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Intrarenal oxygenation: unique challenges and the biophysical basis of homeostasis

Roger G. Evans,[1]* Bruce S. Gardiner,[2] David W. Smith,[2] and Paul M. O'Connor[3]*

[1]*Department of Physiology, Monash University, Melbourne;* [2]*Department of Civil and Environmental Engineering, University of Melbourne, Victoria, Australia; and* [3]*Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin*

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Evans RG, Gardiner BS, Smith DW, O'Connor PM. Intrarenal oxygenation: unique challenges and the biophysical basis of homeostasis. *Am J Physiol Renal Physiol* 295: F1259–F1270, 2008. First published June 11, 2008; doi:10.1152/ajprenal.90230.2008.—The kidney is faced with unique challenges for oxygen regulation, both because its function requires that perfusion greatly exceeds that required to meet metabolic demand and because vascular control in the kidney is dominated by mechanisms that regulate glomerular filtration and tubular reabsorption. Because tubular sodium reabsorption accounts for most oxygen consumption ($\dot{V}O_2$) in the kidney, renal $\dot{V}O_2$ varies with glomerular filtration rate. This provides an intrinsic mechanism to match changes in oxygen delivery due to changes in renal blood flow (RBF) with changes in oxygen demand. Renal $\dot{V}O_2$ is low relative to supply of oxygen, but diffusional arterial-to-venous (AV) oxygen shunting provides a mechanism by which oxygen superfluous to metabolic demand can bypass the renal microcirculation. This mechanism prevents development of tissue hyperoxia and subsequent tissue oxidation that would otherwise result from the mismatch between renal $\dot{V}O_2$ and RBF. Recent evidence suggests that RBF-dependent changes in AV oxygen shunting may also help maintain stable tissue oxygen tension when RBF changes within the physiological range. However, AV oxygen shunting also renders the kidney susceptible to hypoxia. Given that tissue hypoxia is a hallmark of both acute renal injury and chronic renal disease, understanding the causes of tissue hypoxia is of great clinical importance. The simplistic paradigm of oxygenation depending only on the balance between local perfusion and $\dot{V}O_2$ is inadequate to achieve this goal. To fully understand the control of renal oxygenation, we must consider a triad of factors that regulate intrarenal oxygenation: local perfusion, local $\dot{V}O_2$, and AV oxygen shunting.

counter-current exchange; diffusional oxygen shunting; hyperoxia; hypoxia; kidney circulation; kidney disease

BOTH HYPOXIA AND HYPEROXIA (33) can cause tissue damage, so regulation of tissue oxygenation within tight limits is a physiological imperative for all organs and tissues. Tissue hypoxia is a hallmark of the pathogenesis of both acute (9, 101) and chronic (81) renal diseases. Approximately 11% of adults in the United States (19.2 million) have at least one marker of chronic kidney disease, of which a substantial proportion will progress to end-stage renal disease and renal replacement therapy (360,000 in 2003; Ref. 102). Globally, the incidence of end stage renal disease is growing by 8% annually (102) and there are ongoing or emerging epidemics of kidney disease in specific disadvantaged populations such as among Indigenous Australians (42). Furthermore, acute renal injury develops in ~5% of hospitalized patients (76). The economic costs of treating patients with kidney disease are staggering. For example, in the United States the 0.7% of Medicare patients requiring dialysis therapy account for 5% of the Medicare budget (102). One of the messages we wish to convey in this review is that to develop better strategies to prevent and treat kidney disease we require a better understanding of the factors that regulate kidney oxygenation.

The field of renal oxygenation has a long though intermittent history (58, 61, 117). It has reemerged as a strong focus in recent years (81, 83, 89, 101, 108, 119, 123), and, as we will see, a number of new findings have called into question existing dogma regarding the factors that regulate intrarenal oxygenation and cause dysregulation of intrarenal oxygenation in kidney disease.

In this review, we first detail the unique challenges faced by the kidney in the maintenance of homeostasis of intrarenal oxygenation and the biophysical mechanisms that allow these challenges to be met under physiological conditions at the level of the entire organ and at the scale of the microcirculation. We then consider the contribution of renal tissue hypoxia to the pathogenesis of kidney disease and how, armed with new insights into the mechanisms regulating kidney oxygenation, we might improve diagnostic and therapeutic approaches. We present a case to support the concept that arterial-to-venous (AV) oxygen shunting might make an important contribution

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* R. G. Evans and P. M. O'Connor contributed equally to this work.

Address for reprint requests and other correspondence: R. Evans, Dept. of Physiology, PO Box 13F, Monash Univ., Victoria 3800, Australia (e-mail: Roger.Evans@med.monash.edu.au).

to the dynamic physiological regulation of kidney oxygenation and also to the development of renal hypoxia in kidney disease. This is a controversial proposition because much of the evidence supporting a dynamic role of AV O_2 shunting is indirect and recent (46, 55) or based largely on theoretical considerations (84). Nevertheless, we believe that its incorporation into conceptual models of kidney oxygenation may foster rapid advances in this field.

The central thesis of this review is that multiple interacting mechanisms operate in concert to allow tight regulation of intrarenal oxygenation and that dysfunction of these mechanisms makes a major contribution to the pathogenesis of kidney disease. Because of the complexities of these multiple interacting systems, we believe much can be learned from an approach that includes both experimental physiology and computational models grounded in established biophysical principles (18, 43, 112).

Unique Challenges for Regulation of Kidney Oxygenation

Matching supply and demand at the whole organ level. Under normal physiological conditions, ~80% of renal oxygen consumption ($\dot{V}O_2$) is used to drive Na-K-ATPase (36, 53). In turn, Na-K-ATPase drives active transport of not only sodium but also dependent transport processes for glucose, amino acids, and other solutes (36). Because tubular transport processes within the kidney are highly load dependent (36), renal $\dot{V}O_2$ changes in proportion with glomerular filtration rate (GFR), providing an intrinsic regulatory system for maintaining homeostasis of intrarenal oxygenation. For example, when arterial pressure is reduced, the GFR falls and the associated decrease in the filtered load of sodium leads to decreased tubular sodium reabsorption and, therefore, decreased renal $\dot{V}O_2$ (113).

The results of early studies (21, 52, 57, 58, 61, 62, 113, 117) in the field of intrarenal oxygenation led to the conventional wisdom that the flow dependence of renal $\dot{V}O_2$ is the predominant, if not only, mechanism mediating homeostasis of intrarenal oxygenation. That is, dynamic physiological regulation of oxygen in kidney tissue was thought to rely entirely on only two factors: *1*) delivery of oxygen in renal arterial blood (i.e., renal perfusion) and *2*) renal $\dot{V}O_2$ (8, 12; Fig. 1*A*). For example, Levy (57) found that fractional oxygen extraction by the kidney remained stable across a wide range of renal blood flow (RBF), suggesting that changes in oxygen delivery induced by changes in RBF are directly offset by changes in renal $\dot{V}O_2$. However, in many of these classic studies, RBF was altered by maneuvers that alter $\dot{V}O_2$ independently of changes in RBF. For example, RBF was altered by chronic uninephrectomy (61, 117), by changes in renal perfusion pressure that would greatly alter GFR and tubular load (21, 52, 57, 58, 62, 113), or by cooling the kidney, which would reduce tissue metabolic rate (57). More importantly, we now know that the relationship between renal perfusion and $\dot{V}O_2$ is far more complex than was envisaged at the time of these classic studies and that there is ample opportunity for mismatched changes in renal oxygen supply and demand. For example, RBF and GFR (and so total tubular sodium reabsorption) do not always change in parallel under physiological conditions, as evidenced by changes in filtration fraction in response to both vasoconstrictor and vasodilator factors (78). Moreover, altered efficiency of renal $\dot{V}O_2$ can occur, for example, when the profile of sodium reabsorption along the nephron is altered, since the efficiency of tubular sodium reabsorption differs among nephron segments (8, 36). It can also occur when the bioavailability of nitric oxide changes, since nitric oxide inhibits nephron $\dot{V}O_2$ both by inhibiting sodium reabsorption (86) and by increasing the efficiency of nephron oxygen utilization (119). Vascular wall $\dot{V}O_2$ in the kidney also appears to vary with vascular tone (125), adding an additional layer of complexity to the relationship between RBF and total renal $\dot{V}O_2$. Thus it seems unlikely that oxygen supply and demand in the kidney can be matched under all conditions by a simple relationship between renal $\dot{V}O_2$ and RBF.

