Renal Physiology

Editors:

Larissa Bresler, MD, DABMA

Authors:

Kristin G. Baldea, MD

Last Updated:

Wednesday, June 14, 2023

Keywords

kidney, renal, renal blood flow, glomerular filtration rate, acid base metabolism, electrolytes

1. Introduction

A thorough understanding of renal physiology is necessary for all practicing urologists. In this section, the renal physiology that is applicable to the practice of urology is reviewed. Please see the **Kidney, Adrenal, Ureter** section for anatomy.

2. Determinants of Renal Blood Flow and Glomerular Filtration Rate

The renal arteries enter the kidney and then divide into progressively smaller arteries in this order: interlobar, arcuate, interlobular, and afferent arteriole which enters the glomerulus. From the glomerulus, blood is either filtered across the membrane (filtration fraction) or exits via the efferent arteriole. Renal blood flow (RBF) is regulated by changes in vascular resistance of the arteries from the renal artery to the afferent arteriole. RBF is 20% of total cardiac output and flow to the outer cortex of the kidney is 2 to 3 times greater than that to the inner cortex.[1]

Glomerular filtration rate (GFR) is determined by Starling forces as demonstrated in the following equation.

GFR = LpS x (Δ hydrostatic pressure – Δ oncotic pressure)

where Lp= glomerular permeability and S = glomerular surface area.

GFR is altered by 4 factors:

1. <u>Transglomerular hydrostatic pressure (TGP):</u> This is the most significant determinant of GFR. TGP is regulated by the afferent and efferent arterioles which is essentially independent of systemic blood pressure.
2. <u>Renal Plasma Flow (RPF):</u> GFR is directly related to changes in RPF. If RPF increases, then GFR increases. If RPF decreases, then GFR decreases.
3. <u>Glomerular Permeability (Lp):</u> The glomerulus is already at maximal permeability for water and other solutes so an increase in permeability does not change GFR. However, if Lp decreases, then GFR decreases.

4. Oncotic pressure: This is the least relevant variable because plasma proteins are not normally filtered so oncotic pressure should be zero.

Under **NORMAL** physiology conditions GFR is tightly regulated by two mechanisms:

1. Autoregulation: Afferent arteriole tone changes in response to changes in mean arterial pressure (MAP). If MAP increases, afferent arteriole increases to minimize changes in the glomerular pressure. If MAP decreases, afferent arteriole tone decreases to maintain intraglomerular pressure and thus GFR. Autoregulation is effective for a MAP between 40 and 70 mm Hg. The mechanism is not well-understood, but is likely mediated through myogenic stretch receptors in the arteriole wall.[2]

2. Tubuloglomerular feedback (TGF): Cells in the macula dense monitor tubular ultrafiltrate flow rates. If GFR increases, there is increased chloride anion delivery to the distal tubule. This triggers a response which leads to increased afferent arteriole tone with subsequent decrease in RPF, thus GFR.[2]

Under **ABNORMAL** circumstances GFR is regulated by neurohormal responses. For example, if effective circulating volume is significantly reduced, such as in sepsis or hypovolemia, then norepinephrine and angiotensin II maintain GFR through arteriolar vasoconstriction. Renal prostaglandins and nitric oxide offset the vasoconstriction creating a balance between the vasoconstrictive and vasodilatory effects of these hormones (**Table 1**). [1]

