Kidney-Organ Interaction

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6.1 Introduction

The practice of critical care nephrology demands an intimate understanding of the interactions and "crosstalk" that occurs between the kidney and multiple organ systems, in particular the heart, lung, gut, and brain. Accumulating evidence suggests that acute injury and dysfunction to the kidney can incite and propagate cardiac, pulmonary, gastrointestinal, and neurologic injury and dysfunction through a host of mechanisms.

Among patients hospitalized with acute kidney injury (AKI), the therapeutic options to mitigate kidney injury and loss of function once established are relatively limited and largely represent enhanced surveillance and measures to avoid iatrogenic complications and harm. AKI has a high attributable risk of morbidity and mortality.

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H.M. Oudemans-van Straaten et al. (eds.), *Acute Nephrology for the Critical Care Physician*, DOI 10.1007/978-3-319-17389-4_6

Indeed, the hazard of major morbid complications after AKI, including incident chronic kidney disease (CKD) and accelerated progression to end-stage kidney disease (ESKD), along with increased susceptibility to infections/sepsis, malignancy, and fractures and excessive mortality remain elevated long after the initial episode of AKI. This attributable morbidity and mortality may be partially explained by AKI contributing to extrarenal injury/dysfunction to distant organs [1].

Our understanding of the pathophysiological mechanisms underlying this kidney-organ "crosstalk" remains incompletely understood; however, it is likely a complex interaction of patient-specific susceptibilities (i.e., genetic, comorbid disease), acute illness severity, and the extent of organ injury; host responses to injury including dysfunctional inflammatory cascades, oxidative stress, activation of pro-apoptotic pathways, altered molecular expression, and leukocyte trafficking; and the impact of therapeutic interventions aimed to treat critical illness. This chapter will provide a broad overview of the fundamentals of kidney-organ interactions.

6.2 The Kidney and the Heart

The prevalence of cardiac and kidney disease is high and increasing concomitantly with population demographic transition. Importantly, cardiac and kidney disease frequently coexist and together can synergistically modify the risk of major morbidity and premature death and translate into excessive health services use. The "cardiorenal syndrome" is generally characterized by the presence of pathophysiological organ "crosstalk" between the heart and the kidneys, whereby an acute or chronic injury or decompensation in the function of one organ can precipitate injury or dysfunction to the other. A large body of literature from observational studies and clinical trials has clearly shown that acute/chronic heart disease can directly contribute to and/or accelerate acute/chronic worsening of kidney function and vice versa. Recently, a consensus definition and classification scheme for the cardiorenal syndrome was proposed to help standardize its nomenclature with the aim to better understand its underlying pathophysiological mechanisms, epidemiology, and therapeutic approaches. This classification scheme proposed five distinct "cardiorenal" syndrome subtypes (Table 6.1). These subtypes are characterized by important heart-kidney interactions that share a pathophysiological basis, however, have unique discriminating features, in terms of predisposing or precipitating events, risk identification, natural history, and outcomes. In this section, we will focus on the two subtypes of cardiorenal syndrome most likely to be encountered in critical care.

6.2.1 Type I Cardiorenal Syndrome

This subtype is commonly encountered and is characterized by an acute cardiac event or disorder that precipitates AKI. The prototypical conditions contributing to type I CRS are acute decompensated heart failure (ADHF) and acute myocardial infarction (AMI).

Table 6.1 Diagnostic and classification scheme for cardiorenal syndrome

Cardiorenal syndrome (CRS)	A complex pathophysiological disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ
CRS type I (acute cardiorenal syndrome)	Abrupt worsening of cardiac function (e.g., ACS or ADHF) leading to AKI or acute worsening of kidney function
CRS type II (chronic cardiorenal syndrome)	Chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) contributing to progressive and permanent chronic kidney disease
CRS type III (acute renocardiac syndrome)	AKI or abrupt worsening of kidney function contributing to acute cardiac disorder or decompensation
CRS type IV (chronic renocardiac syndrome)	Chronic kidney disease (e.g., diabetic nephropathy) contributing to decreased cardiac function, cardiac hypertrophy, fibrosis, and/or increased risk of adverse cardiovascular events
CRS type V (secondary cardiorenal syndrome)	Systemic condition (e.g., sepsis) contributing to both cardiac and/or kidney injury

ACS acute coronary syndrome, *ADHF* acute decompensated heart failure

The pathophysiological mechanisms contributing to AKI in ADHF and AMI are numerous and complex, however, likely involve alterations to myocardial performance, cardiac output, and systemic and central venous hemodynamics that compromise kidney perfusion and coupled with maladaptive and compensatory neuro-hormonal activation (i.e., activation of the sympathetic nervous system, increased activity of renin-angiotensin-aldosterone, and non-osmotic release of arginine vasopressin). These mechanisms will be further modified not only by the severity of the inciting event but also by preexisting susceptibilities including baseline cardiac and kidney function and presence of chronic kidney disease (CKD). Observational data have confirmed that persistent AKI in ADHF is more likely among those with baseline CKD and diminished renal reserve [2].

