CHAPTER 29

Renal Physiology & Anesthesia

KEY CONCEPTS

1. The combined blood flow through both kidneys normally accounts for 20–25% of total cardiac output.
2. Autoregulation of renal blood flow normally occurs between mean arterial blood pressures of 80 and 180 mm Hg and is principally due to intrinsic myogenic responses of the afferent glomerular arterioles to blood pressure changes.
3. Renal synthesis of vasodilating prostaglandins (PGD_2, PGE_2, and PGI_2) is an important protective mechanism during periods of systemic hypotension and renal ischemia.
4. Dopamine and fenoldopam dilate afferent and efferent arterioles via D_1-receptor activation. Fenoldopam and low-dose dopamine infusion can at least partially reverse norepinephrine-induced renal vasoconstriction.
5. Reversible decreases in renal blood flow, glomerular filtration rate, urinary flow, and sodium excretion occur during both regional and general anesthesia. Acute kidney injury is less likely if an adequate intravascular volume and a normal blood pressure are maintained.
6. The endocrine response to surgery and anesthesia is at least partly responsible for transient fluid retention seen postoperatively in many patients.
7. Compound A, a breakdown product of sevoflurane, has been shown to cause renal damage in laboratory animals. Its accumulation in the breathing circuit is favored by low flow rates. No clinical study has detected significant renal injury in humans during sevoflurane anesthesia; nonetheless, some regulatory authorities recommend fresh gas flow of at least 2 L/min with sevoflurane to prevent this theoretical problem.
8. The pneumoperitoneum produced during laparoscopy causes an abdominal compartment syndrome–like state. The increase in intraabdominal pressure typically produces oliguria (or anuria) that is generally proportional to the insufflation pressures. Mechanisms include central venous compression (renal vein and vena cava); renal parenchymal compression; decreased cardiac output; and increases in plasma levels of renin, aldosterone, and antidiuretic hormone.

The kidneys play a vital role in regulating the volume and composition of body fluids, eliminating toxins, and elaborating hormones, including renin, erythropoietin, and the active form of vitamin D. Factors directly and indirectly related to operative procedures and to anesthetic management frequently have a physiologically significant impact on renal physiology and renal function, and may lead to perioperative fluid overload, hypovolemia, renal insufficiency, and kidney failure, which are major causes of perioperative morbidity and mortality.

Diuretics are frequently used in the perioperative period. Diuretics are commonly administered on a chronic basis to patients with cardiovascular disease, including hypertension and chronic heart failure, and to patients with liver and kidney disease. Diuretics may be used intraoperatively, particularly during neurosurgical, cardiac, major vascular, ophthalmic, and urological procedures. Familiarity with the various types of diuretics, their mechanisms of action, side effects, and potential anesthetic interactions, is therefore essential.

The Nephron

Each kidney is made up of approximately 1 million functional units called nephrons. Anatomically, a nephron consists of a tortuous tubule with at least six specialized segments. At its proximal end (the *renal corpuscle*, composed of a glomerulus and a Bowman's capsule), an ultrafiltrate of blood is formed, and as this fluid passes through the nephron, its volume and composition are modified by both the reabsorption and the secretion of solutes. The final product is eliminated as urine.

Nephrons are classified as *cortical* or *juxtamedullary* (see below), and the renal corpuscles of all nephrons are located in the renal cortex. The six major anatomical and functional divisions of the nephron are the renal corpuscle, the proximal convoluted tubule, the loop of Henle, the distal renal tubule, the collecting tubule, and the juxtaglomerular apparatus (**Figure 29–1** and **Table 29–1**).

The Renal Corpuscle

Each renal corpuscle contains a glomerulus, which is composed of tufts of capillaries that jut into Bowman's capsule, providing a large surface area for the filtration of blood. Blood flow is provided by a single afferent arteriole and is drained by a single efferent arteriole (see below). Endothelial cells of the glomeruli are separated from the epithelial cells of Bowman's capsule only by their fused basement membranes. The endothelial cells are perforated with relatively large fenestrae (70–100 nm), but the epithelial cells interdigitate tightly with one another, leaving relatively small filtration slits (about 25 nm). The two cell types with their basement membranes provide an effective filtration barrier to cells and large-molecular-weight substances. This barrier has multiple anionic sites that give it a net negative charge, favoring filtration of cations relative to anions. A third cell type, called *intraglomerular mesangial cells*, is located between the basement membrane and epithelial cells near adjacent capillaries. These contractile cells regulate glomerular blood flow and also exhibit phagocytic activity. They secrete various substances, absorb immune complexes, and contain contractile proteins that respond to vasoactive substance. Mesangial cells contract, reducing glomerular filtration, in response to angiotensin II, vasopressin, norepinephrine, histamine, endothelins, thromboxane A_2, leukotrienes (C_4 and D_4), prostaglandin F_2, and platelet-activating factor. They relax, thereby increasing glomerular filtration, in response to atrial natriuretic peptide (ANP), prostaglandin E_2, and dopaminergic agonists.

Glomerular filtration pressure (about 60 mm Hg) is normally approximately 60% of mean arterial pressure and is opposed by both plasma oncotic pressure (about 25 mm Hg) and renal interstitial pressure (about 10 mm Hg). Afferent and efferent arteriolar tone are both important in determining glomerular filtration pressure: filtration pressure is directly proportional to efferent arteriolar tone but inversely proportional to afferent tone. Approximately 20% of plasma is normally filtered as blood passes through the glomerulus.

The Proximal Tubule

Of the ultrafiltrate formed in Bowman's capsule 65–75% is normally reabsorbed isotonically (proportional amounts of water and sodium) in the

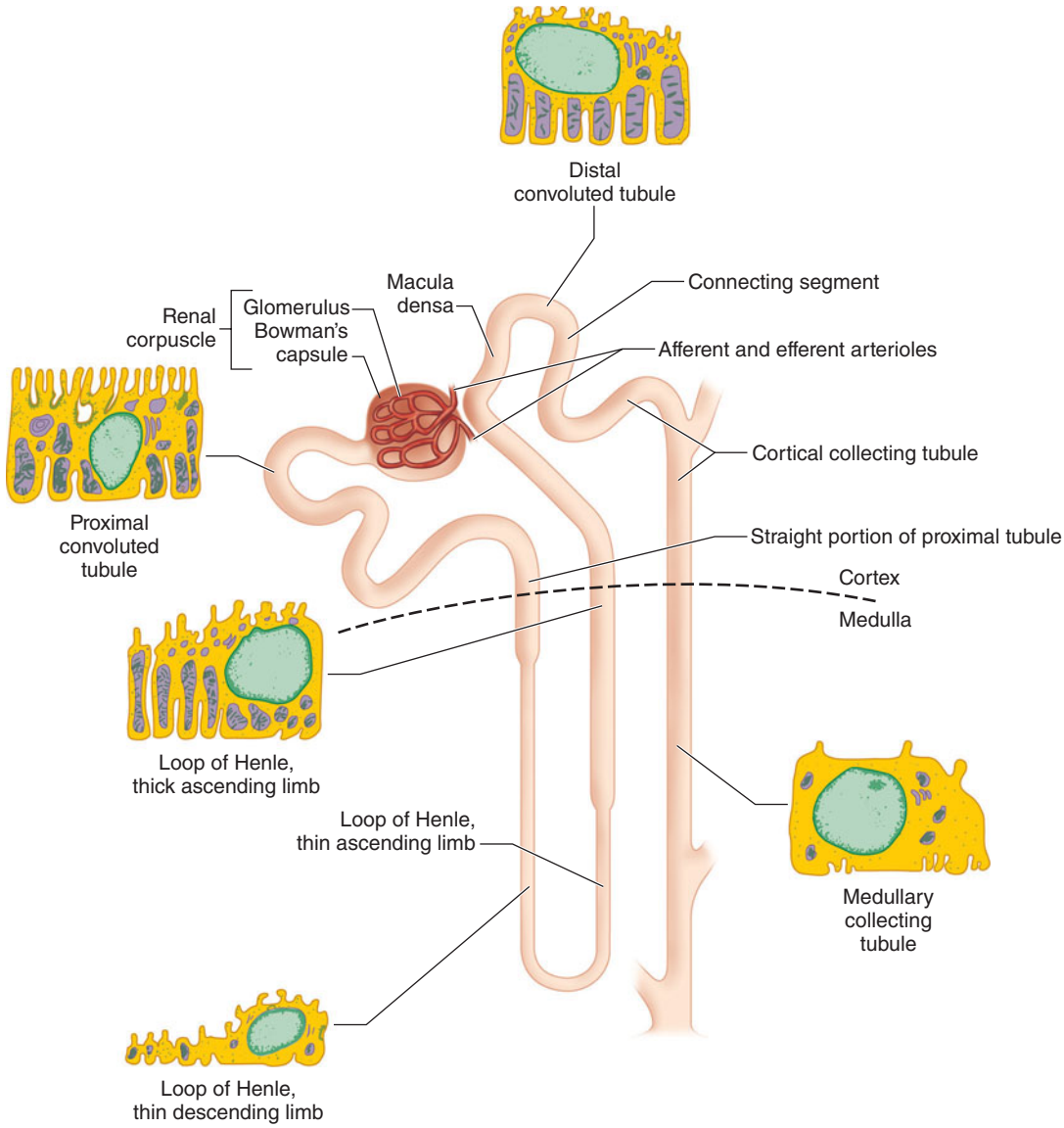

FIGURE 29–1 Major anatomic divisions of the nephron. (Reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 24th ed. McGraw-Hill, 2012.)

