CHAPTER 104

Cardiovascular Problems in Acute Kidney Injury

Martin K. Kuhlmann

OBJECTIVES

This chapter will:

1. Delineate the differences between cardiovascular problems in acute kidney injury and those in chronic kidney disease.
2. Characterize the typical cardiovascular problems occurring in acute kidney injury and their consequences for patient outcome.
3. Review the basic pathophysiologic concepts underlying the development of cardiovascular problems in acute kidney injury.

Kidney and heart disease often coexist; the heart is highly dependent on regulation of salt and water homeostasis by the kidneys, which in turn directly depend on blood flow and pressure generated by the heart. A physiologic organ-to-organ crosstalk between these two organs is necessary to maintain the regular homeostasis and the normal functioning of the human body. During disease states, the damaged organ can induce structural and functional dysfunction in the other organ. Thus acute or chronic cardiac disease can contribute directly to concurrent worsening of kidney function, and vice versa; acute kidney injury can induce a variety of cardiovascular complications, such as decompensated heart failure, acute myocardial infarction, and arrhythmias. The term cardiorenal syndrome (CRS) is used to describe these clinically evident interdependencies between heart and kidneys. Among the five types of CRS, type 3 is defined as acute cardiac complications resulting from an acute decline in kidney function, as it is seen in acute kidney injury (AKI) (Fig. 104.1).[1,2]

CARDIOVASCULAR COMPLICATIONS IN CHRONIC KIDNEY DISEASE

It is well appreciated that the cardiovascular mortality rate is excessively high in end-stage renal disease (ESRD) as a result of accelerated arteriosclerosis and vascular calcifications.[3] The disease process leading to these complications, however, starts during much earlier stages of chronic kidney disease (CKD), and even mild to moderate CKD is associated with increased cardiovascular morbidity and mortality.[4] The evidence is becoming increasingly clear that renal dysfunction not only carries the risk for development of cardiovascular diseases but also is a significant independent risk factor for adverse events in patients with acute illnesses such as myocardial infarction. It has been demonstrated that the presence of mild to moderate renal impairment in these patients increases the rate of adverse outcomes and that the mortality risk increases with declining renal function. For patients with a glomerular filtration rate (GFR) below 81.0 mL/min per 1.73 m^2 of body surface, each 10-unit reduction in baseline estimated GFR is associated with a 10% increase in the relative risk of death or nonfatal cardiovascular complications. Furthermore, rates of reinfarction, congestive heart failure, stroke, and resuscitation are significantly higher in patients with GFRs less than 45 mL/minute per 1.73 m^2 than in those with better renal function.[5] Therefore, among patients who have had a myocardial infarction, any degree of preexisting renal impairment has to be considered a potent and independent risk factor for cardiovascular complications.

The typical cardiovascular problems associated with CKD include vascular and valvular calcifications, left ventricular hypertrophy, left ventricular dilatation, congestive heart failure, arrhythmias, and sudden cardiac death. The exact mechanisms by which chronic renal dysfunction increases the cardiovascular risk are currently under investigation. The progressive increase in cardiovascular risk with worsening GFR is at least partly explained by factors associated with the decline in renal function, such as anemia, oxidative stress, disturbances of calcium-phosphate homeostasis, inflammation, and conditions promoting coagulation. All of these factors are associated with accelerated atherosclerosis and endothelial dysfunction. Another factor, almost unrecognized until recently, is the dialysis procedure. Elegant studies indicate that conventionally administered HD results in recurrent circulatory stress, including myocardial, cerebral, and intestinal hypoperfusion and tissue hypoxia, caused at least in part by a composite loss of individual organ vasoregulatory reserve.[6] The repetitive nature of this injury has a cumulative effect, leading to fixed reductions in left ventricular systolic function and conferring an increased risk of cardiac events, arrhythmia, and mortality.[7]

CARDIOVASCULAR COMPLICATIONS IN ACUTE KIDNEY INJURY

The occurrence of AKI increases the risk for cardiovascular complications and in-hospital death.[8] For a long time it was assumed that the high mortality rate in septic patients with AKI was due mainly to the consequences of sepsis alone and that AKI was only an expression of an aggravated course of the disease. However, it has been recognized that the relationship between sepsis and AKI is more complex than has been appreciated previously.[9] The prognosis for patients in whom AKI develops during an intensive care unit (ICU) stay is worse than that for patients with ESRD referred to ICUs. These differences in outcome between patients with these two forms of kidney disease are not explained by differences in disease severity but rather reflect the additional risk conferred by AKI on top of sepsis.