In both ADHF and AMI, the development of AKI is associated with worse outcomes, higher rehospitalization rates, and increased health-care costs [3, 4]. Moreover, there appears to be a biological gradient between the severity of AKI and risk of death [5, 6]. Among patients reperfused following AMI, those developing AKI tended to have higher plasma norepinephrine, B-natriuretic peptide, and interleukin-6 levels in the 2 weeks after reperfusion compared to those without AKI. Those with AKI show higher risk of in-hospital death and major adverse cardiac events, including greater changes in LV remodeling during recovery. Even small acute changes in serum creatinine modify the risk of death following AMI [6]. Among those developing AKI, greater risk of cardiovascular events such as congestive heart failure (CHF), recurrent AMI, and stroke and need for rehospitalization have been shown [6]. Moreover, patients with AMI complicated by AKI have increased risk of development of incident CKD and accelerated progression to ESKD [7].

6.2.2 Type III Cardiorenal Syndrome

This subtype is characterized by AKI that contributes to the development of acute cardiac injury and/or dysfunction (i.e., AMI, CHF, arrhythmias). While any episode of AKI may predispose to acute cardiac dysfunction and type III CRS, the most common conditions encountered include contrast-induced AKI (CI-AKI), drug-induced nephropathies, AKI after major noncardiac surgery, AKI after cardiac surgery, post-infectious glomerulonephritis, and rhabdomyolysis. The pathophysiological mechanisms of how AKI contributes to acute cardiac injury and/or dysfunction are incompletely understood. An episode of AKI may have effects that depend both on the severity and duration of AKI and that both directly and indirectly predispose to an acute cardiac event. Moreover, baseline patient susceptibility will modify the subsequent risk for cardiac events associated with AKI (i.e., preexisting risk factors and cardiac disease).

Experimental data suggest that cardiac injury may be directly induced by inflammatory mediators release, oxidative stress, apoptosis, and activation of neuroendocrine systems early after AKI [1, 8]. Likewise, AKI may be associated with physiological derangements (i.e., extracellular volume expansion, retention of uremic [cardiotoxic] compounds, metabolic acidosis, electrolyte abnormalities [i.e., hyperkalemia, hypocalcemia]), alterations to coronary vasoreactivity, and ventricular remodeling and fibrosis that indirectly exert negative effects on cardiac performance. AKI may also adversely impact cardiac function by contributing to alternations in drug pharmacokinetics and pharmacodynamics.

CI-AKI serves as a prototypical example of type III CRS. CI-AKI remains a leading cause of iatrogenic kidney injury following diagnostic and interventional procedures and portends adverse effects on prognosis, progression of CKD, and consumption of health resources. While AKI is most often attributable to the administration of radiocontrast media, additional susceptibilities and confounding factors in the population undergoing the procedure are also likely to be contributory (i.e., atheroembolic disease, kidney hypoperfusion, concomitant nephrotoxins). The reported incidence is highly variable depending on the population at risk being evaluated and the type of procedure performed (i.e., emergent, intravascular, type, and volume of contrast media). The natural history of CI-AKI in many patients may follow an asymptomatic rise in serum creatinine with early return to baseline, and these patients would not be expected to fulfill the criteria for type III CRS. However, in an estimated 0.2–1.1 %, AKI progresses to require the initiation of renal replacement therapy (RRT) [9, 10].

In these patients, AKI may be associated with volume overload, retention of uremic solutes, CHF, pulmonary edema, and cardiac arrhythmias. Several factors have been found to independently predict development of more severe AKI after contrast media including older age, preexisting CKD, diabetes mellitus, cerebral vascular disease, heart failure, and volume/dose of contrast media. However, the difficulty in evaluating the epidemiology of type III CRS attributable to CI-AKI or AKI from other causes is that few studies have specifically reported the temporal occurrence of cardiovascular events following AKI.

6.3 The Kidney and the Lung

Kidney and lung injury are highly prevalent in critical illness. These two organ systems are intimately interconnected. Injury and/or dysfunction in either or both of these organ systems can directly incite or exacerbate injury and/or impairment in the other.

6.3.1 Impact of AKI on Lung Function

The loss of metabolic/fluid homeostasis and excretory function characteristic of AKI is associated with the retention of metabolic waste products (i.e., uremic toxins), nonvolatile acids, and the expansion of extracellular volume. This decrement in kidney function can precipitate clinically important and adverse physiological consequences on the normal function of numerous organ systems, in particular the lung [1]. The accumulation of uremic compounds is known to contribute to lung inflammation and injury and has been termed *uremic pneumonitis*. However, this complication of AKI is rarely seen due to earlier initiation and more intensive application of RRT [11]. Metabolic derangement in AKI, such as abnormalities in serum phosphate and calcium level and metabolic acidosis, may also contribute to respiratory muscle weakness and dysfunction [12]. Perhaps the most common life-threatening pulmonary complication associated with AKI is alveolar edema. Expansion of extracellular volume can contribute to increased pulmonary capillary hydrostatic pressure. This coupled with alterations to pulmonary microvascular permeability and reduced serum oncotic pressure can predispose to rapid increases in extravascular lung water [13]. AKI can also contribute to lowering the threshold for accumulation of extravascular lung water [14] along with impaired clearance of alveolar fluid once present. Indeed, lung injury in AKI can occur in the absence of overt volume overload [15]. This is due, in part, to the downregulation of epithelial sodium transporters (ENaC), sodium-potassium adenosine triphosphatases (Na-K-ATPase), and aquaporins at the alveolar-capillary barrier. In further support of the hypothesis that lung injury in AKI represents more than alveolar edema, experimental models of ischemic-/reperfusion-induced AKI have shown lung injury that is characterized by not only pulmonary vascular congestion and interstitial edema but also focal alveolar hemorrhage and inflammatory cell infiltrate [16]. Indeed, the systemic inflammation incited by AKI, including the release and reduced clearance of proinflammatory mediators, is an important mechanism contributing to acute lung injury. Moreover, the magnitude of AKI, both in terms of severity and duration, can also modify the intensity of lung injury.

