Editorial Commentary

Are Kidneys Not Ischemic in Human Renal Vascular Disease?

Robert M. Carey

Atherosclerotic renal artery stenosis (≥60% lumen occlusion) is a relatively common cause of nephropathy and secondary hypertension, and its frequency increases with age and the presence of cardiovascular disease.[1] Renal vascular disease is present in 0.5% to 7.0% of patients over age 65 years, 5.5% of patients with chronic kidney disease, 22.0% of those starting dialysis, 28.0% of those with peripheral vascular disease, 34.0% of elderly patients with congestive heart failure, and up to 50.0% of patients with diffuse atherosclerotic vascular disease.[1,2] Clinically, renal vascular disease presents a series of complex challenges, including limited sensitivity of imaging methods for detection, lack of tests that would conclusively establish the functional significance of the stenotic lesion, absence of reliable predictors of the response to revascularization, and uncertainty regarding the optimal method of treatment (medical, angioplasty/stenting, or surgical revascularization). After discovery, progression of renal vascular disease occurs in ≈50%, and 10% of stenotic vessels become occluded within 5 years.[1] Progression is characterized initially by renal cortical thinning and loss of renal mass with preservation of glomerular filtration rate and later by further loss of renal mass accompanied by reduced glomerular filtration rate.

Traditional pathophysiological concepts of renal vascular disease progression have focused on an initial reduction in renal perfusion pressure followed by renal baroreceptor-stimulated renin release and consequent systemic and intrarenal angiotensin generation, leading to vasoconstriction and enhanced renal sodium reabsorption, both ultimately contributing to chronic hypertension. Implicit in this thinking has been the idea that the impairment of blood flow distal to the stenotic lesion leads to ischemic nephropathy, in which the metabolic demands of the tissue are unable to be met because of tissue hypoxia. However, the contribution of tissue hypoxia to renal damage in renal vascular disease has been controversial, because renal oxygen delivery is among the highest in the body, and <10% of the kidney oxygen supply is required to maintain the metabolic needs of the tissue.[3] Approximately 80% of renal oxygen consumption is used to drive renal tubular Na^+/K^+ ATPase. When renal perfusion pressure falls, as in renal artery stenosis, glomerular filtration rate falls, and the associated decrease in filtered sodium load reduces tubular sodium reabsorption and, thus, decreases renal oxygen consumption.[4] Clearly, we need to know more about the pathophysiology of renal vascular disease and, in particular, about the role of tissue oxygenation in renal damage.

In this issue of *Hypertension*, Gloviczki et al[5] provide a thorough analysis of renal size, function, and central oxygenation by a novel technique, blood oxygen level– dependent MRI, in patients with renal artery stenosis and relatively preserved glomerular filtration rate (65 mL/min per 1.73 m^2) or primary (essential) hypertension. Blood oxygen level–dependent MRI of the kidney has been validated as reflecting tissue oxygen tension and has proven to be a sensitive method of detecting alterations induced by acute renal artery stenosis or furosemide administration in experimental animals and in human renovascular disease.[6–8] The results of the present study demonstrate the surprising finding that, despite a reduction in renal blood flow and kidney volume on the stenotic side, renal cortical and medullary tissue oxygenation is preserved. Because renal venous oxygen levels were elevated in the patients with renal artery stenosis, it is likely that there is reduced renal oxygen consumption on the stenotic side. Because both groups of patients were treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at the time of study, the role of renin-angiotensin system blockade in preserving tissue oxygenation is unknown. In addition, it is well known that increased collateral circulation develops over time in renal artery stenosis, but its role in preserving tissue oxygenation remains undefined.

This study challenges traditional thinking regarding the role of tissue ischemia in renal vascular disease and catalyzes future research on the cellular and molecular mechanisms of preserved renal oxygenation. In particular, the role of NO needs to be clarified. NO increases renal oxygen tension by several mechanisms (Figure). NO increases oxygen delivery by vasodilation. NO also inhibits nephron oxygen consumption both by reducing sodium reabsorption and by increasing the efficiency of nephron oxygen use by competing with oxygen at the level of cytochrome oxidase in mitochondria.[9–12] In a recent study, Palm et al[13] demonstrated that oxygen availability is preserved in the clipped kidney of early 2-kidney, 1-clip Goldblatt hypertensive rats because of NO formation by angiotensin II activation of renal angiotensin II type 2 receptors. In these rats, blood perfusion in the postclip kidney was relatively maintained, and the results suggest that cellular oxygen use may have been downregulated by this pathway. In addition to NO, intrarenal arteriovenous oxygen shunting, which normally blunts the delivery of oxygen to renal tissue, could be reduced in renal vascular hypertension

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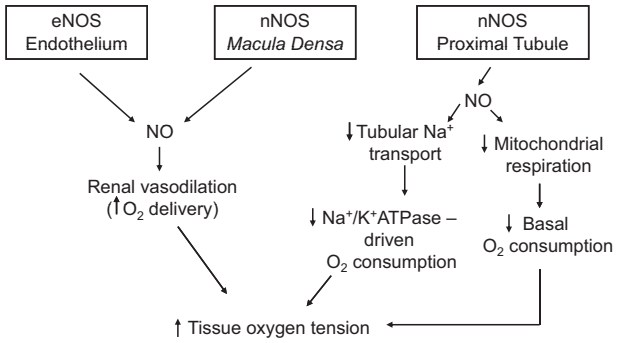

Figure. Schematic depiction of NO regulation of renal oxygenation. eNOS indicates endothelial NO synthase; nNOS, neural NO synthase; Na^{+}/K^{+} ATPase, sodium-potassium adenosine triphosphatase.

and account, at least in part, for the preservation of renal tissue oxygenation.[3]

Irrespective of the mechanisms, the finding that renal tissue oxygenation is preserved, at least in the early stages of renal vascular disease, is a clinically relevant observation. As suggested above, atherosclerotic renal artery stenosis progresses through intermediate stages, often leading to severe renal dysfunction and hypertension. Early preservation of tissue oxygenation, as suggested by the authors, may signal the potential for recovery once the stenosis is anatomically corrected. Beyond that point, however, tissue hypoxia may induce irretrievable renal damage. We do not yet know when that set point occurs clinically, and this information may alter the approach to treatment. Techniques such as blood oxygen level–dependent MRI hold promise to clarify this issue, which will help determine clinical assertiveness toward the early detection of renal vascular disease.

Disclosures

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