

Early Fistula Failure: Back to Basics

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Maintenance of a well-functioning vascular access for hemodialysis is a major challenge in caring for patients with end-stage renal disease (ESRD). Vascular access dysfunction is one of the most important sources of morbidity and contributes substantially to the cost of ESRD care.¹ Vascular access practices have evolved over the past 3 decades, and these changes have been accompanied by an increased understanding of the processes underlying vascular access failure, particularly failure of synthetic arteriovenous (AV) grafts. We now recognize that stenosis, the cause of most episodes of graft thrombosis, is the result of aggressive neointimal hyperplasia. In this issue of *AJKD*, Roy-Chaudhury and colleagues use careful histologic and morphometric analysis to demonstrate that the same lesion may underlie maturation failure of native AV fistulas.²

During the 1980s and 1990s, use of the AV graft became widespread, in large part because of the ability to place grafts in the vast majority of patients regardless of vessel characteristics. An additional advantage of grafts is that, in contrast to native fistulas, they do not require a prolonged period of maturation and thus can usually be used within 1 to 2 weeks after placement. However, as use of grafts increased it became apparent that their advantages are countered by a high rate of thrombosis requiring frequent interventions to restore patency, and an average overall lifespan of only 2 to 3 years.³ Recognition that stenosis at or near the graft-vein anastomosis is present in most thrombosed grafts led to the incorporation of percutaneous angioplasty into approaches for restoring graft patency, and, shortly thereafter, to prophylactic angioplasty of stenoses that are identified prior to thrombosis.⁴⁻⁷ Unfortunately, beneficial effects

of angioplasty are short-lived, and stenosis usually recurs within several months or sooner.^{4,8,9}

Neointimal hyperplasia in stenotic AV grafts has been characterized histologically in previous work by Roy-Chaudhury's group and others.¹⁰⁻¹² The lesion contains smooth muscle cells, myofibroblasts, fibroblasts, and extracellular matrix. Macrophages can be present along the luminal surface of the graft, and microvessel formation is apparent in the intima and adventitia. Multiple factors are thought to contribute to neointimal hyperplasia of AV grafts; these include hemodynamic factors involving alterations in wall shear stress and venous hypertension, differences in compliance between the graft and the downstream vein, inflammation induced by the graft itself, activation of platelets by frequent needle cannulation, and the general vasculopathic state associated with kidney failure. Although there are no pharmacologic or biologic interventions that are clearly effective in preventing graft thrombosis, current investigational approaches are focused on systemic or local administration of antiproliferative agents directed at neointimal hyperplasia.¹³⁻¹⁷

The morbidity and cost associated with complications of synthetic grafts have led to recommendations in clinical practice guidelines for preferential creation of native fistulas, and have triggered major initiatives, such as the Fistula First Program of the Centers for Medicare and Medicaid Services, promoting the use of native fistulas.^{18,19} Although the development of neointimal hyperplasia and stenosis is not unique to grafts, thrombosis rates and the need for interventions, as well as the risk of infection, are lower for fistulas than for grafts. Despite widespread agreement that the native fistula is the best type of vascular access, and a substantial increase during the past few years in the proportion of patients for whom fistula creation is attempted, fewer than half of the patients undergoing hemodialysis in the United States receive dialysis with a fistula.²⁰ Maturation failure, the subject of Dr Roy-Chaudhury's investigation, is probably the most important reason for the low prevalence of native fistulas.

In order to be used for dialysis, a newly created fistula must mature; that is, the artery and vein must undergo dilation and remodeling to

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accommodate the markedly increased blood flow that results from creating the AV anastomosis. Mechanisms underlying fistula maturation failure are not well understood.²¹ Anatomic factors such as the diameters of the feeding artery and draining vein are thought to be important, and it is now considered standard practice to perform preoperative vascular evaluation either with ultrasound or angiography to identify vessels that appear anatomically suitable for fistula creation. However, there is clearly more to maturation than sufficient vessel diameter. For both the artery and vein a minimal diameter appears to be necessary for successful creation of a fistula, but above this threshold, no clear relationship exists between vessel size and fistula outcome.²² Non-anatomic factors that are likely to contribute to maturation failure include the underlying vascular pathology and impaired endothelial function associated with chronic kidney disease, vein trauma from surgical manipulation, and the hemodynamic stresses (ie, altered shear stress and venous hypertension) that result from creating an AV anastomosis.²¹ Importantly, several of these functional factors are potentially modifiable.

Roy-Chaudhury and colleagues examined tissue specimens obtained at the time of surgical revision from venous segments of 4 fistulas that had failed to mature. Three of the fistulas were patent and 1 had thrombosed. Neointimal hyperplasia together with less prominent medial hypertrophy was present in all 4 fistulas. The degree of stenosis was 80% or greater in all of the fistulas, and morphometric measurements revealed an eccentric geometry of the hyperplastic lesion. By immunohistochemistry, the predominant cell type contained both α -smooth muscle actin and vimentin but not desmin, marking it as a myofibroblast; contractile smooth muscle cells were also present but to a lesser degree.