proximal renal tubules (Figure 29–2). To be reabsorbed, most substances must first traverse the tubular (apical) side of the cell membrane, and then cross the basolateral cell membrane into the renal interstitium before entering peritubular capillaries. The major function of the proximal tubule is Na^+ reabsorption. Sodium is actively transported out of proximal tubular cells at their capillary side by membrane-bound Na^+–K^+-adenosine triphosphatase (Na^+–K^+-ATPase) (Figure 29–3). The resulting low intracellular concentration of Na^+ allows passive movement of Na^+ down its gradient from tubular fluid into epithelial cells. Angiotensin II and norepinephrine enhance Na^+ reabsorption in the

TABLE 29–1 Functional divisions of a nephron.[1]

Segment	Function
Renal corpuscle (glomerulus, Bowman's capsule)	Ultrafiltration of blood
Proximal tubule	Reabsorption Sodium[2] chloride Water Bicarbonate Glucose, protein, amino acids Potassium, magnesium, calcium Phosphates,[3] uric acid, urea Secretion Organic anions Organic cations Ammonia production
Loop of Henle	Reabsorption Sodium, chloride Water Potassium, calcium, magnesium Countercurrent multiplier
Distal tubule	Reabsorption Sodium[4] chloride Water Potassium Calcium[5] Bicarbonate Secretion Hydrogen ion[4] Potassium[4] Calcium
Collecting tubule	Reabsorption Sodium[4,6] chloride Water[6,7] Potassium Bicarbonate Secretion Potassium[4] Hydrogen ion[4] Ammonia production
Juxtaglomerular apparatus	Secretion of renin

[1]Adapted from Rose BD: *Clinical Physiology of Acid-Base and Electrolyte Disorders,* 3rd ed. McGraw-Hill, 1989.
[2]Partially augmented by angiotensin II.
[3]Inhibited by parathyroid hormone.
[4]At least partly aldosterone mediated.
[5]Augmented by parathyroid hormone.
[6]Inhibited by atrial natriuretic peptide.
[7]Antidiuretic hormone mediated.

early proximal tubule. In contrast, dopamine and fenoldopam decrease the proximal reabsorption of sodium via D_1-receptor activation.

Sodium reabsorption is coupled with the reabsorption of other solutes and the secretion of H^+ (Figure 29–3). Specific carrier proteins use the low concentration of Na^+ inside cells to transport phosphate, glucose, and amino acids. The net loss of intracellular positive charges, the result of Na^+–K^+-ATPase activity (exchanging $3Na^+$ for $2K^+$), favors the absorption of other cations (K^+, Ca^{2+}, and Mg^{2+}). Thus, the Na^+–K^+-ATPase at the basolateral side of the renal cells provides the energy for the reabsorption of most solutes. Sodium reabsorption at the luminal membrane is also coupled with countertransport (secretion) of H^+. The latter mechanism is responsible for reabsorption of 90% of the filtered bicarbonate ions (see Figure 50–3). Unlike other solutes, chloride can traverse the tight junctions between adjacent tubular epithelial cells, and accordingly, is passively resorbed via its concentration gradient. Active chloride reabsorption may also take place as a result of a K^+–Cl^- cotransporter that extrudes both ions at the capillary side of the cell membrane (Figure 29–3). Water moves passively out the proximal tubule along osmotic gradients. Apical membranes of epithelial cells contain specialized water channels, composed of a membrane protein called aquaporin-1, that facilitate water movement.

The proximal tubules are capable of secreting organic cations and anions. Organic cations such as creatinine, cimetidine, and quinidine may share the same pump mechanism and thus can compete for excretion with one another. Organic anions such as urate, ketoacids, penicillins, cephalosporins, diuretics, salicylates, and most radiocontrast dyes also share common secretory mechanisms. Both pumps probably play a major role in the elimination of many circulating toxins. Low-molecular-weight proteins, which are filtered by glomeruli, are normally reabsorbed by proximal tubular cells, to be metabolized intracellularly.

The Loop of Henle

The loop of Henle consists of *descending* and *ascending* portions. They are responsible for

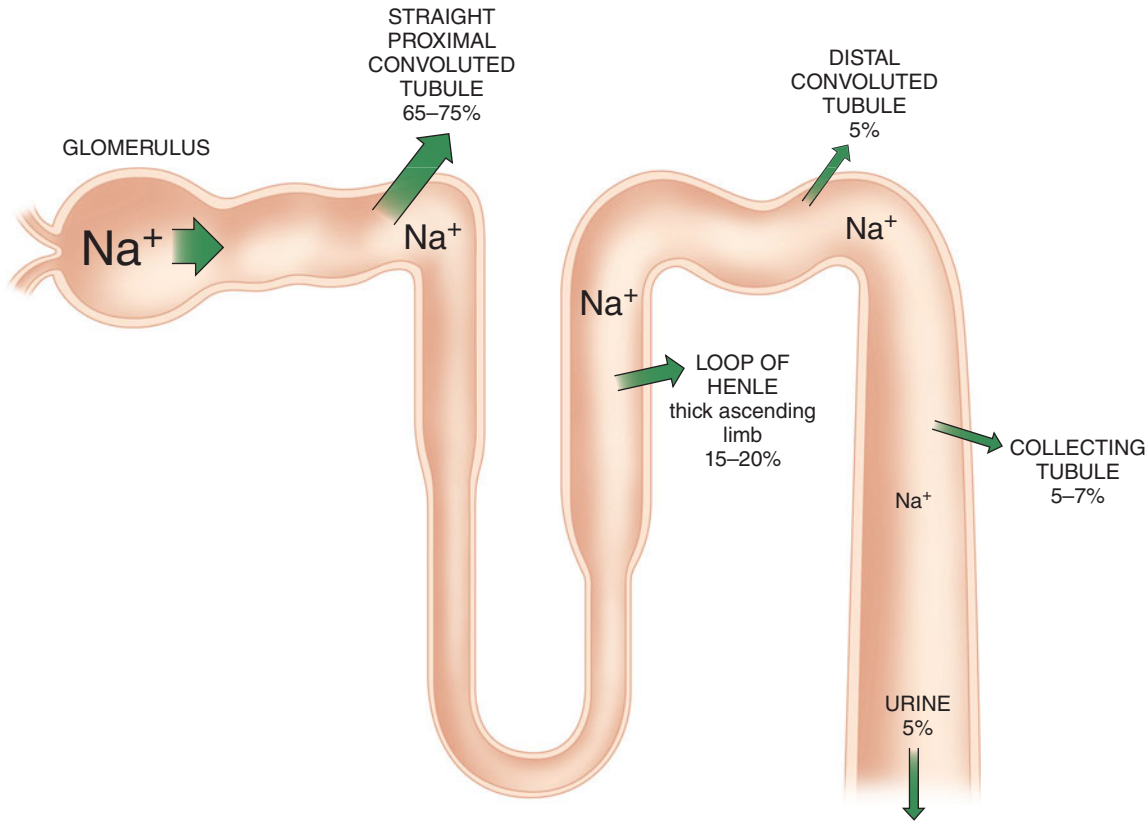

FIGURE 29–2 Sodium reabsorption in the nephron. Numbers represent the percentage of the filtered sodium reabsorbed at each site. (Reproduced, with permission, from Cogan MG: *Fluid and Electrolytes: Physiology and Pathophysiology.* Appleton & Lange, 1991.)

maintaining a hypertonic medullary interstitium and also indirectly provide the collecting tubules with the ability to concentrate urine. The thin descending segment is a continuation of the proximal tubule and descends from the renal cortex into the renal medulla. In the medulla, the descending portion acutely turns back upon itself and rises back up toward the cortex as the ascending portion. The ascending portion consists of a functionally distinct, thin ascending limb, a medullary thick ascending limb, and a cortical thick ascending limb (Figure 29–1). *Cortical* nephrons have relatively short loops of Henle which extend only into the more superficial regions of the renal medulla and often lack a thin ascending limb. *Juxtamedullary* nephrons, which have renal corpuscles located near the renal medulla, possess loops of Henle that project deeply into the renal medulla. Cortical nephrons outnumber juxtamedullary nephrons by approximately 7:1.

