CHAPTER 44

Acute Kidney Injury in Heart Failure

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OBJECTIVES

This chapter will:

1. Review the epidemiology of acute kidney injury in the setting of acute heart failure.
2. Discuss the clinical implications of cardiorenal syndromes.
3. Present emerging information on the determinants of cardiorenal syndromes in acute heart failure.

Heart failure (HF) is a leading cause of adult hospitalization in developed countries with an expanding prevalence pool of patients because of survival after myocardial infarction and advancements in the treatment of HF that prolong survival.[1] Thus with greater numbers of HF patients who over time have more comorbidities such as hypertension, diabetes mellitus, chronic kidney disease (CKD), and older age, there are increasing risks for acute kidney injury (AKI) with every HF hospitalization. In this scenario, AKI in the setting of acute HF (AHF), the term type 1 cardiorenal syndrome has been applied.[2]

PATHOPHYSIOLOGY

Although the differential diagnosis of AKI in HF includes type 1 cardiorenal syndrome, interstitial nephritis, subclinical sepsis, and prerenal azotemia, the most likely cause is type 1 cardiorenal syndrome after the other possibilities are ruled out or determined to be sufficiently unlikely to

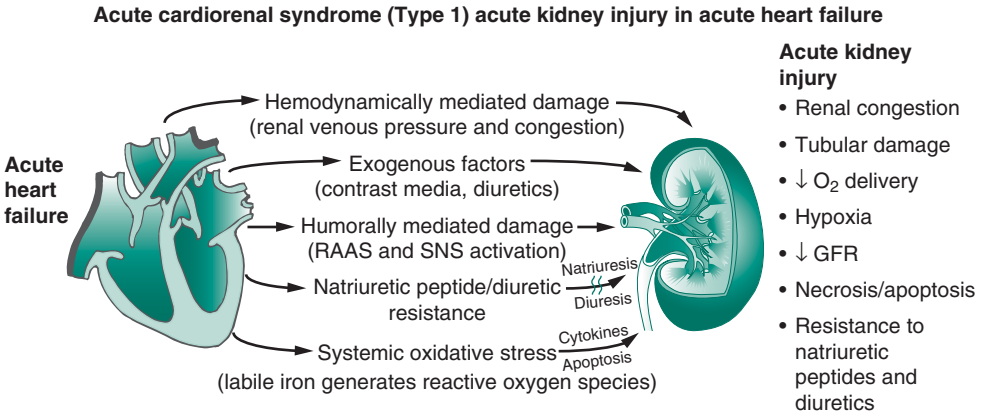


FIGURE 44.1 Pathophysiology of cardiorenal syndromes.

further consider. Because most patients have considerable evidence of volume expansion, it is unlikely that there has been enough volume loss to have caused prerenal azotemia. There is considerable evidence of elevated central venous pressure, which is the strongest hemodynamic determinant of type 1 cardiorenal syndrome, as shown in Fig. 44.1. Although the kidneys may not be receiving enough forward output and there may transiently be a slowed plasma refill from the extravascular space, most AHF patients are very unlikely to be truly volume depleted. Interstitial nephritis can be suggested by urinary eosinophils and the presence of rash and fever; however, it is unlikely because common medications that induce this syndrome typically are not used in HF. In most cases, we are left with a working diagnosis of type 1 cardiorenal syndrome, in which the onset of AHF has led to an attempt at diuresis, which commonly is successful initially, and then a marked reduction in glomerular filtration and urine output follow over the next several days.[3]

