Interventional Nephrology: Novel Devices that Will One Day Change Our Practice

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Summary
There is increasing awareness of vascular access dysfunction as a significant contributor to the morbidity associated with chronic hemodialysis. Over the last several years, interventional nephrologists, in conjunction with our colleagues in vascular surgery, have led the way in the creation of novel devices that are designed to help solve the vascular access problem. The purpose of this review is to describe novel devices in the precommercial stage of development that have the potential to revolutionize the field of dialysis vascular access. These devices include bioengineered blood vessels, access monitoring technology, and advanced anastomotic connectors.


Hemodialysis access dysfunction remains a $1 billion per year problem despite efforts by multiple regional and national entities (1). There is increasing awareness of vascular access dysfunction as a significant contributor to the morbidity associated with chronic hemodialysis, highlighted in recent years by two large National Institutes of Health studies from the Dialysis Access Consortium (DAC) demonstrating poor outcomes for both arteriovenous (AV) fistulas and grafts (2,3). An increased interest in multidisciplinary clinical as well as research efforts to find solutions to vascular access problems continues to emerge as the US hemodialysis patient population rapidly increases (4), but there remains much work to be done.

More than 500,000 people in the United States have ESRD and require dialysis for survival, most of whom are on hemodialysis and have a need for dependable vascular access (5,6). Up to 17% of total spending for hemodialysis per patient per year is associated with hemodialysis access-related morbidity (7). Although it is generally agreed upon that the ideal hemodialysis access should be durable, require few interventions to maintain patency over time, and have minimal risk of infection, maintenance of access requires repeated interventions over time, exacting both an economic as well as physical and emotional toll on patients.

Studies have shown that AV fistulae are superior to prosthetic access when overall patency rates and revisions are considered (8,9). However, the two major complications seen with AV fistula formation are an initial failure to mature, and later venous stenosis followed by thrombosis (10). The DAC fistula study found that 60% of AV fistulae were not suitable for dialysis at 5 months and 20% were thrombosed at 6 weeks. Rates of primary nonfunction, or failure to mature, have been reported up to 50% at some centers, particularly those with aggressive fistula placement policies (11). Perhaps due to the latter problem, the United States continues to have an extremely low AV fistula rate compared with other countries around the world (12).

Interventional nephrology is a nascent subspecialty of nephrology that focuses primarily, but not exclusively, on access care improvement for hemodialysis patients. Before the development of interventional nephrology as a subspecialty field, vascular access care was often fragmented and difficult to navigate with imaging performed by one group, access placement by a surgical subspecialist, and catheter placement and access maintenance typically handled by an interventional radiologist. Coordination of this care often led to delays in dialysis initiation, permanent access placement, and treatment of complications (13). Over the last several years, interventional nephrologists have led the way in the creation of novel devices that are designed to help solve the vascular access problem. The purpose of this review is to describe novel devices in the precommercial stage of development that have the potential to revolutionize the field of dialysis vascular access.

Bioengineered Blood Vessels for Vascular Access
Over the last 3 decades, there has been an interest in the development of bioengineered blood vessels for a variety of uses. The initial focus was on small-caliber arteries used for coronary artery bypass grafting, because synthetic grafts performed poorly when replacing small diameter vessels needed for arterial bypass when the patient lacked sufficient arterial or saphenous vein grafts for the procedure. Polytetrafluoroethylene (PTFE) and Dacron grafts invariably led to increased thrombogenicity and intimal thickening, causing early graft failure and stenosis, consistent with what is commonly seen in the dialysis population (14–16). It was demonstrated that an endothelial cell (EC) monolayer on small-caliber grafts seemed to provide immediate protection from thrombus formation, and investigators began to look at various sources of human ECs, such as those harvested...
from the human umbilical vein, as a source for bioengineered vessel formation (17–19). A great deal of embryonic and adult stem cell research is ongoing in the area of tissue engineering for multiple uses. These unique cells are characterized by their capacity for prolonged undifferentiated proliferation in culture while maintaining the potential to differentiate into derivatives of all three germ layers (20).