Only 25–35% of the ultrafiltrate formed in Bowman's capsule normally reaches the loop of Henle. Once there, 15–20% of the filtered sodium load is normally reabsorbed in the loop of Henle. With the notable exception of the ascending thick segments, solute and water reabsorption in the loop of Henle is passive and follows concentration and osmotic gradients, respectively. In the ascending thick segment, however, Na^+ and Cl^- are reabsorbed in excess of water; moreover, Na^+ reabsorption in this part of the nephron is directly coupled to both K^+ and Cl^- reabsorption (**Figure 29–4**), and $[Cl^-]$ in tubular fluid appears to be the rate-limiting factor. Active Na^+ reabsorption still results from

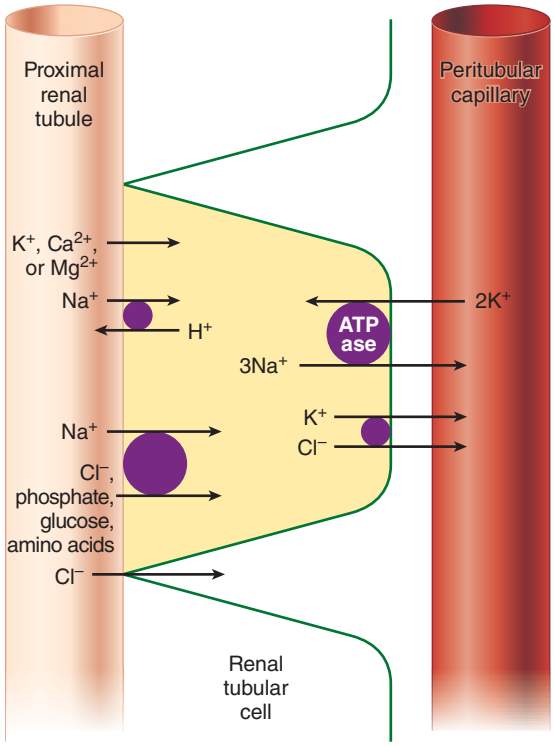

FIGURE 29–3 Reabsorption of solutes in proximal tubules. Note that Na^+–K^+-ATPase supplies the energy for reabsorption of most solutes by maintaining a low intracellular concentration of sodium.

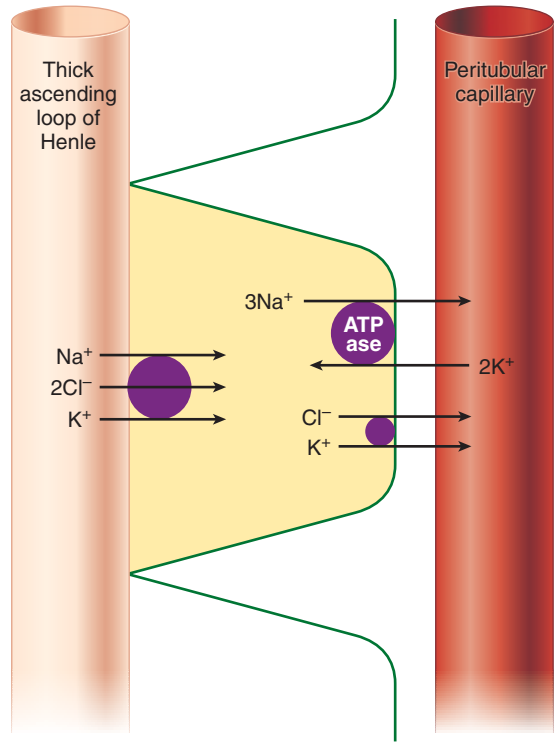

FIGURE 29–4 Sodium and chloride reabsorption in the thick ascending loop of Henle. All four sites on the luminal carrier protein must be occupied for transport to occur. The rate-limiting factor appears to be chloride concentration in tubular fluid.

Na^+–K^+-ATPase activity on the capillary side of epithelial cells.

Unlike the descending limb and the thin ascending limb, the thick parts of the ascending limb are impermeable to water. As a result, tubular fluid flowing out of the loop of Henle is hypotonic (100–200 mOsm/L) and the interstitium surrounding the loop of Henle is therefore hypertonic. A *countercurrent multiplier mechanism* is established such that both the tubular fluid and medullary interstitium become increasingly hypertonic with increasing depth into the medulla (Figure 29–5). Urea concentrations also increase within the medulla and contribute to the hypertonicity. The countercurrent mechanism includes the loop of Henle, the cortical and medullary collecting tubules, and their respective capillaries (vasarecta).

The thick ascending loop of Henle is also an important site for calcium and magnesium reabsorption, and parathyroid hormone may augment calcium reabsorption at this location.

The Distal Tubule

The distal tubule receives hypotonic fluid from the loop of Henle and is normally responsible for only minor modifications of tubular fluid. In contrast to more proximal portions, the distal nephron has very tight junctions between tubular cells and is relatively impermeable to water and sodium. It can therefore maintain the gradients generated by the loop of Henle. Sodium reabsorption in the distal tubule normally accounts for only about 5% of the filtered sodium load. As in other parts of the nephron, the energy is derived from Na^+–K^+-ATPase activity on the capillary side, but on the luminal side Na^+ is reabsorbed by an Na^+–Cl^- carrier. Sodium reabsorption in this segment is directly proportional to Na^+

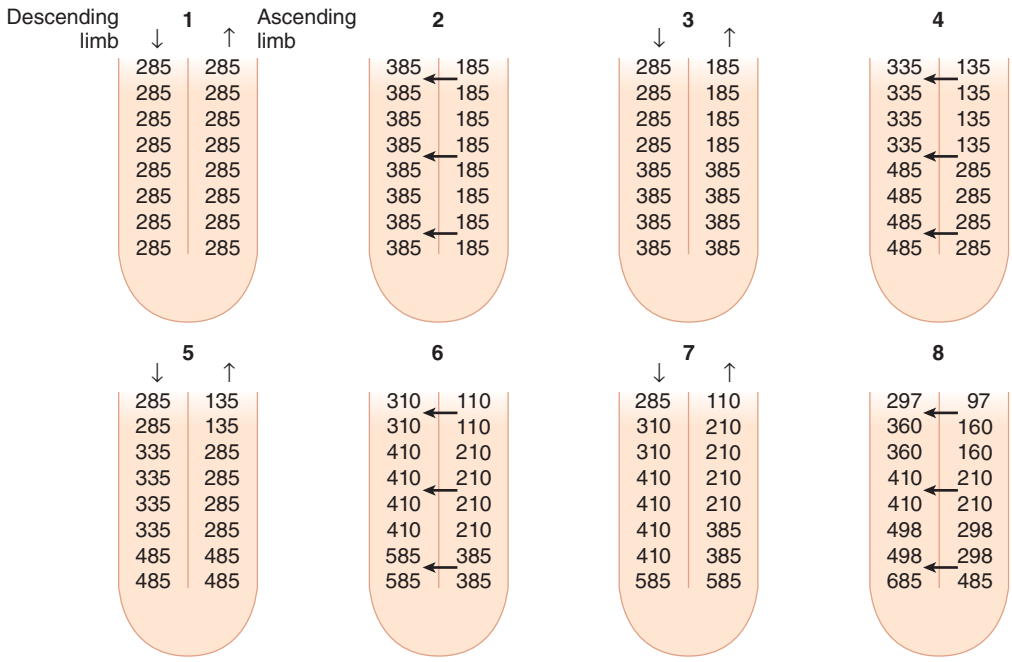

FIGURE 29–5 The countercurrent multiplier mechanism. This mechanism is dependent on differential permeability and transport characteristics between the descending and ascending limbs. The descending limb and the thin ascending limb are permeable to water, Na^+, Cl^-, and urea. The thick ascending limb is impermeable to water and urea, actively reabsorbs Na^+ and Cl^-, and therefore can generate an osmotic gradient. This figure depicts from "time zero," a progressive 200-mOsm/kg gradient between the descending and ascending limbs. Note that as urine flows, the gradient remains unchanged but the osmolality progressively increases at the bottom of the loop. (Reproduced, with permission, from Pitts RF: *Physiology of the Kidney and Body Fluids,* 3rd ed. Year Book, 1974.)

delivery. The distal tubule is the major site of parathyroid hormone–and vitamin D–mediated calcium reabsorption.

The latter portion of the distal tubule is referred to as the *connecting segment*. Although it is also involved in hormone-mediated calcium reabsorption, unlike more proximal portions, it participates in aldosterone-mediated Na^+ reabsorption.

The Collecting Tubule

The collecting tubule can be divided into cortical and medullary portions. Together, they normally account for the reabsorption of 5–7% of the filtered sodium load.

A. Cortical Collecting Tubule

This part of the nephron consists of two cell types: (1) principal cells (P cells), which primarily secrete potassium and participate in aldosterone-stimulated Na^+ reabsorption, and (2) intercalated cells (I cells), which are responsible for acid–base regulation. Because P cells reabsorb Na^+ via an electrogenic pump, either Cl^- must also be reabsorbed or K^+ must be secreted to maintain electroneutrality. Increased intracellular $[K^+]$ favors K^+ secretion. Aldosterone enhances Na^+–K^+-ATPase activity in this part of the nephron by increasing the number of open K^+ and Na^+ channels in the luminal membrane. Aldosterone also enhances the H^+-secreting ATPase on the luminal border of I cells (**Figure 29–6**). I cells additionally have a luminal K^+–H^+-ATPase pump, which reabsorbs K^+ and secretes H^+, and some I cells are capable of secreting bicarbonate ion in response to large alkaline loads.

