A Patient with Recurrent Arteriovenous Graft Thrombosis

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Abstract
Arteriovenous grafts (AVGs) are prone to frequent thrombosis that is superimposed on underlying hemodynamically significant stenosis, most commonly at the graft-vein anastomosis. There has been great interest in detecting AVG stenosis in a timely fashion and performing preemptive angioplasty, in the belief that this will prevent AVG thrombosis. Three surveillance methods (static dialysis venous pressure, flow monitoring, and duplex ultrasound) can detect AVG stenosis. Whereas observational studies have reported that surveillance with preemptive angioplasty substantially reduces AVG thrombosis, randomized clinical trials have failed to confirm such a benefit. There is a high frequency of early AVG restenosis after angioplasty caused by aggressive neointimal hyperplasia resulting from vascular injury. Stent grafts prevent AVG restenosis better than balloon angioplasty, but they do not prevent AVG thrombosis. Several pharmacologic interventions to prevent AVG failure have been evaluated in randomized clinical trials. Anticoagulation or aspirin plus clopidogrel do not prevent AVG thrombosis, but increase hemorrhagic events. Treatment of hyperhomocysteinemia does not prevent AVG thrombosis. Dipyridamole plus aspirin modestly decreases AVG stenosis or thrombosis. Fish oil substantially decreases the frequency of AVG stenosis and thrombosis. In patients who have exhausted all options for vascular access in the upper extremities, thigh AVGs are a superior option to tunneled internal jugular vein central vein catheters (CVCs). An immediate-use AVG is a reasonable option in patients with recurrent CVC dysfunction or infection. Tunneled femoral CVCs have much worse survival than internal jugular CVCs.


Patient Presentation
The following vignette illustrates the numerous challenges in optimizing arteriovenous graft (AVG) patency in hemodialysis patients. A 28-year-old woman initiated peritoneal dialysis when she developed ESRD because of focal glomerular sclerosis. She was hospitalized with an intracerebral bleed caused by a ruptured aneurysm 1.5 years later. A ventricular-peritoneal shunt was placed to treat hydrocephalus, and she was anticoagulated with warfarin to keep the shunt patent. Because of residual left-sided weakness and inadequate family support, she was no longer able to perform peritoneal dialysis. A tunneled central vein catheter (CVC) was placed in the right internal jugular vein, and she was switched to maintenance hemodialysis.

A left forearm arteriovenous fistula (AVF) clotted 2 weeks after its creation. A subsequent looped left upper-arm AVG was successfully cannulated 5 weeks after its creation. It clotted four times during the ensuing 6 months and was treated each time by an interventional radiologist or nephrologist, who performed percutaneous thrombectomy, in conjunction with angioplasty of a venous anastomotic stenosis. The patient resumed hemodialysis with an internal jugular CVC when the AVG failed. A right radiocephalic AVF required surgical revision to promote maturation and was cannulated successfully 7 months after its creation. When it failed 3.5 months later, a new CVC was placed. A subsequent right upper-arm graft failed after 6 months because of irreversible thrombosis, despite undergoing two angioplasties and two thrombectomies. A new CVC was placed in the right femoral vein because an ultrasound had then revealed bilateral thrombosis of the central veins in her chest.

Having exhausted vascular access options in both upper extremities during a 5-year period, she then had an immediate-use AVG (Gore) placed in her left thigh. This AVG required five thrombectomies, two angioplasties, and one surgical revision to maintain its patency for dialysis during the next 3 years. Therefore, over an 8.2-year period of hemodialysis, this patient required five new vascular access surgeries, 12 thrombectomies, four angioplasties, and two surgical revisions. She also underwent 15 CVC placements, exchanges, or removals and was treated for three episodes of catheter-related bacteremia. In summary, she averaged 4.4 vascular access procedures annually and was catheter-dependent for 1.8 years, or 22% of her time on hemodialysis. Unfortunately, she was disqualified for kidney transplant because of morbid obesity.