Over the past decade there have been many attempts to produce a viable bioengineered vessel for both cardiovascular and peripheral vascular surgical uses and for formation of vascular access in the hemodialysis population (21). Blood vessel substitutes were first created by Weinberg and Bell through the seeding of ECs, fibroblasts, and smooth muscle cells on preformed collagen gels in 1986 (22). Burst strength was poor and the vessels were not viable for in vivo implantation but this was an exciting start to the area of tissue engineering of blood vessels. Two decades before this experimentation, Charles Sparks was pursuing animal experiments with siliconized Dacron tubes allowed to “mature” in vivo for 6 weeks to create a subcutaneous tunnel (23).

The PTFE grafts typically used now for development of vascular access are virtually identical to the first chronic-use prosthetic blood vessel used by Scribner in 1961 to create a prosthetic dialysis access, despite the well known deficiencies in function of these grafts (24). Tissue engineering involves several considerations, particularly where vascular access for hemodialysis is concerned. In addition to the proper mechanical and physical properties needed to maintain adequate flow, the vessel must maintain an adequate degradation rate without producing any toxic degradation waste products. There must be suitable cell adhesion, allowing integration into the surrounding tissues, and minimal inflammatory response at the site to prevent thrombogenicity and rapid development of stenosis that precludes adequate flow for use in hemodialysis. These challenges are exponential when one considers repeated cannulation with large bore needles that disrupt hemostasis and remodeling and cause long-term degradation of the engineered tissues as well as high flow rates through the graft required for adequate dialysis.

Tissue engineering, and incorporation of cells into a biodegradable scaffold, has demonstrated promising results for vascular access dilemmas (Figure 1). Stem cells, given the rapid proliferation and inherent ability to self-renew, make tissue engineering a viable option for access creation. Adult stem cells can be isolated from a patient’s own tissue, which limits the ethical issues associated with embryonic stem cells used in much of the early research in this area. Several methods are being studied currently utilizing different cell lines, including bone marrow mononuclear progenitor cells, mesenchymal stem cells from various sources such as bone marrow, skeletal muscle and adipose tissue, and endothelial precursor cells harvested from umbilical cord blood, peripheral blood or bone marrow (25). Some of these cells, specifically, pericytes or perivascular cells that line and interact with the endothelium in capillaries, have demonstrated an ability to regenerate within the graft, developing tissue that mimics native arteries. It is thought that pericytes are perhaps the origin of mesenchymal stem cells (MSCs) due to the expression of MSC markers and the typical location of MSCs in perivascular areas (26).

Figure 1. | Proposed mechanism of vascular transformation of hBMC-seeded biodegradable scaffolds. (A) Early pulse of MCP-1, secreted from seeded hBMCs, enhances early monocyte recruitment to the scaffold. Infiltrating monocytes release multiple angiogenic cytokines and growth factors (i.e., VEGF), which recruit SMCs and ECs to the scaffold. Vascular cells potentially come from circulating progenitors and/or proliferation and migration of mature vascular cells in adjacent vessel segments. ECs and SMCs appropriately organize into a mature blood vessel structure on the luminal surface of the scaffold. As the scaffold degrades, monocytes migrate away, leaving behind a completely autologous neovessel. (B) Immunohistochemical VEGF staining of hBMC-seeded scaffolds at postimplantation weeks 1, 6, and 10 shows continued VEGF expression throughout TEVG development (brown, positive VEGF expression). hBMC, human bone marrow stromal cell; MCP-1, monocyte chemotactic protein-1; VEGF, vascular endothelial growth factor; SMC, smooth muscle cell; EC, endothelial cell. Original magnification, ×400 (19).
safety during a 3-month safety period and then for primary patency at 1 and 6 months. Primary patency was maintained in seven of nine patients at 1 month (78%) and in five of eight patients at 6 months (62.5%), approaching the Dialysis Outcomes Quality Initiative objectives for primary patency (76% across all patients with native AV fistulas at 3 months) in this high-risk cohort (24). One concern with this cohort was that two of three graft failures were due to dilation, despite high initial burst strength of the graft and low expected immune response. This was postulated to be due, in one case, to high postoperative flows and subsequent unwinding of the tissue scaffold. In the other patient, it appeared to be immune-mediated response and perhaps due to use of a different ovine culture medium with higher IgG levels.