B. Medullary Collecting Tubule

The medullary collecting tubule courses down from the cortex through the hypertonic medulla before

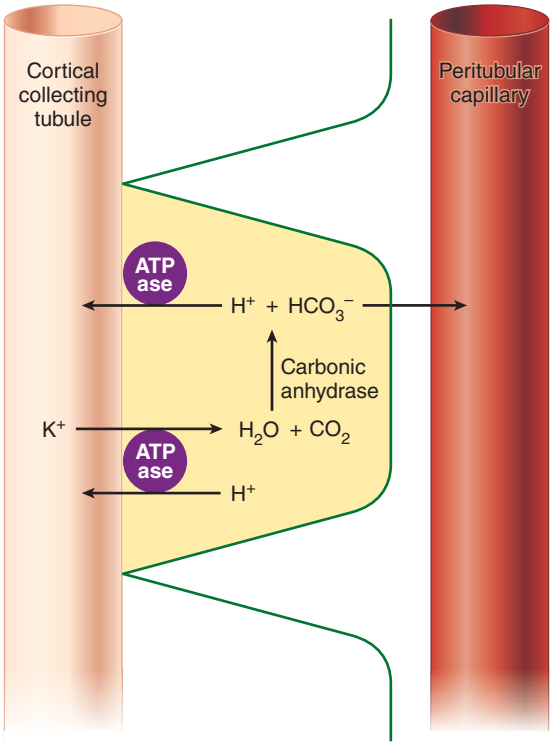

FIGURE 29–6 Secretion of hydrogen ions and reabsorption of bicarbonate and potassium in the cortical collecting tubule.

joining collecting tubules from other nephrons to form a single ureter in each kidney. This part of the collecting tubule is the principal site of action for antidiuretic hormone (ADH), also called arginine vasopressin (AVP). ADH stimulates the expression of a water channel protein, aquaporin-2, in the cell membrane. The permeability of the luminal membrane to water is entirely dependent on the presence of ADH (see Chapter 49). Dehydration increases ADH secretion, rendering the luminal membrane permeable to water. As a result, water is osmotically drawn out of the tubular fluid passing through the medulla, resulting in production of concentrated urine (up to 1400 mOsm/L). Conversely, adequate hydration suppresses ADH secretion, allowing fluid in the collecting tubules to pass through the medulla relatively unchanged and to remain hypotonic (100–200 mOsm/L). This part of the nephron is responsible for acidifying urine; the hydrogen ions secreted are excreted in the form of titratable acids (phosphates) and ammonium ions (see Chapter 50).

C. Role of the Collecting Tubule in Maintaining a Hypertonic Medulla

Differences in permeability to urea in the cortical and medullary collecting tubules account for up to half the hypertonicity of the renal medulla. Cortical collecting tubules are freely permeable to urea, whereas medullary collecting tubules are normally impermeable. In the presence of ADH, the innermost part of the medullary collecting tubules becomes even more permeable to urea. Thus, when ADH is secreted, water moves out of the collecting tubules and the urea becomes highly concentrated. Urea can then diffuse out deeply into the medullary interstitium, increasing its tonicity.

The Juxtaglomerular Apparatus

This small organ within each nephron consists of a specialized segment of the afferent arteriole, containing juxtaglomerular cells within its wall, and the end of the thick, ascending cortical segment of the loop of Henle, the macula densa (Figure 29–7). Juxtaglomerular cells contain the enzyme renin and are innervated by the sympathetic nervous system. Release of renin depends on β_1-adrenergic sympathetic stimulation, changes in afferent arteriolar wall

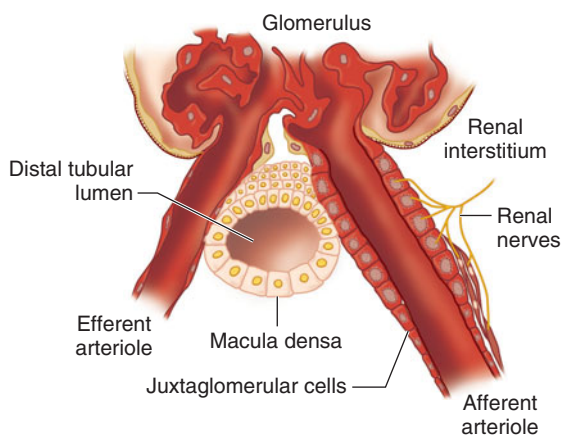

FIGURE 29–7 The juxtaglomerular apparatus. (Reproduced, with permission, from Ganong WF: *Review of Medical Physiology,* 20th ed. McGraw-Hill, 2001.)

pressure (see Chapter 49), and changes in chloride flow past the macula densa. Renin released into the bloodstream catalyzes the conversion of angiotensinogen, a protein synthesized by the liver, to angiotensin I. This inert decapeptide is then rapidly converted, primarily in the lungs, by angiotensin-converting enzyme (ACE) to form the octapeptide angiotensin II. Angiotensin II plays a major role in blood pressure regulation (see Chapter 15) and aldosterone secretion (see Chapter 49). Proximal renal tubular cells have converting enzyme as well as angiotensin II receptors. Moreover, intrarenal formation of angiotensin II enhances sodium reabsorption in proximal tubules. Some extrarenal production of renin and angiotensin II also takes place in the vascular endothelium, the adrenal glands, and the brain.

The Renal Circulation

Renal function is intimately related to renal blood flow (RBF). In fact, the kidneys are the only organs for which oxygen consumption is determined by blood flow; the reverse is true in other organs. The combined blood flow through both kidneys normally accounts for 20–25% of total cardiac output. Approximately 80% of RBF normally goes to cortical nephrons, and only 10–15% goes to juxtamedullary nephrons. The renal cortex extracts relatively little oxygen, having an oxygen tension of about 50 mm Hg, because of the relatively high blood flow with a mostly filtration function. In contrast, the renal medulla maintains high metabolic activity because of solute reabsorption and requires low blood flow to maintain high osmotic gradients. The medulla has an oxygen tension of only about 15 mm Hg and is relatively vulnerable to ischemia.

Redistribution of RBF away from cortical nephrons with short loops of Henle to larger juxtamedullary nephrons with long loops occurs under certain conditions. Sympathetic stimulation, increased levels of catecholamines and angiotensin II, and heart failure can cause redistribution of RBF to the medulla and is associated with sodium retention.

In most individuals, each kidney is supplied by a single renal artery arising from the aorta. The renal artery then divides at the renal pelvis into interlobar arteries, which in turn give rise to arcuate arteries at the junction between the renal cortex and medulla (**Figure 29–8**). Arcuate arteries further divide into interlobular branches that eventually supply each nephron via a single afferent arteriole. Blood from each glomerular capillary tuft is drained via a single efferent arteriole and then travels alongside adjacent renal tubules in a second *peritubular* system of capillaries. In contrast to the glomerular capillaries, which favor filtration, peritubular capillaries are primarily "reabsorptive." Venules draining the second capillary plexus finally return blood to the inferior vena cava via a single renal vein on each side.

RENAL BLOOD FLOW & GLOMERULAR FILTRATION

Clearance

The concept of clearance is frequently used in measurements of RBF and the glomerular filtration rate (GFR). The renal clearance of a substance is defined as the volume of blood that is completely cleared of that substance per unit of time (usually, per minute).

Renal Blood Flow

Renal plasma flow (RPF) is most commonly measured by *p*-aminohippurate (PAH) clearance. PAH at low plasma concentrations can be assumed to be completely cleared from plasma by filtration and secretion in one passage through the kidneys. Consequently,

$$\text{RPF} = \text{Clearance of PAH} = \left(\frac{[\text{PAH}]_U}{[\text{PAH}]_P}\right) \times \text{Urine flow}$$

where $[\text{PAH}]_U$ = urinary concentration of PAH and $[\text{PAH}]_P$ = plasma PAH concentration.

If the hematocrit (measured as a decimal rather than as a percent) is known, then

$$\text{RBF} = \frac{\text{RPF}}{(1 - \text{Hematocrit})}$$

RPF and RBF are normally about 660 and 1200 mL/min, respectively.