Clinical Management

We are in the midst of an HF chronic disease pandemic with the aging of populations in the Western world.[1] Survivorship in the settings of long-standing hypertension, myocardial infarction, valvular disease, and with myocardial disease has led to an increased prevalence pool of patients with established HF. Approximately half of patients with HF have reduced left ventricular ejection fraction (LVEF) or HFrEF and the other half as HF with preserved LVEF or HFpEF. HFrEF can be attributed to myocardial ischemia or prior infarction in two thirds of cases, whereas approximately half of those with HFpEF have a significant contribution to their illness because of ischemia as a result of coronary artery disease (CAD).[4] Because of the considerable overlap among hypertension, diabetes, other risk factors, CAD, and myocardial disease with CKD, it is a common occurrence to find patients who have both HF (either HFrEF or HFpEF) with evidence of CKD manifest by a reduced estimated glomerular filtration rate (eGFR) < 60 mL/min/1.72 m^2 or by the presence of albuminuria (≥30 mg/g albumin:creatinine ratio in spot urine) or by the detection of structural abnormalities in the kidneys or urologic tract (e.g., polycystic kidney disease, unilateral kidney).[5] In addition, it is well known that in the setting of acute HF (AHF) decompensation, that AKI occurs in approximately 25% of hospitalized patients (type 1 cardiorenal syndrome).[2] Finally, it is possible that HF itself sets up renal pathophysiology in a way to manifest reduced eGFR or albuminuria. This scenario has been termed type 2 cardiorenal syndrome.[6] Thus there is a considerable interface between cardiac and renal function in health and disease. This chapter provides a framework to understand the kidney in HF from a graphical and pictorial perspective.

Hemodynamics, Renal Blood Flow, Glomerular Filtration

A normal human body has approximately 5 L of blood volume and at rest a cardiac output of 3 to 5 L per minute. Cardiac output can increase to approximately 35 L per minute with aerobic exercise such as running. There is an important Frank-Starling relationship between end-diastolic volume and forward stroke work, which is analogous to the volume per contraction that would partially perfuse the kidneys. At rest the parasympathetic system via acetylcholine release predominates over the sinoatrial node and maintains heart rate in the 50 to 100 beats per minute range. In athletes, parasympathetic tone can be more pronounced and result in even lower sinus rates. With exercise the sympathetic nervous system via the release of norepinephrine predominates and the sinus node rate increases. In addition, contractility of the myocardium becomes more forceful resulting in greater ventricular systolic pressures. The mechanisms by which cardiac output increase are driven by the sympathetic nervous system and include increases in heart rate, end-diastolic volume, and stroke volume. For these responses to occur there must be increased venous return to the heart.

At rest approximately 60% of blood volume is in the venous system at any given time (Fig. 44.2). The veins have much thinner walls than arteries and thus have a much greater capability to dilate, resulting in pooling of blood volume. The tunica media in veins is innervated by the sympathetic nervous system and stains intensely for norepinephrine from sympathetic neuromuscular terminals, which works to control venous tone in minute-to-minute regulation of venous return to the heart, which does have an important pressure relationship to the overall cardiovascular system. The right-sided chambers, pulmonary circulation, and then left-sided systemic chambers are highly dependent on venous return dynamically in terms of their hemodynamic performance.

The kidneys receive arterial blood flow through the renal arteries, which arise from the abdominal aorta just distal to the superior mesenteric artery. Each kidney receives approximately 600 mL/min of flow, and together RBF

