Recent advances in renal hemodynamics: insights from bench experiments and computer simulations

Anita T. Layton

Department of Mathematics, Duke University, Durham, North Carolina

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Renal Autoregulation

The generally stable glomerular filtration rate (GFR) is a result of renal autoregulation, as is the protection of glomerular capillaries from excessive intravascular pressure and shear stress. Renal autoregulation is mediated by several mechanisms (10, 27, 33). One such mechanism is the myogenic response, with which a rise in intravascular pressure elicits a local stretch-dependent constriction that generates a compensatory increase in vascular resistance (32). Another key autoregulatory mechanism is the tubuloglomerular feedback (TGF), which is a negative feedback response that balances glomerular filtration with tubular reabsorptive capacity (10, 27, 33). These renal autoregulatory mechanisms are believed to simultaneously insulate kidney function from variations in blood pressure and to protect glomerular capillaries from potential barotrauma. Indeed, impaired renal autoregulation (4, 61) and the resulting elevation in glomerular capillary pressure (28, 52) are thought to play an essential role in the pathogenesis of the progressive glomerular injury and sclerosis that has been observed in most chronic renal diseases, including diabetic nephropathy. The relative contributions of myogenic response and TGF in protecting glomerular capillaries from barotrauma remain controversial.

A notable feature of the afferent arteriolar myogenic mechanism is that the response times for vasoconstriction and vasodilation differ significantly. Loutzenhiser and coworkers (44, 45) observed that the initial delay in the activation of pressure-dependent vasoconstriction was ∼0.3 s, with the response profile approximated by an exponential having a time constant of 4 s. In contrast, vasodilation has a longer initial response approximated by an exponential having a time constant of 1 and 14 s. A modeling study by Edwards and Layton (14) suggests that the faster vasoconstriction can be attributed to the kinetic behavior of the voltage-activated L-type channels. If these observations are accurate, then the afferent arteriole would respond to high-frequency pressure fluctuations in blood pressure with a sustained vasoconstriction that is determined not by mean arteriolar pressure but by systolic pressure (44, 45). It is noteworthy that Just and Arendshorst (34) observed a stronger and faster dilator response than constrictor response, in direct contrast to the kinetics reported by Loutzenhiser and coworkers (44, 45). An explanation for this discrepancy has yet to be determined.

TGF regulates distal tubular sodium load by adjusting the tone of the afferent arteriole and glomerular filtration rate in response to changes in NaCl concentration of the tubular fluid reaching the macula densa (5). TGF is regulated by a number of factors, including angiotensin (ANG) II (81), adenosine triphosphate (ATP) (31, 65), atrial natriuretic factor (29), nitric oxide (NO) (42), and superoxide (O2−) (43). In addition, recent studies by Liu and coworkers (20, 87) suggest that aldosterone, via its effects on NO and O2−, may play an important role in the control of TGF response. Aldosterone increases O2− production in the macula densa; O2− then scavenges NO and buffers the effect of NO on TGF activity.