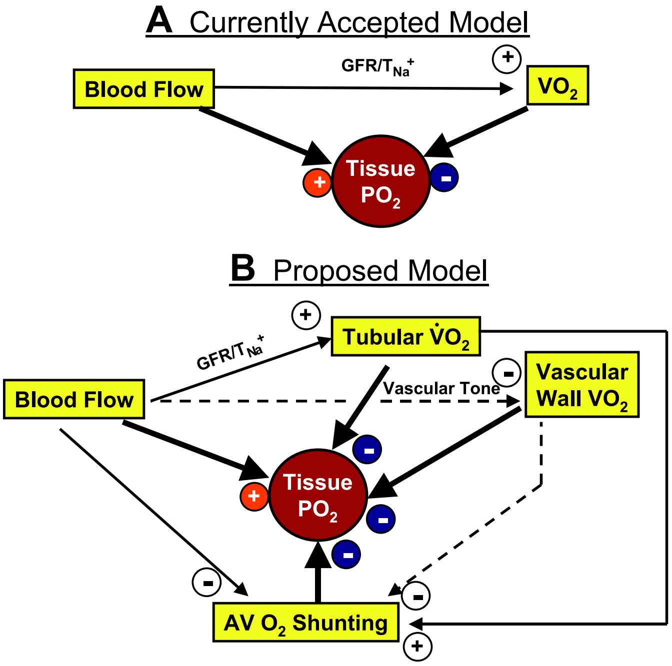

Fig. 1. Two schematic models of control of renal tissue oxygen tension (P_{O_2}). In the currently accepted model (*A*), changes in blood flow directly affect tissue P_{O_2} through changes in the supply of oxygen through advection to capillaries, where oxygen then diffuses to tissue. Changes in blood flow in the kidney also have an indirect effect of tissue P_{O_2} because of associated changes in glomerular filtration rate (GFR) and tubular sodium reabsorption (T_{Na^+}) and, therefore, resultant changes in renal oxygen consumption ($\dot{V}O_2$). The proposed model (*B*) also includes the influence of arterial-to-venous (AV) O_2 shunting, which acts to limit delivery of oxygen to renal tissue, and considers the effects of changes in renal blood flow (RBF), and the differential effects of changes in tubular and vascular $\dot{V}O_2$, on this process. Circulatory transit time falls as RBF increases, which should in turn limit the time available for AV diffusion, and so the quantity of oxygen shunted. Tubular $\dot{V}O_2$ creates the driving force for AV oxygen shunting, the AV P_{O_2} gradient, so increased tubular $\dot{V}O_2$ should also increase shunting. In contrast, oxygen consumption by the vascular wall should modulate AV oxygen shunting by extracting O_2 from the shunting pathway and thus changing the P_{O_2} gradient in the wall. Arguably, renal vasodilatation should increase AV oxygen shunting both by increasing tubular $\dot{V}O_2$ and reducing vascular wall $\dot{V}O_2$. Direct effects on tissue oxygenation are color coded: red for factors that increase it and blue for factors that reduce it. Solid lines represent well-established mechanisms, while dashed lines indicate those that remain speculative.

In light of these considerations, we (55) recently reexamined the mechanisms that mediate the dynamic regulation of intrarenal oxygenation in studies in which RBF was altered by renal arterial infusion of vasoactive agents in anesthetized rabbits. Our experimental approach was based on the fact that changes in RBF induced by acetylcholine and angiotensin II were not matched by parallel changes in renal $\dot{V}O_2$ (Fig. 2). Indeed, these vasoactive agents had remarkably little effect on total renal $\dot{V}O_2$, even though they had profound effects on GFR and sodium reabsorption. Thus maintenance of stable renal $\dot{V}O_2$ under these experimental conditions was likely attributable at least partly to changes in the efficiency of tubular oxygen utilization for sodium reabsorption. However, despite stable renal $\dot{V}O_2$, renal tissue oxygen tension (PO_2) remained conspicuously stable as RBF (and so renal oxygen delivery) was varied from ~30% below basal to ~30% greater than its basal level. Renal venous PO_2, however, increased as RBF increased and decreased as RBF fell. Our experiment showed that the flow dependence of renal $\dot{V}O_2$ cannot completely account for dynamic regulation of intrarenal oxygenation under all experimental conditions. Rather, our findings could be explained if AV oxygen shunting in the kidney changes in proportion to RBF (Fig. 3), thus providing an additional mechanism for maintenance of homeostasis of intrarenal oxygenation in the face of physiologically relevant changes in renal perfusion.

A-V oxygen shunting in the renal cortex. The chief function of the kidney, filtration of plasma and formation of urine, dictates that RBF, and in particular blood flow in the renal cortex, is much greater than that which would be necessary to meet the metabolic requirements of the kidney. Thus the kidneys comprise <1% of body weight but receive ~25% of cardiac output (36, 84). In terms of energy mass balance, basal RBF is approximately fivefold greater than basal coronary blood flow, yet at rest the cardiac $\dot{V}O_2$ is approximately double that of the kidneys (83). Therefore, in the absence of specific mechanisms to limit oxygen delivery to renal tissue, PO_2 in renal cortical tissue should be high. This would be expected to drive production of reactive oxygen species such as superoxide and lead to oxidative stress, since superoxide production in kidney tissue is highly dependent on oxygen availability (15). However, mammalian kidney tissue is not hyperoxic; cortical PO_2 is 15–50 mmHg (6, 11, 55, 56, 120), similar to skeletal muscle PO_2 (115), while medullary PO_2 can be even lower (PO_2 = 5–25 mmHg; Refs. 12, 85). In the mammalian kidney, the phenomenon or AV oxygen shunting appears to act as a structural antioxidant mechanism to blunt delivery of oxygen to renal tissue (84). In the avian kidney, in which there is little opportunity for counter-current exchange of oxygen between arteries and veins, an alternative mechanism appears to operate, with most blood flow to the kidney being of venous origin (34).