Further investigation of tissue-engineered blood vessels (TEBVs) in the United States was conducted by Tillman et al. to determine whether scaffold-based TEBVs could withstand the hemodynamic and mechanical challenges of chronic dialysis access. TEBVs were constructed using decellularized arterial scaffolds seeded with autologous ovine ECs, and then preconditioned to arterial pressure and flow in a bioreactor for 2 weeks before ovine implantation to create carotid artery to jugular vein AV grafts (Figure 2). Grafts were allowed to heal for 1 month before initiating percutaneous needle puncture 3 days per week and the wall geometry and graft patency was monitored via duplex imaging. Grafts were either explanted for histologic analysis at 2 months or followed for up to 6 months until venous outflow stenosis threatened patency. In this study, despite high flow, only modest wall dilation (<6%) was demonstrated at 4 months after implantation and needle access was well tolerated with only one small pseudoaneurysm occurring. Histologic analysis in the group explanted at 2 months demonstrated repopulation of the outer wall by host cells and healing of needle sites by cellular ingrowth and new matrix deposition along the tract. Ultimately, all six models that were not explanted at 2 months developed venous anastomotic stenosis, ranging from 3.3 to 5.6 months after implantation (27).

The research on new bioengineered vessels is encouraging, but the primary question for the practicing nephrologist remains—Is a TEBV access better than the traditional PTFE graft in people who are not candidates for fistula creation? If so, is there a viable commercially available product? Based on research done by Prichard et al. in conjunction with the makers of the tissue-engineered vascular graft Humacyte, there may be a viable product in the pipeline. Humacyte is a human tissue-engineered vascular graft (TEVG) with compliance between that of a native artery and vein, made of extracellular matrix proteins that confers resistance to inflammation and makes them highly biocompatible. The grafts are acellular, which allows them to be stored in simple refrigeration for up to 1 year. In a study utilizing a baboon model and comparing TEVGs with PTFE grafts, the TEVGs were found to have less venous intimal hyperplasia, with a correlation between intimal hyperplasia in the first 2 weeks and the rate of blood flow through the graft. The flow rates and venous dilation of the TEVGs reached a plateau at 4 weeks, suggesting that the venous remodeling and intimal hyperplasia largely occurred within the first month of implantation. The TEVGs appeared to be resistant to major triggers for intimal hyperplasia demonstrated in PTFE grafts, including an abundant macrophage population and the compliance mismatch between PTFE grafts and the outflow tract (28). Phase II manufacturing trials and clinical trials in humans are currently ongoing, and further data will be needed to determine whether TEVGs are ready for primetime.

**Biosensors for Access Monitoring**

There has been a great deal of investigation focused on prediction of stenosis and subsequent thrombosis in AV fistulas and grafts. It has been known since the 1980s that low blood flows through a fistula are associated with an increased incidence of subsequent failure of that fistula. Both the absolute flow rates and the rate of change in flow over time have been studied and found to be predictive of