AVG Placement and Cannulation
Surgeons create an AVG by interposing a hollow synthetic tube in a looped configuration, with one end anastomosed to the side of an artery and the other end to the side of a vein (Figure 1). The AVG is typically cannulated 2–3 weeks after its placement, once the
surgical wound has healed. The initial cannulation is performed with 15-gauge needles inserted at a 45° angle with a dialysis blood flow of 450 ml/min.

**Why Do AVGs Clot?**

Virchow’s triad (venous stasis, endothelial injury, and hypercoagulability) describes the three factors predisposing to venous thrombosis. The first two are the major contributors to AVG thrombosis. When patients undergo percutaneous thrombectomy of a clotted AVG, imaging studies almost always reveal an underlying hemodynamically significant (>50%) stenosis. The stenotic location is most commonly observed at the venous anastomosis, but it may also be found in the draining vein, central vein, feeding artery, or within the AVG itself (1–3). Successful restoration of AVG patency requires both mechanical thrombectomy and successful angioplasty of the underlying stenosis. These observations suggest that AVG thrombosis is a direct consequence of critical stenosis. This assumption is clearly an oversimplification, however, because only a fraction of AVG with hemodynamically significant stenosis will clot in the absence of a preemptive angioplasty. For example, in one prospective study of patients with >50% AVG stenosis documented by angiogram, only 30% of AVGs clotted during the ensuing 6 months without preemptive angioplasty (4). In other words, stenosis is necessary, but not sufficient, to cause AVG thrombosis. Unfortunately, there is no reliable test to distinguish between an AVG with underlying stenosis that is destined to clot and one that will remain patent without an intervention.

**Can One Identify AVGs with Significant Stenosis by Noninvasive Methods?**

An angiogram is the definitive test to identify AVG stenosis, but it is invasive and expensive. Therefore, it is desirable to have a simple, reproducible, noninvasive test to identify patients who are likely to have AVG stenosis. Patients with an abnormal test would then be referred for an angiogram, and if it reveals hemodynamically significant stenosis, a preemptive angioplasty would be performed. The noninvasive tests for stenosis fall into two broad categories. Clinical monitoring consists of tests that can be performed in the dialysis unit without requiring special equipment or extensive staff training. AVG monitoring includes physical examination of the AVG (abnormal bruit, edema distal to the AVG); observations during the hemodialysis session (difficulty in cannulation, prolonged bleeding from the needle puncture site); and unexplained decrease in the delivered Kt/V on a constant dialysis prescription (3,5). Monitoring is simple and cheap, but it is dependent on having the dialysis staff implement it consistently.

AVG surveillance is a method that requires either specialized equipment or extensive staff training. There are three major types of AVG surveillance. Static dialysis venous pressure measures the intragraft pressure before initiation of the dialysis session (6). The ratio of intragraft to systemic systolic pressure is normally <0.4. A ratio >0.6 is suspicious for AVG stenosis. Flow monitoring measures the access blood flow using ultrasound dilution (7). With the arterial and venous lines reversed, ice saline is injected rapidly into the graft, and the rate of increase in blood temperature is used to calculate the blood flow. An access flow <600 ml/min, or one that has decreased by >25% from the previous baseline, is considered suspicious for AVG stenosis. Finally, duplex ultrasound requires a visually apparent focus of narrowing, in conjunction with a ratio of the peak systolic velocity on either side of the stenosis being >2 (8). Static dialysis venous pressures and flow monitoring are typically performed by a trained individual at monthly intervals, and duplex ultrasound is usually done quarterly. A number of studies have evaluated the positive predictive value of an abnormality of clinical AVG monitoring or surveillance for the presence of hemodynamically significant stenosis. The values were 69%–93% for clinical monitoring (80% for physical examination, 69% for unexplained decrease in Kt/V, and 66% for difficulties encountered during the dialysis session) (3,5,8–10), 92% for static dialysis venous pressure (6), 87%–100% for flow monitoring (11,12), and 80% for duplex ultrasound (5).