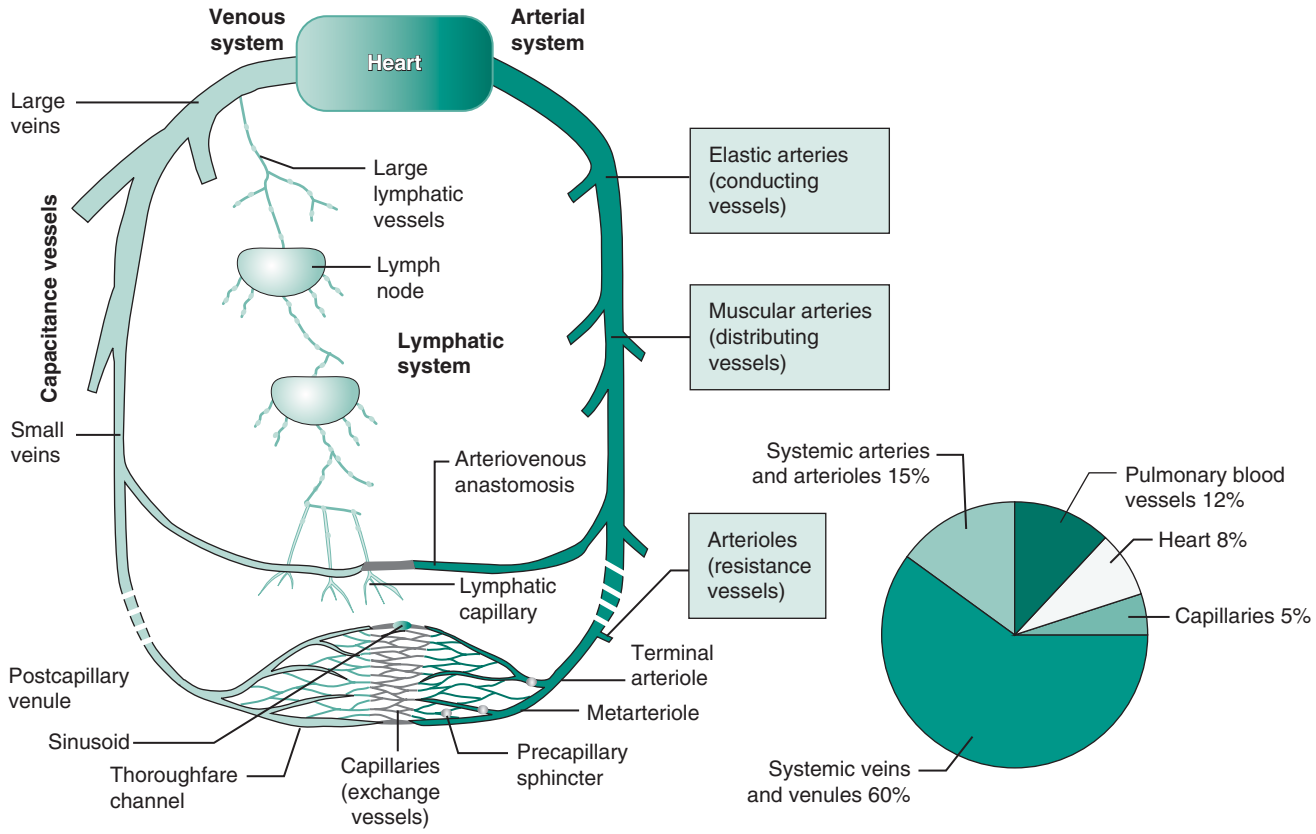


FIGURE 44.2 Distribution of blood volume by vascular component.

represents approximately 20% of cardiac output. The renal artery subdivides into segmental branches, then arcuate branches, and ultimately to afferent arterioles that deliver blood to the glomerular tuft and reconstitute as efferent arterioles, which go on to form the peritubular network, vasa recta, and then subsegmental and segmental renal veins, which converge on the main renal veins back to the inferior vena cava. This valveless system carries a large blood volume back to the heart and thus is vulnerable to changes in forward perfusion pressure, back pressure, or changes in organ fluid content. Because the kidneys are in the retroperitoneal space, unlike other viscera, there is lesser tolerance for organ expansion in the setting or organ edema. Multiple studies have shown that measures of central venous pressure, inferred renal venous pressure, and reduced outflow is a strong determinant of type 1 cardiorenal syndrome in patients with AHF.[7]

