Superoxide in AVF dysfunction: a new target for intervention

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Submitted 25 September 2012; accepted in final form 3 October 2012

Adequately functioning vascular access is an absolute requisite for patients receiving hemodialysis. Among the three currently available (fistulae, grafts, and tunneled catheters) vascular accesses, the arteriovenous fistula (AVF) is considered the “gold standard” and is the most common mode of vascular access (9, 16). AVF has several advantages that include lower risk of infections and clot formation, better blood flow, and hence superior effectiveness of dialysis and higher longevity compared with other vascular access modalities (16). Nevertheless, the rates of inadequate AVF maturation and functional failure are alarmingly high (16). Such failure rates translate to significant morbidity, hospitalization, and mortality. Furthermore, the yearly health care costs for vascular access-related morbidity are well over one billion dollars in the United States alone (2, 11). The number of patients requiring hemodialysis has increased remarkably in the past few decades. Therefore, there is an urgent need to study the underlying mechanisms of AVF dysfunction to enable implementation of novel preventive and therapeutic strategies to improve quality of care in hemodialysis patients.

The major cause of AVF failure is either unsuccessful maturation or venous stenosis of a matured AVF. Although several mechanisms have been proposed for AVF malfunction, venous stenosis resulting from neointimal hyperplasia within the perianastomotic region is undoubtedly the most common cause of AVF failure in hemodialysis patients. Despite the magnitude of this clinical challenge, there are no effective preventive and/or therapeutic measures to adequately address this condition. In an attempt to decipher the pathobiological pathways that lead to AVF venous stenosis and AVF failure, animal models have been designed that closely mimic the human lesion and hemodynamic features (1, 5, 7). These studies demonstrate that the venous stenosis is associated with several pathological characteristics such as smooth muscle cell migration and proliferation, monocyte/macrophage infiltration, fibrosis, and microangiogenesis that may be accompanied by thrombosis and/or calcification and upregulation of a number of inflammatory genes (10–12).

While a strong body of evidence suggests that disproportionate reactive oxygen species, in particular superoxide anions, are involved in the pathogenesis of a number of vascular injury and remodeling conditions (3, 4, 13), whether such derangements could account for the AVF failure has not been comprehensively explored. In an issue of the American Journal of Physiology-Renal Physiology, Tsapenko and colleagues (15) investigated the pathogenic role of superoxide anion in venous stenosis in a rat model of femoral AVF. The authors report significant augmentation of superoxide anion levels at one week postcreation of the AVF in the venous limb. Such increment was attributed to both increased generation and decreased dismutation of the superoxide anions due to reduced total superoxide dismutase expression and activity. Superoxide dismutase is an antioxidant enzyme that converts two superoxide anions into a molecule of hydrogen peroxide (decomposed and neutralized by glutathione peroxidase and catalase) and one molecule of oxygen. This concept was further validated by either unchanged or increased levels of glutathione peroxidase and catalase, respectively. Interestingly, the authors also report evidence of significant tyrosine nitration in all three layers of the veins as well as infiltrating leukocytes in the AVF. This observation highlights the increased generation of peroxynitrite, a product of superoxide anion interaction with nitrogen oxide. Under a number of pathological conditions, nitric oxide synthase (NOS) activity becomes uncoupled, leading to increased production of superoxide anion. Indeed, NOS uncoupling has been implicated in vasculopathies such as atherosclerosis. To validate evidence of such uncoupling, the authors demonstrate that the tetrahydrobiopterin (BH4)-to-dihydrobiopterin (BH2) ratio (a reliable marker of NOS uncoupling) is significantly reduced in the venous segment of the AVF.

To elucidate other downstream effects of increased superoxide anion generation, several potential candidate pathways were investigated. Intriguingly, only Src and its phosphorylation of NOS uncoupling Hemodynamic stress Inflammatory mediators

![Fig. 1. Oxidative stress pathways in arteriovenous fistula (AVF) dysfunction. Increased superoxide anion in the venous limb of AVF can activate Src, which in turn can increase superoxide generation. Uncoupling of nitric oxide synthase (NOS), hemodynamic stress, and inflammatory mediators can also contribute to increase superoxide generation. Tempol, a scavenger of superoxide anion, and potentially other antioxidants can block this pathway, leading to attenuation of AVF dysfunction. SOD, superoxide dismutase.](http://www.ajprenal.org)
REFERENCES


DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: A.Z. interpreted results of experiments; A.Z. and A.A. prepared figures; A.Z. and A.A. drafted manuscript; A.Z. and A.A. edited and revised manuscript; A.Z. and A.A. approved final version of manuscript; A.A. conception and design of research.

ACKNOWLEDGMENTS

This work was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grants R01 DK-59600 and the O’Brien Center P30 DK-079337 (to A. Agarwal).