**EDITORIAL**

Dialysis Vascular Access Intervention and the Search for Biomarkers

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doi: 10.1681/ASN.2015090982

Hemodialysis vascular accesses are often referred to by any one of a triad of tropes: *lifeline* because of their indispensability for hemodialysis; *Achilles’ heel* since access complications contribute substantially to the morbidity and mortality in this patient population; and *Cinderella* as the field of vascular access has never received its merited attention. Understanding the basis for access complications and failure and developing strategies that effectively mitigate both sets of adverse outcomes are necessary objectives in improving the wellbeing of patients maintained on chronic hemodialysis.1

Of the available vascular accesses, the least desired is the central venous catheter, and the most favored is the arteriovenous fistula (AVF). Even for the AVF, the outcomes are dismal, with 30%–60% of the created AVFs never usable for hemodialysis2,3; recent analyses indicate that the median cumulative patency for AVFs (placed as the first access) is 7.4 months, which increases to 61.9 months when primary AVF failures are excluded.4 Moreover, a significant subset of functioning AVFs requires endovascular or surgical procedures to achieve and/or maintain such functionality; AVFs that require intervention to achieve maturation have decreased cumulative survival compared with AVFs that successfully mature on their own.5 Arteriovenous grafts (AVGs) are generally placed when available veins are inadequate for AVFs, and, in a quite limited number of specific settings, there is a gathering sense that an AVG may be a reasonable alternative to the AVF, even when there is venous adequacy.6 AVGs are usable sooner than AVFs and exhibit one half of the primary failure rates of AVFs, but they require substantially more endovascular interventions than AVFs to maintain patency.6,7

For both AVFs and AVGs, loss of luminal patency occurs mainly in the juxta-anastomotic venous segment and is driven by an encroaching neointimal hyperplasia, which predisposes to thrombosis.1,7,8 Endovascular intervention can address both processes by removing thrombus and dilating constricting segments. Such access salvaging, however, comes at a price: in the course of endovascular intervention, the vasculature is inevitably injured, with attendant proliferative and inflammatory responses. Recurrent stenosis and thrombosis may thus ensue along with the need for another procedure to maintain access patency, thereby instigating a cyclical dependency on endovascular interventions.7 In a substantial number of accesses with significant stenosis, however, and for quite unclear reasons, thrombosis does not occur; intervening in this subset of stenosing accesses may not only serve little purpose but incurs the risk of causing thrombosis and/or an unremitting reliance on intermittent interventions to maintain access functionality.7 A serum biomarker that predicts the response to endovascular interventions may thus aid in determining when and in whom to intervene, especially given the inability of periodic monitoring and surveillance to reliably forecast access thrombosis.7

In this issue of the *Journal of the American Society of Nephrology*, the study of Wu et al.9 takes a step in this direction by linking serum levels of the uremic toxin, indoxyl sulfate, to specific outcomes after access intervention. In this observational study, patients who required angioplasty for access dysfunction were prospectively recruited over a 3-year period, with 175 and 131 of the recruited patients having AVGs and AVFs, respectively.9 After a median follow-up of 32 months, 68% of patients had restenosis requiring another intervention, 50% had access thrombosis, and 8% had access failure. Patients with thrombosis of AVGs exhibited greater serum levels of free and total indoxyl sulfate than those patients without AVG thrombosis. Moreover, absolute and tertiles of free indoxyl sulfate levels in serum independently predicted AVG thrombosis.9

This association between the baseline level of a specific uremic toxin and the propensity for postintervention AVG thrombosis is particularly germane to the generally accepted notion that the uremic milieu contributes to underlying vascular disease, of which at least four basic phenotypes are recognized: atherosclerosis, arterial stiffness, vascular calcification, and abnormal vascular repair with a propensity to neointimal hyperplasia.10 By virtue of its proinflammatory and pro-oxidant actions and its inhibitory effects on repair and regeneration of the injured endothelium, indoxyl sulfate is implicated in the pathogenesis of these vasculopathies.11 More recently, indoxyl sulfate is implicated in a fifth phenotype: the increased risk for thrombosis in CKD, especially after endovascular procedures.12–15 The thrombogenic effect of indoxyl sulfate resides in its capacity to stimulate expression of tissue factor in endothelial and smooth muscle cells,12–15 tissue factor representing a potent trigger for the
extrinsic coagulation pathway. Thrombosis is also driven by tissue factor–enriched microparticles originating from the injured endothelium. Thus, the association observed by Wu et al.9 is congruent with the recognition of increased thrombogenicity induced by elevated levels of indoxyl sulfate in CKD, and possibly represents an effect elicited by increased expression of tissue factor.

Wu et al.9 did not observe an association between serum indoxyl sulfate levels and the rate of restenosis in AVGs, negative findings that are also of interest. A possible explanation may reside in the following speculation. Restenosis largely reflects smooth muscle cell (and myofibroblast) proliferation, and both proliferative and antiproliferative effects of indoxyl sulfate on smooth muscle cells have been described in vitro. Additionally, indoxyl sulfate has been shown to induce cell cycle inhibitors (p53 and p21) and cellular senescence in vascular smooth muscle cells in vitro, along with analogous findings in vivo. If these senescence–promoting, antiproliferative effects of indoxyl sulfate on smooth muscle cells are the pertinent actions manifested after endovascular intervention, then higher indoxyl sulfate levels may exert a brake on processes that promote smooth muscle cell proliferation; these countervailing, growth–inhibitory effects of indoxyl sulfate may thus lead to a dissociation of serum levels of indoxyl sulfate and rates of restenosis. It is also notable that neither outcome in AVFs—thrombosis nor restenosis—as noted by Wu et al.9 correlated with serum levels of indoxyl sulfate. It is conceivable that indoxyl sulfate likely evinces thrombogenic effects in veins that are more damaged or anomalous in some way. In this regard, AVGs are generally selected rather than AVFs when available veins are suboptimal because of size or other reasons. Additionally, the venous segment in an AVG is downstream not to a native artery but to a synthetic conduit, a situation that may exaggerate stress responses in veins, including thrombogenic stress as imposed by indoxyl sulfate.

In addition to these pathogenetic implications, this association of indoxyl sulfate levels with thrombosis in AVGs after intervention raises therapeutic considerations. As recently reviewed, AVG outcomes (largely on the basis of thrombosis) are not improved by either anticoagulants (warfarin) or the reduction in homocysteine levels; are inconsistently and weakly benefited by antiplatelet agents; and, as shown in a limited number of studies, may be improved by fish oil. Such unprepossessing responsivity to these pharmacologic approaches may reflect the failure to target what may be a critical initiator of thrombosis in AVGs, namely, indoxyl sulfate. In this regard, there is substantial interest in orally administered agents that can reduce serum levels of indoxyl sulfate by serving as adsorbents (such as AST-120) or other approaches targeted to the gut microbiota. These studies thus raise the possibility that strategies designed to reduce serum levels of indoxyl sulfate, and thereby vitiate the downstream effects, offer a therapeutic approach in improving AVG outcomes, especially in AVGs in need of repeated interventions.

ACKNOWLEDGMENTS

K.A.N. thanks Ms. Kara Zelinske for secretarial expertise.

This work was supported by the National Institutes of Health Grant DK70124.

DISCLOSURES

None.

REFERENCES