Intrarenal autoregulatory mechanisms maintain renal blood flow (RBF) and glomerular filtration rate (GFR) independent of renal perfusion pressure (RPP) over a broad range systemic arterial pressure (80–180 mm Hg).[8] Such autoregulation is mediated largely by the myogenic control over tone in the afferent arteriole, which supplies blood to the glomerular tuft. The glomerulus is a unique vascular structure with multiple layers that constitute the filtration barrier between plasma and urine, including (1) glycocalyx, (2) fenestrated endothelium, (3) basement membrane, (4) foot of podocytes, (5) epithelial basement membrane, and (6) urogenital epithelial cells. The glomerulus also houses the mesangium, juxtaglomerular apparatus, and macula densa cells, which serve a variety of regulatory processes. The mesangial cells have cytosolic contractile proteins that enable the mass of mesangial cells to change shape and regulate blood flow into the glomerulus via the afferent arteriole. Angiotensin II is an important regulator of this function. The juxtaglomerular complex refers to the close proximity of the distal convoluted tubule and the afferent and efferent arterioles, where more densely staining distal tubular and interstitial cells are termed macula densa cells because of their dense cytosolic granules containing renin. Thus the anatomy and normal physiology of renal perfusion and glomerular filtration is particularly responsive to changes in forward flow and venous return. In addition, the peritubular network is the site where renal tubules in close proximity to the tubular lumen and the blood capillary interface regulate sodium, chloride, ammonium, and bicarbonate in the urine. Each distal convoluted tubule is drained into a collecting duct, and thus each collecting duct services approximately 4 to 8 nephrons. The principal cell in the collecting duct has two major functions that are relevant in HF: (1) effector response to intranuclear signaling from aldosterone, which positions the cell in response to distal delivery of sodium in the urine to reclaim sodium and to dump potassium and (2) effector response to cell surface activation of vasopressin 2 receptors to arginine vasopressin, which activates aquaporin channels on the lumen surface to reclaim water. Because of the close proximity of the collecting ducts to the vasa recta, both of these systems work to deliver large amounts of sodium and water to the bloodstream when these hormonal systems are activated.

In summary, the kidneys are positioned to be the most hemodynamically and neurohormonally responsive to changes in blood volume, flow, perfusion, back pressure, sodium, water, and neurohormonal stimulation in the setting of HF. As a result, chronic and acute renal filtration function

are two of the most important parameters in the prognosis and management of patients with all forms of HF.

Neurohormonal Activation

It is beyond the scope of this chapter to discuss in detail the role of each neurohormone that is participating in normal physiology, as well as the pathophysiology of HF. In brief, multiple important regulatory systems are activated in HF that work toward preserving perfusion to the brain at the expense of the kidneys and direct the maximal amount of sodium and water reclamation as possible despite the adverse consequences of responses. The sympathetic nervous system via peripheral synapses at the neuromuscular junction within afferent and efferent renal arterioles, as well as mesangial cells, acts through the release of norepinephrine, which stimulates both α- and β-adrenergic receptors. These effects result in a decrease in RBF, an increase in intraglomerular pressure, and increased sodium retention. Norepinephrine is a stimulus for juxtaglomerular cells to release renin, which is the starting point for the renin angiotensin system. In addition to norepinephrine, epinephrine and dopamine as precursor molecules have effects on the kidneys primarily in the proximal and distal tubule with varying effects depending on the family of receptors. In general, epinephrine and norepinephrine stimulate the reabsorption of salt and water. However, dopamine, acting on a different family of receptors, can stimulate natriuresis and diuresis. In general, the epinephrine and norepinephrine effects are more powerful, and the net effect of sympathetic stimulation to the kidneys is release of renin, reduction in RBF, increased salt and water retention, and a slightly reduced eGFR.

The renin angiotensin system is integral to renal physiology with not only the production and release of renin but also the direct effects of angiotensin II on the renal vasculature and renal tubular cells. The results of angiotensin II include efferent arteriolar vasoconstriction, salt and water retention, and reductions in RBF. Because intraglomerular pressure is elevated, angiotensin II results in maintenance or slight increases in eGFR.

Norepinephrine and angiotensin II stimulate the chromaffin cells in the adrenal glands to synthesize and release aldosterone. Aldosterone has a powerful effect on the principal cells in the collecting ducts to reabsorb sodium, provided there is adequate delivery of urinary sodium to the distal nephron, as well as release potassium into the urine. In the setting of HF, the result of activation of the sympathetic nervous system and the renin-angiotensin-aldosterone axis is salt and water retention and over a long period of time, renal fibrosis, and drop out of nephrons with a reduction in eGFR.