Naturally, this organ crosstalk and associated clinical complications may be aggravated in critical illness due to concurrent widespread systemic inflammation (i.e., sepsis, major trauma) and diminished baseline physiological reserve due to preexisting chronic lung, cardiac, or kidney disease and in response to resuscitation (i.e., large-volume resuscitation). Among patients receiving mechanical ventilation, the development of AKI has been associated with impaired or delayed weaning,

Table 6.2 Potential mechanisms of impaired kidney function associated with mechanical ventilation

Alterations to cardiovascular function	Reduced cardiac output
	Reduced renal blood flow
	Altered distribution of intrarenal blood flow
	Elevated inferior vena cava and renal vein pressure
Alterations to neuro-hormonal function	Sympathetic nervous system activation
	Renin-angiotensin-aldosterone system stimulation
	Reduced atrial natriuretic peptide secretion
	Increased (non-osmotic) arginine vasopressin secretion
Exaggerated effects of mechanical ventilation	Intravascular volume depletion
	Impaired baseline myocardial performance
	Alterations to pulmonary compliance
	Prior chronic kidney disease
	Prior chronic pulmonary disease

higher likelihood of tracheostomy, and prolongation of ICU stay [17]. Those patients developing lung injury and respiratory failure necessitating mechanical ventilation, concurrent with or following an episode of AKI, have worse outcome and increased risk of mortality [18, 19].

6.3.2 Impact of Lung Injury on the Kidney

Lung injury, such as acute respiratory distress syndrome (ARDS), can contribute to downstream kidney injury and dysfunction through a number of mechanisms including impaired gas exchange, systemic and regional hemodynamic alterations, systemic inflammation, and the application of mechanical ventilation (Table 6.2).

Abnormalities in gas exchange are common among critically ill patients with lung injury. These patients often receive supplemental oxygen, noninvasive ventilatory support, or invasive mechanical ventilation when respiratory failure ensues, with the aim of correcting hypoxemia and restoring near-normal gas exchange. However, this is often challenging or not possible, and many patients may have residual hypoxemia or hypercapnea in the setting of ARDS and lung-protective ventilation and/or permission hypercapnea. The exact mechanisms by which hypoxemia contributes to AKI are incompletely understood and, however, are likely multifactorial and relate to altered cardiovascular function, renal microcirculatory dysfunction, neuro-hormonal activation, and circulating systemic inflammatory mediators [20]. Small clinical studies have suggested that hypoxemia may impair renal autoregulation and glomerular filtration rate (GFR) and contribute to sodium and water retention, while reversal of hypoxemia may improve renal blood flow (RBF) [21, 22]. Hypercapnea has also been associated with impaired kidney function, attributed to alterations in RBF and renovascular resistance; however, experimental data have been inconsistent [23]. Further, acute hypercapnea can also

Table 6.3 Mechanisms of ventilator-induced lung injury (VILI)

Volutrauma	Ventilation with excessive tidal volume or end-expiratory volumes
Barotrauma	Ventilation with excessive end-inspiratory or plateau pressures
Atelect-trauma	Ventilation below the lower inflection point on the pressure-volume curve with cyclic opening and closing of alveoli
Biotrauma	Local and systemic release of inflammatory mediators in response to mechanical stress and disruption of alveoli

contribute to or worsen existing acidemia. The combined impact of hypoxemia and hypercapnea may act synergistically to impair kidney function [24].

Lung injury may be the result of primary lung disease (i.e., aspiration, contusion) or a systemic process (i.e., pancreatitis, sepsis); however, the application of mechanical ventilation is well recognized as a potentially important precipitant or exacerbating factor in lung injury. Ventilator-induced lung injury (VILI) is attributable to the use of excessive end-inspiratory pressures and volumes coupled with the added effects of barotrauma, atelect-trauma, and biotrauma (Table 6.3). The mechanical disruption of the alveolar-capillary barrier from excessive pressure-volume loading during positive pressure ventilation can induce the release of local inflammatory mediators into the systemic circulation [25]. This inflammation due to VILI can contribute to downstream end-organ injury, including AKI [26]. In a murine model of lung injury, the application of injurious MV was associated with increased expression of IL-6 in kidney tissue, increased evidence of renal tubular apoptosis, and impaired kidney function [27, 28].

6.4 The Kidney in the Abdominal Compartment

The kidneys are encapsulated organs, located in the retroperitoneal space of the abdominal compartment. Therefore, alterations in the abdomen can seriously disturb kidney function. This section discusses the impact of elevated intra-abdominal pressure (IAP), deranged splanchnic and renal hemodynamics, and abdominal organ dysfunction on renal function in critically ill patients.