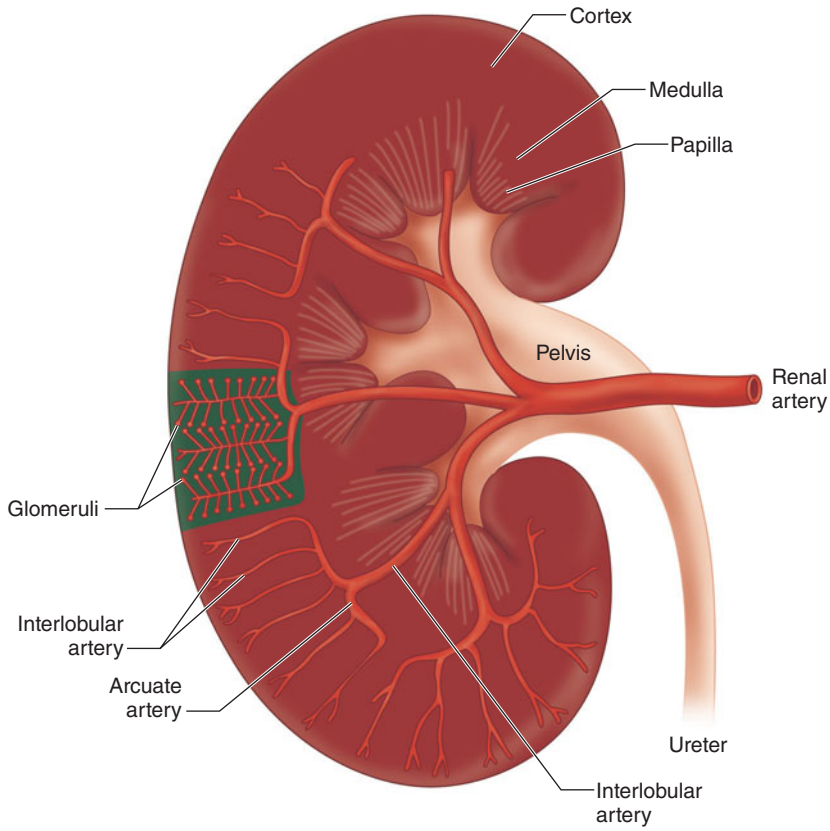

FIGURE 29–8 The renal circulation. (Reproduced, with permission, from Leaf A, Cotran RS: *Renal Pathophysiology.* Oxford University Press, 1976.)

Glomerular Filtration Rate

The GFR, the volume of fluid filtered from the glomerular capillaries into Bowman's capsule per unit time, is normally about 20% of RPF. Clearance of inulin, a fructose polysaccharide that is completely filtered but is neither secreted nor reabsorbed, is a good measure of GFR. Normal values for GFR are about 120 ± 25 mL/min in men and 95 ± 20 mL/min in women. Although less accurate than measuring inulin clearance, creatinine clearance is a much more practical measurement of GFR (see below). Creatinine clearance tends to overestimate GFR because some creatinine is normally secreted by renal tubules. Creatinine is a product of phosphocreatine breakdown in muscle. Creatinine clearance is calculated as follows:

$$\text{Creatinine clearance} = \frac{([\text{Creatinine}]_U \times \text{Urinary flow rate})}{[\text{Creatinine}]_P}$$

where $[\text{creatinine}]_U$ = creatinine concentration in urine and $[\text{creatinine}]_P$ = creatinine concentration in plasma.

The ratio of GFR to RPF is called the *filtration fraction* (FF) and is normally 20%. GFR is dependent on the relative tones of both the afferent and efferent arterioles (see above). Afferent arteriolar dilation or efferent arteriolar vasoconstriction can increase the FF and maintain GFR, even when RPF decreases. Afferent arteriolar tone appears to be responsible for maintaining a relatively constant GFR over a wide range of blood pressures.

Control Mechanisms

Regulation of RBF represents a complex interplay between intrinsic autoregulation, tubuloglomerular balance, and hormonal and neuronal influences.

A. Intrinsic Regulation

2 Autoregulation of RBF normally occurs between mean arterial blood pressures of 80 and 180 mm Hg and is principally due to intrinsic myogenic responses of the afferent glomerular arterioles to blood pressure changes. Within these limits, RBF (and GFR) can be kept relatively constant by afferent arteriolar vasoconstriction or vasodilation. Outside the autoregulation limits, RBF becomes pressure dependent. Glomerular filtration generally ceases when mean systemic arterial pressure is less than 40–50 mm Hg.

B. Tubuloglomerular Balance and Feedback

Tubuloglomerular feedback plays an important role in maintaining constant GFR over a wide range of perfusion pressures. Increased tubular flow tends to result in reduced GFR; conversely, decreased tubular flow tends to result in increased GFR. Although the mechanism is poorly understood, the macula densa appears to be responsible for tubuloglomerular feedback by inducing reflex changes in afferent arteriolar tone and possibly glomerular capillary permeability. Angiotensin II probably plays a permissive role in this mechanism. Local release of adenosine, which occurs in response to volume expansion, may inhibit renin release and dilate the afferent arteriole.

C. Hormonal Regulation

Increases in afferent glomerular arteriolar pressure stimulate renin release and formation of angiotensin II. Angiotensin II causes generalized arterial vasoconstriction and secondarily reduces RBF. Both afferent and efferent glomerular arterioles are constricted, but because the efferent arteriole is smaller, its resistance becomes greater than that of the afferent arteriole; GFR therefore tends to be relatively preserved. Very high levels of angiotensin II constrict both arterioles and can markedly decrease GFR. Adrenal catecholamines (epinephrine and norepinephrine) directly and preferentially increase afferent arteriolar tone but usually do not cause marked decreases in GFR because these agents also increase renin release and angiotensin II formation. Relative preservation of GFR during increased aldosterone or catecholamine secretion appears at least partly to be mediated by angiotensin-induced prostaglandin synthesis because it can be blocked by inhibitors of prostaglandin synthesis such as nonsteroidal antiinflammatory drugs (NSAIDs).

3 Renal synthesis of vasodilating prostaglandins (PGD_2, PGE_2, and PGI_2) is an important protective mechanism during periods of systemic hypotension and renal ischemia.

ANP is released from atrial myocytes in response to atrial distention. ANP is a direct smooth muscle dilator and antagonizes the vasoconstrictive action of norepinephrine and angiotensin II. It preferentially dilates the afferent glomerular arteriole, constricts the efferent glomerular arteriole, and relaxes mesangial cells, effectively increasing GFR (see Chapter 49). ANP also inhibits both the release of renin and angiotensin-induced secretion of aldosterone, and antagonizes the action of aldosterone in the distal and collecting tubules.

D. Neuronal and Paracrine Regulation

Sympathetic outflow from the spinal cord at the level of T4–L1 reaches the kidneys via the celiac and renal plexuses. Sympathetic nerves innervate the juxtaglomerular apparatus (β_1) as well as the renal vasculature (α_1). This innervation is largely responsible for stress-induced reductions in RBF (below). α_1-Adrenergic receptors enhance sodium reabsorption in proximal tubules, whereas α_2 receptors decrease such reabsorption and promote water excretion.

4 Dopamine and fenoldopam dilate afferent and efferent arterioles via D_1-receptor activation. Unlike dopamine, fenoldopam is selective for the D_1-receptor. Fenoldopam and low-dose dopamine infusion can at least partially reverse norepinephrine-induced renal vasoconstriction. Activation of D_2-receptors on presynaptic postganglionic sympathetic neurons can also vasodilate arterioles through inhibition of norepinephrine secretion (negative feedback). Dopamine is formed extraneuronally in the proximal tubule cells from circulating L-3,4-dihydroxyphenylalanine (L-dopa). Dopamine is released into the tubule where it can bind dopaminergic receptors to reduce proximal reabsorption of Na^+.

Effects of Anesthesia & Surgery on Renal Function

Acute kidney injury (AKI) is a common perioperative problem. It occurs in 1–5% of all hospitalized patients and is a major contributor to increased hospital length of stay, markedly increasing morbidity, mortality, and cost of care. Patients may develop AKI and kidney failure secondary to intrinsic kidney disease (Table 29–2). Risk factors for AKI in the perioperative setting include preexisting renal impairment, diabetes mellitus, cardiovascular disease, hypovolemia, and use of potentially nephrotoxic medication by elderly patients. The risk index in Table 29–3 identifies preoperative predictors of AKI following general surgery.

Clinical studies attempting to define the effects of anesthetic agents on renal function are complicated and difficult. However, several conclusions can be stated:

5 1. Reversible decreases in RBF, GFR, urinary flow, and sodium excretion occur during both regional and general anesthesia.

TABLE 29–2 Causes of acute kidney injury secondary to intrinsic kidney disease.[1]

Vascular Effects	Renal Parenchymal Effects
Hemodynamic effects	**Glomerular diseases**
Acute kidney failure (eg, in elderly patients and those taking nonsteroidal antiinflammatory drugs [NSAIDs])	Rapidly progressive glomerulonephritis (systemic vasculitis, Goodpasture's disease, systemic lupus erythematosus, other forms of glomerulonephritis)
Contrast agent–induced (producing renal vasoconstriction and avid sodium retention)	Hemolytic uremic syndrome
Hepatorenal syndrome	Cryoglobulinemia
Cirrhosis (producing intense renal vasoconstriction and sodium retention)	**Malignant hypertension**
Impaired renal perfusion and autoregulation	Untreated primary ("essential") hypertension
Angiotensin-converting enzyme inhibitors, NSAIDs	Chronic glomerulonephritis
plus	**Acute tubular necrosis**
Atherosclerotic renal vascular disease or hypovolemia	Surgery (general, cardiac, vascular) Obstetric complications
Abdominal compartment syndrome	Sepsis
Postoperative abdominal exploration	Acute heart failure
Tense ascites	Burns
Atheroembolism ("cholesterol embolism")	**Rhabdomyolysis**
Angiography	Post–crush injury
Anticoagulation	Drug overdose
Thrombolysis	Status epilepticus
Renal embolism	**Osmotic damage to proximal tubular cells**
Endocarditis	Sucrose-containing intravenous immunoglobulin solutions
Cardiac thrombus	**Acute pyelonephritis**
Renal vein thrombosis	Infection (eg, in patients with diabetes and partial obstruction from papillary necrosis)
Malignancy	**Myeloma**
Preexisting nephritis syndrome	Cast nephropathy
	Light-chain deposition disease
	Amyloidosis
	Sepsis
	Interstitial nephropathy
	Drug-induced (aminoglycosides, amphotericin, and many other agents)
	Acute interstitial nephritis
	Urate nephropathy
	Chemotherapy for acute leukemia or lymphoma
	Hypercalcemia
	Sarcoidosis
	Milk-alkali syndrome

[1]Data from Armitage AJ, Tomson C: Acute renal failure. Medicine (UK ed. Abingdon) 2003;31:43.

