

## Predicting the Functionality and Form of a Dialysis Fistula

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Management of ESRD by chronic hemodialysis requires the ready and recurrent accessing of a segment of the circulatory system with a relatively large luminal diameter and high rate of blood flow. Introduced 50 years ago, the surgically created, native arteriovenous fistula (AVF) provides an ingenious way of achieving such vascular access, and is preferred to others so employed, the arteriovenous graft (AVG) and the central venous catheter (CVC).<sup>1</sup> Compared with the AVG, the endogenous AVF avoids an exogenous, synthetic conduit; is less reliant on repeated interventions to maintain vascular patency; and exhibits a functionality that may be more durable.<sup>2</sup> Compared with the CVC, the use of the AVF is attended by lower rates of infection and hospitalization, and less morbidity and mortality.<sup>2</sup>

To reliably sustain chronic hemodialysis, the AVF, once created, needs to undergo in the ensuing weeks a biologic process referred to as “maturation.”<sup>3</sup> This process involves functional and structural adaptations that culminate in three desired, and, indeed, obligatory outcomes. First, substantial augmentation in AVF blood flow is needed in order for the access to enable effective hemodialysis. Second, enhanced resilience of the venous wall is required such that the vein can withstand not only the augmented blood flow and pressure to which it is exposed following AVF creation, but also the intermittent trauma of recurrent needle-puncturing. Third, prothrombotic processes, predictably triggered as the endothelium is injured during AVF creation, must be held in check; otherwise, thrombogenesis would compromise luminal patency and trigger inflammation, both of which are inimical to the maturational process.

Vasodilation and outward remodeling of the artery and vein are critical steps in ensuring successful AVF maturation.<sup>3</sup> In the immediate phase after AVF creation, blood flow through the feeding artery increases because peripheral resistors are bypassed. Such augmentation in blood flow increases shear stress on the vasculature. The vasculature detects increased shear stress *via* endothelial mechanoreceptors, and responds to such stress by vasodilation, the latter tending to return shear

stress to normal. Augmentation in luminal diameter is achieved structurally as well as functionally, because of outward remodeling of the artery and vein. Remodeling of the venous wall also toughens an otherwise flaccid structure into one that tolerates hemodynamic stress and repeated accessing for dialysis. How these maturational processes develop is very much dependent on vascular production of the vasodilator, nitric oxide (NO): NO is elaborated in increased amounts in response to shear stress; is antithrombogenic and anti-inflammatory; and is linked to downstream mediators of the outward remodeling process.<sup>4–6</sup>

This obligatory choreography of sequential steps for successful AVF maturation often does not occur, and, in certain studies, as many as 60% of created AVFs fail to mature. In a limited subset of AVFs, lesions militating against maturation exist, and may be corrected; for example, a juxta-anastomotic stenotic lesion, obstructing arterial inflow to the vein, may be dilated by angioplasty; conversely, venous tributaries siphoning blood flow away from the main vein can be ligated. However, for the majority of dysfunctional AVFs, maturational failure is neither easily understood nor predicted, and insights into either would significantly advance the field.

The farsighted Hemodialysis Fistula Maturation study was undertaken to address these specific issues.<sup>7</sup> This National Institutes of Health–supported study recruited from seven centers in the United States some 600 patients who were followed prospectively for up to 4 years after AVF creation. Drawing upon data so garnered, the study of Allon *et al.*, contained in this issue of the *Journal of the American Society of Nephrology*, reports new and important findings.<sup>8</sup> Allon *et al.* examined the extent to which tests of arterial vasodilation, arterial stiffness, and venous capacitance, performed before AVF creation, associated with AVF blood flow and venous diameter, determined 6 weeks after AVF creation.<sup>8</sup> Notably, such an association was evinced by indices assessing arterial vasodilator capacity, specifically, flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (NMD). However, such an association was not observed with other indices such as those evaluating stiffness of central or peripheral arteries (pulse wave velocity) or the capacity of veins to dilate (venous occlusion plethysmography).<sup>8</sup> The failure to discern associations between these AVF outcomes and certain tests (pulse wave velocity and venous occlusion plethysmography), while possibly reflecting the relative insensitivity and other aspects of these specific tests, nonetheless, underscores the positive association observed with FMD and NMD. FMD largely reflects endothelium-dependent vasodilation, whereas NMD assesses the capacity of arterial smooth muscle cells to respond to NO-generating compounds, and is endothelium-independent. That FMD and NMD associated with desired changes in the AVF following its creation highlights the importance of the integrity of vasodilator responses in enabling AVF maturation, at least as assessed at the 6-week timepoint.<sup>8</sup>

AVFs are created in the uremic setting, and the evidence is now incontrovertible that CKD, *per se*, predisposes to a