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**Figure 2.** Preimplant specimens and operative images. Images of lyophilized decellularized scaffold (A) and a preimplant EC-lined scaffold stained with the nuclear stain DAPI, which demonstrates an endothelial monolayer present on the scaffold lumen at the time of implant (B). Operative photograph of bioengineered graft (C) placement in a loop configuration between carotid artery and jugular vein overlying the sternocleidomastoid muscle. Side view image of mature AV graft at 2 months postimplantation depicting the visible subcutaneous graft and dilated proximal vein (D) (27). EC, endothelial cell; DAPI, 4′,6-diamidino-2-phenylindole; CA, carotid artery; JV, jugular vein; SCM, sternocleidomastoid muscle; AV, arteriovenous.
access failure (29–31). Unfortunately, there is no one “gold standard” method for measuring access flow that can successfully predict when a patient needs to be referred for further investigation by an interventional nephrologist. On-line thermodilution monitors have been used with some success but are not available in all centers and require compatible equipment (32). Ultrasonic measurements such as those obtained with the Transonic Flow-QC Hemodialysis Monitor allow for measurement of flow rates and recirculation rates by calculating the transit times of ultrasonic beams relative to bi-directional flow within the access (33). These measurements can be helpful predictors of access complications, particularly when tracked over time, but are susceptible to operator error and require the time of trained staff to assess flows, which may only be done when clinical problems with the access are apparent.

It is widely accepted that a standardized approach to vascular access monitoring is helpful to predict access complications and prevent thrombosis. When coupled with a program that provides percutaneous intervention and correction of stenosis, access thrombosis rates decline from between 50% and 75%. Data show that intervention results in AV fistula thrombosis rates of 0.1–0.2/patient-year rather than 0.2–0.4 at baseline and AV graft thrombosis rates of 0.5/patient-year versus 0.8–1.2 at baseline (34,35). Current data support the Kidney Disease Outcomes Quality Initiative guidelines recommending that all patients undergo a program of regular access monitoring, preferably incorporating access flow measurements, coupled with appropriate referrals for prompt imaging and elective stenosis correction for accesses with decreased flows.

A new device has been studied in heart failure patients to provide wireless pulmonary artery hemodynamic monitoring to predict intracardiac and pulmonary artery pressures before the onset of clinical symptoms of congestion and the need for hospitalization. The CardioMEMS heart failure monitor (Figure 3) is a small pressure sensor consisting of electronic components housed within a hermetically sealed, fused silica capsule with two wire loops of nitinol attached at either end to prevent migration of the device. Pressure applied to the sensor causes deflections on the pressure-sensitive surface and results in a characteristic shift in the resonant frequency. The internal coil allows for electromagnetic coupling to the sensor by an external antenna that is held against the patient’s side or back in the approximate area of sensor deployment. The antenna powers the device, continuously measures its resonant frequency, and converts the shifts in frequency into a real-time pressure waveform that can easily be downloaded and interpreted (36). Initial data from the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III Patients (CHAMPION) trial published in 2011 suggest that the device is safe, with 98% of the 550 patients at 64 centers in the United States free of device-related and system-related complications and without pressure sensor failures. The results of this large trial in New York Heart Association Class III patients demonstrated definitive reduction in heart failure hospitalizations (37).

Although the CardioMEMS has not been studied in the hemodialysis population, it seems reasonable that real-time hemodynamic measurements with pressure waveform data would be quite successful in monitoring hemodialysis access flow rates and provide data suggestive of an early stenosis much sooner than the current monitoring strategies. The device is designed to withstand relatively high pressures within the pulmonary artery and is easily deployed percutaneously. It could be readily placed near the anastomosis where cannulation is typically not performed and valuable flow data could be obtained. In the future, it is hoped that further study in the hemodialysis population will determine the usefulness of this sensor and other intravascular hemodynamic monitoring devices in detecting and predicting access complications.

