Nonmaturation of new arteriovenous fistulas (AVFs) remains a major barrier to increasing AVF use in hemodialysis patients (1). Our current clinical paradigm views nonmaturing AVF as a plumbing problem, with efforts directed at augmenting access flow by surgical or percutaneous interventions (2–4). Unfortunately, the very same interventions utilized to salvage surgical or percutaneous interventions (2–4) with efforts directed at augmenting access flow, which in turn promotes recurrent intimal hyperplasia, rapid re-stenosis, shortened cumulative AVF survival, and the need for frequent interventions to maintain long-term AVF patency for dialysis (5,6). Vascular access research in humans and experimental models reported in the past few years highlights the complex biologic factors involved in AVF nonmaturation. These studies raise the exciting potential of identifying specific pharmacologic interventions to promote AVF maturation. A symposium held at the 2012 American Society of Nephrology Kidney Week in San Diego, California, highlighted new paradigms in our understanding of the mechanisms of AVF nonmaturation, and their implications for prevention of this problem. We invited the speakers at that symposium to amplify on their lectures for this Moving Points in Nephrology collection.

Our current understanding of the pathogenesis of AVF nonmaturation distinguishes between upstream and downstream events (7). “Upstream events” result in the initial vascular injury, which in turn produces “downstream events” (a biologic response to the initial injury leading to neointimal hyperplasia, stenosis, and ultimately AVF failure) (Figure 1). The initial injury may be caused by surgical injury to the vessels during AVF creation, as well as hemodynamic shear stress near the anastomotic site. The magnitude of vascular injury and the resultant biologic response is likely modified by numerous factors, including genetic predisposition, uremia, and preexisting vascular pathology.

Creation of an AVF results in a nonphysiologic condition whereby the low-pressure vein is exposed to the high-pressure artery, resulting in shear stress and vascular injury. The shear stress in a new AVF is not evenly distributed. Rather, it is localized to the juxta-anastomotic region (within approximately 2 cm of the artery-vein anastomosis). Imaging studies of nonmaturing AVF typically demonstrate focal stenosis in the juxta-anastomotic region (2,3). Most vascular surgeons create the anastomosis with a 90° angle between the vein and the artery. Elegant computational modeling of radiocephalic AVF has demonstrated disrupted flow at the swing segment of the vein and in the arterial segment proximal to the anastomosis (8). Moreover, varying the angle of the anastomosis in this model dramatically alters the shear stress. As the angle is decreased from 90° to 30°, there is a progressive decrease in shear stress, which may attenuate the vascular injury, neointimal hyperplasia, and development of juxta-anastomotic stenosis (9). The clinical relevance of these experimental findings was supported by a recent observational clinical study, in which changing the anastomotic angle of AVF from 90° to 30° reduced early juxta-anastomotic stenosis from 40% to 10% (10). Similarly, the Optiflow device may decrease vascular injury by fixing the angle at 60° (11). It is unknown whether the shear stress differs between brachiocephalic and radiocephalic AVF, because the former have a considerably lower nonmaturation rate than the latter (12). The article by Dr. Remuzzi amplifies on the relationship between AVF configuration, shear stress, and development of juxta-anastomotic AVF stenosis.

Neointimal hyperplasia is the final common pathway in the pathogenesis of juxta-anastomotic AVF stenosis. It develops within 3 weeks in experimental models of AVF (13–16), and has been documented in a small number of hemodialysis patients who underwent surgical revision due to AVF nonmaturation 2–6 months after their initial AVF creation (17,18). Experimental models have evaluated the role of some specific mediators in regulating neointimal hyperplasia after AVF creation. The initial biologic response to injury entails migration of myofibroblasts and smooth muscle cells from the adventitia and media into the intima, leading to subsequent aggressive neointimal hyperplasia (7). Numerous regulators mediate or modulate this biologic response, including cell cycle regulators, cytokines, chemokines, vasoactive molecules, adhesion molecules, and metallic matrix metalloproteinases. For example, heme oxygenase-1 (HO-1) has antiproliferative properties. HO-1 knockout mice exhibit accelerated neointimal hyperplasia of their AVF, highlighting the physiologic role of HO-1 in attenuating neointimal hyperplasia (13). The clinical relevance of these experimental findings was demonstrated by...
an observational study from Taiwan, which evaluated the association of AVF survival with HO-1 length polymorphisms in hemodialysis patients (19). A promoter gene regulates the transcription of HO-1. G-T length polymorphisms of this promoter affect HO-1 expression. The L/L genotype (longer GT repeats) is associated with a lower rate of HO-1 transcription than the S/S genotype (shorter GT repeats). Compared with the patients with the S/S genotype, those with the L/L genotype have shorter AVF patency.