Because static dialysis venous pressure and flow monitoring may vary between repeated measurements, the typical approach is to look for trends (e.g., progressive increase in the intragraft to systemic systolic pressure or progressive decreases in the access blood flow) before referring the patient for an angiogram. In practice, this typically requires 2–3 months of repeated measurements before the angiogram is obtained. When stenosis progresses rapidly, it is quite possible for the AVG to clot before surveillance has identified a likely stenosis. In fact, approximately 25% of AVGs clot before an abnormal surveillance test has been obtained and confirmed (13,14).
Does Stenosis Surveillance with Preemptive Angioplasty Prevent AVG Thrombosis?

The rationale of AVG surveillance is to identify stenosis in a timely fashion and perform a preemptive angioplasty before the AVG clots. Such an approach makes sense intuitively. In fact, numerous observational studies have reported that implementation of routine AVG stenosis surveillance, in conjunction with preemptive angioplasty, markedly lowers the frequency of AVG thrombosis in comparison with a historical period without AVG surveillance (6,9,10,15–17). More recently, six randomized clinical trials (RCTs) have evaluated this research question (4,5,12,18–20) (Figure 2). These studies used different surveillance methods (static dialysis venous pressure, flow monitoring, or duplex ultrasound), whereas the control group underwent clinical monitoring alone (21). As one would expect, the frequency of angioplasty was always higher in the surveillance group than in the control arm. Thrombosis-free AVG survival was the primary end point in five of the studies, and none found a significant difference in this outcome between the surveillance arm and controls. In addition, five of the studies evaluated cumulative AVG survival (time to permanent failure), and only one demonstrated superior AVG survival in the surveillance group. Finally, a meta-analysis of these RCTs concluded that AVG surveillance with preemptive angioplasty does not prevent AVG thrombosis (22).

Why Surveillance with Preemptive Angioplasty Does Not Prevent AVG Thrombosis

AVG stenosis is caused by aggressive neointimal hyperplasia (23). The vascular injury caused by balloon angioplasty induces accelerated intimal hyperplasia, resulting in rapid restenosis (24). As a consequence, stenosis recurs in approximately 20% of AVGs within 1 week of angioplasty and in 40% within 1 month (11,12). In other words, the very intervention used to treat the underlying stenosis to prevent AVG thrombosis leads to rapidly recurrent stenosis that places the patient at risk for AVG thrombosis. As previously mentioned, we do not know which AVGs with hemodynamically significant stenosis are likely to clot and which ones will remain patent without a preemptive angioplasty. Therefore, the current sledgehammer approach results in elective angioplasty in all AVGs. Angioplasty may prevent AVG thrombosis in some AVGs that are destined to clot, but at the same time provoke thrombosis in other AVGs with stable stenosis. The net effect

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Figure 2. | Effect of AVG stenosis surveillance with preemptive angioplasty on AVG thrombosis: Observational versus randomized studies.

(A) Observational studies reporting on the frequency of graft thrombosis that occurred during a historical control period and after implementation of stenosis monitoring or surveillance. Thrombosis decreased during the intervention period in all of the studies. (B) The frequency of graft thrombosis in the graft surveillance group and the control group that was observed in randomized clinical trials. The rate of thrombosis was not significantly different between the randomized groups in these studies. AVG, arteriovenous graft; CM, clinical monitoring; DVP, dialysis venous pressure; FM, flow monitoring; SVP, static dialysis venous pressure; US, ultrasound. Reprinted from reference 21, with permission.
is no change in the overall frequency of AVG thrombosis despite a large increase in angioplasty procedures (i.e., added cost without benefit).