In an elegant study, Peti-Peterdi (62) demonstrated that TGF activation triggers a calcium wave, which spreads across the mesangial cell field and reaches the afferent arteriole. Intercellular communication pathways are an integral component of that calcium wave and of signal transmission in the juxtaglomerular apparatus (JGA), inasmuch as TGF calcium wave propagation can be prevented by gap junctional coupling inhibitors (62). Gap junctions comprise of connexin (Cx) subunits. In particular, the Cx protein Cx40, which is highly expressed in extraglomerular mesangial cells, has been proposed to be a facilitator of calcium signal transmission across the JGA (39, 76, 85). The role of Cx40 in TGF calcium wave propagation can be prevented by gap junctional coupling inhibitors (62). Gap junctions comprise of connexin (Cx) subunits. In particular, the Cx protein Cx40, which is highly expressed in extraglomerular mesangial cells, has been proposed to be a facilitator of calcium signal transmission across the JGA (39, 76, 85). The role of Cx40 in TGF calcium wave propagation can be prevented by gap junctional coupling inhibitors (62). Gap junctions comprise of connexin (Cx) subunits. In particular, the Cx protein Cx40, which is highly expressed in extraglomerular mesangial cells, has been proposed to be a facilitator of calcium signal transmission across the JGA (39, 76, 85). The role of Cx40 in TGF calcium wave propagation can be prevented by gap junctional coupling inhibitors (62). Gap junctions comprise of connexin (Cx) subunits. In particular, the Cx protein Cx40, which is highly expressed in extraglomerular mesangial cells, has been proposed to be a facilitator of calcium signal transmission across the JGA (39, 76, 85). The role of Cx40 in TGF calcium wave propagation can be prevented by gap junctional coupling inhibitors (62). Gap junctions comprise of connexin (Cx) subunits. In particular, the Cx protein Cx40, which is highly expressed in extraglomerular mesangial cells, has been proposed to be a facilitator of calcium signal transmission across the JGA (39, 76, 85). The role of Cx40 in TGF calcium wave propagation can be prevented by gap junctional coupling inhibitors (62). Gap junctions comprise of connexin (Cx) subunits. In particular, the Cx protein Cx40, which is highly expressed in extraglomerular mesangial cells, has been proposed to be a facilitator of calcium signal transmission across the JGA (39, 76, 85). The role of Cx40 in TGF calcium wave propagation can be prevented by gap junctional coupling inhibitors (62). Gap junctions comprise of connexin (Cx) subunits. In particular, the Cx protein Cx40, which is highly expressed in extraglomerular mesangial cells, has been proposed to be a facilitator of calcium signal transmission across the JGA (39, 76, 85). The role of Cx40 in TGF calcium wave propagation can be prevented by gap junctional coupling inhibitors (62). Gap junctions comprise of connexin (Cx) subunits. In particular, the Cx protein Cx40, which is highly expressed in extraglomerular mesangial cells, has been proposed to be a facilitator of calcium signal transmission across the JGA (39, 76, 85).
of Cx40 reduces TGF responsiveness by ~30%. Nonetheless, the fact that TGF response is not completely eliminated suggests either the involvement of a Cx other than Cx40 in TGF or an extracellular transmission pathway.

How is renal autoregulation affected by changes in dietary salt? A key TGF signal is Cl\(^-\), the transport of which is mediated by Na-K-Cl cotransport (NKCC). A recent study by Schiessl et al. (70) indicates that a low-salt diet induces a shift from the isoform NKCC2-A to NKCC2-B primarily in the cortical thick ascending limb and macula densa cells. Given the markedly different ion affinities and reabsorptive capacities of its splice variants, the diet-induced shift in NKCC2 expression is believed to significantly impact NaCl reabsorption. To assess the validity of that hypothesis, Edwards et al. (13) used a theoretical approach: they developed a highly detailed computational model of the macula densa cell and thick ascending limb transport. Results of that modeling study suggest that the enhanced expression of NKCC2-B, which has a higher affinity for Cl\(^-\) than NKCC2-A, in the cortical thick ascending limb, where luminal Cl\(^-\) concentration is low especially with a low-salt diet, significantly enhances salt reabsorption in the thick limb and reduces salt delivery to the macula densa. Simulation results also predict that the NKCC2 isoform shift hyperpolarizes the macula densa basolateral cell membrane, which, taken in isolation, may inhibit the release of the TGF signal, thereby causing excessive early distal salt delivery and renal salt loss during a low-salt diet. That damaging effect may be prevented by an asymmetric TGF response that is more sensitive to flow increases (13).