**Novel Anastomotic Connectors**

There are robust data to support the idea that cuffed, double lumen silicone catheters are the least ideal type of access, and it is generally accepted that they should be avoided when possible due to high rates of infection and dysfunction (38). Unfortunately, this is the most convenient and rapidly obtainable type of access available and is often the initial access used for patients initiated on hemodialysis after an AKI event or without previous planning for hemodialysis. With infections accounting for between 15% and 30% of all deaths in hemodialysis patients, second only to cardiovascular mortality, and infection leading to approximately 20% of hospital admissions in this population (39), tunneled catheter placement is clearly not an optimal strategy for permanent access.
PTFE grafts enjoy the benefits of being easy to place and essentially ready to use, but are prone to higher rates of thrombosis, stenosis, and infection than AV fistulae. Data from the Dialysis Outcomes Quality Initiative Analysis have suggested a primary patency rate of 50% at 1 year for PTFE grafts (10), whereas other authors report primary patency rates as low as 23% at 1 year and 4% at 2 years, consistent with findings from the large DAC study reported in 2009 (2,40). Nevertheless, AV graft placement may be an ideal choice for certain populations, even preferable to the AV fistula in certain subsets of patients, as some studies have shown (41–43). Moreover, when failure of the AV fistula to mature is taken into consideration, AV grafts have very similar patency outcomes to AV fistulae and are usable much sooner (44). Thus, as catheter avoidance becomes a primary focus of the post-“fistula first” era, AV graft placement is being cast in a new light.

A novel AV graft anastomotic device called the InterGraft (Phraxis Inc, St. Paul, MN) is currently being developed. The device is designed to provide a percutaneous solution to the vascular access conundrum that general nephrologists and their patients face. Even if referred early to general nephrology, 80% of patients begin dialysis with a catheter in the United States (38). Part of the reason for this is the logistical delay associated with surgical evaluation, anesthesia clearance, scheduling of operating room time, and finally AV fistula maturation time (or nonmaturation in half of the cases). The purpose of the InterGraft device is to afford interventionalists a percutaneous AV graft creation solution to the logistical delays.

Yevzlin et al. recently reported on a canine experiment of AV graft creation using the InterGraft device, which was invented by Dr. Yevzlin. The investigators hypothesized that a subcutaneous AV graft can be percutaneously delivered in a canine model to sustain flow at 3 hours postinsertion. Furthermore, they hypothesized that percutaneous intervention can be performed on the device safely. A 25-kg dog was anesthetized and prepped in the usual nonsterile fashion. Heparin (50 U/kg) was administered to the animal. Using percutaneous techniques (Figure 4 and Table 1) and two novel connectors for the venous and arterial anastomoses (Figure 5), a standard AV graft was tunneled under the skin of the animal and was used to connect the femoral artery and femoral vein.

Angiography immediately postintervention revealed patent flow from the femoral artery to the femoral vein of the animal at a BP of 65/35 mmHg. Percutaneous intervention was then performed with a 5×40 mm angioplasty balloon on the arterial and venous anastomoses without difficulty. The angiogram was repeated at 3.5 hours postimplantation and revealed patent brisk flow through the AV graft (Figure 6). This study shows for the first time that a percutaneous AV graft can be created and flow can be sustained at ≥3 hours postintervention. Given the importance of using any and all interventional strategies to decrease catheter use, a chronic animal study to test the ability to cannulate this type of AV graft for up to 20 weeks is planned for 2013.

The Optiflow implant device (Bioconnect Systems, Ambler, PA) is another novel anastomotic device designed to protect the perianastomotic region from the development of stenosis and improve the hemodynamics of the AV fistula (Figures 7–9). Although it is not a percutaneously deliverable device (it requires traditional surgery), the device is designed for end-to-side AV fistula creation and has been tested for safety and clinical performance in a study population of 94 patients in Hungary, Greece, Paraguay, and the United Kingdom with encouraging results. There were 88 patients evaluated for patency through 42 days; 5 patients had an immediate technical failure and 1 died from a non-device–related cardiac event before the patency evaluation. There have been no further technical failures since the device deployment technique was subsequently revised. Of these 88 patients, 89% had a patent fistula at 42 days and 78% were patent at 90 days. Fistula maturation data are available for 38 patients in the UK arm of the study, with a 70% unassisted maturation at 42 days postimplantation, defined as a venous
There has been some concern about the complications associated with dislodging the Optiflow device during subsequent percutaneous interventions, specifically balloon angioplasty, and current recommendations are to use a maximum balloon diameter compatible with the Optiflow device (3 or 4 mm, depending on the specific device used for anastomosis). The balloon also must be fully deflated before retraction to prevent the device from being inadvertently dislodged after the intervention. A field safety notice was issued by Bioconnect, the makers of the device, in August 2012, to address these concerns and provide recommendations regarding angioplasty (46). Further investigation regarding safety and utility of this product is certainly warranted, but it is an encouraging step toward increasing primary patency and decreasing perianastomotic stenosis, particularly in more challenging fistula creations.