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vasculopathy characterized by any one or combination of the following changes: endothelial dysfunction, impaired arterial compliance, atherosclerosis, aberrant calcification, compromised reparative capacity, a propensity toward neointimal hyperplasia, and venous disease.<sup>9–11</sup> Numerous pathogenetic factors are contributory, including systemic hypertension, the preponderating effect of vasoconstrictors over vasodilating species, dyslipidemia, uremia, insulin resistance and other metabolic abnormalities, inflammation, disturbances in mineral metabolism, and oxidative stress, among others.<sup>9–11</sup> With so many factors potentially compromising vascular behavior and structure, it is perhaps not surprising that successful outcomes after AVF creation often do not occur. Such failure not only delays the availability of a usable AVF, but also incurs dependency on a CVC and leaves one less site for subsequent AVF placement. Reliably predicting the chances for successful maturation of a contemplated AVF would thus aid in deciding whether the AVF (or an AVG) should be placed. It is tempting to suggest that the findings of Allon *et al.* raise the consideration that diagnostic strategies founded on the adequacy of arterial vasodilation, and used to complement ultrasound vascular mapping, may assist in predicting the likelihood of effective AVF maturation.

Experimental studies attest to the importance of NO in AVF maturation. In an AVF model in the rat with intact kidney function, arterial expression of endothelial nitric oxide synthase (eNOS) and inducible NOS (iNOS) is increased, and chronic NOS inhibition reduces AVF blood flow, prevents outward remodeling, and exacerbates neointimal hyperplasia.<sup>6</sup> Genetic eNOS deficiency in a murine AVF model (intact kidney function) interrupts the normalization of shear stress following AVF creation, blunts the upregulation of metalloproteinases, and impairs outward remodeling, the latter posited as a metalloproteinase-dependent process.<sup>4</sup> The NOS system, however, may be compromised by uremia in several ways. First, as reported in some studies, expression of eNOS and phosphorylated eNOS may be decreased in CKD. Second, reduced tetrahydrobiopterin is a necessary cofactor for effective coupling of eNOS such that NO is generated; when tetrahydrobiopterin is oxidized, as can occur in the oxidizing milieu of uremia, eNOS becomes uncoupled, yielding superoxide anion rather than NO.<sup>5</sup> Third, CKD and accompanying oxidative stress may denature soluble guanylate cyclase, the receptor for NO, thereby impairing the ability of soluble guanylate cyclase to instigate the vasodilatory effects of NO.<sup>12</sup> Fourth, uremia is attended not only by oxidative stress, but also by increased systemic levels of asymmetric dimethylarginine, an endogenous NOS inhibitor.<sup>10</sup> Elevated systemic levels of asymmetric dimethylarginine may associate with an increased risk for cardiovascular disease in uremia, as well as poor outcomes in AVFs such as a greater risk for recurrent stenosis after angioplasty.<sup>13</sup> Thus, the impairment in FMD and NMD observed in the patient population studied by Allon *et al.* likely arises from uremic perturbations that reduce, respectively, either the generation of, or the responsiveness to NO. Such functional impairment in the NOS system in uremia may be targeted by therapeutic strategies.

Therapies aimed at improving AVF blood flow may also involve vasodilator species other than NO. For example, either isoform of the vasodilator heme oxygenase (HO) system improves AVF blood flow, as does the acute administration of the product of HO activity, carbon monoxide; additionally, the chronic upregulation of HO-1 increases AVF blood flow and decreases venous histologic disease.<sup>14</sup>

As enunciated and substantiated a century ago by the masterpiece “*On Growth and Form*” written by the Scottish polymath D’Arcy Wentworth Thompson, biologic growth and structure generally conform to mechanical and other physical principles.<sup>15</sup> Successful AVF maturation provides another notable example supporting this concept: for example, Ohm’s law explains the immediate increase in blood flow after AVF creation; Poiseuille’s law accounts for vasodilation when wall shear stress is increased; and Laplace’s law (expanded) elucidates why, when vessel radius is increased, the vessel wall may thicken so as to mitigate wall tension. Obedience to these and other physical laws underpinning successful AVF maturation, however, requires preservation of homeostatic responses in the vasculature, despite the hypertensive, uremic, oxidative, inflammatory, and other stresses imposed on the vasculature in CKD. In this regard, the study of Allon *et al.* uncovers flow-mediated and NO-mediated dilation as vascular responses that associate with adaptive AVF changes favoring successful maturation. In so doing, Allon *et al.* have highlighted the integrity of innate vascular behavior as a salient consideration in AVF maturation, and have uncovered possible targets for future therapeutic strategies.

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## DISCLOSURES

None.

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See related article, "Association between Preoperative Vascular Function and Postoperative Arteriovenous Fistula Development," on pages 3788–3795.