6.4.1 Intra-abdominal Hypertension and Abdominal Compartment Syndrome

There has been increasing focus on the detrimental effects of elevated IAP in AKI [29]. IAP is normally between 5 and 7 mmHg in healthy individuals and $\leq$10 mmHg in critically ill adults, measured supine at end-expiration, zeroed at the level where the midaxillary line crosses the iliac crest [30]. By consensus, intra-abdominal hypertension (IAH) is defined as a sustained increase in IAP $\geq$12 mmHg, and abdominal compartment syndrome (ACS) as a sustained increase >20 mmHg with new organ dysfunction/failure [30]. The most important risk factors for these

conditions are shock/hypotension, resuscitation with a large amount of fluids, and worsening respiratory status [31]. Therefore, it should not be surprising that IAH is common among critically ill patients and associated with worse outcome [32]. However, it is less clear whether the relationship between IAH and organ dysfunction represents cause and effect and if prevention/treatment of IAH might improve organ function and prognosis.

6.4.2 Elevated Intra-abdominal Pressure and Renal Function

Elevated IAP influences renal function in different ways. First, IAH might lead to a significant decrease in RBF as renal perfusion pressure equals mean arterial pressure minus IAP [33]. Further, higher intrarenal vascular resistance (organ compression) shunts blood away from the kidneys. This is of particular concern for the renal medulla, which receives only ~12 % of the RBF, exacerbated by neurohumoral activation [34]. Indeed, AKI through ischemic tubular necrosis is probably the most common complication in the ICU necessitating RRT. Second, the combination of systemic venous congestion and elevated IAP decreases the glomerular filtration gradient [35]. Because the kidney is an encapsulated organ, a pressure rise in the venous system translates into a higher renal interstitial and Bowman's capsular pressure, directly impeding glomerular filtration [36, 37]. Intriguingly, in advanced heart failure – presumably because of low renal perfusion – the kidneys are extremely sensitive to even small elevations in IAP (8–10 mmHg) [38]. Moreover, decreasing IAP in such cases, through ultrafiltration or paracentesis, can dramatically improve renal function [38]. Extrapolating these findings to the general ICU population, recent evidence suggests that a comprehensive management strategy with appropriate use of an open abdomen in patients at risk significantly improves survival from IAH/ACS [39].

6.4.3 Gut Microbiota and the Intestinal Barrier Function

A new area of research is the role of gut microbiota in AKI. It has been clearly established that bacterial fermentation processes in the large intestines are an important source of tightly protein-bound toxins such as p-cresyl sulfate and indoxyl sulfate [40]. Because of this protein binding, such toxins are difficult to clear from the circulation, even by means of hemodialysis [41]. They may accelerate kidney dysfunction, and plasma levels are correlated to all-cause mortality [42, 43]. This offers a strong rationale for targeting gut microbiota and toxin production in the bowel compartment with future therapies.

In normal circumstances, the gut has an important barrier function, preventing entrance of toxins and microorganisms into the systemic circulation. However, especially when abdominal perfusion is impaired, like in advanced heart failure or patients with IAH, this function might become compromised [44]. Indeed, it has been shown that the intestinal morphology, permeability, and function are substantially altered in heart failure [45, 46]. Consequently, leakage of lipopolysaccharides

in the systemic circulation may cause further hemodynamic compromise leading to a detrimental vicious cycle [44, 47]. As the ICU clusters, the most vulnerable patients with regard to hemodynamic compromise, kidney and organ dysfunction, this is likely an underrecognized problem and should be an area of further research. Only recently, IAP has been identified as a potential missing link in patients with cardiorenal syndrome, and the term cardio-abdominal-renal syndrome (CARS) was coined [44].

6.4.4 Hepatorenal Syndrome

AKI is a fearsome complication in patients with decompensating liver cirrhosis, where it occurs in ~20 %, and is associated with poor outcome [48]. Patients with cirrhosis are susceptible to developing AKI because of the progressive vasodilatory state and reduced effective blood volume. Hepatorenal syndrome is initiated by portal hypertension and may be triggered by bacterial infections, nonbacterial systemic inflammatory reactions, excessive diuresis, gastrointestinal hemorrhage, diarrhea, nephrotoxic agents, or IAH [49]. Orthotopic liver transplantation is the best current treatment and leads to a gradual recovery of renal function in the vast majority of patients.

6.4.5 Conclusions

The kidneys are well-perfused organs, located inside the retroperitoneal space of the abdomen. Elevated IAP may seriously disrupt systemic and renal hemodynamics, which might cause renal dysfunction and loss of intestinal barrier function with subsequent entry of toxins into the systemic circulation. A more thorough understanding of kidney-organ interactions in the abdominal compartment may hopefully lead to new therapeutic targets to better preserve renal function in critically ill patients. Within this regard it is important to consider IAP as a missing link in patients with congestive heart failure developing worsening kidney function. This condition has been termed as CARS.

6.5 The Kidney and the Brain

The kidney and brain are vital organs protected in health by an autoregulated blood supply. Both organs play a role in regulating sodium and water balance in the body and visceral sympathetic nervous system activity.