Arginine vasopressin is secreted by the hypothalamus in response to cardiac afferent signaling to the brain in HF. Vasopressin stimulates V_2 receptors on the principal cell (Fig. 44.3) in the collecting duct, thus stimulating aquaporin channel expression and activation, which work to reclaim free water from the collecting duct. This vasopressin effect raises urine osmolality, lowers plasma osmolality, and represents an inappropriate release of antidiuretic hormone, which can cause hyponatremia in HF patients. When this occurs, this is a poor prognostic sign indicating that systems that work to maintain the plasma concentration of sodium near 140 mEq/L have failed and that short-term cardiac compensation, as well as some degree of brain edema, is imminent. These changes are common in the setting of multiple hormonal dysregulation including a relative deficiency/resistance to erythropoietin and anemia. Thus

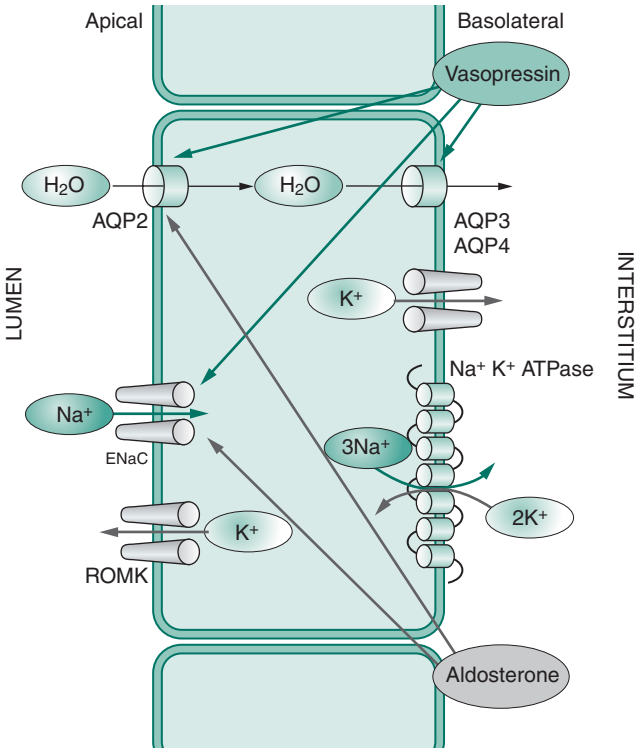


FIGURE 44.3 Principal cell in the collecting duct of the kidney and site of action of arginine vasopressin.

there is a vicious cycle of multiple abnormalities that are caused by HF, which beget worsened HF symptoms and are associated with decompensation.

Endothelins (ET-1, ET-2, ET-2) are derived from ET precursor (big ET), which is produced by renal tubular cells, and to a lesser extent endothelial and most other cell lines in the kidney, and is a powerful paracrine factor that works on ET-A and ET-B receptors. ET-1 is a potent vasoconstrictor peptide involved in normal renal physiology and pathology, including constriction of cortical and medullary vessels (ET-A), mesangial cell contraction (ET-A), stimulation of extracellular matrix production and fibrosis (ET-B), and inhibition of sodium and water reabsorption along the collecting duct (ET-B).[9] Although endothelin receptor antagonists have not proven to be effective in the treatment of HF, they have found a role in the treatment of pulmonary hypertension and at very low doses may be effective in reducing the progression of CKD.[10]

Adenosine is another important paracrine substance in the kidney that is produced by multiple cell lines and acts on a family of receptors. Although short-lived in the circulation, adenosine can activate four subtypes of G protein-coupled adenosine receptors: A(1), A(2A), A(2B), and A(3). The adenosine A1 receptor on proximal tubular cells when stimulated results in reabsorption of salt and water and in addition, via tubuloglomerular feedback, increases afferent arterial tone and reduces glomerular blood flow resulting in a reduction in eGFR. Recently, adenosine 2B receptors have been associated with renal fibrosis in models after renal ischemia.[11] Thus adenosine and its effects on receptors, as well as their differential expression, probably plays roles in hemodynamics, salt and water balance, as well as response to ischemic injury. Dual adenosine A1/A2B inhibition may be a potential therapeutic target for HF in the future.[12]

