commentary

and growth factors, such as insulin or VEGF, and can be transduced via different postreceptor signaling pathways.[8] Kajimoto et al.[3] showed that treatment of human umbilical vein endothelial cells with ADMA in high-L-NAME culture conditions leads to a dose-dependent decrease in both basal and VEGF-stimulated activation of eNOS via Ser1177 phosphorylation. The pathway leading to Ser1177 phosphorylation of eNOS in response to VEGF engages the VEGF2 receptors insulin receptor substrate-1 (IRS-1) and phosphatidilinositol-3′-kinase (PI3K)/Akt. However, in this study, Akt activation induced by VEGF treatment was not inhibited by ADMA. Another pathway, documented in glomerular endothelial cells by Feliers et al., involves activation of PI3K and extracellular signal-regulated kinases 1 and 2 (ERK1/2);[9] and Kajimoto et al.[3] report inhibition of ERK1/2 activation by ADMA.

Although these data require substantial validation by molecular and pharmacological manipulation of the various kinases, it is tempting to speculate that ADMA may have a selective inhibitory rather than a promiscuous toxic effect on signaling kinases, leading to decreased eNOS activation (Figure 1). Also, follow-up studies that comprehensively examine all of the known eNOS phosphorylation sites and the signaling molecules engaged in response to different agonists are critical to understand the potentially complex effects of ADMA on eNOS activation. For example, a promising candidate may be Ser144, which is phosphorylated by ERK1/2, resulting in an altered ability of eNOS to bind the prolyl isomerase Pin1, which in turn negatively impacts eNOS activity.[10]

Understanding which signaling pathways leading to reduced eNOS activity are affected by ADMA may lead in the future to the design of better therapies to reduce the effects of ADMA in addition to the current efforts to minimize ADMA accumulation in CKD and other pathological conditions. Therefore, the study by Kajimoto et al.[3] is important, as it opens new avenues to investigate molecular mechanisms responsible for vascular and renal effects of ADMA via eNOS inhibition beyond the old rivalry between ADMA and L-arginine as substrates of choice for catalysis by eNOS.

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From basic anatomic configuration to maturation success

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The arteriovenous fistula is the preferred vascular access for hemodialysis patients because of its low complication rate and lower costs, but it still has unacceptable failure rates. Krishnamoorthy et al. implicate the geometry of the fistula in the temporal and spatial variations occurring in two of the most important parameters of fistula maturation, blood flow and vessel diameter.

Patients with end-stage renal disease who require long-term hemodialysis need a reliable vascular access. The arteriovenous fistula is the access of choice owing to its long patency rate and low complication profile.[1] It is created by the direct anastomosis of adjacent artery and vein. Fistulae

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capable of maintaining a minimum blood flow rate between 450 and 500 ml/min are considered 'mature' and suitable for dialysis. The problem resides in that many fistulae fail to mature (up to 66% at 2 years).[2] In fact, arteriovenous fistula failure is the most important cause of morbidity in the hemodialysis population, which is currently more than 300 000 in the United States alone.[3] Despite the magnitude of the problem, there have been no major advances in the field of hemodialysis vascular access for the past three decades, and only a modest increased rate of scholarly activity in this area has been lately seen.[4] Therefore, there is still an unmet necessity of basic studies to assess the role
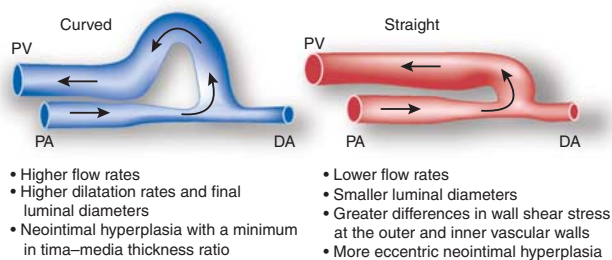
Figure 1 | Characteristics of curved and straight fistulae. Arrows indicate the direction of blood flow. DA, distal artery; PA, proximal artery; PV, proximal vein.

of hemodynamics, anatomy, and biology in arteriovenous fistula maturation.