6.5.1 Hyponatremia

Hyponatremia may occur following acute cerebral damage, with reports of an incidence of 56 % postsubarachnoid hemorrhage, but may also develop posttraumatic brain injury. Mortality increases as serum sodium falls, increasing as serum sodium

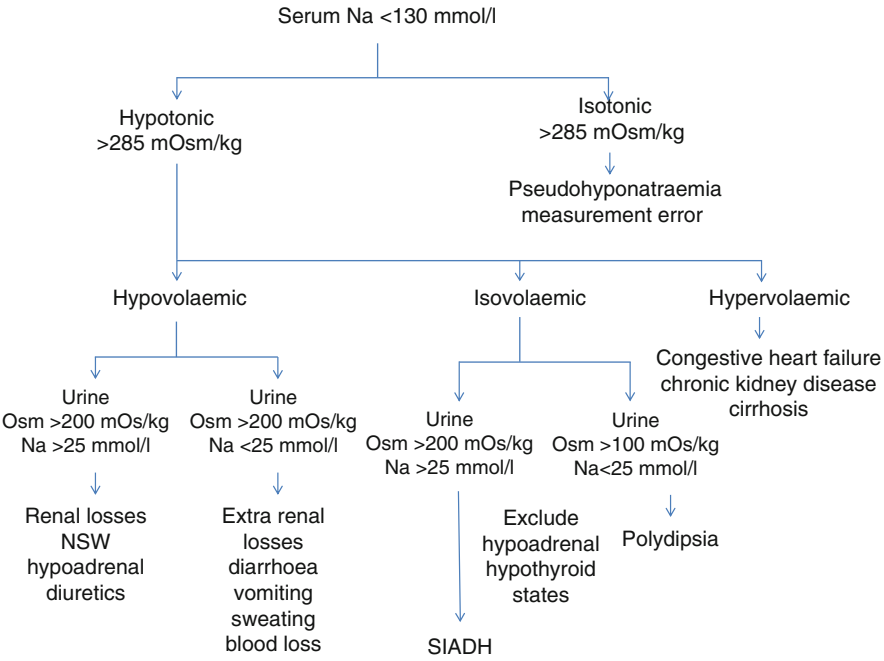

Fig. 6.1 Investigating hyponatremia in the brain-injured patient. Clinically examine patients and determine volume status, and review daily weights and serial estimations of fluid intake and output charts, then check serum osmolality, hematocrit, urea, creatinine, and urate and urinary osmolality and electrolytes. Measure liver function tests and thyroid, adrenal, and natriuretic hormones as required

falls from <130 to <120 mmol/L from 11 to 25 % [50]. Vasopressin release from the hypothalamus, termed syndrome of inappropriate antidiuretic hormone release (SIADH) and leads to water retention by the kidney, is the most common cause of hyponatremia (60–70 %), but cerebral salt wasting, now termed nephrogenic sodium wasting (NSW), may also develop (6–10 %). Both conditions cause hyponatremia, and although physical examination may help to discriminate between these conditions, with SIADH patients typically being euvolemic [51] and those with NSW having signs of extracellular volume depletion, in clinical practice, it may be difficult to distinguish between these conditions and, in a small proportion of cases, both conditions may be present (5 %). Similarly biochemical investigation may also be unhelpful as both conditions will have a reduced serum osmolality (<285 mOsmo/kg), with a relatively increased urinary sodium (>25 mmol/l) and urinary osmolality (>200 mOsmo/kg) (Fig. 6.1). However, patients with NSW should have increased urea, creatinine, and hematocrit due to intravascular volume depletion, whereas they should be normal or lowered in SIADH due to relative water retention [52]. In both conditions serum urate is typically reduced. It is important to make the correct diagnosis as instituting the standard treatment for SIADH, namely, water restriction and

a vasopressin receptor antagonist, can lead to permanent ischemic cerebral damage and mortality in patients with NSW, who require a controlled increase in serum sodium, approximately 8 mmol/day, using hypertonic saline in combination with fludrocortisone [53].

6.5.2 Hypernatremia

Cranial diabetes insipidus can develop acutely posttraumatic brain injury, pituitary surgery or infarction, stroke, cerebral tumor, and infection (meningitis or encephalitis), although most cases are idiopathic and are thought to be autoimmune. Initially patients are polyuric, passing a dilute urine (<150 mOsm/kg) due to a failure of vasopressin release but after 4–5 days may then become transiently oliguric due to the release of stored ADH from the hypothalamus, before a chronic state ensues [54]. The conscious patient typically compensates by drinking large volumes of water, but the unconscious patient may develop profound life-threatening hypernatremia.

For patients with acute hypernatremia (<48 h), rapid lowering of serum sodium by 1 mmol/h by the administration of hypotonic fluids does not increase the risk of cerebral edema, whereas those with hypernatremia of unknown or longer duration a slower pace of correction, aiming for around 10 mmol/L/day is important to prevent cerebral edema. As the risk of cerebral edema also depends upon the volume infused, then smaller volumes of more hypotonic fluids are advantageous [55].

$$\text{Water deficit} = \text{Total body water} \times \left(\left(\text{Current serum sodium} / 140 \right) - 1 \right).$$

6.5.3 Acute Kidney Injury and the Brain

Acute kidney injury typically leads to systemic inflammation, exacerbated by reduced cytokine clearances. Cytokines and other inflammatory mediators may gain entry to the brain through the fenestrated vascular endothelium in the floor of the third ventricle, leading to appetite suppression and increasing the risk of delirium [56]. Increasing osmolality and inflammation as renal failure progressively leads to the disruption of the blood-brain barrier. In addition, kidney failure leads to the accumulation of the waste products of nitrogen metabolism, with organic acids accumulating in the brain, resulting in changes in both neuronal intracellular osmolality and neurotransmitter levels [57]. So, if untreated, patients become encephalopathic with classic slow wave brain electrical activity (loss of alpha and beta waves, with predominance of theta and delta wave activity) [58] (Fig. 6.2).

Patients with kidney failure are at greater risk of drug-induced encephalopathy, as many drugs are transported from the brain by organic acid transporters, and due to the competition for these transporters, clearance from the brain is delayed leading to accumulation.