AV O_2 shunting occurs in tissues where arteries and veins are arranged in close proximity in a counter-current fashion (e.g., skeletal muscle and kidney; Refs. 94, 95). Evidence for AV O_2 shunting in nonrenal tissues such as skeletal muscle includes the greater PO_2 of venous than capillary blood (107) and direct visualization of AV oxygen transfer (49). Mathematical models also support its existence (14, 45, 104, 110). It is driven by the AV PO_2 difference and facilitated by the close anatomical association of arteries and veins, as occurs most strikingly in the kidney (31, 32, 80, 84). Nordsletten et al. (80)

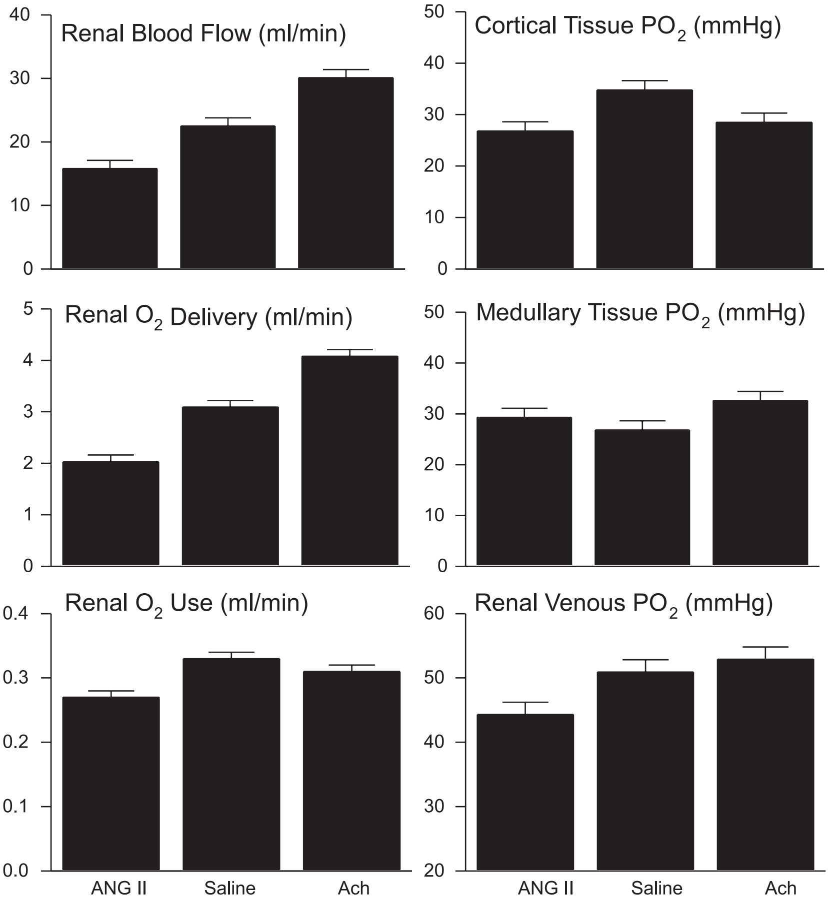

Fig. 2. Relationships between RBF and renal oxygenation in anesthetized rabbits (n = 8; means ± within-subject SE). Renal tissue PO_2 did not vary with RBF within the physiological range (±30%), despite the fact that oxygen delivery and renal venous PO_2 changed and renal oxygen consumption ($\dot{V}O_2$) did not. Data were obtained during renal arterial infusion of angiotensin II (Ang II), saline, and acetylcholine (Ach). Original data from Leong et al. (55).

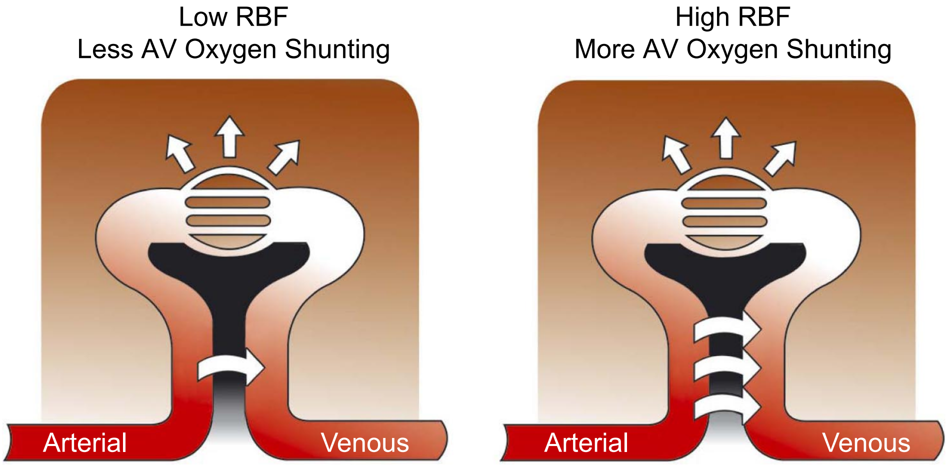

Fig. 3. Renal AV oxygen shunting is a structural antioxidant mechanism and also contributes to dynamic regulation of intrarenal oxygenation. Because of AV oxygen shunting, much of the oxygen entering the kidney never enters the renal microcirculation, instead diffusing from arterial blood to the closely associated veins. The data shown in Fig. 2 are consistent with the hypothesis that AV oxygen shunting increases in proportion with increased RBF and is reduced when RBF falls, at least under the conditions of this experiment (curved arrows). This mechanism helps maintain stable renal tissue oxygen tension. Figure modified from O'Connor et al. (84).

have recently produced a three-dimensional reconstruction of the renal vasculature using images from high resolution computer tomography. Their data show that an intimate relationship exists between intrarenal arteries and veins along the entire renal circulation up to and including the interlobular vessels (80).

There are three major lines of evidence for the existence of renal AV oxygen shunting. First, nearly 50 yr ago Levy and Sauceda (60), in an ingenious experiment, measured the respective transit times for oxygen and hemoglobin (and thus erythrocytes) across the renal circulation by measuring the optical density of renal venous blood. They labeled hemoglobin by methylation, which increases its optical density, while oxygenation of hemoglobin reduces its optical density. When they administered blood into the renal artery supplemented with oxygen and/or erythrocytes containing methhemoglobin, they found the transit time for oxygen was always less than that for erythrocytes. This can only be explained by the existence of a diffusional shunt for oxygen that bypasses at least some of the circulation (Fig. 4*A*). Initially, they proposed that AV oxygen shunting was confined to the medullary circulation. However, their experimental findings were reproduced even when the medulla was cooled to reduce medullary perfusion, providing strong evidence that AV shunting of oxygen also occurs in the cortical circulation. Secondly, Schurek et al. (103) found that the P_{O_2} of blood in glomerular capillaries increased relatively little during pure oxygen breathing. Thirdly, and most definitively, Welch and colleagues (120) demonstrated that the P_{O_2} of blood in the renal vein exceeds that of blood in the efferent arteriole (120; Fig. 4*B*), while Schurek et al. (103) demonstrated that it exceeds that of blood in glomerular capillaries.

Recent observations suggest that renal AV oxygen shunting might not just be a static process, but rather a dynamic process that contributes to maintenance of homeostasis of intrarenal oxygenation under physiological conditions and probably also to renal pathologies associated with disturbed intrarenal oxygenation. We have already discussed our recent evidence that renal AV oxygen shunting acts to stabilize renal tissue P_{O_2} when RBF changes within the physiological range (55; Figs. 2 and 3). In addition, Johannes et al. (46) recently provided strong evidence that the amount of oxygen shunted from arteries to veins in the kidney increases during normovolaemic hemodilution. They found that renal cortical tissue P_{O_2} fell during normovolemic hemodilution to a much greater extent than did the P_{O_2} of renal venous blood. They reasoned that the increased "gap" between tissue and venous P_{O_2} during hemodilution indicated increased AV oxygen shunting. Mathematical models of AV oxygen shunting predict such a phenomenon, because the high affinity of hemoglobin for oxygen acts to hinder diffusional shunting (104, 126).

