Multitasking: a challenge for the kidney

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Renal erythropoietin (EPO) production is controlled chiefly by the abundance of hypoxia-inducible factor-2α (HIF-2) and thus kidney tissue oxygen tension (PO2) (4). Therefore, from an evolutionary perspective, the function of the kidney as the body’s “critmeter” (1) must have provided selection pressure for renal tissue PO2 to be sensitive to blood oxygen content. But the kidney has other functions, too, so the selection pressures that have driven the evolution of the mammalian kidney have been complex. Nevertheless, there is now a wealth of evidence that the kidney is more sensitive to acute hypoxemia and anemia than other organs, a paradoxical situation given that renal blood flow is so far in excess of renal oxygen consumption (2). Multiple factors may contribute to the susceptibility of the kidney to hypoxia when oxygen delivery is challenged, including counter-current shunting of oxygen in the cortex and medulla (10), limitations of oxygen diffusion to tissue at the level of the peritubular capillaries (8), and the remarkable reluctance of the renal vasculature to dilate when faced with acute renal hypoxia (2).

The susceptibility of the kidneys to hypoxia may be a critical factor in the development of acute kidney injury (AKI), particularly in the setting of major surgery (11). For example, AKI is common after cardiac surgery requiring cardiopulmonary bypass, a medical procedure that results in acute hemodilution (6). Furthermore, the risk of AKI in this setting is greatly exacerbated by preoperative anemia and appears to progressively increase with the degree of intraoperative anemia (reviewed in Ref. 3). Thus, there is a strong imperative for us to increase our understanding of the effects of both acute and more prolonged anemia, and their interactions, on renal oxygenation and its determinants. One important limitation of previous relevant studies in the field of “kidney oxygenation” is that they have largely focused on the effects of acute hemodilution. There has been little previous effort to assess effects of prolonged anemia. Prolonged anemia could potentially be associated with adaptive or maladaptive responses that could modulate the response of kidney oxygenation. This deficit in our knowledge is important because chronic anemia is highly prevalent globally, particularly in low-to-middle-income countries (7). Anemia is also highly prevalent in patients with chronic kidney disease (CKD), a condition that greatly exacerbates the risk of AKI (5). In the current issue of American Journal of Physiology–Regulatory, Integrative and Comparative Physiology, Mistry and colleagues begin the process of filling this knowledge-gap (9).

Mistry and colleagues employed a novel approach. They administered a red blood cell (RBC)-specific antibody to mice to induce moderate anemia. Anemia progressively developed across 4 days after administration of the antibody (to a nadir hemoglobin of 89 g/l), with hemoglobin recovering to control levels (~145 g/l) by 14 days after antibody administration. They found that moderate subacute anemia was associated with profound renal tissue hypoxia and a marked upregulation of EPO mRNA. Using a transgenic mouse in which a luciferase reporter gene is fused to the oxygen degradation-dependent region of HIF-1α, they also generated evidence of increased HIF-1α abundance during subacute anemia. Critically, just as they had shown previously in acute hemodilutional anemia of a similar severity, renal blood flow did not increase in subacute anemia (12). In contrast to the kidney, they could not detect a reduction in tissue PO2 in the brain during subacute anemia. Maintenance of cerebral oxygenation is likely explained by increased cerebral perfusion as evinced by increased blood flow in the internal carotid artery. Thus, just as appears to be the case in acute hemodilutional anemia, the kidney appears to be particularly sensitive to development of hypoxia during subacute anemia, whereas the brain is relatively well protected because it mounts a robust hyperemic response. It seems likely, although it remains to be directly tested, that the same will be true in chronic anemia.

Two other sets of observations reported by Mistry and colleagues are worthy of mention. First, despite their inability to detect hypoxia in brain tissue in subacute anemia using the highly sensitive method of phosphorescence lifetime oximetry, they observed an increase in HIF-dependent mRNA transcription. Thus, it is likely that some level of subtle hypoxia developed in the brain. This is a nice reminder that biological mechanisms are sometimes more sensitive bioassays than the physiologist’s most cutting-edge measurement tools. Second, Mistry and colleagues found evidence for hierarchical regulation of EPO expression during subacute anemia, with the kidney exhibiting the greatest response, followed by the brain and liver, and no evidence of a response in the heart. The profound response of the kidney makes sense on the basis that it is the body’s critmeter. Nevertheless, the mechanisms underlying the differential regulation of EPO across various organs and the physiological significance of this differential regulation will provide the impetus for future work in the field.

We believe that the new model of subacute anemia described in the current paper could provide a platform for future studies to investigate the mechanistic links between renal tissue hypoxia and the development of both AKI and CKD. If renal tissue hypoxia is a major driver of CKD, we might expect CKD to develop in mice given more chronic treatment with the anti-
body used by Mistry and colleagues. Furthermore, if renal tissue hypoxia is a major factor that renders patients with CKD susceptible to AKI, mice treated with this antibody should be more sensitive to AKI than control mice. We believe these hypotheses merit testing.

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DISCLOSURES
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AUTHOR CONTRIBUTIONS
J.P.N. and R.G.E. conceived and designed research; J.P.N. and R.G.E. drafted manuscript; J.P.N. and R.G.E. edited and revised manuscript; J.P.N. and R.G.E. approved final version of manuscript.

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