Can Stent Deployment Improve AVG Outcomes after Angioplasty?
One potential approach to improve AVG patency after angioplasty is to deploy a stent at the stenotic site. By providing a rigid scaffold inside the vessel, this may delay AVG restenosis. The efficacy of this approach was evaluated in an RCT in which patients with hemodynamically significant stenosis at the AVG venous anastomosis were allocated to receive either conventional angioplasty or angioplasty in conjunction with deployment of a stent graft (25). All patients underwent protocol angiograms 2 and 6 months after the initial intervention. The patients in the stent group had superior 6-month patency of the stenotic site and the entire access circuit. Importantly, the study design likely led to many superfluous angioplasties when there was no clinical indication to perform an angiogram. Moreover, the frequency of AVG thrombosis did not differ between the two groups. Given the high expense of stent grafts (approximately $2000 each) and their unproven benefit in terms of preventing AVG thrombosis, their routine deployment to treat AVG stenosis cannot be justified at this time (26). Two larger ongoing RCTs, RENOVA (flair endovascular stent graft post-approval trial) and REVISE (Gore Viabahn endoprosthesis versus percutaneous transluminal angioplasty to revise arteriovenous grafts at the venous anastomosis in hemodialysis patients) are evaluating two different brands of stent grafts to assess whether they improve AVG patency after angioplasty of a venous anastomotic stenosis. Once the results of these RCTs are available, it will be possible to reappraise the indications for stent deployment in patients with AVG stenosis.

Potential Pharmacologic Interventions to Prevent AVG Thrombosis or Failure
There has been great interest in identifying pharmacologic approaches to prevent AVG stenosis and thrombosis. The published studies to date have evaluated the efficacy of warfarin, high-dose folic acid, antiplatelet agents, and fish oil (Table 1).

Anticoagulation
In a Canadian double-blinded RCT, warfarin failed to prevent AVG thrombosis, but produced a major bleed in approximately 10% of the patients (27). The futility of warfarin is highlighted in the present patient, who experienced recurrent AVG thrombosis despite long-term anticoagulation while maintaining a therapeutic international normalized ratio. It is sometimes argued that anticoagulation may still be useful in the subset of patients who experience frequent AVG thrombosis because such patients may differ from those with less-frequent AVG thrombosis. For example, a retrospective, case-control study of 419 hemodialysis patients with and without vascular access thrombosis identified a genetic or acquired thrombophilia (e.g., factor V Leiden, lupus anticoagulant, prothrombin gene mutation, hyperhomocysteinemia, antithrombin III deficiency) in a higher proportion of patients with access thrombosis compared with those without access thrombosis (55% versus 39%) (28). Nonetheless, simply demonstrating an association between thrombophilia and access thrombosis does not establish that the thrombophilic disorder is responsible for AVG thrombosis or that anticoagulation would prevent AVG thrombosis. Answering this question would require an RCT of anticoagulation in hemodialysis patients with thrombophilia who receive a new AVG. Until such a study has been performed, anticoagulation of such patients cannot be justified. Rather, the focus should be on pharmacologic approaches to prevent neointimal hyperplasia and stenosis (the underlying pathology leading to AVG thrombosis).

Antiplatelet Agents
Dipyridamole, an antiplatelet agent, also inhibits the proliferation of vascular smooth muscle cells in vitro, suggesting that it may prevent neointimal hyperplasia, stenosis, and thrombosis in AVGs (29). In a single-center, double-blinded RCT, dipyridamole decreased AVG thrombosis by approximately 50% (30). A much larger, multicenter, double-blinded RCT observed that aspirin plus long-acting dipyridamole improved primary unassisted AVG survival by approximately 18% (31). In another RCT, aspirin plus clopidogrel did not prevent AVG thrombosis thrombosis-free AVG, but doubled the frequency of bleeding complications (32).

Therapy to Treat Hyperhomocysteinemia
Homocysteine levels are extremely high in hemodialysis patients, and vascular access thrombosis has been associated with homocysteine levels (33), suggesting that decreasing plasma homocysteine may prevent vascular access thrombosis. Two RCTs evaluated this question by administering high doses of vitamin B. In one study a high (15 mg) daily dose of folic acid lowered plasma homocysteine levels without preventing access thrombosis (34). Likewise, a second RCT that used high doses of folic acid, pyridoxine, and cyanocobalamin to lower plasma homocysteine did not observe a reduction in AVG thrombosis (35). These two RCTs highlight an important principle: just because a therapy treats an underlying thrombophilia does not necessarily mean that it will prevent AVG thrombosis.