Both TGF and the myogenic response regulate glomerular filtration, in response to different signals, by affecting the afferent arteriolar tone. The individual contributions of these two mechanisms have been assessed by Sgouralis and Layton (71) using a detailed computational model of renal hemodynamics. The question is, given a perturbation in renal perfusion pressure, to what extent does each mechanism contribute to the stabilization of GFR? Their model simulations indicate a significant contribution of TGF to overall autoregulation only with a narrow band of perfusion pressure values (80–110 mmHg). The two autoregulatory mechanisms leave their marks on nephron blood flow even in the absence of pressure perturbations, by generating sustained oscillations in arteriolar muscle tone, with a frequency of ~30 mHz for TGF and ~150 mHz for the myogenic response. A fascinating feature of these oscillations is that clusters of nearby nephrons, presumably with different characteristics and thus slightly different inherent frequencies, exhibit transient (not permanent) synchronization. Using laser speckle contrast imaging, Holstein-Rathlou et al. (26) found similar frequencies within small clusters of two or three nephrons, with larger clusters of nephrons with synchronized oscillations forming and dissolving. To better understand internephron interactions and synchronization, Marsh et al. (46) developed a computational model of 16 interacting nephrons. Their simulation results suggest that, despite the differing characteristics among the nephrons, some degree of synchrony persists, which triggers the formation of a self-organization system of nephrons. Nonetheless, owing to the asymmetry in the renal vascular network, that synchronization is not robust and can dissipate following a perturbation.

**Renal Oxygenation**

The mechanisms underlying the development of renal hypoxia in many disease states have yet to be elucidated. That difficulty may be attributable, in part, to the fact that the kidney is a complex organ with unique three-dimensional organization of functional units. Anatomic studies in the medulla of rodent kidneys have revealed a highly structured organization of nephrons and vessels; that spatial organization is believed to play a key role in the oxygenation of the renal medulla (59). In the inner stripe of the outer medulla, descending vasa recta and some of the ascending vasa recta are isolated within tightly packed vascular bundles, separated from the thick ascending limbs and collecting ducts (3, 38). That arrangement continues into the upper inner medulla, where collecting ducts form clusters that exclude descending vasa recta (57, 58, 83). The structural organization of nephrons and vessels likely facilitates preferential interactions among neighboring structures and leads to radial gradients in solute concentrations. That is, for a given medullary cross section, interstitial solute concentrations may be different within versus outside the vascular bundles or collecting duct clusters. Now because the vascular bundles and collecting duct clusters are small, those concentration differences are likely small too and may even be negligible for solutes like NaCl, which reaches a high concentration within the renal medulla. However, for a solute with a much smaller baseline concentration, like O\(_2\), that “small” radial concentration gradient may still be substantial relative to baseline. Thus it may be argued that the structural organization of nephrons and vessels within the renal medulla may result in the sequestration of O\(_2\) within the vascular bundles (59).

Despite receiving ~25% of the cardiac output, the mammalian kidney has low O\(_2\) levels, with tissue O\(_2\) tension of ~20 and 10 mmHg in the outer and inner medulla, respectively (51). Thus the kidney is susceptible to hypoxia. Its low O\(_2\) tension can be attributed in part to the high metabolic demands of the Na\(^+-K^+\) -ATPase, which drives salt reabsorption and accounts for a substantial fraction of the O\(_2\) consumption (QO\(_2\)) in the medulla. In the outer medulla, the compartmentalization of medullary blood flow within the vascular bundle is believed to help preserve O\(_2\) supply to the inner medulla, but it also lowers the O\(_2\) tension in the interbundle regions. Because the thick limbs are found outside of the vascular bundles where O\(_2\) supply is low, they are particularly vulnerable to hypoxic injuries. Indeed, recent modeling studies have suggested that the thick ascending limb cells, particularly those of superficial nephrons, operate near hypoxia (8, 19). Also noteworthy are modeling studies of Edwards and coworkers (18, 84) that examine the distribution of medullary NO, taking into account the structural arrangements of the vascular bundles. Those studies demonstrate that differential NO concentrations may selectively alter medullary perfusion in different regions.