Table 1. InterGraft percutaneous insertion

<table>
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<tr>
<th>Procedure</th>
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<tr>
<td>Via a maximum incision size of 1 cm, tunnel an ePTFE graft</td>
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<tr>
<td>Obtain access to femoral vein and artery using standard Seldinger technique, place sheaths</td>
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<tr>
<td>Confirm size of target artery and vein using angiography (Figure 5)</td>
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<tr>
<td>Deliver and deploy the VIG connector</td>
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<tr>
<td>Attach PTFE graft to VIG</td>
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<tr>
<td>Deliver and deploy the AIG connector (sheath already in place)</td>
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<tr>
<td>Insert 0.014–0.018” guide wire</td>
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<tr>
<td>Place 0.014–018” guide wire across target arterial anastomosis site (wire tip should be advanced approximately 10 cm into the artery)</td>
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<tr>
<td>Insert AIG delivery system over the wire, then remove the first stop</td>
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<tr>
<td>Retract sheath back until it contacts the second stop</td>
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<tr>
<td>Inflate the AIG balloon</td>
</tr>
<tr>
<td>Pull back balloon until it engages tines</td>
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<tr>
<td>Continue to slowly and gently pull back the balloon and the delivery system, until resistance is first felt.</td>
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<tr>
<td>Confirm with fluoroscopy that tines are fully seated against the wall</td>
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<tr>
<td>Retract delivery system sheath to deploy the proximal portion of the connector</td>
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<tr>
<td>Inflrate balloon</td>
</tr>
<tr>
<td>Remove AIG delivery system, observe flow</td>
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<tr>
<td>Unclamp VIG/AV graft</td>
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<tr>
<td>Allow PTFE graft to fill with blood</td>
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<tr>
<td>Using similar technique, connect AIG to PTFE graft, advancing the PTFE graft over the AIG. Unclamp AIG to provide flow through the entire arteriovenous circuit</td>
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<tr>
<td>Perform fluoroscopy of AV circuit</td>
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<tr>
<td>Suture the incision sites</td>
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PTFE, polytetrafluoroethylene; VIG, venous InterGraft; AIG, arterial InterGraft; AV, arteriovenous.

Figure 5. | Diagram of venous and arterial connectors of the InterGraft device.

Figure 6. | Angiogram at 3.5 hours postimplantation of the InterGraft device. The arterial anastomosis is an end to side technique, thus preserving distal arterial flow.

Figure 7. | Optiflow implant. Schematic demonstrating the precise control attainable over the geometry of the arteriovenous anastomosis (45).

outflow segment of ≥5 mm in diameter and blood flows of ≥500 ml/min as measured by ultrasonography (45).

There has been some concern about the complications associated with dislodging the Optiflow device during
Mositis perioperatively (45).

Over the next several years, as bundled payments for hemodialysis begin to take access type into consideration, general and interventional nephrologists will have to work together to find cost effective, creative solutions to the vascular access problem. The novel, precommercial devices described in this review may one day change the way vascular access care is practiced in the United States and around the world.

Disclosures
A.S.Y. is the inventor of the IntraGraft device and founder of Phraxis, Inc.

References