Determinants of AV oxygen shunting. Collectively, the new experimental observations we have discussed (46, 55) suggest that regulation of intrarenal oxygenation might depend not only on the matching of changes in RBF with changes in renal $\dot{V}_{O_2}$ but also on the influence of AV oxygen shunting on oxygen delivery to kidney tissue (Fig. 1*B*). There are likely complex interactions between these three factors.

Renal $\dot{V}_{O_2}$ creates the driving force for AV oxygen shunting, the P_{O_2} gradient between blood in renal arteries and veins, so AV oxygen shunting should be enhanced when renal $\dot{V}_{O_2}$ increases. As discussed earlier, most kidney $\dot{V}_{O_2}$ is attributable to tubular sodium reabsorption, so renal $\dot{V}_{O_2}$ (and thus shunting) should increase when RBF (and so GFR) increases. However, $\dot{V}_{O_2}$ factored for sodium reabsorption can also change under physiological (55) and pathophysiological (89, 119) conditions. This phenomenon likely arises from both changes in the efficiency of sodium reabsorption itself and changes in oxygen utilization for other cellular processes. It has important implications for our understanding of the biophysical basis of AV oxygen shunting, because it allows renal $\dot{V}_{O_2}$ to change in ways both dependent on RBF and independent of RBF.

RBF should also have effects on AV oxygen shunting independent of its effects on renal $\dot{V}_{O_2}$. First, changes in RBF will alter circulatory transit time in the renal circulation and, therefore, the time available for diffusive transport of oxygen from arteries to veins. This will act to reduce AV oxygen shunting when RBF increases, but our findings suggest that it instead increases (Figs. 2 and 3). Currently, we have no adequate explanation for this paradox. One possibility is that diffusion equilibrium is reached at some point in the renal circulation, so that AV oxygen shunting ceases beyond this point. Changes in RBF might then be expected to alter the point at which the diffusion equilibrium is reached; reductions in flow moving the point of diffusion equilibrium to more

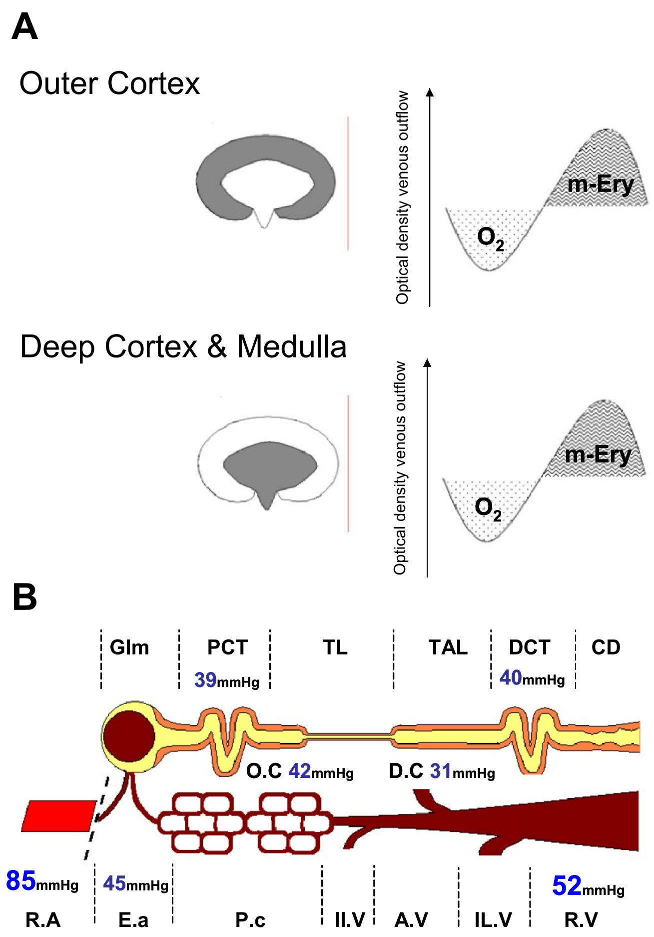

Fig. 4. Two critical pieces of evidence for the existence of AV oxygen shunting in the kidney. *A*: studies by Levy and Imperial (59) using the isolated blood perfused kidney of the dog. They injected a bolus of blood into the renal artery in which the erythrocytes were labeled with methemoglobin (m-Ery), and blood oxygen tension was increased by equilibration with 95% O_2-5% CO_2. Methemoglobin increased the optical density of blood while increased oxygen saturation of hemoglobin decreased it. They always found a biphasic response, with optical density of renal venous blood first decreasing and then increasing, indicating that oxygen traverses the renal circulation faster than erythrocytes. Cooling the renal cortex (grey, *top*) or medulla (grey, *bottom*) to selectively reduce regional kidney perfusion did not change this finding, indicating that oxygen shunting occurs in both the cortex and medulla. *B*: oxygen tension measured at various levels of the renal circulation and nephron using miniaturized oxygen electrodes (120). Note that the oxygen tension of blood in the renal vein exceeds that of blood in the efferent arteriole. Glm, glomerulus; PCT, proximal convoluted tubule; TL, thin limb; TAL, thick ascending limb; DCT, distal convoluted tubule; CD, collecting duct; O.C, outer cortex; D.C, deep cortex; R.A, renal artery; E.a, efferent arteriole; P.C, peritubular capillaries; II.V, interlobular vein; A.V, arcuate vein; IL.V, interlobar vein; R.V, renal vein.

proximal vascular elements and increases in flow moving the point to more distal vascular elements. This putative mechanism is analogous to that which allows glomerular filtration to be flow dependent under conditions in which glomerular filtration pressure equilibrium is reached at some point along the glomerular capillary network (70). Another possibility is that oxygen consumption by the vascular wall has a profound effect on renal AV O_2 shunting. The question of how much oxygen is consumed by the vascular wall is currently a matter of intense controversy (35). Furthermore, in the absence of direct experimental data or quantitative analysis it is unclear what quantitative effects vascular wall $\dot{V}_{O_2}$ might have on AV oxygen shunting. Nevertheless, the vascular wall does consume oxygen in driving vasomotion and endothelial nitric oxide synthesis (105, 114, 125). There is evidence that this produces P_{O_2} gradients across the arterial wall of as much as 25 mmHg in large arterioles (~100 μm) and 10 mmHg in small arterioles, at least in skeletal muscle (105). Vasodilatation reduces these gradients, reflecting reduced vascular smooth muscle $\dot{V}_{O_2}$. The resultant increase in oxygen tension at the outside wall of arterial vessels could in turn enhance AV oxygen shunting by increasing the effective P_{O_2} gradient driving shunting. Another way of considering this concept is that vascular wall $\dot{V}_{O_2}$ extracts oxygen from the shunting pathway, so decreasing vascular wall $\dot{V}_{O_2}$ as a fraction of the total kidney $\dot{V}_{O_2}$ should lead to an increase in the contribution AV O_2 shunting makes to the various oxygen transport pathways in the kidney. Thus in our experiment where RBF was increased through vasodilatation, shunting may have increased in part because of reduced vascular wall $\dot{V}_{O_2}$. Conversely, when RBF was decreased during vasoconstriction, shunting may have decreased in part because of increased vascular wall $\dot{V}_{O_2}$. This prediction is consistent with our findings (Figs. 2 and 3). However, such predictions must be made with care, as oxygen diffusion between "connected" counter-current flows (Fig. 3) is complex and poorly understood. The P_{O_2} levels in the artery, vein, and wall and, therefore, the driving force for shunting are all linked together with RBF and vascular and tubular $\dot{V}_{O_2}$. These multiple interactions provide great potential for counterintuitive behavior. Regardless, it is now clear that to understand intrarenal oxygenation we require a deeper knowledge of how the three chief regulatory factors, perfusion, oxygen consumption, and AV oxygen shunting, interact in physiological and pathophysiological settings (Fig. 1*B*).