Table 1: Vasoactive Substances that Control Renal Artery Tone

Action	Substance	Notes
Vasoconstriction	Angiotensin II	Important to maintain GFR in conditions that decrease RBP such as renal artery stenosis and dietary sodium restriction.
	Norepinephrine	Vasoconstricts all major vascular beds in the kidney thus renal function is preserved when used as a pressor agent in the face of systemic vasodilation.
	Vasopressin	At low doses used for management of septic shock, it does not change RBF, thus renal function is preserved. It can induce renal ischemia at higher doses.
	Endothelin	Most potent vasoconstrictor identified. Also stimulated aldosterone secretion and decreases RBF and GFR.
	Atrial natriuretic peptide	Synthesized in the atria in response to stretching (volume expansion). Increases GFR and natriuresis in the kidney without a change in RBF.
Vasodilation	Nitric oxide	NO synthesized in the vascular endothelium diffuses into vascular smooth muscle cells leading to smooth muscle relaxation.
	Carbon monoxide	Heme oxygenase catalyzes the rate-limiting step in heme degradation, resulting information of carbon monoxide. Produces vasodilation in the kidney and is renoprotective from oxidant injury.
	Prostaglandin E2	Offsets action of angiotensin II in the afferent arteriole. Causes potent vasodilation.

3. Anatomy of Renal Tubules

The renal tubule is divided into sections and each is specialized in two basic functions: reabsorption (transport from lumen to blood) or secretion (transport from blood to lumen) (**Figure 1**).[1]
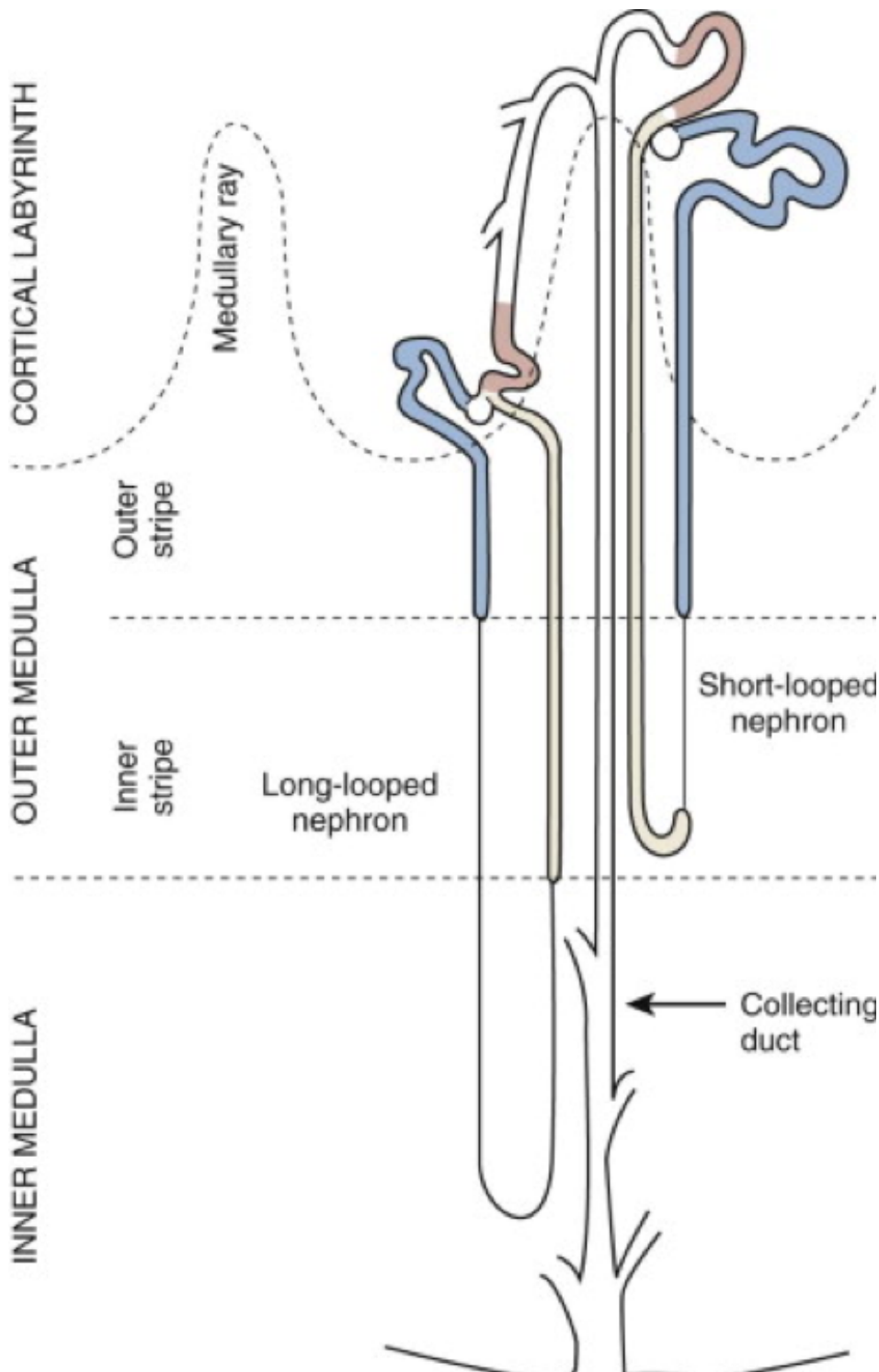