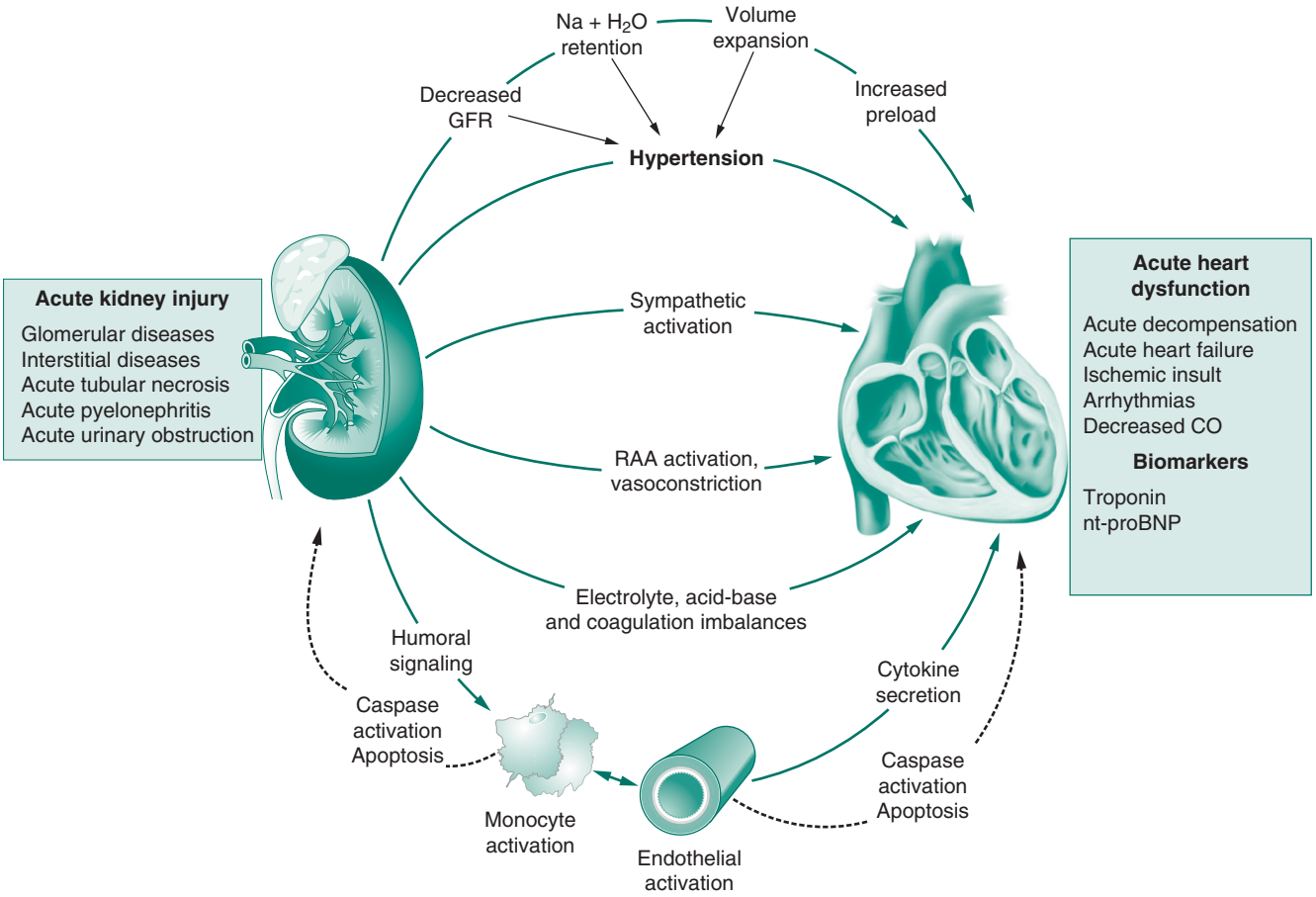

FIGURE 104.1 Pathophysiologic interactions between heart and kidney in type 3 cardiorenal syndrome. *BNP,* brain natriuretic peptide; *CO,* cardiac output; *GFR,* glomerular filtration rate; *RAA,* Renin-Angiotensin-Aldosterone System.

BOX 104.1

Spectrum of Cardiovascular Problems in Acute Kidney Injury

- Hypotension
- Hemodynamic instability
- Congestive heart failure
- Decreased cardiac contractility
- Myocardial ischemia
- Cardiac arrhythmias
- Pulmonary edema
- Respiratory failure
- Acute respiratory distress syndrome (ARDS)

Compared with sepsis patients without AKI, those with AKI have a higher incidence of hemodynamic instability and leukocytosis.[8] Hemodynamic instability is one of the most common cardiovascular problems seen in patients with AKI. Other problems include the wide spectrum of conditions and disorders leading to cardiac and pulmonary dysfunction, which are among the most common causes of death in patients with AKI (Box 104.1). Patients with AKI more frequently require vasoactive medication, mechanical ventilation, cardiopulmonary resuscitation, and treatment of acid-base disturbances. Hypotension, congestive heart failure, respiratory failure, plasma potassium levels, and plasma bicarbonate levels have been shown to be of significant prognostic value for in-hospital death of AKI patients.[10] From several studies examining outcomes and prognostic factors in AKI, it can be concluded that the development of cardiovascular dysfunction in patients with AKI has an important impact on survival in the ICU.[8,11] Furthermore, dialysis-requiring AKI alone is associated with a 1.7-fold higher risk of coronary events, which is similar to the risk conferred by diabetes alone.[87] This complex array of cardiovascular problems in patients with AKI does not necessarily reflect an increased severity of the underlying illness but rather is mediated by traditional and nontraditional complications of AKI.