TABLE 29–3 Acute kidney injury risk index for patients undergoing general surgery.[1,2]

Risk Factor
• Age ≥56 y
• Male sex
• Active congestive heart failure
• Ascites
• Hypertension
• Emergency surgery
• Intraperitoneal surgery
• Renal insufficiency—mild or moderate[3]
• Diabetes mellitus—oral or insulin therapy

[1]Reproduced, with permission, from Kheterpal S, Tremper KK, Heung M, et al: Development and validation of an acute kidney injury risk index for patients undergoing general surgery. Results from a national data set. Anesthesiology 2009;110:505.

[2]Risk Index classification is based on the number of risk factors present: class I (0–2 risk factors), class II (3 risk factors), class III (4 risk factors), class IV (5 risk factors), class V (≥6 risk factors).

[3]Preoperative serum creatinine >1.2 mg/dL.

2. Such changes are usually less pronounced during regional anesthesia.
3. Most of these changes are indirect and are mediated by autonomic and hormonal responses to surgery and anesthesia.
4. AKI is less likely when an adequate intravascular volume and a normal blood pressure are maintained.
5. There is no evidence that currently utilized vapor anesthetic agents cause AKI in patients. However, several studies have reported that compound A, a breakdown product of sevoflurane, produces renal toxicity when administered at low flow rates in laboratory animals.

INDIRECT EFFECTS

Cardiovascular

Most inhalation and intravenous anesthetics produce concentration-dependent cardiac depression or vasodilation; therefore they are capable of decreasing systemic blood pressure. Depending on the level of sympathetic blockade, spinal or epidural anesthesia may cause a drop in systemic blood pressure secondary to decreased cardiac output as a result of decreased sympathetic tone. This leads to increased pooling of blood and decreased systemic vascular resistance, decreased heart rate, and decreased cardiac output. Decreases in blood pressure below the limits of autoregulation reduce RBF, GFR, urinary flow, and sodium excretion, and this adverse impact on renal function can be reversed by administration of pressor agents and intravenous fluids.

Neurologic

Increased sympathetic tone commonly occurs in the perioperative period as a result of anxiety, pain, light anesthesia, and surgical stimulation. Heightened sympathetic activity increases renal vascular resistance and activates several hormonal systems (see below), reducing RBF, GFR, and urine output.

Endocrine

Endocrine changes during sedation and general anesthesia are a component of the stress response induced by factors that may include anxiety, pain, surgical stimulation, circulatory depression, hypoxia, acidosis, and hypothermia. Increases in epinephrine and norepinephrine, renin, angiotensin II, aldosterone, ADH, adrenocorticotropic hormone, and cortisol are common. Catecholamines, ADH, and angiotensin II all reduce RBF by inducing renal arterial constriction. Aldosterone enhances sodium reabsorption in the distal tubule and collecting tubule, resulting in sodium retention and expansion of the extracellular fluid compartment. Nonosmotic release of ADH also favors water retention and may result in hyponatremia. The endocrine response to surgery and anesthesia is at least partly responsible for transient fluid retention seen postoperatively in many patients.

DIRECT ANESTHETIC EFFECTS

The direct effects of anesthetics on renal function are minor compared with the secondary effects described above.

Volatile Agents

Halothane, sevoflurane, desflurane, and isoflurane decrease renal vascular resistance. As previously noted, compound A, a breakdown product of sevoflurane, has been shown to cause renal

damage in laboratory animals. Its accumulation in the breathing circuit is favored by low flow rates. No clinical study has detected significant renal injury in humans during sevoflurane anesthesia; nonetheless, some regulatory authorities recommend fresh gas flow of at least 2 L/min with sevoflurane to prevent this theoretical problem.

Intravenous Agents

Opioids and propofol exhibit minor, if any, effects on the kidney when used alone. Ketamine minimally affects renal function and may, relative to other anesthetic agents, preserve renal function during hemorrhagic hypovolemia. Agents with α-adrenergic blocking activity may prevent catecholamine-induced redistribution of RBF. Drugs with antidopaminergic activity—such as metoclopramide, phenothiazines, and droperidol—may impair the renal response to dopamine. Inhibition of prostaglandin synthesis by NSAIDs such as ketorolac prevents renal production of vasodilatory prostaglandins in patients with high levels of angiotensin II and norepinephrine; attenuation of prostaglandin synthesis in this setting may result in AKI. ACE inhibitors block the protective effects of angiotensin II and may result in reductions in GFR during anesthesia.

Other Drugs

Many medications, including radiocontrast agents, used in the perioperative period can adversely affect renal function, particularly in the setting of preexisting renal dysfunction (Table 29–4). Mechanisms of injury include vasoconstriction, direct tubular injury, drug-induced immunological and inflammatory responses, and renal microvascular or tubular obstruction. In addition to intravenous hydration, pretreatment with *N*-acetylcysteine (600 mg orally every 12 h in four doses beginning prior to contrast administration) has been shown to decrease the risk of radiocontrast agent–induced AKI in patients with preexisting renal dysfunction. *N*-Acetylcysteine's protective action may be due to its free radical scavenging or sulfhydryl donor (reducing) properties. Fenoldopam, mannitol, loop diuretics, and low-dose dopamine infusion do not help maintain renal function or confer protection against AKI, and *N*-acetylcysteine has not been shown to be protective in the perioperative setting except in patients who receive radiocontrast dyes.

TABLE 29–4 Drugs and toxins associated with acute kidney injury.[1]

Type of Injury	Drug or Toxin
Decreased renal perfusion	Nonsteroidal antiinflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors, radiocontrast agents, amphotericin B, cyclosporine, tacrolimus
Direct tubular injury	Aminoglycosides, radiocontrast agents, amphotericin B, methotrexate, cisplatin, foscarnet, pentamidine, heavy metals, myoglobin, hemoglobin, intravenous immunoglobulin, HIV protease inhibitors
Intratubular obstruction	Radiocontrast agents, methotrexate, acyclovir, sulfonamides, ethylene glycol, uric acid, cocaine, lovastatin
Immunological–Inflammatory	Penicillin, cephalosporins, allopurinol, NSAIDs, sulfonamides, diuretics, rifampin, ciprofloxacin, cimetidine, proton pump inhibitors, tetracycline, phenytoin

[1]Reproduced, with permission, from Anderson RJ, Barry DW: Clinical and laboratory diagnosis of acute renal failure. Best Pract Res Clin Anaesthesiol 2004;18:1.

DIRECT SURGICAL EFFECTS

In addition to the physiological changes associated with the neuroendocrine stress response to surgery, certain surgical procedures can significantly alter renal physiology. The pneumoperitoneum produced during laparoscopy creates an abdominal compartment syndrome–like state. The increase in intraabdominal pressure typically produces oliguria (or anuria) that is generally proportional to the insufflation pressures. Mechanisms include central venous compression (renal vein and vena cava); renal parenchymal compression; decreased cardiac output; and increases in plasma levels of renin, aldosterone, and ADH. Abdominal compartment syndrome can also be produced by

severe intraabdominal tissue edema, with a similar adverse impact on renal function via the same mechanisms (see Chapter 39).

Other surgical procedures that can significantly impair renal function include cardiopulmonary bypass (see Chapter 22), cross-clamping of the aorta (see Chapter 22), and dissection near the renal arteries (see Chapter 31). The potential effects of neurosurgical procedures on ADH physiology are discussed in Chapters 27 and 49.

Diuretics

Diuretics increase urinary output by decreasing the reabsorption of Na^+ and water. Although classified according to their mechanism of action, many diuretics have more than one such mechanism; hence this classification system is imperfect. Only major mechanisms will be reviewed here.

The majority of diuretics exert their action on the luminal cell membrane from within the renal tubules. Because nearly all diuretics are highly protein bound, relatively little of the free drug enters the tubules by filtration. Most diuretics must therefore be secreted by the proximal tubule (usually via the organic anion pump) to exert their action. Impaired delivery into the renal tubules accounts for resistance to diuretics in patients with impaired renal function.