There are several mediators of vasodilation of the peritubular network in the renal medulla including nitric oxide, bradykinin, and prostaglandins.[13] These substances may be produced by vascular, tubular, or interstitial satellite cells and appear to be important in maintaining the integrity of blood flow and tissue structure in the tubules and peritubular network. Nitric oxide synthase is present in renal tubular cells and appears to be important in maintaining normal salt and water homeostasis as it relates to blood pressure regulation.[14] Bradykinin opposes the effects of aldosterone at the distal nephron epithelial Na channel (ENaC) and results in natriuresis.[15] Prostaglandin E(2) is a major renal cyclooxygenase-derived metabolite of arachidonic acid and interacts with four G protein-coupled receptors: EP(1), EP(2), EP(3), and EP(4). EP(1) expression predominates in the collecting duct where it inhibits Na(+) absorption, contributing to natriuresis. The EP(2) receptor regulates vascular reactivity in the peritubular network. The EP(3) receptor also is expressed in vessels as well as in the thick ascending limb and collecting duct, where it partially antagonizes the effect of aquaporin channels in reclaiming water from the collecting duct. EP(4) may regulate glomerular tone and renal renin release. Thus PGE(2) can be thought of as a buffer, preventing excessive responses to physiologic perturbations in the setting of HF. As a result, the use of nonsteroidal antiinflammatory agents, which impair the production of PGE(2), has been associated with worsened outcomes in patients with HF.[16]

Cell Signaling in Cardiorenal Failure

It has been increasingly appreciated that beyond hemodynamics and neurohormonal derangements (see Fig. 44.1), that HF is a condition in which production of cell signaling peptides (interleukins, tumor necrosis factor, intracellular transforming growth factor-β) may play a role in directing cell differentiation and proliferation of fibroblasts in the deposition of collagen and tissue fibrosis. In addition, some cell signaling molecules may mediate acute tubular dysfunction in the setting of AHF (IL-6, IL-18). The net result may be progressive and simultaneous renal and cardiac fibrosis termed type 4 cardiorenal syndrome. Although the production of cell signaling peptides from adipocytes, endothelial cells, hepatocytes, and immune cells has been termed "inflammation," this term does not appropriately represent the processes observed in HF. Inflammation classically involves four elements: (1) white blood cells, (2) complement, (3) antibodies, and (4) cytokines. Thus "inflammation" probably does not describe the abnormal cell signaling that is occurring in the heart and kidney, as reflected in the measurement of cytokines or their downstream effects, including tubular and myocardial cell dysfunction, apoptosis, and replacement fibrosis. As the kidneys fail in the setting of HF, these effector actions can be partially lost, causing additional derangements that may become clinically relevant (e.g., hyperphosphatemia, hyperparathyroidism).

Renal Response to Diuretics

Diuretics are a mainstay in the treatment of HF for the relief of systemic congestion and to initiate plasma refill of salt and water from the interstitial space into the venous vasculature. There are a host of diuretics that have different and specific location of action along the nephron with key issues with respect to their physiologic response in HF (Fig. 44.4). All available diuretics are tightly bound by albumin and do not undergo glomerular filtration. To work they must get secreted by the S2 segment of the proximal tubule into the urine. Hypoalbuminemia results in an increased volume of distribution of diuretics and lesser delivery to the kidneys and is one of many factors related to decreased diuretic responsiveness. Carbonic anhydrase inhibitors (e.g., acetazolamide) work in the proximal tubule and cause loss of sodium bicarbonate and thus create a metabolic acidosis. Because of these effects and the relatively large opportunity for upregulation of sodium absorption in the remaining nephron, carbonic anhydrase inhibitors are not a mainstay of therapy for either acute or chronic HF. However, loop diuretics (e.g., furosemide, bumetanide, torsemide, ethacrynic acid) are relied upon in most patients with HF at some time or another for the relief of congestion. These agents are the most powerful diuretic class, causing the excretion of 20% to 25% of filtered sodium load.[17] Loop diuretics are secreted by organic anion transporters (OATs), which are expressed in proximal tubule cells and then work in the urinary lumen of the loop of Henle to impair sodium reuptake in the thick ascending limb, which is a major site of sodium reclamation from urine.[18] Furosemide is catabolized by proximal tubular cells and can accumulate in the blood if there is CKD or AKI. Bumetanide and torsemide are broken down by the liver and do not accumulate in renal failure.