Figure 1: Organization of the renal tubule.[1]

1. The ***proximal convoluted tubule (PCT)*** reabsorbs 60% of the total glomerular filtrate. With the process of *glomerulotubular balance* the PCT can adjust reabsorption in

response to changes in GFR to maintain constant reabsorptive fractions. The PCT reabsorbs 65% of the filtered sodium, potassium, and calcium; 80% of the filtered phosphate, water, and bicarbonate; 100% of the filtered glucose and amino acids; and it secretes numerous drugs and toxins that are too large to be filtered. [1] The PCT also generates ammonia from glutamine, which is necessary for urinary acidification.

In proximal renal tubular acidosis (Type 2), the reabsorption of bicarbonate is lowered and large amounts of sodium bicarbonate are delivered distally. The distal tubule has a low capacity to reabsorb this bicarbonate excess. Instead, the distal tubule secretes hydrogen ions which bind the bicarbonate resulting in decreased ammonium and reduction in titratable acid secretion. The urine becomes alkaline and rich in bicarbonate and a hyperchloremic metabolic acidosis develops. The acidosis is self-limited because acid production and excretion ultimately become equal at the reduced pH. Clinically, the effects are osteomalacia, rickets, abnormal intestinal calcium absorption, and decreased vitamin D metabolism. [3]

2. The *loop of Henle* consists of three segments; the thin descending limb (DLH), the thin ascending limb (ALH), and the thick ascending limb (TALH). The major function of the loop is to reabsorb sodium chloride in excess of water, creating an extremely concentrated medullary interstitium in order to excrete concentrated urine.

The DLH has high water permability due to abundant expression of aquaporin-1. The ALH is water impermeable, but highly permable for sodium chloride and urea, so reabsorption of these solutes occurs passively along the osmotic gradient that was established by the DLH. The TALH lacks aquaporins and is also impermeable to water, but is very active in terms of solute reabsorption. Sodium reabsorption along the TAHL, in the absence of water reabsorption, is critical to the formation of the interstitial concentration gradient.

A critical function of the kidney is to preserve body water. This is accomplished through the osmotic reabsorption of water in the collecting tubule and excretion of hyperosmolar urine. Human kidneys can produce a urine concentration up to 1200 mOSm/kg. [1] The loop of Henle is able to produce an interstitial osmotic gradient using *countercurrent multiplication*.

The basic steps of countercurrent multiplication:[1]
   1. Sodium chloride is reabsorbed in the ascending limbs of the loop of Henle, making the medullary interstitium hyperosmolar.
   2. Due to the hairpin configuration of the loop, the concentration of the luminal fluid can be progressively multiplied to as much as 1200 mOsm/kg, increasing the interstitial osmolarity further.
   3. In the presence of antidiuretic hormone (ADH), urea diffuses from the medullary collecting tubule into the interstitium, increasing the interstitial osmolarity even further. With increased interstitial osmolarity, water reabsorption in the DLH increases, increasing luminal solute concentration in

the ascending limbs and making step 1 more efficient.