OSMOTIC DIURETICS (MANNITOL)

Osmotically active diuretics are filtered at the glomerulus and undergo limited or no reabsorption in the proximal tubule. Their presence in the proximal tubule limits the passive water reabsorption that normally follows active sodium reabsorption. Although their major effect is to increase water excretion, in large doses, osmotically active diuretics also increase electrolyte (sodium and potassium) excretion. The same mechanism also impairs water and solute reabsorption in the loop of Henle.

Mannitol is the most commonly used osmotic diuretic. It is a six-carbon sugar that normally undergoes little or no reabsorption. In addition to its diuretic effect, mannitol appears to increase RBF. The latter can wash out some of the medullary hypertonicity and interfere with renal concentrating ability. Mannitol appears to activate the intrarenal synthesis of vasodilating prostaglandins. It also appears to be a free radical scavenger.

Uses

A. Prophylaxis Against Acute Kidney Injury in High-Risk Patients

Many clinicians continue to administer mannitol for renal protection and, less frequently, to convert oliguric acute kidney failure to nonoliguric kidney failure, with the goal of lowering associated morbidity and mortality. However, there is no evidence that such use of mannitol provides renal protection, lessens the severity of AKI, or lessens the morbidity or mortality associated with AKI when compared with correction of hypovolemia and preservation of adequate renal perfusion alone. In addition, high-dose mannitol can be nephrotoxic, especially in patients with renal insufficiency.

B. Evaluation of Acute Oliguria

Mannitol will augment urinary output in the setting of hypovolemia but will have little effect in the presence of severe glomerular or tubular injury. However, the optimal initial approach to evaluation of acute oliguria is to correct hypovolemia and optimize cardiac output and renal perfusion.

C. Acute Reduction of Intracranial Pressure & Cerebral Edema

See Chapter 27.

D. Acute Reduction of Intraocular Pressure in the Perioperative Period

See Chapter 36.

Intravenous Dosage

The intravenous dose for mannitol is 0.25–1 g/kg.

Side Effects

Mannitol solutions are hypertonic and acutely raise plasma and extracellular osmolality. A rapid intracellular to extracellular shift of water can transiently increase intravascular volume and precipitate

cardiac decompensation and pulmonary edema in patients with limited cardiac reserve. Transient hyponatremia and reductions in hemoglobin concentration are also common and represent acute hemodilution resulting from rapid movement of water out of cells; a modest, transient increase in plasma potassium concentration may also be observed. It is also important to note that the initial hyponatremia does not represent hypoosmolality but reflects the presence of mannitol (see Chapter 49). If fluid and electrolyte losses are not replaced following diuresis, mannitol administration can result in hypovolemia, hypokalemia, and hypernatremia. The hypernatremia occurs because water is lost in excess of sodium. As noted above, high-dose mannitol can be nephrotoxic, especially in patients with renal insufficiency.

LOOP DIURETICS

The loop diuretics include furosemide (Lasix), bumetanide (Bumex), ethacrynic acid (Edecrin), and torsemide (Demadex). All loop diuretics inhibit Na^+ and Cl^- reabsorption in the thick ascending limb. Sodium reabsorption at that site requires that all four sites on the Na^+–K^+–$2Cl^-$ luminal carrier protein be occupied. Loop diuretics compete with Cl^- for its binding site on the carrier protein (see Figure 29–4). With a maximal effect, they can promote excretion of 15–20% of the filtered sodium load. Both urinary concentrating and urinary diluting capacities are impaired. The large amounts of Na^+ and Cl^- presented to the distal nephron overwhelm its limited reabsorptive capability. The resulting urine remains hypotonic, probably due to rapid urinary flow rates that prevent equilibration with the hypertonic renal medulla or due to interference with the action of ADH on the collecting tubules. A marked increase in diuresis may occur when a loop diuretic is combined with a thiazide diuretic, especially metolazone.

Loop diuretics also increase urinary calcium and magnesium excretion. Ethacrynic acid is the only loop diuretic that is not a sulfonamide derivative, and thus may be the diuretic of choice in patients allergic to sulfonamide drugs. Torsemide may have an antihypertensive action independent of its diuretic effect.

Uses

A. Edematous States (Sodium Overload)

These disorders include heart failure, cirrhosis, the nephrotic syndrome, and renal insufficiency. When given intravenously, these agents can rapidly reverse cardiac and pulmonary manifestations of fluid overload.

B. Hypertension

Loop diuretics may be used as adjuncts to other hypotensive agents, particularly when thiazides (below) alone are ineffective.

C. Evaluation of Acute Oliguria

The response to a small dose (10–20 mg) of furosemide may be useful in differentiating between oliguria resulting from hypovolemia and oliguria resulting from redistribution of RBF to juxtamedullary nephrons. Little or no response is seen with hypovolemia, whereas resumption of normal urinary output occurs with the latter. However, the optimal initial approach to evaluation of acute oliguria is to correct hypovolemia and optimize cardiac output and renal perfusion.

D. Conversion of Oliguric Kidney Failure to Nonoliguric Failure

As with mannitol, discussed earlier, many clinicians continue to administer loop diuretics for renal protection and to convert oliguric acute kidney failure to nonoliguric kidney failure, despite lack of evidence that such use provides renal protection, lessens the severity of AKI, or lessens the morbidity or mortality associated with AKI, when compared with correction of hypovolemia and preservation of adequate renal perfusion alone.

E. Treatment of Hypercalcemia

See Chapter 49.

F. Rapid Correction of Hyponatremia

See Chapter 49.

Intravenous Dosages

The intravenous doses are furosemide, 10–100 mg; bumetanide, 0.5–1 mg; ethacrynic acid, 50–100 mg; and torsemide 10–100 mg.

Side Effects

Increased delivery of Na^+ to the distal and collecting tubules increases K^+ and H^+ secretion at those sites and can result in hypokalemia and metabolic alkalosis. Marked Na^+ losses will also lead to hypovolemia and prerenal azotemia; secondary hyperaldosteronism often accentuates the hypokalemia and metabolic alkalosis. Urinary calcium and magnesium loss promoted by loop diuretics may result in hypocalcemia or hypomagnesemia, or both. Hypercalciuria can result in stone formation. Hyperuricemia may result from increased urate reabsorption and from competitive inhibition of urate secretion in the proximal tubule. Reversible and irreversible hearing loss has been reported with loop diuretics, especially furosemide and ethacrynic acid.

THIAZIDE & THIAZIDE-LIKE DIURETICS

This group of agents includes thiazides, containing a benzothiadiazine molecular structure, and also thiazide-like drugs with similar actions but without the benzothiadiazine structure, including chlorthalidone (Thalitone), quinethazone (Hydromox), metolazone (Zaroxolyn), and indapamide (Lozol). These diuretics act at the distal tubule, including the connecting segment, and inhibition of sodium reabsorption at this site impairs diluting but not concentrating ability. They compete for the Cl^- site on the luminal Na^+–Cl^- carrier protein. When given alone, thiazide and thiazide-like diuretics increase Na^+ excretion to only 3–5% of the filtered load because of enhanced compensatory Na^+ reabsorption in the collecting tubules. They also possess carbonic anhydrase–inhibiting activity in the proximal tubule, which is usually masked by sodium reabsorption in the loop of Henle and which is probably responsible for the marked diuresis often seen when they are combined with loop diuretics. In contrast to their effects on sodium excretion, thiazide and thiazide-like diuretics augment Ca^{2+} reabsorption in the distal tubule. Indapamide has some vasodilating properties and is the only thiazide or thiazide-like diuretic with significant hepatic excretion.

Uses

A. Hypertension

Thiazide and thiazide-like diuretics are often selected as first-line agents in the treatment of hypertension (see Chapter 21), and they have been shown to improve long-term outcomes in this disorder.

B. Edematous Disorders (Sodium Overload)

These drugs are used to treat mild to moderate edema and congestive heart failure related to mild to moderate sodium overload.

C. Hypercalciuria

Thiazide and thiazide-like diuretics are often used to decrease calcium excretion in patients with hypercalciuria who form renal stones.

D. Nephrogenic Diabetes Insipidus

The efficacy of these agents in this disorder reflects their ability to impair diluting capacity and increase urine osmolality (see Chapter 49).

Intravenous Dosages

These agents are only given orally.

Side Effects

Although thiazide and thiazide-like diuretics deliver less sodium to the collecting tubules than loop diuretics, the increase in sodium excretion is enough to enhance K^+ secretion and frequently results in hypokalemia. Enhanced H^+ secretion can also occur, resulting in metabolic alkalosis. Impairment of renal diluting capacity may produce hyponatremia. Hyperuricemia, hyperglycemia, hypercalcemia, and hyperlipidemia may also be seen.

POTASSIUM-SPARING DIURETICS

These are weak diuretic agents and characteristically do not increase potassium excretion. Potassium-sparing diuretics inhibit Na^+ reabsorption in the collecting tubules and therefore can maximally excrete only 1–2% of the filtered Na^+ load. They are usually used in conjunction with more potent diuretics for their potassium-sparing effect.