Medullary circulation and maintenance of medullary oxygenation. While parts of the renal medulla, especially the papilla, have a high anaerobic capacity, almost all segments of the medullary nephron appear to rely at least in part on oxidative metabolism (16). Of particular note, the renal medullary thick ascending limb, the segment responsible for formation of the medullary interstitial NaCl gradient, has a high respiratory rate and a mitochondrial density similar to cardiac myocytes. However, just as the functions of the renal cortex dictate that this tissue is richly perfused, the functions of the renal medulla dictate that blood flow is limited. The maintenance of a relatively low medullary blood flow (MBF) appears to be critical for maintaining the cortico-medullary solute gradient and, therefore, urinary concentrating mechanisms (88). Furthermore, the level of MBF appears to be a critical determinant of the fine control of tubular sodium reabsorption and, therefore, long-term control of arterial pressure, through regulation of renal interstitial hydrostatic pressure (17, 27, 74). Accordingly, there must be considerable trade-off, in the control of MBF, between the physiological imperatives of the regulation of the cortico-medullary solute gradient and renal interstitial hydrostatic pressure (and so normal tubular function) and the supply of oxygen within the renal medulla.

Blood is supplied to the renal medulla from the vasa recta capillaries that arise from the efferent arterioles of juxtamedullary glomeruli, which comprise ~10% of all glomeruli in the kidney (88). Thus while all blood flow to the kidney enters the renal cortex, only ~10% of this enters the renal medulla (88).

Blood flow in the outer and inner medulla is ~40 and 10%, respectively, of that in the cortex (88). The bulk of the direct diffusive supply of oxygen to the medullary nephrons is likely drawn from the plexus of small intermingled capillaries that arise within the renal medulla rather than the vasa recta themselves. The unique anatomy of the renal capillaries has been suggested to underlie much of the susceptibility of the kidney to acute renal ischemic injury, particularly within the renal medulla. Rosen et. al (99) point out that much of the blood supplying the capillaries that feed the medullary tissue with oxygen is derived from the ascending vasa recta, which drain the deeper and less well-oxygenated regions of the renal medulla. In effect, much of the medullary tissue is supplied with a mix of "venous" and arterial blood.

Another factor that limits the delivery of oxygen to the renal medulla is the counter-current arrangement of the major medullary blood vessels, the descending and ascending vasa recta. This allows counter-current diffusion of oxygen from blood flowing into the medulla in the descending vasa recta to blood flowing out of the medulla in the ascending vasa recta, analogous to AV oxygen shunting in the cortex. A mathematical model of this phenomenon indicates it is a major factor limiting oxygen delivery to the renal medulla (126). Medullary hematocrit is also low relative to arterial blood, further limiting medullary oxygen supply (98). As a result of these factors, coupled with the relatively high metabolic demand of the medullary thick ascending limb, small alterations in local blood flow and/or local $\dot{V}\text{O}_2$ could potentially result in tissue hypoxia and cellular injury (39).

Regulation of medullary tissue Po_2 has been thought to rely heavily on tight control of oxygen delivery through MBF (25, 83). Indeed, there is good evidence that paracrine and autocrine factors act in concert to regulate MBF in the face of altered medullary metabolic activity (25). The relative insensitivity of the medullary circulation to many vasoconstrictor stimuli has also been proposed as an adaptive mechanism that protects the medulla from hypoxic damage (25). However, such a strategy is unlikely to be successful because medullary hypoxia occurs during moderate ischemia of the renal cortex, even when medullary perfusion is maintained at normal levels (85). The mechanisms that link medullary oxygenation with cortical perfusion remain to be determined but could potentially involve AV oxygen shunting (Fig. 5). Cortical hypoxia will lead to reduced oxygen content of blood in interlobular veins draining the renal cortex, which then drain into arcuate and interlobar veins before exiting the kidney via the main renal vein. Thus the driving force for AV oxygen shunting will be increased not only in vascular elements specific to the cortical circulation but also in vascular elements common to both the cortical and medullary circulations (interlobar, arcuate, and proximal interlobular). Thus medullary hypoxia may occur during cortical ischemia, even when MBF is maintained, because oxygen is "stolen" from arterial blood at a point upstream from the divergence of the cortical and medullary circulations by AV oxygen shunting. This hypothesis remains to be formally tested.

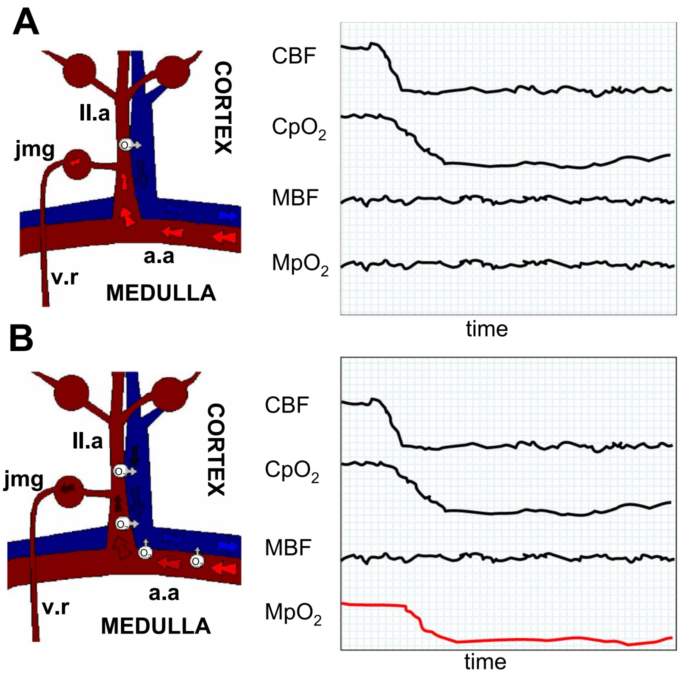

Fig. 5. Hypothesis: potential role of AV oxygen shunting in the dependence of medullary oxygen tension on cortical oxygen tension. *A*: expected effects of cortical ischemia if AV oxygen shunting occurs predominantly in interlobular arteries beyond the origin of the afferent arterioles of juxtamedullary glomeruli. Under these conditions, medullary oxygenation would be expected to be relatively independent of cortical oxygenation. *B*: expected effects of cortical ischemia if AV oxygen shunting occurs in vessels proximal to the origin of the juxtamedullary afferent arterioles. Blood in interlobular veins draining the hypoxic cortex will be relatively de-oxygenated during cortical ischemia, so increasing the gradient driving AV oxygen shunting in proximal interlobular, arcuate and interlobar vessels. This could lead to medullary hypoxia during cortical ischemia, even if medullary perfusion is perfectly maintained, as we have observed experimentally (85); a.a, arcuate artery; vr., vasa recta; jmg, juxtamedullary glomerulus; Il.a, interlobular artery, MBF, medullary blood flow; CBF, cortext blood flow.