Renal tissue hypoxia has been demonstrated during the acute phase of reperfusion after ischemia induced by blocking the aorta that supplies the kidney (40, 41, 72). However, these observations appear to be in disagreement with clinical studies that indicate relatively well-preserved oxygenation in the non-functional transplanted kidney (54, 63). Thus the question is: to what extent can acute kidney injury occur in the absence of wide-spread renal tissue hypoxia? To answer that question, Abdelkader et al. (1) measured renal O\(_2\) delivery, QO\(_2\), and...
cortical and inner medullary tissue $P_{O_2}$ during reperfusion after a period of ischemia localized to the kidney. They detected no significant reductions in tissue $P_{O_2}$ in the renal cortex or inner medulla, a result that may be explained by the simultaneous decreases in glomerular filtration and $Q_{O_2}$. Nonetheless, pimonidazole adduct immunohistochemistry indicates localized tissue hypoxia in the outer medulla, which allows for the possibility of hypoxia contributing to acute kidney injury.

Tissue $P_{O_2}$ is frequently assessed by data obtained using blood oxygen level-dependent (BOLD) MRI, an imaging technique where the concentration of deoxygenated hemoglobin molecules is reflected by tissue signal (53). BOLD MRI data are known to be influenced by various factors, including blood perfusion, hematocrit, intrinsic spin-spin relaxation rate, and oxygen permeability. To improve the extraction of tissue $P_{O_2}$ from renal BOLD data, Zhang et al. (86) developed a multistep data analysis method. First, Monte Carlo simulations are performed to estimate blood oxygen saturation (SHb) from BOLD signals. Then an oxygen transit model is used to convert SHb to tissue $P_{O_2}$. Their method was validated using a porcine model and appears promising for use in human subjects.

The ratio of Na$^+$ reabsorption ($T_{Na}$) to $Q_{O_2}$ represents a measure of the metabolic efficiency. $T_{Na}/Q_{O_2}$ is reduced in diabetes (56), hypertension (11), and chronic kidney disease (11). These observations have been interpreted as evidence for inefficiency utilization of oxygen for $T_{Na}$ in those pathophysiological states, due to shift in $T_{Na}$ to less efficient nephron segments or to mitochondrial dysfunction [as discussed in a recent review (7)]. However, it is important to note that $Q_{O_2}$ has two components, one that depends on $T_{Na}$ denoted $Q_{O_2}^{Na}$, and the other does not, denoted $Q_{O_2}^{basal}$. With this notation, $T_{Na}/Q_{O_2}$ can be written as $T_{Na}/(Q_{O_2}^{Na} + Q_{O_2}^{basal})$. It can be seen that a drop in metabolic efficiency for $T_{Na}$ is clearly reflected in the ratio $T_{Na}/Q_{O_2}$ only if $Q_{O_2}^{basal}$ is negligible compared with $Q_{O_2}^{Na}$; otherwise, any changes in $Q_{O_2}^{basal}$ would have minimal effect on $Q_{O_2}$ and $T_{Na}/Q_{O_2}$. To estimate the fractional contributions of $Q_{O_2}^{basal}$ to $Q_{O_2}$, Evans et al. (16) performed a systematic review and conducted additional experiments in anesthetized rabbits. They estimated that under physiological conditions, $Q_{O_2}^{basal}/Q_{O_2}$ varies hugely from 0 to 81.5%; that fraction depends, in part, on fractional sodium excretion (FE$Na$). Linear regression analysis predicted $Q_{O_2}^{basal}/Q_{O_2}$ of 12.7–16.5% when FE$Na$ = 1%. Given these estimates, Evans et al. concluded that $T_{Na}/Q_{O_2}$ should be interpreted cautiously, because $Q_{O_2}^{basal}$ is by no means negligible and may actually vary in ways that can be difficult to predict (16). As a result, it is conceivable that significant changes in $T_{Na}/Q_{O_2}$ may occur when $T_{Na}$ changes, even if metabolic efficiency remains unaltered.