Fish Oil
The active component of fish oil, omega-3 fatty acids, has antiproliferative and antioxidant properties, which may help prevent AVG thrombosis (36). A small, single-center RCT demonstrated a markedly lower rate of AVG thrombosis in patients treated with fish oil versus placebo (37). A larger, multicenter, double-blinded RCT observed that fish oil halved the frequency of AVG thrombosis and angioplasty (38).

Local Drug Delivery Systems
There has been an ongoing interest during the last few years in developing local drug delivery systems that would provide a high concentration of an antiproliferative drug at the site of stenosis, while minimizing the potential toxicity associated with systemic administration of such drugs (39). Such an approach has been beneficial in a number of experimental animal models of AVGs (e.g., using a paclitaxel- or rapamycin-eluting wraps), but no large-scale RCTs in patients with AVGs have been completed.
Once All Upper-Extremity Options for Permanent Vascular Access Have Been Exhausted, What Is the Best Access Option?

A subset of hemodialysis patients, such as the one described in the current patient presentation, experience multiple failed vascular accesses and ultimately exhaust all options for permanent vascular access in the upper extremities. Assuming that peritoneal dialysis is not a viable option, such patients may continue hemodialysis with a long-term tunneled CVC. Alternatively, the surgeon can create an AVG in the thigh. A recent observational study compared the long-term access outcomes in a large cohort of hemodialysis patients with tunneled internal jugular CVCs versus thigh AVGs (40). Infection-free survival at 1 year was 79% for thigh AVGs versus 21% for CVCs. Cumulative access survival at 1 year was 62% for thigh AVGs versus 31% for CVCs. Therefore, in this clinical scenario, thigh AVGs are a much superior option that is associated with fewer infections and more prolonged access survival. In patients with a patent artery but an occluded central vein, another access option is placement of a hemodialysis reliable outflow graft (41).

What Is the Role of an Immediate-Use AVG?

Conventional polytetrafluoroethylene (PTFE) AVGs typically require 2–3 weeks before they can be safely cannulated. In contrast, immediate-use AVGs are made of polyurethane and include a special middle layer with a nonpermeable self-sealable coat that permits them to be safely cannulated within 24 hours of their placement (42). Under what circumstances is the use of immediate-use AVG justified? One scenario is the situation in which CVC dysfunction recurs rapidly (within days) and repeatedly, such that it impairs adequate delivery of dialysis. A second scenario is a patient with frequent catheter-related bacteremia necessitating multiple courses of antibiotics, thereby delaying placement of the AVG (43). At one large dialysis center, immediate-use AVGs accounted for only 3.5% of all AVGs placed during a 5-year period (44). Compared with standard PTFE AVGs, the immediate-use AVGs have a similar cumulative patency. However, they had a higher frequency of AVG infection, particularly if they were placed in the thigh (44).

What Vascular Access Options Are Possible When All Permanent Access Options Have Been Exhausted and Central Thoracic Veins Are Occluded?

Once a patient has exhausted all options for permanent vascular access options in all four extremities, that patient remains CVC-dependent unless peritoneal dialysis is feasible. Approximately 5% of hemodialysis patients fall into this category (45). Central vein stenosis and thrombosis are common complications of long-term CVCs (46). Once the patient develops bilateral occlusion of the central veins in the chest, central veins at other locations are used for vascular access. The most commonly used choice is the femoral artery. Unfortunately, femoral CVCs are short-lived and far inferior to those placed in the internal jugular vein. At one clinical center, the 6-month patency of CVCs (from initial placement to removal or exchange) was only 14% for femoral CVCs compared with 67% for internal jugular CVCs (47). Moreover, 26% of patients with femoral CVCs developed ipsilateral deep vein thrombosis requiring anticoagulation (47). Other less commonly used sites for CVCs...
include transhepatic CVCs and translumbar CVCs placed into the inferior vena cava (48,49).