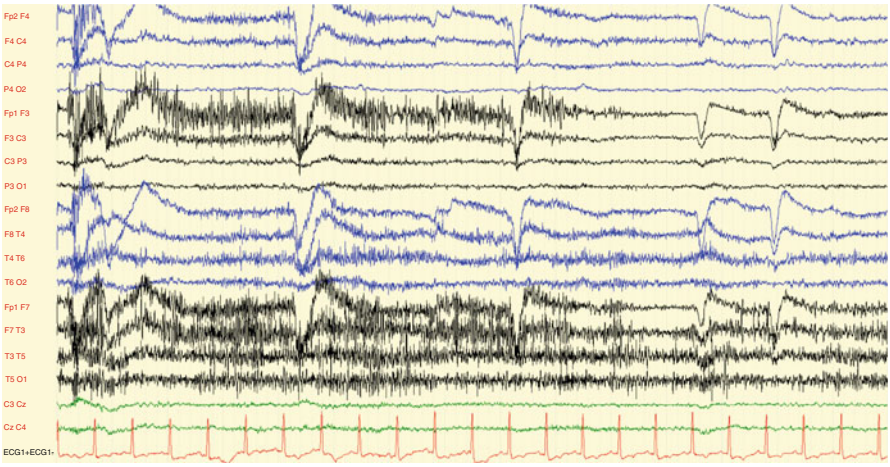

Fig. 6.2 Electrical encephalography from a patient with uremic encephalopathy showing absent normal faster alpha and beta activity with predominance of slower theta and delta wave activity

Initially kidney transplant recipients may develop an acute psychosis due to high doses of steroids and also an acute encephalopathy due to immunophyllin neurotoxicity (tacrolimus > cyclosporin) [59], and treatment of acute rejection with the newer anti-lymphocyte antibody therapies. Thereafter, continued immunosuppression to maintain kidney transplant function increases the risk of cerebral infections, including viral encephalitis and listerial and fungal meningitis [60].

6.5.4 Conditions Affecting Both the Kidney and Brain

The brain and kidney can both be acutely affected by infections (bacterial, leptospirosis; viral, Epstein-Barr virus, human immunodeficiency virus; and protozoal, malaria) and also by systemic vasculitides (polyarteritis nodosa, microscopic polyangiitis). Other conditions including sarcoidosis can cause chronic disease in both organs, and some patients with adult polycystic kidney disease are predisposed to intracerebral aneurysms.

Conclusions

The kidney interacts with virtually all organ systems in the body. Acute injury to the kidney can clearly contribute to cardiac, pulmonary, gastrointestinal, hepatic, and neurologic injury and/or dysfunction through a host of mechanisms. Likewise, primary injury and/or dysfunction to any of these organ systems can directly and indirectly contribute to kidney injury and impairment.

Key Messages

The Kidney and the Heart

- Kidney and cardiac diseases commonly coexist. Injury and/or dysfunction in either organ system can synergistically cause injury and/or dysfunction in the other.
- Acute cardiac events (i.e., ADHF, AMI) can contribute to AKI through hemodynamic, neuroendocrine, and inflammation mechanisms.
- AKI can directly and indirectly contribute to acute cardiac events through complications related to loss of kidney excretory function, along with neuro-hormonal activation and systemic inflammation.

The Kidney and the Lung

- The kidney and lung are commonly injured in critical illness.
- In AKI, the loss of kidney excretory function expands extracellular volume to increase the risk of pulmonary capillary hydrostatic pressure. This is exacerbated by downregulation of key fluid transport molecules in the alveoli, alterations to microvascular permeability, and reduced serum oncotic pressure, which further lower the threshold for alveolar edema and impair alveolar fluid clearance.
- Mechanical ventilation, through alterations in intrathoracic pressures and systemic hemodynamics and through exacerbation of lung injury, can contribute to AKI and negatively impact kidney function.

The Kidney and the Abdominal Compartment

- Normal IAP is $\leq$10 mmHg in critically ill patients.
- IAH (sustained IAP >12 mmHg) is frequently associated with AKI through multiple pathways (fluid overload, low perfusion, neurohumoral).
- Elevated IAP is considered an important contributor in patients with congestive heart failure and worsening kidney function, and this is termed CARS.
- Gut microbiota and toxins may play a role in the development of AKI and form an area for future research.
- Hepatorenal syndrome needs to be considered in patients with cirrhosis and worsening kidney function.

The Kidney and the Brain

- Nephrogenic sodium wasting is a potential cause of hyponatremia in patients with acute brain injury and infections and must not be confused with SIADH.
- Cranial diabetes insipidus may develop acutely following acute brain injury and pituitary surgery, causing hypernatremia.

- Renal transplant patients are at increased risk of drug-induced encephalopathy and psychotic reactions during the first weeks post transplantation.
- In the longer-term renal transplant, patients are immunocompromised and remain at risk of cerebral infections.