Use of bolus loop diuretics is equally as effective as continuous infusion for AHF, but with less adverse effects such as hyponatremia and hypotension.[19,20] A principal mechanism of loop diuretic resistance is hypertrophy of thick ascending limb renal tubular cells with upregulation of sodium channel number and function that counteracts the inhibition of the loop diuretic.[21] Thiazide diuretics exert their mechanism of action in the distal convoluted tubule, where they impair reuptake of sodium from the lumen. The thiazide group and metolazone are moderately potent diuretics, resulting in the excretion of 5% to 8% of filtered sodium.[15] Chlorothiazide intravenously and metolazone orally are the most commonly used thiazide diuretics in HF, but usually in conjunction with loop diuretics and as part of "sequential nephron blockade" with pharmacologic agents. Diuretics that work proximal to the collecting duct have the potential for causing hypokalemia if distal urinary sodium delivery is increased, because this stimulates the epithelial sodium channel (ENaC) to reabsorb sodium and under the control of aldosterone, and causes the renal outer medullary potassium (ROMK) channels to excrete potassium in the principal cells. The "potassium-sparing" drugs are considered mildly potent, causing the excretion of only 2% to 3% of filtered sodium.[15] They spare potassium because they work at the collecting duct and do not influence delivery of sodium to the principal cell as discussed above. Triamterene and amiloride block ENaC on the lumen side of the collecting ducts, whereas mineralocorticoid receptor antagonists work in the principal cells to partially block the effects of endogenous aldosterone, and as a result there is less ENaC and ROMK activity with lesser degrees of potassium excretion.

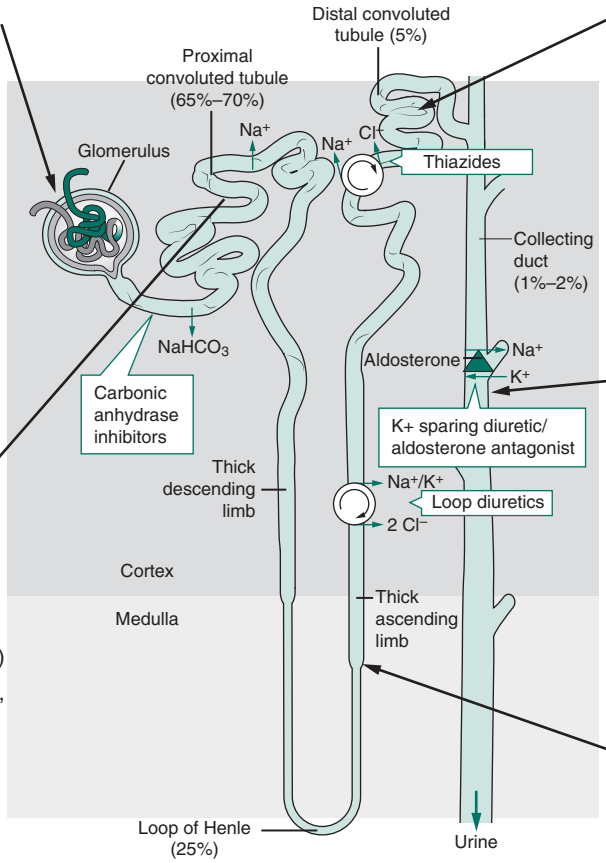
It is common in severe HF to deploy loop diuretics, a thiazide, and an MRA agent for control of congestion and for symptom relief in the same patient. As a consequence of sequential nephron blockade with diuretics, volume depletion can occur and electrolyte disturbances most commonly hyperkalemia are frequent and must be anticipated with prudent use of the laboratory.[22] Hyperkalemia has multiple causes in the setting of HF including CKD, diabetes, and the use of drugs to treat HF. There is a clear