The traditional cardiovascular complications of AKI are those related to direct consequences of renal dysfunction, such as hyperkalemia, acidosis, uncontrolled uremia, or volume overload.[12] Hyperkalemia can cause life-threatening dysrhythmias, whereas severe acidosis may impair cardiac contractility, reduce vasopressor responsiveness, and contribute to the susceptibility for arrhythmias. Volume overload, which is considered the main factor contributing to patient mortality and morbidity in AKI, is associated with a number of adverse events, including increased intraabdominal pressure, which may delay kidney function recovery, pulmonary edema, which may predispose to lung inflammation and pneumonia, and gut edema, which may lead to bacterial translocation and sepsis.[13] Uncontrolled uremia, on the other hand, may cause pericarditis or upper gastrointestinal bleeding because of impaired platelet function. The mutual "end points" of these traditional adverse cardiovascular events in AKI include myocardial infarction, stroke, and heart failure.[14]

Although traditional complications can be managed by modern renal replacement therapy (RRT), it is the nontraditional complications of AKI that appear to be mainly responsible for the high mortality rate. These nontraditional complications include respiratory failure, cardiac complications, and sepsis, all of which mainly occur in the context of a systemic inflammatory response syndrome (SIRS) triggered or potentiated by AKI. Similar to other systemic illnesses, induction of SIRS eventually results in a dysregulation of the immune system. The inflammatory response to AKI may induce direct injury to the lung capillary endothelium and promote fluid extravasation into the interstitium. In addition to the traditional cardiovascular effects, AKI also may have direct deleterious effects on the heart, inducing acute LV dilatation and alterations of various functional parameters, including LV relaxation times and fractional shortening. Experimental studies have described cardiac histologic changes such as cellular apoptosis and capillary vascular congestion after renal ischemia reperfusion injury or glycerol-induced rhabdomyolysis; AKI also has been shown to lead to cardiac hypertrophy and increased cardiac macrophage accumulation. Cardiocyte apoptosis has been suggested to play a role in promoting these changes along with increased mitochondrial fragmentation and stimulation of inflammatory mediators. These effects likely contribute to short- and long-term deleterious cardiac complications associated with AKI.[15]

