Pathophysiology of Stenosis Within AV Fistulas and Mechanisms of PTA

Despite widespread treatment of AV access stenosis with PTA, we have a limited understanding of what we are treating, why it responds to dilation, and if lesion characteristics can be used to guide treatment.

BY KATE STEINER, BSc, MBBS, MRCP, FRCR

Percutaneous transluminal angioplasty (PTA) is an established treatment for arteriovenous (AV) access stenosis in the setting of dialysis fistula dysfunction. PTA is safe and effective and can be performed as an outpatient procedure with a short recovery time. The National Kidney Foundation 2006 update on vascular access states, "Treatment of hemodynamically significant stenosis prolongs the use-life of the [AV access]." It is usually a relatively quick procedure depending on lesion location and type.

Although there is evidence that AV access PTA is both safe and effective, there is limited understanding of AV access stenosis. Most studies refer to AV access stenoses in native dialysis fistulas as a uniform group, sometimes even including polytetrafluoroethylene graft venous anastomotic stenosis. However, evidence now suggests that there are different types of AV access stenoses, and perhaps different lesion types should be treated differently.

Some lesions respond well to PTA and have relatively low restenosis rates, whereas other lesions (eg, those at the cephalic arch, those involving surgical “swing points,” or those at a polytetrafluoroethylene graft-venous anastomosis) have higher restenosis rates. Should treatment strategies for lesions with higher restenosis rates differ from lesions elsewhere?

PATHOPHYSIOLOGY AND ULTRASOUND CHARACTERIZATION OF AV ACCESS STENOSIS

When an AV fistula is created, a connection is made between a high-pressure arterial system and a low-pressure venous system. Vessel wall stress occurs and causes nitrous oxide release and vein dilation. When these mechanisms are favorable, the vein dilates and produces a usable fistula. However, high shear stress gradients and compliance mismatch, as well as traumatic balloon dilation, can lead to endothelial cell damage and intimal hyperplasia. Surgical injury, uremia, and traumatic needle insertion are also recognized causes and contributors to venous neointimal hyperplasia.

Histopathologists examining the juxta-anastomotic vein in the setting of fistula failure have described venous neointimal hyperplasia and adverse vascular remodeling (venous constriction). It is not yet clear whether failure of maturation secondary to a juxta-anastomotic stenosis occurs secondary to adverse vascular remodeling (venous constriction) or intimal hyperplasia or a combination of both. Venous neointimal hyperplasia is well recognized at the AV graft-venous anastomosis and in mature fistulas with stenoses. In 2004, Chang et al described an increase in the proliferation index of the intima and media in aggressive restenotic lesions after angioplasty.
Different appearances of AV access stenosis on ultrasound have been described. In 2012, Yamamoto et al described three types of stenosis seen on ultrasound in the outflow vein of AV grafts: a vascular constriction type, a neointimal proliferation type, and a third type that has features of both constriction and neointimal proliferation. This group assessed patency rates with bare-metal stent placement and found higher patency rates in the vascular constriction type of stenosis when compared to the other two types of stenosis.

This author’s observations confirm the three different types of AV stenosis reported by Yamamoto et al: a type with the appearance of neointimal proliferation/venous neointimal hyperplasia (Figure 1), a type with a more fibrotic appearance/vascular constriction (Figure 2), and a mixed type where there is vascular constriction with intimal hyperplasia (Figure 3).

In summary, there are most likely different subgroups of AV access stenosis. Most previous reports only look at the degree of stenosis but rarely consider lesion type.
More research is needed before we will know whether we should adopt different treatment strategies according to the type of stenosis. Some types of stenosis may be best treated with conventional PTA alone or alternative treatments including drug-coated balloons, covered stents, or surgery.

MECHANISM OF ANGIOPLASTY IN AV ACCESS STENOsis

The mechanism of angioplasty in coronary arteries and in peripheral artery disease has been studied histologically and by intravascular ultrasound (IVUS). Less is known about the mechanism of angioplasty in dialysis access stenosis. In 1991, Davidson et al used IVUS to evaluate 38 PTA procedures, and vessel dissection was observed in 42%, arterial stretch in 50%, and elastic recoil in 50%. Elastic recoil occurred most commonly when treating central venous lesions. IVUS was not able to differentiate between the adventitia, media, and intima of the vein wall.

Studies from coronary arterial models have shown that angioplasty can cause endothelial and smooth muscle cell injury, which results in migration of smooth muscle cells and myofibroblasts from the media to the intima where they proliferate, resulting in intimal hyperplasia. There may be a difference in response to injury within an arterialized vein, and aggressive restenosis may be observed. There is evidence that fibroblasts migrate from the adventitia, given that adventitial-derived fibroblasts and myofibroblasts are seen in neointimal hyperplasia at the AV graft anastomosis. Kim et al demonstrated that venous smooth muscle cells are more sensitive to antiproliferative agents, such as paclitaxel, when compared with arterial smooth muscle cells. In a review of vascular access dysfunction from a cellular and molecular viewpoint, Roy-Chaudhury et al described the histology of AV access stenosis and mechanisms of neointimal hyperplasia and discussed implications for antiproliferative therapy, including local drug delivery via drug-coated balloons or stents.