In summary, AVGs have relatively poor long-term patency and usually fail as a result of irreversible thrombosis superimposed on underlying stenosis. AVG surveillance can detect stenosis before thrombosis and can lead to timely pre-emptive angioplasty. However, surveillance with pre-emptive angioplasty did not prevent AVG thrombosis in RCTs. Several pharmacologic approaches to preventing AVG stenosis and thrombosis have been evaluated.

Questions
Manish K. Saha, MD (Nephrology Fellow at University of Alabama at Birmingham)

Has anybody looked at using drug-eluting stents, such as those used for coronary artery disease, to prevent AVG failure?

Answer
Sirolimus-eluting stents have been shown to reduce intimal hyperplasia in a porcine model of an AVG (50). To date, there have been no clinical studies evaluating this approach in hemodialysis patients with an AVG. In addition, an ongoing open-label, single-center, RCT of 40 hemodialysis patients revealed superior 6-month primary access patency in patients treated with a paclitaxel-coated angioplasty balloon compared with those treated with a standard angioplasty balloon (51). Larger clinical trials are indicated before this approach can be recommended.

Vinay N. Krishna, MD (Nephrology Fellow at University of Alabama at Birmingham)

Can preoperative venous mapping predict outcomes of AVF and AVG?

Answer
Preoperative vascular mapping assists surgeons in selecting the type and location of vascular access. It provides information about arterial and venous diameters and stenosis or thrombosis of the draining vein (52). Use of arteries or veins <1.5 mm in diameter is associated with higher AVF nonmaturation (53), prompting most surgeons to require arterial diameters ≥2 mm and venous diameters ≥2.5 mm. However, using even higher vascular diameters does not lower AVF nonmaturation (54). The effect of preoperative vascular diameters on AVG survival has not been reported. However, access survival is comparable for AVGs placed in the thigh and in the upper extremity, even though the former use considerably larger vessels (55). The possibility that vascular function tests may be better predictors of AVF outcome is currently being investigated (56).

James C. Harms, MD (Nephrology Fellow at University of Alabama at Birmingham)

Are any patient characteristics associated with AVG stenosis or thrombosis?

Answer
AVF nonmaturation or early failure is associated with older age, female sex, forearm location, and cardiovascular disease (57–60). In contrast, no clinical factors have been associated with early AVG failure. Therefore, for example, a recent prospective, multicenter study of 354 patients with new AVGs did not observe an association of early AVG failure with patient age, sex, race, diabetes, cardiovascular disease, body mass index, or access location (61).

Claretha N. Lyas, MD (Nephrology Fellow at University of Alabama at Birmingham)

Are there any genetic factors that predispose to early access failure?

Answer
Heme-oxygenase-1 polymorphisms were associated with AVF failure in one report (62). Thrombophilia (genetic abnormalities associated with a hypercoagulable state, such as factor V Leiden, prothrombin mutation, or decreased activity of protein S or C) was present in 9% of 219 patients undergoing AVF creation and was associated with a 2.2-fold higher risk for AVF failure (63). Another prospective study of 479 patients with new AVFs investigated the association of AVF failure with 43 single-nucleotide polymorphisms (SNPs) in 26 candidate genes related to proliferation, inflammation, endothelial function, vascular remodeling, coagulation, and calcium/phosphate metabolism (64). Only two of the candidate SNPs studied (one for factor V and one for LDL receptor-related protein 1), accounting for 17% of the study cohort, were associated with AVF failure. Finally, a third study of 354 patients with new AVGs evaluated whether AVG failure was associated with 48 SNPs associated with nine candidate genes (61). Factor V polymorphisms, found in 47% of the patients, were associated with a 1.7-fold higher risk of AVG failure. Should patients with frequent AVG thrombosis be screened for such genetic abnormalities? Genetic screening is expensive, and it is not known whether anticoagulation of these individuals would prevent future AVG thrombosis. In the absence of an RCT, such an approach cannot be recommended.

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Disclosures
None.

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