This study is important because it provides the first demonstration of neointimal hyperplasia in fistulas with maturation failure. The histologic findings reported by Roy-Chaudhury et al complement recent observations by others that stenosis is a frequent angiographic finding in nonmaturing fistulas.^{23,24} However, unlike many of the fistulas in angiography series, the fistulas examined in the present study had never been cannulated for dialysis. Thus, we can conclude that processes involved in the development of

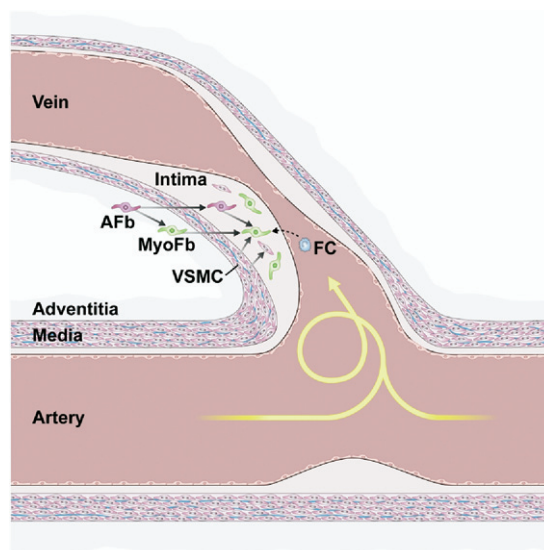


Figure 1. Eccentric venous neointimal hyperplasia at the juxta-anastomotic site of an arteriovenous (AV) fistula may occur at regions of low or oscillating wall shear stress and lead to failed fistula maturation. These regions of altered wall shear stress typically occur at the “heel” of the AV anastomosis as well as at the arterial wall opposite the opening of the fistula. The thickened neointima is composed of a variety of cells, including myofibroblasts (MyoFb), vascular smooth muscle cells (VSMC), endothelial cells involved in neovascularization, and inflammatory cells (the latter two are not shown), as well as extracellular matrix. Denuded areas of endothelium may also be seen. Myofibroblasts, a principal component of the neointima, are specialized synthetic and contractile cells involved in wound healing. Ultrastructurally, these cells contain α -smooth muscle actin coupled to extracellular fibronectin by a fibronexus junction that helps to provide support for injured tissue while the tissue is remodeled and new matrix formed. Myofibroblasts may originate from several sources including differentiation and migration of adventitial fibroblasts (AFb), dedifferentiation and migration of VSMC within the media, transdifferentiation from endothelial cells or possibly infiltration from circulating bone marrow-derived fibrocytes (FC). Regulating myofibroblast formation, proliferation, and migration may be key for controlling the eccentric neointimal hyperplasia that leads to fistula failure.

neointimal hyperplasia are independent of needle insertion into the vein, compression of the vein to promote coagulation after needle removal, or hemodynamic alterations induced by the dialysis machine blood pump. The observation that the lesions are eccentric is consistent with a role of hemodynamic stresses in the development of neointimal hyperplasia since those stresses should be distributed in a nonuniform manner along the circumference of the vein. The cellular phenotyping suggests that the composition of neointimal hyperplasia is similar whether it occurs in ve-

nous segments of nonmaturing fistulas or in venous segments downstream of synthetic grafts. Moreover, the abundant presence of myofibroblasts within the neointima is consistent with (but does not prove) a role for the adventitia as a source of cells for neointimal proliferation (Fig 1). This suggests that new therapies using perivascular delivery systems may hold promise in preventing fistula maturation failure.

The study has limitations that should be noted. The small sample size prevents conclusions about the frequency with which neointimal hyperplasia is present in fistulas with maturation failure. Additionally, one cannot exclude the possibility that stenoses were present in the veins before fistula creation. Although the degree of stenosis in each fistula appeared substantial by histologic examination, the hemodynamic significance of the lesion was not evaluated before the samples were obtained. Moreover, the investigators did not provide information about distance between the AV anastomosis and stenosis, or the orientation of the eccentric lesions with respect to the feeding artery. Such information might have enabled some evaluation of existing hypotheses about rheologic and hemodynamic influences on development of neointimal hyperplasia. Finally, the identification of myofibroblasts as the predominant cell type could have been further confirmed by ultrastructural studies looking for typical features such as the specialized focal adhesion complexes known as the fibronexus.^{25,26}

As is the case with most new observations, the findings of Roy-Chaudhury et al raise many questions. Most importantly, what are the triggers for such a marked hyperplastic response early after fistula creation? How important is preexisting vascular disease present in many individuals with chronic kidney disease? How important is the surgical trauma associated with mobilizing the vein or creating the anastomosis? How important are the relative orientations of the artery and vein making up the fistula? What is the source of the cells that populate the neointima and what would happen to the fistula if their migration, proliferation, or both were inhibited? These are not easy questions to answer, and it is likely that multiple factors interact to set the stage for neointimal hyperplasia. Roy-Chaudhury's group clearly recognizes the need for investigating the basic biology and physiol-

ogy of fistula maturation and maturation failure. Such efforts are crucial for identifying interventions to improve vascular access outcomes.

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