References

1. Grams ME, Rabb H. The distant organ effects of acute kidney injury. Kidney Int. 2012;81(10):942–8.
2. Aronson D, Burger AJ. The relationship between transient and persistent worsening renal function and mortality in patients with acute decompensated heart failure. J Card Fail. 2010;16(7):541–7.
3. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, et al. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. Am J Cardiol. 2000;85(9):1110–3.
4. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, et al. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. Eur J Heart Fail. 2008;10(2):188–95.
5. Smith GL, Vaccarino V, Kosiborod M, Lichtman JH, Cheng S, Watnick SG, et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? J Card Fail. 2003;9(1):13–25.
6. Jose P, Skali H, Anavekar N, Tomson C, Krumholz HM, Rouleau JL, et al. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. J Am Soc Nephrol. 2006;17(10):2886–91.
7. Newsome BB, Warnock DG, McClellan WM, Herzog CA, Kiefe CI, Eggers PW, et al. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. Arch Intern Med. 2008;168(6):609–16.
8. Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. J Am Soc Nephrol. 2003;14(6):1549–58.
9. Weisbord SD, Hartwig KC, Sonel AF, Fine MJ, Palevsky P. The incidence of clinically significant contrast-induced nephropathy following non-emergent coronary angiography. Catheter Cardiovasc Interv. 2008;71(7):879–85.
10. Weisbord SD, Mor MK, Resnick AL, Hartwig KC, Sonel AF, Fine MJ, et al. Prevention, incidence, and outcomes of contrast-induced acute kidney injury. Arch Intern Med. 2008;168(12):1325–32.
11. Hopps HC, Wissler RW. Uremic pneumonitis. Am J Pathol. 1955;31(2):261–73.
12. Bush A, Gabriel R. The lungs in uraemia: a review. J R Soc Med. 1985;78(10):849–55.
13. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical, Trials N, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564–75.
14. Slutsky RA, Day R, Murray M. Effect of prolonged renal dysfunction on intravascular and extravascular pulmonary fluid volumes during left atrial hypertension. Proc Soc Exp Biol Med. 1985;179(1):25–31.
15. Kramer AA, Postler G, Salhab KF, Mendez C, Carey LC, Rabb H. Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. Kidney Int. 1999;55(6):2362–7.

16. Hassoun HT, Grigoryev DN, Lie ML, Liu M, Cheadle C, Tuder RM, et al. Ischemic acute kidney injury induces a distant organ functional and genomic response distinguishable from bilateral nephrectomy. Am J Physiol Renal Physiol. 2007;293(1):F30–40.
17. Vieira Jr JM, Castro I, Curvello-Neto A, Demarzo S, Caruso P, Pastore Jr L, et al. Effect of acute kidney injury on weaning from mechanical ventilation in critically ill patients. Crit Care Med. 2007;35(1):184–91.
18. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med. 1998;104(4): 343–8.
19. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med. 2002;30(9):2051–8.
20. Aksu U, Demirci C, Ince C. The pathogenesis of acute kidney injury and the toxic triangle of oxygen, reactive oxygen species and nitric oxide. Contrib Nephrol. 2011;174:119–28.
21. Howes TQ, Deane CR, Levin GE, Baudouin SV, Moxham J. The effects of oxygen and dopamine on renal and aortic blood flow in chronic obstructive pulmonary disease with hypoxemia and hypercapnia. Am J Respir Crit Care Med. 1995;151(2 Pt 1):378–83.
22. Reihman DH, Farber MO, Weinberger MH, Henry DP, Fineberg NS, Dowdeswell IR, et al. Effect of hypoxemia on sodium and water excretion in chronic obstructive lung disease. Am J Med. 1985;78(1):87–94.
23. Anderson RJ, Rose Jr CE, Berns AS, Erickson AL, Arnold PE. Mechanism of effect of hypercapnic acidosis on renin secretion in the dog. Am J Physiol. 1980;238(2):F119–25.
24. Rose Jr CE, Kimmel DP, Godine Jr RL, Kaiser DL, Carey RM. Synergistic effects of acute hypoxemia and hypercapnic acidosis in conscious dogs. Renal dysfunction and activation of the renin-angiotensin system. Circ Res. 1983;53(2):202–13.
25. Chiumello D, Pristine G, Slutsky AS. Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. Am J Respir Crit Care Med. 1999;160(1):109–16.
26. Meduri GU, Headley S, Kohler G, Stentz F, Tolley E, Umberger R, et al. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. Chest. 1995;107(4):1062–73.
27. Gurkan OU, O'Donnell C, Brower R, Ruckdeschel E, Becker PM. Differential effects of mechanical ventilatory strategy on lung injury and systemic organ inflammation in mice. Am J Physiol Lung Cell Mol Physiol. 2003;285(3):L710–8.
28. Imai Y, Parodo J, Kajikawa O, de Perrot M, Fischer S, Edwards V, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA. 2003;289(16):2104–12.
29. Malbrain ML, Chiumello D, Pelosi P, Bihari D, Innes R, Ranieri VM, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med. 2005;33(2):315–22.
30. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39(7):1190–206.
31. Holodinsky JK, Roberts DJ, Ball CG, Blaser AR, Starkopf J, Zygun DA, et al. Risk factors for intra-abdominal hypertension and abdominal compartment syndrome among adult intensive care unit patients: a systematic review and meta-analysis. Crit Care. 2013;17(5):R249.
32. Vidal MG, Ruiz Weisser J, Gonzalez F, Toro MA, Loudet C, Balasini C, et al. Incidence and clinical effects of intra-abdominal hypertension in critically ill patients. Crit Care Med. 2008;36(6):1823–31.
33. Wauters J, Claus P, Brosens N, McLaughlin M, Malbrain M, Wilmer A. Pathophysiology of renal hemodynamics and renal cortical microcirculation in a porcine model of elevated intra-abdominal pressure. J Trauma. 2009;66(3):713–9.