    4. Due to high interstitial osmolality the water is passively reabsorbed in the medullary collecting tubule.

3. The *distal convoluted tubule (DCT)* is primarily involved in sodium and calcium reabsorption. The DCT accounts for 10% to 15% of the calcium reabsorption which is regulated by parathyroid hormone and vitamin D. [1]

In distal renal tubular acidosis (Type 1), the distal tubule is unable to secrete hydrogen ions and thus cannot produce a urine pH less than 5.4. Urine pH in this condition ranges from 5.4 to 6.5 depending on the severity of the transport defect. The resulting systemic hyperchloremic metabolic acidosis causes an increase in bone reabsorption leading to increased urinary calcium and nephrocalcinosis due to the low solubility of the excess calcium in mildly alkaline urine. [3]

4. The *collecting tubule* is composed of two major cell types: *principal cells* are involved in sodium chloride reabsorption and *intercalated cells* are involved with acid secretion. Both cell types are involved in potassium regulation. The water permeability of the collecting tubules is typically low, but can be greatly increased in the presence of ADH due to insertion of preformed aquaporin-2 water channels into the luminal membrane. A section of the medullary collecting tubule has a high permability for urea which allows a high concentration of urea to develop in the interstitium, thus sustaining the osmotic gradient that is responsible for water reabsorption and urinary concentration.

4. Disturbances of Acid-base Metabolism

The human body must maintain a blood pH of 7.35 to 7.45, anything outside this range will compromise a number of physiological functions. The 2 main compounds that determine blood pH are carbonic acid (as related to the carbon dioxide content of alvelolar air) and plasma bicarbonate.[4] Simple acid-base disturbances are described below. Mixed acid-base disorders involve respiratory or metabolic compensation.

Metabolic acidosis: In order to determine etiology, the anion gap must be calculated using the equation below. The normal range is 9 to 14 mEq/L. The appropriate compensatory response is increased ventilation with decreased pCO_2.[4]

ANION GAP = [Na – (Cl + HCO3)]

A. *Normal anion gap metabolic acidosis:* The primary change is a reduction in plasma bicarbonate. Causes include GI tract losses (ex. chronic diarrhea) and renal losses.[4]

B. *Elevated anion gap metabolic acidosis:* The primary change is the addition of an acid to the blood. Examples of acids include ketones (diabetic ketoacidosis or starvation states), lactate (lactic acidosis), urea (renal failure) and drugs (methanol, aspirin). [1]

Metabolic alkalosis: Caused by either losing too much acid or retaining too much bicarbonate. Etiologies include vomiting, prolonged nasogastric tube suction and diuretic use. The appropriate

respiratory compensation is reduced ventilation with increased pCO_2.[4]

Respiratory acidosis: Caused by hypoventilation due to sedative drugs or chronic lung disease. The appropriate compensatory response is increased plasma bicarbonate.

Respiratory alkalosis: The most common cause in surgical patients is sepsis.[4] Other common causes of hyperventilation are pain, anxiety, head trauma and excessive mechanical ventilation. The appropriate compensatory response is lowering of plasma bicarbonate. [1]

5. Electrolytes

The preservation of basic cellular function depends ultimately on the body's ability to maintain a relative equilibrium in regards to fluid and electrolyte balance between the intracellular and extracellular component. If the balance is offset, physiologic consequences are observed (**Table 2**).

Table 2: Electrolyte Disturbances[1,4]