Taken together, AKI has to be viewed as a systemic disease affecting multiple organs including lung, heart, liver, intestines, and brain. Traditional and nontraditional complications together lead to a diverse array of complications such as sepsis, respiratory failure, and heart failure that contribute to the increased mortality in AKI patients.

PATHOPHYSIOLOGY OF CARDIOPULMONARY DYSFUNCTION IN ACUTE KIDNEY INJURY

In health, a strong physiologic interaction between renal and cardiovascular function operates to control extracellular fluid volume and arterial blood pressure. Renal failure modifies most of the factors regulating cardiovascular function through direct hemodynamic effects, neurogenic reflexes, and circulating hormones. The main players involved in these interactions are the renin-angiotensin system (RAS), nitric oxide (NO), and the sympathetic nervous system (SNS). AKI affects each of these systems separately, with consequences for cardiovascular function.

Renin-Angiotensin-Aldosterone System

In general, a decrease in renal perfusion pressure results in the activation of the renin-angiotensin-aldosterone (RAAS) with favorable effects on systemic vasoconstriction and volume retention. At the same time, RAAS activation also may have unfavorable effects, such as the formation of reactive oxygen species (ROS), an increase in gene expression of proinflammatory substances, and activation of the SNS.[16] In AKI inappropriate RAAS stimulation contributes to angiotensin II release, vasoconstriction, and dysregulation of extracellular fluid volume homeostasis. Angiotensin II may play a direct role in modifying myocardial structure and function, contribute to cellular hypertrophy, and precipitate apoptosis in cardiac myocyte cultures. It is also responsible for the activation of several cell signaling pathways, including oxidative stress, inflammatory mediators release, and extracellular matrix regulation. Angiotensin II may lead to ROS formation via activation of the enzyme NADPH oxidase.[17]

Nitric Oxide/Reactive Oxygen Species System

NO contributes to the renal control of extracellular fluid volume and arterial blood pressure by causing vasodilatation, natriuresis, and desensitization of the tubuloglomerular feedback.[18] Superoxide, the most aggressive ROS, on the other hand, may have the opposite effect on extracellular fluid volume control and may increase blood pressure. Although NO and ROS are balanced in health, the balance in AKI is shifted toward an increased production of ROS, with a depletion of antioxidants and reduced availability of NO. The resulting oxidative stress has been shown to increase sympathetic nervous system activity, shifting the inflammatory response toward production of proinflammatory cytokines.[16]

Sympathetic Nervous System

Although peripheral and central sympathetic nerve activity are known to be increased in CKD, induction as well as repression of sympathetic activity may occur in AKI. Sympathetic nervous system (SNS) activation stimulates the RAAS, increases the production of ROS, and induces proinflammatory cytokine production.[16] Catecholamines play an important role in maintaining blood pressure by controlling heart rate, myocardial contractility, and the tone of resistance vessels. Whereas sudden, excessive sympathetic activity may induce cardiomyocyte apoptosis, with subsequent hypertrophy and focal myocardial necrosis, chronic sympathetic overactivity may cause β-adrenoceptor insensitivity, a reduction in heart rate variability, and increased susceptibility to arrhythmias. Activation of the SNS also may impair myocardial function through several mechanisms, such as direct effects of norepinephrine, disturbances in myocardial calcium homeostasis, and an increase in myocardial oxygen demand.[1] In animal studies, the pressor responses to norepinephrine and the chronotropic responses to right cervical sympathetic and vagal nerve stimulation were diminished, suggesting that AKI induces cardiovascular depression.[19] This "acquired resistance" to norepinephrine may be responsible for the higher doses of adrenergic substances required in patients with sepsis complicated by AKI.