Heterogeneity of tissue Po_2 and local oxygen exchange. Oxygenated arterial blood is distributed via the renal capillaries to the renal parenchyma by the processes of convection of oxygen bound to hemoglobin, dispersion of the red blood cells as they are convected, and diffusion of unbound oxygen. To prevent local hypoxia and cellular injury, these processes together must ensure that sufficient oxygen is delivered to meet local cellular metabolic demand. Local oxygen tension within the kidney is heterogeneous (69) and will depend on numerous factors including local blood flow, the rate and spatial distribution of oxygen metabolism, the distance to the nearest blood supply, the relative permeability of the surrounding tissue to oxygen, and, importantly with respect to AV oxygen shunting, the oxygen saturation of hemoglobin delivered to the renal capillary beds.

Oxygen delivery to mitochondria and cellular hypoxia. Cellular oxygen consumption creates the driving force for cellular oxygen uptake. Therefore, when cellular $\dot{V}\text{O}_2$ increases, cellular oxygen uptake increases. However, this also reduces local extracellular Po_2 and so limits oxygen diffusion to neighboring cells. A similar phenomenon occurs within cells, with regard to delivery of oxygen to mitochondria. Aw et al. (1) demonstrated that half-maximal oxidation (p50) of cytochrome $c + c1$ in intact resting renal proximal tubular cells is 3.6 μM oxygen. The p50 in isolated mitochondria however, is much less, occurring between 0.02 and 0.5 μM (i.e., <1 mmHg; Refs. 1, 87). The discrepancy between findings in intact cells and isolated mitochondria is likely accounted for by the presence of oxygen gradients within the cell (1) in large part due to the oxygen sink arising from the mitochondria themselves. That is, as mitochondria utilize oxygen, the oxygen concentration of the surrounding cytosol falls, reducing the diffusion of oxygen further into the cell and to more distant mitochondria. The critical Po_2 of renal cells (the extracellular Po_2 at which cellular oxygen utilization becomes limited) in vitro has been reported to be between 10 and 20 mmHg (3). Similar values have been reported for renal cortical and medullary tissue in vivo (79). Importantly, the critical Po_2 of intact cells is close to the range of tissue Po_2 observed in many regions of the kidney, particularly in the medulla, suggesting that even mild bouts of hypoxia are likely to limit oxidative metabolism and alter tubular function in these regions.

Based on the concepts discussed above, it could be expected that increased tubular ion transport activity and enhanced metabolic ATP demand would drive cellular hypoxia by increasing the rate of utilization of oxygen by mitochondria. In agreement with this concept, Aw et al. (1) demonstrated that either the addition of the sodium ionophore nystatin or the mitochondrial uncoupler FCCP significantly increased the p50 for cytochrome oxidation in intact renal proximal tubular cells. Furthermore, the activity of Na-K-ATPase in rat medullay thick ascending limb cells is highly correlated with the susceptibility of these cells to hypoxic injury (24).

Tubular hypertrophy may also limit the diffusion of oxygen in renal epithelial cells. In addition to increasing tubular transport activity, stimuli such as protein loading or reduced renal mass also result in significant cellular hypertrophy, which is in turn accompanied by mitochondrial hypertrophy (44). Thus the increased susceptibility of hypertrophied cells to hypoxic injury may be due not only to an increase in transport related mitochondrial oxygen utilization but also to increased mitochondrial mass. The development of local cellular hypoxia through cellular hypertrophy, in the absence of systemic renal hypoxia, may provide an explanation for the seemingly paradoxical results of some studies investigating the role of tissue hypoxia in the remnant kidney model of chronic kidney disease. Using oxygen mirco-electrodes to measure tissue O_2 tension, Priyadarshi et al. (97) demonstrated a 73% increase in both cortical and medullary tissue Po_2 in rats subjected to 5/6ths nephrectomy. In contrast, Manotham et al. (72), using the cellular specific hypoxic probe pimonidazole, demonstrated an increase in hypoxic cell staining in the renal cortex of rats in the early phase of the remnant kidney model. As tubular hypertrophy is known to occur in the remaining nephrons in the 5/6ths nephrectomy model, one possibility for the discrepancy between the results of these two studies may be that Manotham et al. observed the development of local cellular hypoxia in response to cellular and mitochondrial hypertrophy, while Priyadarshi et al. observed an increase in systemic renal interstitial Po_2 associated with an increase in renal oxygen delivery relative to $\dot{V}o_2$.

To conclude, the kidney is a heavily respiring organ in which oxygen is supplied to the parenchyma via a complex capillary network. Po_2 in the cellular microenvironment may depend not only on the relative rate of whole organ oxygen delivery to metabolic demand but may be highly dependent on the barriers to diffusion of oxygen through the parenchyma as well as local rates of cellular oxygen consumption and related micro-oxygen gradients. As regions of local tissue and cellular hypoxia could plausibly occur in the absence of significant whole organ hypoxia, identification and characterization of renal hypoxia may require multiple experimental approaches at multiple scales. Mathematical modeling may assist the planning and interpretation of these experimental approaches.

Reconciling the endocrine (erythropoietin) and exocrine functions of the kidney. In most tissues, blood flow is tightly regulated by tissue oxygenation. For example, hypoxia in tissues such as the brain (7) and skeletal muscle (23) causes vasodilatation and increased perfusion. Similarly, hyperoxia can induce vasoconstriction, particularly in brain tissue, which in turn limits tissue oxygen delivery (Fig. 6). In contrast, RBF is relatively insensitive to the effects of hypoxia and hyperoxia (54, 55; Fig. 6). This makes adaptive sense, since it allows control of renal perfusion to be dominated by the need for regulation of renal excretory function. It also makes adaptive sense for the role of the kidney as the "critmeter" of the body, since it allows changes in arterial blood Po_2 to be transmitted to renal tissue and so regulate erythropoietin synthesis and secretion.

Erythropoietin directs the proliferation and differentiation of erythroid precursors into erythrocytes, making it the chief hormonal factor that regulates hematocrit (108). Under physiological conditions, erythropoietin is expressed almost exclusively in the peritubular fibroblasts of the juxtamedullary cortex, although in states of chronic anemia of nonrenal origin it is also expressed in more superficial regions of the cortex (22). Erythropoietin synthesis is regulated chiefly by the bioavailability of hypoxia inducible factor-1, which is in turn inversely related to Po_2 (75, 108), although other oxygen-sensing mechanisms also likely play some role (22), including extrarenal mechanisms (118). As outlined elegantly in a recent review (38), the existence of a critmeter in the renal cortex makes sense from a teleological perspective for a number of reasons. Perhaps most important among these is the fact that the kidney extracts only ~10% of oxygen delivered in the renal artery, so the oxygen-hemoglobin dissociation curve is relatively steep in the renal cortex. Thus increased fractional oxygen extraction induced by anemia (46) will result in large