Reduced GFR:

Barriers	Potential solution
Abnormal glomerular hemodynamics	Discontinue NSAIDs, consider holding ACEI/ARB
Low cardiac output	Hemodynamic support
Chronic kidney disease or functional renal hypoperfusion	Increase LD dose

Proximal tubule hyperfunction:

Barriers	Potential solution
Neuro-hormonal activation	ACEI/ARB
Sodium-avid states	Increased LD doses, proximal tubule diuretics (i.e., acetazolamide)
Postdiuretic effect	Multiple daily doses, continuous LD infusion
Excessive daily sodium intake	Sodium restriction



Distal tubule hypertrophy:

Barriers	Potential solution
Rebound sodium retention	Sequential nephron blockade (combination diuretic therapy)

Distal nephron hyperfunction:

Barriers	Potential solution
Excessive aldosterone-mediated sodium retention	Aldosterone antagonist, K^+-sparing diuretic (ENaC blocker)
Excessive vasopressin-mediated water retention	Vasopressin antagonist, free water restriction

Loop of Henle hyperfunction:

Barriers	Potential solution
Braking effect	Higher LD doses

FIGURE 44.4 Sites of action of diuretics in the nephron.

relationship between the development of hyperkalemia and mortality in patients with critical illness including HF. The drug class most commonly implicated is the MRAs; however, many drugs in combination work to sufficiently suppress the release of aldosterone from the adrenal gland and or antagonize its effects at the collecting ducts to result in insufficient elimination of potassium from the body.[23] Thus there is a risk-to-benefit equation that must be balanced in patients with HF, CKD, and hyperkalemia. Novel strategies employing agents to enable greater gastrointestinal elimination (patiromer calcium, sodium zirconium cyclosilicate) may play a role in the future in the enablement of drugs that antagonize the renin-angiotensin-aldosterone axis.

PROGNOSIS

Our patient had several clinical features that predict a poor prognosis. Her baseline renal filtration function was moderately impaired and as a result was at risk for inpatient and short-term postdischarge death or rehospitalization.[24] In multivariate modeling, reduced eGFR or stage of CKD is in general the most important prognostic variable in the setting of HF and is more important than LVEF, type of cardiomyopathy, and treatment received in terms of prognosis for death or hospitalization.[25] The development of type 1 cardiorenal syndrome, which occurs in approximately 25% of patients with AHF, is an additional poor prognostic sign and has a four- to sevenfold increased risk for death, the need for renal replacement therapy, worsened CKD after discharge, and outpatient mortality.[25]

CONCLUSION

The renal system is integral to the cardiovascular system in health and disease. In the setting of HF, those patients with preserved renal function who do not develop significant reductions in the setting of AHF enjoy good responses to diuretics and optimal outcomes. Those patients with CKD at baseline and who develop AKI in the setting of hospitalization for HF have increased rates of in-hospital complications, including volume overload, hyperkalemia, and death. In addition, they face increased risks of readmissions and longer-term mortality, including pump failure and arrhythmic death. Future research into novel diagnostic and therapeutic targets is likely to yield advances in the field of HF given the very close relationships between the cardiovascular and renal organ systems.

Key Points

1. In approximately 25% of patients with acute heart failure, acute kidney injury develops during the

hospitalization, and this is termed type 1 cardiorenal syndrome.
2. Neurohormonal activation is a hallmark of type 1 acute cardiorenal syndrome and involves the sympathetic nervous system, renin-angiotensin-aldosterone system, arginine vasopressin, endothelin, and many other systems that are maladaptive in the setting of acute heart failure.
3. Type 1 cardiorenal syndrome is associated with increased central venous congestion and has been linked consistently to longer lengths of stay, rehospitalization, and mortality.
4. Sequential nephron blockade of sodium reabsorption can be a strategy to consider in patients who have refractory congestion. This strategy involves use of loop diuretics, high potency thiazides, and MRA agents. Patients have to be very carefully monitored with frequent assessment of electrolytes with this strategy.

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