1. Aldosterone Antagonists (Spironolactone & Eplerenone)

Spironolactone (Aldactone) and eplerenone are direct aldosterone receptor antagonists in collecting tubules. They inhibit aldosterone-mediated Na^+ reabsorption and K^+ secretion. Both agents have been shown to improve survival in patients with chronic heart failure. Aldosterone may produce gynecomastia in male patients due to its antiandrogenic properties.

Uses

These agents may be used as adjuvants in the treatment of refractory edematous states associated with secondary hyperaldosteronism (see Chapter 49). Spironolactone is particularly effective in patients with ascites related to advanced liver disease. They have become part of the standard medical management of chronic heart failure.

Intravenous Dosage

These agents are only given orally.

Side Effects

These agents can result in hyperkalemia in patients with high potassium intake or renal insufficiency and in those receiving β blockers or ACE inhibitors. Metabolic acidosis may also be seen. Eplerenone lacks spironolactone's side effects of gynecomastia and sexual dysfunction.

2. Noncompetitive Potassium-Sparing Diuretics

Triamterene (Dyrenium) and amiloride (Midamor) are not dependent on aldosterone activity in the collecting tubule. They inhibit Na^+ reabsorption and K^+ secretion by decreasing the number of open sodium channels in the luminal membrane of collecting tubules. Amiloride may also inhibit Na^+–K^+-ATPase activity in the collecting tubule.

Uses

In patients with hypertension, these agents are often combined with a thiazide or similar diuretic to minimize hypokalemia produced by the other agent. They have been added to more potent loop diuretics in congestive heart failure patients with marked potassium wasting.

Intravenous Dosages

These agents are only given orally.

Side Effects

Amiloride and triamterene can cause hyperkalemia and metabolic acidosis similar to that seen with spironolactone (see above). Both can also cause nausea, vomiting, and diarrhea. Amiloride is generally associated with fewer side effects, but paresthesias, depression, muscle weakness, and cramping may occasionally be seen. Triamterene on rare occasions has resulted in renal stones and is potentially nephrotoxic, particularly when combined with nonsteroidal antiinflammatory agents.

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase inhibitors such as acetazolamide (Diamox) interfere with Na^+ reabsorption and H^+ secretion in proximal tubules. They are weak diuretics because the former effect is limited by the reabsorptive capacities of more distal segments of nephrons. Nonetheless, these agents significantly interfere with H^+ secretion in the proximal tubule and impair HCO_3^- reabsorption.

Uses

A. Correction of Metabolic Alkalosis in Edematous Patients

Carbonic anhydrase inhibitors often potentiate the effects of other diuretics.

B. Alkalinization of Urine

Alkalinization enhances urinary excretion of weakly acidic compounds such as uric acid.

C. Reduction of Intraocular Pressure

Inhibition of carbonic anhydrase in the ciliary processes reduces the formation of aqueous humor and, secondarily, intraocular pressure. Carbonic anhydrase inhibitors, including oral or intravenous acetazolamide, oral methazolamide (Neptazane), and ophthalmic topical brinzolamide (Azopt) and dorzolamide (Trusopt) are often used to treat glaucoma.

Intravenous Dosage

For acetazolamide, the intravenous dose is 250–500 mg.

Side Effects

Carbonic anhydrase inhibitors generally produce only a mild hyperchloremic metabolic acidosis because of an apparently limited effect on the distal nephron. Large doses of acetazolamide have been reported to cause drowsiness, paresthesias, and confusion. Alkalinization of the urine can interfere with the excretion of amine drugs, such as quinidine. Acetazolamide is frequently used for prophylaxis against mountain sickness.

OTHER "DIURETICS"

These agents may increase GFR by elevating cardiac output or arterial blood pressure, thereby increasing RBF. Drugs in this category are not primarily classified as diuretics because of their other major actions. They include methylxanthines (theophylline), cardiac glycosides (digitalis), fenoldopam (Corlopam), inotropes (dopamine, dobutamine), and intravenous crystalloid and colloid infusions. Methylxanthines also appear to decrease sodium reabsorption in both the proximal and distal renal tubules.

CASE DISCUSSION

Intraoperative Oliguria

A 58-year-old woman is undergoing radical hysterectomy under general anesthesia. She was in good health prior to the diagnosis of uterine carcinoma. An indwelling urinary catheter is placed following induction of general anesthesia. Total urinary output was 60 mL for the first 2 h of surgery. After the third hour of surgery, only 5 mL of urine is noted in the drainage reservoir.

Should the anesthesia provider be concerned?

Decreases in urinary output during anesthesia are very common. Although decreases may be expected owing to the physiological effects of surgery and anesthesia, a urinary output of less than 20 mL/h in adults generally requires evaluation.

What issues should be addressed?

The following questions should be answered:

1. Is there a problem with the urinary catheter and drainage system?
2. Are hemodynamic parameters compatible with adequate renal function?
3. Could the decrease in urinary output be directly related to surgical manipulations?

How can the urinary catheter and drainage system be evaluated intraoperatively?

Incorrect catheter placement is not uncommon and should be suspected if there has been a total absence of urine flow since the time of catheter insertion. The catheter may be inadvertently placed and inflated in the urethra in men or the vagina in women. Catheter displacement, kinking, obstruction, or disconnection from the reservoir tubing can all present with features similar to this case, with complete or near-complete cessation of urinary flow. The diagnosis of such mechanical problems requires retracing and inspecting the path of urine (often under the surgical drapes) from the catheter to the collection reservoir. Obstruction of the catheter can be confirmed by an inability to irrigate the bladder with saline through the catheter.

What hemodynamic parameters should be evaluated?

Decreased urinary output during surgery is most commonly the result of hormonal and hemodynamic changes. In many instances, a decrease in intravascular volume (hypovolemia), cardiac output, or mean arterial blood pressure is responsible. Redistribution of renal blood flow from the renal cortex to the medulla may also play a role.

Intravascular volume depletion can rapidly develop when intravenous fluid replacement does not match intraoperative blood loss and insensible fluid loss. Oliguria requires careful assessment of intravascular volume to exclude hypovolemia. An increase in urinary output following an intravenous fluid bolus is highly suggestive of hypovolemia. In contrast, oliguria in patients with a history of congestive heart failure may require inotropes,

vasodilators, or diuretics. Intravascular volume status is often difficult to optimize, and goal-directed hemodynamic and fluid therapy utilizing arterial pulse contour analysis (eg, LIDCO Rapid, Vigileo FloTrak), esophageal Doppler, or transesophageal echocardiography should be considered when accurate determination of hemodynamic and fluid volume status is critically important, as in patients with underlying heart, kidney, or advanced liver disease (see Chapter 5). In addition to providing more accurate assessment of the patient's volume and hemodynamic status than that obtained with central venous pressure monitoring, these modalities avoid the risks associated with central venous access procedures and with pulmonary artery catheter placement and use.

When mean arterial blood pressure drops below the lower limit of renal autoregulation (80 mm Hg), urinary flow may become blood pressure dependent. The latter may be particularly true in patients with chronic systemic hypertension, in whom renal autoregulation occurs at higher mean arterial blood pressures. Reductions in anesthetic depth, intravenous fluid boluses, or the administration of a vasopressor or inotrope may increase blood pressure and urinary output in such instances.

Otherwise normal patients may exhibit decreased urinary output in spite of normal intravascular volume, cardiac output, and mean arterial blood pressure. A small dose of a loop diuretic (eg, furosemide, 5–10 mg) usually restores normal urinary flow in such instances—although such therapy does not convey protection against acute kidney injury.

How can surgical manipulations influence urinary output?

In addition to the neuroendocrine response to surgery, mechanical factors related to the surgery itself can alter urinary output. This is particularly true during pelvic surgery, when compression of the bladder by retractors, unintentional cystotomy, and ligation or severing of one or both ureters can dramatically affect urinary output. Retractor compression combined with a head-down (Trendelenburg) position commonly impedes emptying of the bladder. Excessive pressure on the bladder will often produce hematuria.

When mechanical problems with the urinary catheter drainage system and hemodynamic factors are excluded (see above), a surgical explanation should be sought. The surgeon should be notified so that the position of the retractors can be checked, the ureters identified, and their path retraced in the operative area. Intravenous methylene blue or indigo carmine dyes (excreted in urine) are useful in identifying the site of an unintentional cystotomy or the end of a severed ureter. Note that the appearance of dye in the urinary drainage reservoir does not exclude unilateral ligation of one ureter. Methylene blue and, to a much lesser extent, indigo carmine, can transiently give falsely low pulse oximeter readings (see Chapter 6). Excessive insufflation pressure during laparoscopic procedures can result in abdominal compartment syndrome, reducing renal blood flow.

What was the outcome?

After the integrity of the urinary catheter and drainage system was checked, 2 L of lactated Ringer's solution along with 250 mL of 5% albumin and 10 mg of furosemide were administered intravenously, but failed to increase urinary output. Indigo carmine was given intravenously, and the proximal end of a severed left ureter was subsequently identified. A urologist was called and the ureter was reanastomosed.

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