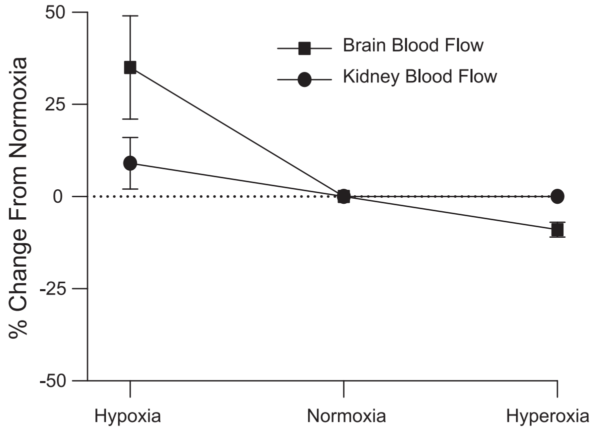

Fig. 6. Contrasting changes in blood flow in response to hypoxia and hyperoxia in the brain and kidney. Responses to hypoxia are from our own unpublished studies in anesthetized and artificially ventilated rabbits. Blood flow in the frontal cortex was measured by laser Doppler flowmetry, while kidney blood flow was measured by transit-time ultrasound flowmetry. Rabbits were made hypoxic by changing the ventilator gas mixture from 21% oxygen (room air) to 10% oxygen. Responses to hyperoxia come from studies by Kolbitsch et al. (51) and Flemming et al. (30).

reductions in renal tissue Po_2 and so is a strong signal for increased erythropoietin synthesis. There is also recent evidence that AV oxygen shunting in the kidney is enhanced in anemic states, which would act to augment renal hypoxia and so amplify the signal for erythropoietin synthesis (46).

However, now we are left with a paradox, because changes in perfusion of the cortex and medulla that occur as part of the renal response to challenges to homeostasis of fluid and electrolyte balance should also lead to changes in the delivery of oxygen to renal tissues. Such changes in renal oxygen delivery could potentially confound the maintenance of homeostasis of intrarenal oxygenation and in particular the control of erythropoietin synthesis. Halperin et al. (38) have argued that the "flow-dependence" of renal $\dot{V}o_2$ acts to maintain stable renal tissue Po_2 in the face of changes in renal hemodynamics. That is, since most oxygen consumption in the kidney is attributable to tubular sodium reabsorption, kidney $\dot{V}o_2$ often varies with RBF (36), so that kidney tissue oxygenation changes little when RBF changes under physiological conditions. Indeed, this concept is supported by the observations that moderate reductions in RBF have little effect on erythropoietin synthesis (see Ref. 118). However, this analysis relies on the assumptions that the filtration fraction remains relatively constant under physiological conditions and that renal $\dot{V}o_2$ always changes in response to altered RBF in a way that negates the effects of altered oxygen delivery. However, the physiological regulation of the GFR is often associated with changes in filtration fraction (78) and renal $\dot{V}o_2$ does not always vary in direct proportion to RBF (55). Nevertheless, renal tissue Po_2 can remain remarkably stable in the face of changes in RBF within the physiological range (i.e., ± ~30% of baseline), even if there is a mismatch between changes in oxygen delivery and demand (55, 85). As we have discussed in this review, recent findings (55) suggest that an additional mechanism contributes to dynamic regulation of intrarenal oxygenation in the face of changes in renal perfusion; renal AV oxygen shunting (Figs. 2 and 3).

Intrarenal Oxygenation in Disease States

Over the last three decades medical research has facilitated dramatic advances in the treatment of acute and chronic ischemia and hypoxia in the heart, but the same cannot be said for the treatment of kidney disease (76). This limited success is due in part to the complexity, and our incomplete understanding, of the factors governing intrarenal oxygenation. Nevertheless, some recent advances have been made, in large part because of the recognition that increased oxygen utilization in the kidney, not just reduced oxygen delivery to kidney tissue, contributes to the pathogenesis of kidney disease. Indeed, there is now strong evidence that reduced efficiency of mitochondrial oxygen utilization caused by oxidative stress and reduced nitric oxide bioavalability contributes to renal hypoxia in a diverse range of renal pathologies (89, 119). Further advances should also arise from an increased understanding of the effect of AV oxygen shunting on intrarenal oxygenation in disease states.

Acute renal injury. A range of factors can lead to acute renal injury, such as renal ischemia/reperfusion (9), allograft rejection (20), endotoxic and hemorrhagic shock (116), severe anemia (116), or hemodilution during medical procedures such as cardiopulmonary bypass (37, 106) and nephropathy induced by chemicals such as radiocontrast agents and other nephrotoxins (41, 101). Often, in a clinical context, a number of these factors are present (116). Renal tissue hypoxia is an important common feature of acute renal injury (101) and is a major driver of the cascade of events leading to cellular injury and vascular and tubular dysfunction (9). The outer medulla is particularly susceptible to hypoxic damage, due both to the relatively large $\dot{V}o_2$ of outer medullary tubular elements (e.g., thick ascending limbs and S3 segments of proximal tubules) and the relatively poor supply of oxygen by the outer medullary vasculature (12, 101).

Until recently, most interest has focused on the role of renal ischemia in the hypoxia associated with acute renal injury, but it is becoming increasingly clear that increased $\dot{V}o_2$ and perhaps also reduced oxygen delivery due to enhanced AV oxygen shunting also contribute. Indeed these three factors make variable contributions, depending on the underlying cause of kidney injury. For example, injection of radiocontrast agents into the kidney circulation causes renal hypoxia, particularly in the medulla (67). This may in part be mediated by reduced local blood flow (65), perhaps secondary to release of endothelin peptides (66). However, there is also evidence that contrast agents can increase blood flow in the outer medulla (40). Radiocontrast-induced medullary hypoxia can be reversed by the loop diuretic furosemide, indicating that it is at least partially dependent on increased oxygen use for tubular transport (40). Similarly, renal tissue hypoxia in anemia (46), after blockade of production of nitric oxide and/or prostanoids (101) and in response to nephrotoxins such as amphotericin (101), appears at least partly due to increased renal $\dot{V}o_2$. Johannes et al. (46) have also provided compelling evidence that enhanced renal AV O_2 shunting in anemia contributes to the development of renal hypoxia, presumably because the high affinity of oxygen for hemoglobin normally acts to retard AV oxygen shunting.

Consideration of the importance of the relative roles of the triad of factors (Fig. 1*B*); renal $\dot{V}o_2$, local perfusion, and AV oxygen shunting in acute renal injury has important implications for its clinical management, which to date has largely been based on the aim to augment GFR to return it to the normal range (101). The problem with this approach is that enhancing GFR will also increase kidney $\dot{V}o_2$ and so potentially worsen intrarenal oxygenation. Rosenberger et al. (101) have championed the potential use of loop diuretics in acute renal failure, since they reduce $\dot{V}o_2$ in medullary tubular elements. This approach is most likely to be successful when at least some level of medullary perfusion and oxygen delivery is maintained and when the majority of tubular ATP production is directed toward powering sodium transport. In pathologies in which medullary hypoxia is prolonged or where active sodium transport is not the chief cause of cellular ATP depletion, such as during mitochondrial dysfunction, loop diuretics may have little efficacy. Indeed, the balance of evidence suggests that these agents have only limited clinical efficacy (2). Consideration has also been given to the need to maintain perfusion of the renal medulla during acute renal injury to maximize delivery of oxygen to medullary tissue. However, as discussed earlier, maintenance of medullary perfusion may not prevent the development of renal hypoxia during moderate to severe cortical ischemia (Fig. 5).