AV ACCESS STENOSES: PATENCY RATES FROM THE ANASTOMOSIS TO RIGHT ATRIUM

Patency rates may vary depending on the type of stenosis, (neointimal hyperplasia vs vascular constriction vs a combination of both), but it is well recognized that patency rates vary according to the site of stenosis within the access circuit. For example, there are high recurrence rates for cephalic arch stenoses. The perianastomotic vein (the anastomotic and juxta-anastomotic vein) is an area that can be treated with either PTA or surgery. A prospective study evaluating 112 PTA procedures demonstrated primary patency rates of 75%, 51%, and 41% at 6, 12, and 18 months, but secondary patency rates of 94%, 90%, and 90% at 6, 12, and 18 months, respectively. More recently, Patane et al used drug-coated balloons to treat juxta-anastomotic stenoses in 26 patients with radiocephalic fistulas and demonstrated primary patency rates of 96% and 82% at 6 and 12 months.

The cephalic arch is a region with high restenosis and rupture rates. Various treatment strategies have been applied, including PTA, cutting-balloon angioplasty, bare-metal stents, and stent grafts. Higher primary patency rates have been demonstrated after stent graft implantation.

Figure 4. B-mode ultrasound image demonstrating a cephalic arch stenosis and a diameter reduction of the vein and less neo-intimal hyperplasia (white arrow) as compared with Figure 1 (A). Fistulagram for the same patient demonstrating a cephalic arch stenosis (white arrows) prior to fistulaplasty (B).
but primary assisted patency rates are similar, with more interventions in cases when PTA is used.\(^8\)

The pathophysiology of cephalic arch stenosis is not well understood. High flow across the cephalic arch may contribute, and flow reduction surgery is a recognized treatment of cephalic arch stenosis, reducing the number of PTA interventions.\(^11\) The cephalic vein passes through the deltopectoral and clavicular pectoral fascia, which may limit vein dilation or exert pressure. Whether these stenoses are secondary to a more fibrotic stenosis or venous intimal hyperplasia or a combination of both is unknown. The high pressure needed at inflation and the relatively higher rate of cutting-balloon use suggest a fibrotic stenosis; however, a high recurrence rate implies a process involving venous intimal hyperplasia with or without aggressive inflammation and fibrosis (Figure 4).

The central veins also have high recurrence rates, but rupture rates are lower in the central veins as compared to the cephalic arch. Central venous stenosis is often associated with previous central venous catheter placement or transvenous pacemaker leads. Both are thought to cause venous trauma, resulting in endothelial cell damage followed by intimal hyperplasia, smooth muscle cell migration, inflammation, and fibrosis. PTA has a high technical success rate but a low primary patency rate and a relatively low primary assisted patency rate. More recently, a primary assisted patency rate of 75% at 24 months was demonstrated by Jones et al using covered stent grafts where PTA had failed to maintain patency.\(^12\) As demonstrated by Davidson et al, elastic recoil following PTA is relatively more common when treating the central veins.\(^5\)

The graft-venous anastomosis is an area in which venous intimal hyperplasia has been demonstrated by histopathologists. A large, prospective, randomized controlled trial demonstrated a statistically significantly higher primary patency rate of 51% at 6 months when stent grafts were used compared with 23% using PTA.\(^13\) In the presence of neointimal hyperplasia, covered stent grafts may be more effective because stent graft deployment results in vessel wall stretch and covers neointimal hyperplasia.

The surgical swing point of a basilic vein transposition is a relatively common site for stenosis with high recurrence rates, but the literature is scant in evaluating the pathophysiology, treatment outcomes, and treatment strategies in this region. This may reflect relatively low rates of basilic vein transposition at some centers, depending on surgical expertise, and perhaps collaborative work across centers is needed to produce trials and data with sufficient numbers.

**CONCLUSION**

There is mounting evidence that AV access stenoses are a heterogeneous group of lesions that are characterized by varying degrees of vascular constriction and/or neointimal hyperplasia. This may explain patency differences for PTA at various sites in the AV access circuit. If there is little neointimal hyperplasia at a stenotic site, will drug-coated balloons prevent restenosis, or will plain balloon angioplasty be effective? Should venous intimal hyperplasia be treated differently than constricting stenoses? Can ultrasound appearance guide treatment strategies? Are stent grafts, drug-coated balloons, drug-eluting stents, or, in the future, biodesorbable scaffolds better at treating certain types of AV access stenoses than PTA alone? These are important questions that need to be answered by trials and studies, taking into consideration evolving concepts regarding the histology and pathophysiology of AV access stenosis.  

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Kate Steiner, BSc, MBBS, MRCP, FRCR  
Department of Radiology  
The Lister Hospital  
Stevenage, United Kingdom  
kate.steiner@nhs.net  
**Disclosures:** None.