Disturbance	Early Symptoms	Late Symptoms	Causes
Hypernatremia	Lethargy, irritability, confusion, weakness	Seizures, cerebral edema, coma, death	Euvolemic: impaired thirst, excessive sweating
			Hypovolemic: diuretics, diarrea, vomiting
			Hypervolemic: iatrogenic sodium delivery
Hyponatremia	Nausea, vomiting, fatigue, lethargy, irritability, headache	Muscle weakness, cramps, seizures, altered mental status, coma, death, cerebral edema and tentorial herniation	Isotonic: hyperproteinemia or hyperlipidemia
			Hypotonic: adrenal insufficiency, hypothyroidism, SIADH, congestive heart failure, cirrhosis
			Hypertonic: hyperglycemia, glycine or mannitol administration
Hyperkalemia	Muscle weakness, malaise, palpitations	Cardiac conduction disturbances, asystole, death	Impaired urinary excretion, mineralocorticoid or aldosterone deficiency, type IV renal tubular acidosis, spironolactone, ACE

			spironolactone, ACE inhibitors, rhabdomyolysis, massive blood transfusion, profound acidosis, tumor lysis syndrome
Hypokalemia	Ileus, muscle weakness, fatigue, parasthesias	Tetany, flaccid paralysis, hyporeflexia, ventricular tachycardia/ fibrillation, death	GI losses (vomiting, nasogastric tube suction), diuretics, hyperaldosteronism, diminished enteral intake
Hypercalcemia	Nausea, vomiting, constipation, fatigue, depression, confusion, muscle weakness	Nephrolithiasis, renal dysfunction, cardiac arrhythmias, shortened QT	Bone destruction, increase GI absorption, hyperparathyroidism, increased vitamin D from granulomatous disease
Hypocalcemia	Perioral numbness and tingling, muscle spasm	Tetany, laryngeal spasm, seizures, prolonged QT interval, torsades de pointes, complete heart block	Chronic renal failure, following parathyroidectomy
Hyperphosphatemia	Usually asymptomatic	Metastatic calcification of organs leading to widespread organ dysfunction	Renal insufficiency

Hypophosphatemia	Usually asymptomatic	Muscle weakness, cardiomyopathy, rhabdomyolysis, skeletal demineralization, respiratory insufficiency	Increased renal excretion, decreased intestinal absorption, intracellular shifts
Hypermagnesemia	Nausea, vomiting, cutaneous flushing	Muscle weakness, paralysis, cardiac conduction abnormalities	Renal insufficiency, iatrogenic (renacidin TM administration)
Hypomagnesemia	Weakness, tremors, irritability	Delirium, coma	Malabsorption, starvation, chronic diarrhea, hypercalcemia, chronic alcoholism

6. Water Homeostasis

Plasma osmolality is defined as the concentration of solute per kilogram of water. The normal range of plasma osmolality is 275-295 mOsm/kg H_2O. This normal range is regulated by osmoreceptors in the hypothalamus. When increases in plasma osmolality are sensed by these receptors, the posterior pituitary is stimulated to release ADH. This leads to thirst stimulation and increased permeability to water in the renal collecting ducts, which both effectively increase the extracellular volume.[1]

7. Abbreviations:

Renal Blood Flow (RBF)
Glomerular Filtration Rate (GFR)
Transglomerular hydrostatic pressure (TGP)
Renal Plasma Flow (RPF)
Glomerular Permeability (Lp)
Mean arterial pressure (MAP)
Tubuloglomerular feedback (TGF)
Proximal convoluted tubule (PCT)
Thin descending limb of Henle (DLH)
Thin ascending limb of Henle (ALH)
Thick ascending limb of Henle (TALH)
Antidiuretic hormone (ADH)
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Distal convoluted tubule (DCT)

References

1   Shoskes DA and McMahon AW. Renal Physiology and Pathophysiology. In: Kavoussi L, Novick A, Partin A, Peters C, eds. Campbell-Walsh Urology. 10th ed. Philadelphia, PA: Elsevier-Saunders; 2012:1025-1046.

2   ☆ Gilbert BR and Vaughan ED. A Urologist's View of Renal Pathophysiology Part I. AUA Update Series. 1988;VII(25):194-199.

3   ☆ Gilbert BR and Vaughan ED. A Urologist's View of Renal Pathophysiology Part 2. AUA Update Series. 1988;VII(26):202-207.

4   ☆ Novak TE, SM: Fluid, electrolyte and acid-base abnormalities in urological practice. AUA Update Series 2006; 25.