not only see incremental improvements in CVCs and AVGs, but also stark changes to the way hemodialysis access is achieved with inventions like the endoAVF and HeRO. Obtaining and sustaining optimal durable vascular access for hemodialysis is a complex and challenging task, but these innovations promise to build on our current quality of hemodialysis access.

Author details

Nidharshan S. Anandasivam* and Tessa K. Novick
Department of Internal Medicine, Dell Medical School at the University of Texas at Austin, Austin, TX, United States

*Address all correspondence to: nidharshan17@gmail.com

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