New Insights into Dialysis Vascular Access: Introduction

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Optimizing vascular access outcomes continues to pose a tremendous challenge to nephrologists, surgeons, and radiologists who provide medical care to patients on hemodialysis. There is a huge discrepancy between the optimal vascular access outcome proposed by national guidelines (1) and the reality. Thus, for example, whereas the guidelines suggest that most patients should initiate hemodialysis with a mature arteriovenous fistula (AVF), approximately 80% of patients in the United States start dialysis with a central vein catheter (2). This discrepancy reflects both a poor understanding of the pathobiology of vascular access failure and a failure of the complex processes of care required to achieve optimal outcomes. Numerous studies published during the past few years have investigated both aspects of vascular access. In recognition of the huge clinical and economic effect of vascular access failure, the National Institutes of Diabetes, Digestive and Kidney Diseases convened a 2-day workshop in September of 2015 to address this critical topic (http://www.niddk.nih.gov/news/events-calendar/Pages/hemodialysis-vascular-access-2015.aspx). This workshop included nephrologists, surgeons, radiologists, basic scientists, and industry representatives with a common interest in vascular access research. This Moving Points series features three reviews related to topics presented at this workshop (3–5).

There is widespread consensus that a mature AVF is the access of choice for most patients on hemodialysis (1). However, a substantial proportion of new AVFs fails to mature adequately to be cannulated reproducibly with two large-bore needles thrice weekly and deliver the high blood flow required to achieve the target dialysis dose (Kt/V) (6,7). AVF maturation requires a sustained increase in the diameter and blood flow rate of the feeding artery and the draining vein to enable successful cannulation and adequate blood flow through the extracorporeal dialysis circuit (physiologic AVF maturation). Efforts to reduce AVF nonmaturation have been hampered by our poor understanding of its pathophysiology.

Previous animal and human studies of AVF nonmaturation have focused primarily on endothelial dysfunction and the venous neointimal hyperplasia that develops near the surgical anastomosis and leads to flow-limiting stenosis (inward remodeling). Experimental studies have identified a number of bioactive substances that modulate neointimal hyperplasia (8,9). This enhanced understanding of the pathobiology of neointimal hyperplasia may lead to novel pharmacologic therapies to promote AVF maturation. At the same time, there has been a growing recognition of the importance of the biologic processes leading to a sustained increase in the AVF lumen (outward remodeling). Ultimately, AVF maturation may depend on the balance between inward and outward remodeling (10).

On the one hand, AVFs may mature, despite the development of anastomotic stenosis, as long as there is adequate outward remodeling. Thus, for example, in one clinical study, although AVF nonmaturation was more frequent in patients with stenosis than in those without stenosis, two thirds of AVFs with stenosis still matured without treatment of the stenosis (11). On the other hand, if outward remodeling is inadequate, an AVF will fail to mature, even in the absence of neointimal hyperplasia.

More recent studies have focused on the mechanisms of outward remodeling. Therapies that promote AVF maturation in animal models may not necessarily be effective in humans with AVF. Ultimately, only clinical trials will be able to establish potential pharmacologic approaches to enhancing AVF maturation. Ongoing trials are evaluating both therapies to prevent neointimal hyperplasia as well as ones to enhance outward remodeling. Two recent examples are the use of sirolimus-eluting wraps to prevent neointimal hyperplasia in new AVFs (12) and local application of elastase to the anastomotic site to promote sustained vasodilation (13). The paper by Lee and Misra (3) summarizes the exciting advances in our understanding of the complex pathophysiology of AVF nonmaturation.

Whereas the pathologic changes occurring after AVF maturation have long been recognized, there has been a more recent appreciation of preexisting arterial and venous pathology in patients with CKD. The vascular pathology described has included preexisting arterial and venous intimal hyperplasia, medial fibrosis, and arterial microcalcification (14–17). Several studies have evaluated whether these preexisting lesions contribute to poor AVF outcomes. Preexisting arterial and venous intimal hyperplasia may
predispose to accelerated neointimal hyperplasia after AVF creation and thereby, lead to critical juxta–anastomotic stenosis and AVF nonmaturation. Preexisting arterial medial fibrosis and microcalcification may increase vascular stiffness, thereby limiting arterial dilation required for outward remodeling. Preexisting arterial intimal hyperplasia was associated with inferior AVF survival in one study (14), whereas preexisting venous intimal hyperplasia was not associated with juxta–anastomotic AVF stenosis at 6 weeks or clinical AVF maturation (11). Preexisting arterial microcalcification was not associated with postoperative AVF stenosis, AVF nonmaturation, or unassisted AVF patency in one prospective study (17). Finally, a study of patients receiving an arteriovenous graft (AVG) unexpectedly found that the frequency of AVG interventions (angioplasty, thrombectomy, or surgical revision) was actually lower in patients with greater preexisting arterial or venous intimal hyperplasia, arterial medial fibrosis, or arterial microcalcification (18). The manuscript by Vazquez-Padron and Allon (4) provides an overview of vascular pathology in patients with CKD and its relationship to vascular access outcomes.

Finally, notwithstanding the national guidelines on vascular access, there remains considerable uncertainty about their implementation. For example, the guidelines suggest that AVF creation should occur at least 6 months before the expected time of hemodialysis initiation to allow adequate time for AVF development and possible subsequent interventions to promote maturation (1). However, predicting time to dialysis remains notoriously difficult. If this time interval is underestimated, the patient is likely to initiate dialysis with a catheter. However, if the interval is overestimated, the patient may die before needing dialysis or have a very slow progression of kidney disease, such that the AVF is not needed. Several observational studies have reported that only about 70% of patients with CKD and predialysis access surgery will initiate dialysis within 2 years, with the remainder either dying before starting dialysis or surviving without a need for dialysis (19–21). Moreover, the patient outcomes are substantially affected by patient age, such that older patients with CKD have slower progression of their kidney disease and are less likely to die before they require dialysis (19).

In addition, there has been a growing sense that, although AVF may be the preferred vascular access, there may be subpopulations of patients in whom an AVG may be a better choice (22,23). In particular, AVG may be preferred in older patients who have already initiated dialysis with a catheter, have a high likelihood of AVF nonmaturation, or have had a prior failed AVF (22). The manuscript by Woo and Lok (5) addresses in detail issues related to the timing of vascular access surgery and the choice of access in patients with CKD and dialysis.

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