34. Janssen WM, Beekhuis H, de Bruin R, de Jong PE, de Zeeuw D. Noninvasive measurement of intrarenal blood flow distribution: kinetic model of renal 123I-hippuran handling. Am J Physiol. 1995;269(4 Pt 2):F571–80.
35. Dupont M, Mullens W, Tang WH. Impact of systemic venous congestion in heart failure. Curr Heart Fail Rep. 2011;8(4):233–41.
36. Maxwell MH, Breed ES, Schwartz IL. Renal venous pressure in chronic congestive heart failure. J Clin Invest. 1950;29(3):342–8.
37. Gottschalk CW, Mylle M. Micropuncture study of pressures in proximal tubules and peritubular capillaries of the rat kidney and their relation to ureteral and renal venous pressures. Am J Physiol. 1956;185(2):430–9.
38. Mullens W, Abrahams Z, Francis GS, Taylor DO, Starling RC, Tang WH. Prompt reduction in intra-abdominal pressure following large-volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure. J Card Fail. 2008;14(6):508–14.
39. Cheatham ML, Safcsak K. Is the evolving management of intra-abdominal hypertension and abdominal compartment syndrome improving survival? Crit Care Med. 2010;38(2):402–7.
40. Evenepoel P, Meijers BK, Bammens BR, Verbeke K. Uremic toxins originating from colonic microbial metabolism. Kidney Int Suppl. 2009;114:S12–9.
41. Meyer TW, Leeper EC, Bartlett DW, Depner TA, Lit YZ, Robertson CR, et al. Increasing dialysate flow and dialyzer mass transfer area coefficient to increase the clearance of protein-bound solutes. J Am Soc Nephrol. 2004;15(7):1927–35.
42. Bammens B, Evenepoel P, Keuleers H, Verbeke K, Vanrenterghem Y. Free serum concentrations of the protein-bound retention solute p-cresol predict mortality in hemodialysis patients. Kidney Int. 2006;69(6):1081–7.
43. Niwa T, Nomura T, Sugiyama S, Miyazaki T, Tsukushi S, Tsutsui S. The protein metabolite hypothesis, a model for the progression of renal failure: an oral adsorbent lowers indoxyl sulfate levels in undialyzed uremic patients. Kidney Int Suppl. 1997;62:S23–8.
44. Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WH, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol. 2013;62(6):485–95.
45. Arutyunov GP, Kostyukevich OI, Serov RA, Rylova NV, Bylova NA. Collagen accumulation and dysfunctional mucosal barrier of the small intestine in patients with chronic heart failure. Int J Cardiol. 2008;125(2):240–5.
46. Magnusson M, Magnusson KE, Sundqvist T, Denneberg T. Impaired intestinal barrier function measured by differently sized polyethylene glycols in patients with chronic renal failure. Gut. 1991;32(7):754–9.
47. Charalambous BM, Stephens RC, Feavers IM, Montgomery HE. Role of bacterial endotoxin in chronic heart failure: the gut of the matter. Shock. 2007;28(1):15–23.
48. Hartleb M, Gutkowski K. Kidneys in chronic liver diseases. World J Gastroenterol. 2012;18(24):3035–49.
49. Kramer L, Horl WH. Hepatorenal syndrome. Semin Nephrol. 2002;22(4):290–301.
50. Wright WL. Sodium and fluid management in acute brain injury. Curr Neurol Neurosci Rep. 2012;12(4):466–73.
51. Esposito P, Piotti G, Bianzina S, Malul Y, Dal Canton A. The syndrome of inappropriate antidiuresis: pathophysiology, clinical management and new therapeutic options. Nephron Clin Pract. 2011;119(1):c62–73; discussion c73.
52. Maesaka JK, Imbriano LJ, Ali NM, Ilamathi E. Is it cerebral or renal salt wasting? Kidney Int. 2009;76(9):934–8.
53. Yee AH, Burns JD, Wijdicks EF. Cerebral salt wasting: pathophysiology, diagnosis, and treatment. Neurosurg Clin N Am. 2010;21(2):339–52.
54. Di Iorgi N, Napoli F, Allegri AE, Olivieri I, Bertelli E, Gallizia A, et al. Diabetes insipidus–diagnosis and management. Horm Res Paediatr. 2012;77(2):69–84.
55. Chanson P, Salenave S. Treatment of neurogenic diabetes insipidus. Ann Endocrinol. 2011; 72(6):496–9.

56. Liu M, Liang Y, Chigurupati S, Lathia JD, Pletnikov M, Sun Z, et al. Acute kidney injury leads to inflammation and functional changes in the brain. J Am Soc Nephrol. 2008;19(7): 1360–70.
57. Palkovits M, Sebekova K, Gallatz K, Boor P, Sebekova Jr K, Klassen A, et al. Neuronal activation in the CNS during different forms of acute renal failure in rats. Neuroscience. 2009; 159(2):862–82.
58. Adachi N, Lei B, Deshpande G, Seyfried FJ, Shimizu I, Nagaro T, et al. Uraemia suppresses central dopaminergic metabolism and impairs motor activity in rats. Intensive Care Med. 2001;27(10):1655–60.
59. Mammoser A. Calcineurin inhibitor encephalopathy. Semin Neurol. 2012;32(5):517–24.
60. Senzolo M, Ferronato C, Burra P. Neurologic complications after solid organ transplantation. Transpl Int. 2009;22(3):269–78.