**Renal Hemodynamics Under Pathophysiological Conditions**

There is much interest in better understanding the mechanisms by which renal autoregulation is impaired in diseases such as diabetes or hypertensive, and progress has been made. Myogenic response is known to be impaired under some pathophysiological conditions and disease models. One example is the Dahl salt-sensitive (SS) rats. These rats, when challenged with a high-salt diet, quickly develop glomerulosclerosis and proteinuria (67, 68). In a recent study, Ge et al. (22) report that the production of 20-hydroxyecosatetraenoic acid (20-HETE), a potent vasoconstrictor, is reduced in the renal vasculature of Dahl SS rats. In a related study (64), also performed on Dahl SS rat, Ren et al. indicate that a decrease in 20-HETE leads to the impairment of the constriction of the afferent arteriole and its autoregulatory response. Together, these findings suggest that endogenous formation of 20-HETE in the renal microcirculation may play a key role in modulating the autoregulatory response of the afferent arteriole. These studies further provide evidence that the susceptibility of SS rats to the development of hypertension-induced renal injury may be attributed, in part, to the deficiency in the renal production of 20-HETE. One implication of these results is that strategies that increase 20-HETE may restore the myogenic response (64).

Renal autoregulation is impaired in diabetes, one of the leading causes of end-stage renal disease (15, 50, 82). The onset of diabetes is characterized by glomerular hyperfiltration (12). One open question concerns the roles of ANG II and adenosine receptors for controlling baseline renal blood flow or tubular Na$^+$ transport in diabetes. Accordingly, Patinha et al. (60) studied the functions of these receptors in control and 2-wk streptozotocin-diabetic rats after intrarenal infusion of an ANG II AT$_1$ receptor antagonist and an adenosine A1 receptor antagonist, separately or simultaneously. Their findings suggest that, via a unifying mechanism, ANG II and adenosine provide strict tonic control of renal blood flow and tubular Na$^+$ transport; that result was obtained in both control and diabetic kidneys. Furthermore, glomerular hyperfiltration was observed as a consequence of increased vascular AT$_1$ receptor activities, independently of any effect of adenosine A1 receptors.

NO mediates vasodilation, increases renal blood flow, and inhibits renal $Q_{O_2}$; taken together, NO can contribute to the increase of renal tissue oxygenation. Thus derangement of NO metabolism may be involved in the pathogenesis of diabetes and the progression to diabetic nephropathy (36, 37, 88). Hueper et al. (30) conducted the first study that determines the effect of systemic NO synthesis inhibition on systemic blood pressure and vascular conductance in a rat model of diabetic nephropathy. They used diffusion tensor imaging and BOLD imaging to conduct a noninvasive investigation of the intrarenal effects of NO metabolism. Following NO synthesis inhibition by nitro-1-arginine methyl ester (L-NAME) injection, they found a significant decrease in vascular conductance and increase of mean arterial pressure in control animals. In contrast, the systemic vascular reactivity upon L-NAME injection was significantly attenuated in diabetic rats, with minimal changes observed in mean arterial pressure and vascular conductance.

As previously noted, TGF balances glomerular filtration with tubular reabsorptive capacity and elicits a reciprocal effect of distal NaCl delivery on single nephron glomerular filtration rate. This negative feedback is typically robust and remain intact under most circumstances. One exception to this rule is the subtotal nephrectomy (STN) rat model, where TGF responses were found to be highly variable and frequently paradoxical (73). It was suggested that this observation can be attributed to the need for the STN kidney to deal with a large excretory burden, per nephron. Under this circumstance, the kidney may opt to reduce the priority that is normally given to stabilizing nephron function (73). Singh and Thomson (74) tested that theory, with a focus on the effect of dietary salt, by conducting micropuncture studies. Their findings indicate that

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a high-salt diet leads to an anomalous TGF response in the STN kidney, which facilitates the delivery of both NaCl and fluid to the distal nephron.

**REFERENCES**