The presence of myocardial depressant substances in the plasma of patients with chronic as well as acute renal failure, which can be removed by hemofiltration, has been long recognized.[20,21] Although for many years the origin of these myocardial depressant substances was obscure, many indications now point to substances that resemble proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), which exert distinct effects on cardiac function.

Taken together, disturbances in the heart-kidney axis in AKI lead to a dysbalance between oxidants and antioxidants with consequent activation of the RAAS and SNS. Eventually, each of these alterations by itself and, even more, the combination of these disturbances result in a common pathway—the enhanced release of inflammatory mediators. The body's cytokine machinery may in fact be the pathophysiologic driving force for cardiovascular problems in AKI.

Cytokine-Mediated Effects of Acute Renal Failure on Cardiac Function

Critically ill patients with AKI have levels of proinflammatory and antiinflammatory cytokines much higher than those measured in anuric patients with ESRD.[22] The kidney seems to play an important role as an inflammatory focus or mediator in AKI. A sudden reduction in renal function because of renal ischemia or other injury results in a systemic increase in pro- and antiinflammatory cytokine levels.[23] The induction of a proinflammatory environment, however, cannot be explained solely by the loss of the renal cytokine-degrading activity alone. Renal and extrarenal production of cytokines is increased in AKI with prominent cytokine production in liver and spleen.[24] The volume overload resulting from diminished urine output also may be a mediator of plasma cytokine elevation in AKI—a scenario similar to that observed in patients with congestive heart failure.[25]

During AKI, there is an increased amount of cardiac and systemic TNF and IL-1 along with an increased expression of ICAM-1 messenger RNA, selectin, complement activation, ROS, nuclear factor-κB activation, and Toll-like receptor-related pathway.[26] Cytokines may exert an impact on myocardial function through direct effects on myocyte contractility. Proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 and the immunomodulatory cytokine IL-2 typically are considered to impart negative inotropic effects. The nature and pattern of the inotropic response is complex, consisting of an immediate response within minutes that can be either stimulatory or depressant, and a delayed response lasting hours to days that is uniformly cardiodepressant and dependent on the production of secondary mediators. This delayed response may be mainly responsible for the cardiac dysfunction observed during the course of AKI.[27] Similar dose-dependent cardiovascular depression and negative inotropy have been observed in patients with malignancies in which biologic TNF-α and IL-2 were used for immunomodulatory therapy.[28] TNF-α–induced cardiac myocyte apoptosis and neutrophil infiltration play an important role in the pathophysiology of myocardial infarction and can lead to lethal heart dysfunction.[29]

Although AKI alone can be viewed as a state of sustained chronic augmentation of proinflammatory cytokine expression, such increased expression will be even more pronounced in cases in which AKI complicates other diseases with increased cytokine production, such as sepsis. In summary, proinflammatory cytokines can be considered to impart negative inotropic and cardiodepressant effects, thereby contributing significantly to the occurrence of any of the wide spectrum of cardiovascular problems in AKI.

Coronary Vasoregulation in Acute Renal Failure

Myocardial ischemia frequently complicates AKI. Coronary vasoregulation is important for preservation of coronary blood flow and myocardial oxygen supply during sudden changes in blood pressure. Coronary reserve may be reduced as a result of increases in left ventricular mass, circulating neurohumoral factors, and anemia. Animal studies revealed that coronary vascular tone, coronary reserve, and vessel reactivity are diminished markedly in AKI, indicating an impaired function of the coronary vasculature. Consequently, during AKI, small increases in myocardial oxygen demand presumably will induce subendocardial ischemia as a result of a limited capacity to increase oxygen supply. These factors will contribute to the higher risk for adverse coronary events and the increased cardiovascular mortality risk in patients with acute renal failure if increases in myocardial oxygen demand cannot be met because of limited coronary vascular reserve.[30]