Krishnamoorthy et al.[5] (this issue) deal once again with the apparently simple but complex relationship between the basic anatomic shape of the fistula and two important parameters of fistula maturation, blood flow and diameter. Using ultrasound and computed tomographic scan, these authors measured temporal changes in configuration, internal diameter, and blood flow occurring in straight and curved fistulae that were created in experimental pigs (Figure 1). They revealed the superiority of the curved over the straight fistula to deliver higher venous diameters and blood flood rates at 28 days after surgery. These outcomes are broadly in line with those previously reported by this team (Roy-Chaudhury's team) when they described how the complex patters of wall shear stress within the venous limb of the fistula determined the pathological remodeling of the vessel wall.[6,7] On that occasion, they calculated a complete wall stress profile for the curved configuration and correlated it with luminal stenosis. They found a profound relationship between the wall shear stress profile of the curved and straight fistula and the histological architecture of the vessel. Interestingly, there was a local wall shear stress variation with time at outer and inner walls of both fistulae that explained the eccentric histological pattern of intima–media thickening found in the failed fistula. Undoubtedly, in these studies Roy-Chaudhury's team have created sufficient grounds for a human study aimed at proving the impact of surgical configuration on fistula failure, whose outcomes could help configure better parameters to facilitate long-term fistula patency. In fact, since the first description of a side-to-side anastomosis between radial artery and cephalic

vein in the wrist by Brescia et al.,[8] very few modifications in the basic type of anastomosis have been made. Perhaps the major change was the introduction of the side-to-end (artery-to-vein) anastomosis. This type of anastomosis has the advantage that it is technically feasible even in cases in which the distance between the artery and the vein does not permit side-to-side anastomosis. Another advantage of the side-to-end anastomosis is the lower risk of venous hypertension and swelling of the hand.

It is important to note that the work of Krishnamoorthy et al.[5] becomes relevant in the absence of studies intended to elucidate how geometric and hemodynamic factors such as anastomosis length and angle, vessel diameter, and flow distribution patterns determine fistula maturation. Only a few attempts have been made to assess the impact of fistula geometry on stenosis in hemodialysis patients. Perhaps one of the most representative studies is that published by Sivanesan et al. more than a decade ago.[9] This team identified sites of stenosis in radiocephalic arteriovenous fistulae and related the findings to various clinical and geometrical parameters. They measured postoperatively the anastomotic length and angle in 25 consecutive fistulae using duplex and color-flow ultrasonography. In agreement with the data of Krishnamoorthy et al.,[5] this report identified stenosis that developed just proximal to the curved segment of the cephalic vein where the vein straightens out as the most aggressive and progressive stenosis.

It is important also to note that the study by Krishnamoorthy et al.[5] has its own limitations. One is the lack of chronic kidney disease in the experimental model, which is a deleterious factor for vascular remodeling.[10] This can be a minor issue if

it is taken into consideration that histological lesions developed in non-uremic pigs are quite similar to those seen in human tissues.[11] A second limitation is the lack of histological examination in curved and straight fistulae to establish the cause–effect relationship between the variations in blood flow and diameter and the architecture of the vessel. Nonetheless, these authors have previously shown that fistula configuration indeed is translated into histological differences.[6] A third limitation is that pig fistulae lack the collateral veins or tributaries that in humans help dissipate pressure in the presence of an outflow obstruction and prevent a marked increase in pressures. Branches also inevitably produce flow disturbances and regions of flow separation that can potentially modify the development of stenotic lesions.

In conclusion, this study evidences that the geometric conformation of the fistula can determine its successful maturation. Now, is it time to modify the basic anastomotic design of the fistula? What would be the impact on maturation if newly native fistulae included curvatures in the proximal region of the vein? For now the answers remain uncertain, but the findings of Krishnamoorthy et al.[5] warrant future studies to demonstrate the plausibility of designing an optimal anatomic configuration for human fistulae that minimizes the failure rate. If this can be achieved, new recommendations and scientifically validated approaches that optimize fistula geometry while ensuring a proper and timely maturation of the fistula are foreseen (Figure 1).

DISCLOSURE
The authors declared no competing interests.

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