More recent research has focused on preexisting vascular pathology in hemodialysis patients, and its potential contribution to the pathogenesis of neointimal hyperplasia in new AVFs. Several arterial and venous abnormalities have been described in patients undergoing vascular access creation, including venous intimal hyperplasia, arterial intimal hyperplasia, arterial medial fibrosis, arterial calcification, and venous calcification (18,20–23). A plausible hypothesis is that preexisting vascular pathology predisposes to accelerated neointimal hyperplasia and juxtaanastomotic stenosis in patients receiving a new AVF. A pilot Korean study reported significantly decreased AVF patency in patients with preexisting arterial intimal hyperplasia compared with that observed in patients without this pathology (23). A second study found no association of preexisting arterial medial fibrosis or arterial calcification with AVF nonmaturation (18). In contrast, a third study observed a lower frequency of arteriovenous graft (AVG) interventions in patients with preexisting arterial or venous pathology, suggesting a protective effect against neointimal hyperplasia in vascular access (24). These contradictory findings suggest that the cellular mechanisms leading to neointimal hyperplasia after AVF creation differ from those leading to the preexisting vascular abnormalities in uremic patients. Dr. Lee’s article provides a comprehensive overview of the mediators and modulators of neointimal hyperplasia, and the experimental evidence on how they affect AVF maturation.

What are the potential pharmacologic interventions to prevent vascular access failure? The only drug that has been evaluated for prevention of AVF nonmaturation is clopidogrel (25). A multicenter randomized clinical trial allocated patients to receive either clopidogrel or placebo for 6 weeks after AVF surgery. The frequency of AVF thrombosis within 6 weeks was significantly lower in patients receiving clopidogrel (12.2% versus 19.5%; P=0.02), but AVF nonmaturation was similar in both groups (61.8% versus 59.5%; P=0.40). Four randomized studies have evaluated pharmacologic interventions to prevent AVG failure (stenosis or thrombosis). Neither warfarin nor aspirin + clopidogrel prevented AVG thrombosis, but both drug regimens increased the risk of bleeding complications (26,27). Dipyridamole + aspirin produced a modest, but significant, prolongation of primary unassisted AVG survival (28). Finally, fish oil decreased the frequency of angioplasty and thrombosis in new AVG (29).

Systemic administration requires achieving relatively high blood drug levels in order to ensure sufficient anti proliferative effects at the target site (arteriovenous anastomosis for AVF and venous-graft anastomosis for AVG). These high systemic levels may expose the patients to significant adverse effects. There has been considerable interest in devising local drug delivery systems that would achieve a high drug level at the target site, while minimizing the risk of systemic drug toxicity (30). Potential local drug delivery systems, such as topical administration, adventitial wraps, cell implants, and gene delivery systems, have been evaluated in animal models. A limited number of phase 1/2 clinical trials have tested such therapies in dialysis patients. These pilot studies have included allogeneic endothelial cell implants (31), sirolimus-eluting collagen membranes (32), and pancreatic elastase (33). These small studies demonstrated the feasibility and safety of a variety of local drug delivery systems. However, large multicenter randomized clinical trials will be required to evaluate the clinical efficacy of these interventions in preventing vascular access failure. Drs. Terry and Dember have written a comprehensive review of new pharmacologic therapies in the horizon that may improve vascular access outcomes.

Acknowledgments

This manuscript was supported by funding from a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant (R01-DK-085027) to Dr. Allon.

Disclosures
None.

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