We hypothesize that the development of mismatches in medullary perfusion and tissue oxygen tension may be more deleterious than parallel decreases in perfusion and tissue oxygenation. For example, the maintenance of medullary perfusion in the acutely damaged kidney will likely be associated with the maintenance of glomerular filtration and the production of tubular fluid in the juxtamedullary nephrons that supply the renal medulla. This, in turn, will maintain tubular sodium transport and oxygen consumption in long-looped nephrons. Thus, paradoxically, during conditions of medullary hypoxia cellular ATP depletion may occur more rapidly in medullary nephron segments if perfusion (and so tubular sodium delivery) is maintained than if tubular perfusion and, therefore, ATP usage is reduced.

In summary, hypoxic damage, particularly in the outer medulla, is a hallmark of the pathogenesis of acute renal injury. Medical management of acute renal injury has long focused on the maintenance of renal function (i.e., GFR). We submit that instead it should focus on maintenance of intrarenal oxygenation and minimizing the potential for mismatching of tubular oxygen delivery and energy demand. Thus to successfully prevent or treat acute renal injury we must consider the triad of factors that regulate intrarenal oxygenation (perfusion, $\dot{V}O_2$, and AV oxygen shunting) and in many cases the driving forces of increased cellular $\dot{V}O_2$ (Fig. 1*B*).

Chronic renal disease. Compared with acute renal injury, intrarenal oxygenation in chronic renal failure has been relatively little studied. Fine and colleagues (29, 81) have proposed that renal hypoxia is a common pathway in the progression of chronic kidney disease. They have proposed the “two capillary circulations” hypothesis (28), whereby hypoxia results from *1*) decreased perfusion in damaged capillaries, and *2*) increased $\dot{V}O_2$ associated with hyperfiltration in remaining nephrons. In support of this concept, much evidence now indicates that renal capillary dysfunction is an important factor in the initiation of renal hypoxia and kidney disease (48). Hypoperfusion and rarefaction of renal capillaries have been demonstrated in a number of renal disease models including hypertension (68), aging (111), and reduced renal mass (47, 72, 73). Loss of renal capillary density also occurs after recovery from acute renal injury. For example, renal ischemia/reperfusion is associated with loss of capillary density in both the cortex and medulla (5). Importantly, reduced peritubular capillary perfusion and capillary density after recovery from acute renal injury has been associated with the development of local tissue hypoxia and the progression of renal disease (4, 5, 13). Capillary dysfunction and rarefaction in chronic renal disease, or after acute renal insults, result in regions of local hypoxia and cellular injury in the kidney (109). Local areas of hypoxic injury may stimulate renal inflammation (100), the production of reactive oxygen species (64), and the deposition of extracellular matrix (71), further limiting the supply and diffusion of oxygen within the kidney. Further, progression of renal disease stimulates hypertrophy of remaining functional nephrons increasing the critical nephron PO_2 and promoting progression of cellular hypoxia within the kidney and renal disease (77). Given the accumulation of evidence indicating that injury to the renal microvasculature contributes to the initiation and progression of renal disease, future studies aimed at determining the mechanisms underlying microvascular dysfunction and hypoxia in the diseased kidney will undoubtedly be of major clinical importance in the prevention of chronic renal disease.

Renal dysfunction in diabetes and hypertension: the importance of oxidative stress and reduced nitric oxide bioavailability. The last decade has witnessed a huge growth in our understanding of the roles of nitric oxide and superoxide in the pathogenesis of hypertension- (124) and diabetes-induced end organ damage (26, 89, 96). One of the consequences of renal oxidative stress in these conditions is renal tissue hypoxia (89, 119, 120). There is now strong evidence that this tissue hypoxia arises chiefly because of reduced nitric oxide bioavailability in large part due to nitric oxide quenching by superoxide (89, 119). Nitric oxide can increase renal oxygenation by increasing oxygen delivery through vasodilatation (10) and reducing $\dot{V}O_2$ by inhibiting tubular sodium reabsorption (86) and also by competing with oxygen at the level of cytochrome oxidase within mitochondria (50). However, it is becoming increasingly clear that it is the relative absence of this latter effect of nitric oxide that is most important in the development of renal hypoxia in diabetes and hypertension, because it results in reduced efficiency of oxygen utilization for sodium reabsorption (89, 120).

One issue that has not been considered previously, in relation to chronic renal pathologies associated with oxidative stress and reduced nitric oxide bioavailability, is the effect of the consequent increase in renal tubular $\dot{V}O_2$ on AV oxygen shunting. As we have described earlier in this review, renal $\dot{V}O_2$ provides the driving force for AV oxygen shunting; the difference in oxygen tension between arterial and venous blood. Thus while reduced perfusion and increased $\dot{V}O_2$ can themselves contribute to tissue hypoxia, oxygen delivery is partially dependent on $\dot{V}O_2$ because changes in $\dot{V}O_2$will alter AV oxygen shunting (Fig. 1*B*). The degree to which this phenomenon contributes to regulation of intrarenal oxygenation in health and disease remains to be determined. Clearly mathematical modeling has an important role to play in uncovering the complex interplay between these processes.

Important recent findings with implications for treatment of kidney disease. A number of recent findings in the field of intrarenal oxygenation have potential implications for the clinical management of chronic kidney disease. First, renal tissue hypoxia in diabetes and multiple forms of hypertension can be ameliorated by scavengers of reactive oxygen species (63, 90, 121, 122), suggesting that such treatments may have a place in preventing renal injury in chronic hypertension and diabetes. Second, increased hepatic arginine metabolism also appears to make a major contribution to reduced renal nitric oxide bioavailability in diabetes and, in turn, associated tissue hypoxia in the renal medulla (92). This observation provides a mechanistic basis for the use of arginine supplementation in diabetic nephropathy. Third, AT_1-receptor blockade acutely increases renal cortical PO_2 (82) and, if given chronically, upregulates mitochondrial nitric oxide synthase activity in the kidney and reduces respiratory chain activity (93). It also protects against the development of mitochondrial dysfunction in Type 1 diabetes (19). Collectively, these data provide a mechanistic basis for the use of AT_1-receptor antagonists to prevent dysregulation of intrarenal oxygenation in chronic renal disease. The potential roles of AT_2-receptors in control of intrarenal oxygenation also need to be considered, since Palm et al. (91) recently provided strong evidence that AT_2-receptor mediated nitric oxide release sustains renal perfusion and oxygenation in experimental renovascular hypertension.

Conclusion

The kidney faces unique challenges in the maintenance of homeostasis of intrarenal oxygenation. Intrarenal oxygenation is regulated by the maintenance of a fine balance between demand and delivery. At least in the mammalian kidney, this balance could not be achieved without AV oxygen shunting, which allows the functional requirement of the kidney for rich perfusion to be met without the development of tissue hyperoxia (84). The price paid for this protection from tissue hyperoxia is that the kidney is susceptible to tissue hypoxia. More recent observations indicate that renal AV oxygen shunting may not merely be a "structural antioxidant defense mechanism" but may also contribute to the dynamic regulation of intrarenal oxygenation in the face of changes in RBF (55) and also to the development of renal hypoxia in anemic states (46). Renal hypoxia is a salient feature of diverse renal pathologies, including various forms of acute renal injury, chronic renal disease, hypertension and diabetes. Reduced renal perfusion and increased $\dot{V}O_2$ are major contributors to renal hypoxia in these conditions. Theoretical considerations suggest that increased AV oxygen shunting may exacerbate tissue hypoxia in these conditions, but as yet this has not been investigated experimentally or by mathematical modeling. We hope this review has made a case for such studies.

GRANT

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