Pulmonary Injury in Acute Renal Failure

Pulmonary complications, particularly noncardiogenic acute lung injury, acute respiratory distress syndrome (ARDS), and respiratory failure, commonly are associated with AKI and contribute to mortality.[31,32] Respiratory failure requiring mechanical ventilation occurs twice as often in patients with AKI than in similarly ill patients without AKI and is even more frequent in AKI patients requiring RRT.[11] Respiratory function is an area in which traditional and nontraditional complications of AKI produce devastating consequences. In experimental studies, renal ischemia-reperfusion injury increases pulmonary vascular permeability and induces interstitial edema, alveolar hemorrhage, and red blood cell sludging.[33] Because the lung has the largest microcapillary network in the body, it responds to circulating proinflammatory signals with activation of lung macrophages, secretion of proinflammatory cytokines, recruitment of neutrophils and macrophages, and resultant lung injury.[32] Respiratory failure in AKI is the result of extravasation of fluid into the lung interstitium and alveoli because of cardiogenic or noncardiogenic mechanisms. Cardiogenic pulmonary failure is due mainly to volume overload, whereas noncardiogenic edema occurs as a result of direct injury to lung capillary endothelium, mediated by cytokine-induced inflammation and regional neutrophil recrtuitment.[34]

Acute renal failure also may promote directly lung injury independent of volume retention by downregulating the pulmonary expression of sodium channels and aquaporins.[35] These molecular derangements may have detrimental effects on lung fluid balance, especially in the settings of antecedent or concurrent structural injury of the lung. Impaired pulmonary fluid handling may impede lung function acutely, thus increasing the susceptibility of the lung to injury, particularly during mechanical ventilation.

DIRECT EFFECTS OF RENAL REPLACEMENT THERAPY ON CARDIOVASCULAR COMPLICATIONS

RRT may contribute to short-term as well as long-term cardiovascular complications in AKI. Not until recently the phenomenon of myocardial stunning during hemodialysis treatment was recognized clinically. The occurrence of myocardial stunning has been described in patients with ESRD receiving dialysis and is characterized by organ hypoperfusion and tissue hypoxia. Intradialytic cardiac hypoperfusion leads to disturbances of left ventricular wall contractility and myocardial ischemia. In ESRD patients recurrent episodes of intradialytic myocardial ischemia result in a chronic decrease in left ventricular ejection fraction, a higher risk of decompensated heart failure, and increased cardiac mortality. Higher ultrafiltration volumes (>250 mL/hr) and frequency of intradialytic hypotensive episodes are key factors associated with myocardial stunning. Although there are no clinical data, it is evident from daily clinical practice that intradialytic hypotension occurs frequently in severely ill patients with AKI. Therefore myocardial stunning during dialysis for AKI is likely to be common and may be an important mechanism that contributes to the short- and long-term cardiac mortality associated with AKI.[6,34]

Although untreated AKI often is associated with elevated plasma phosphate levels, patients on RRT carry an increased risk of developing hypophosphatemia.[12] Hypophosphatemia is associated with respiratory muscle weakness and impaired myocardial performance and may affect short-term and long-term cardiovascular outcome in severely ill AKI patients.

CONCLUSION

Acute renal failure is associated with a wide array of cardiovascular problems that are assumed to be related mainly to elevated circulating levels of proinflammatory cytokines. These mediators of acute and chronic inflammation exert unfavorable effects on cardiac contractility, coronary perfusion, and, last but not least, pulmonary vascular permeability. The onset of acute renal failure, with or without concomitant severe illness, has to be regarded as an additional risk factor for increased cardiovascular morbidity and mortality. RRT may contribute to short- and long-term cardiovascular complications of AKI through recurrent myocardial stunning.

Key Points

1. Acute renal failure promotes cardiovascular instability and cardiac dysfunction.
2. The occurrence of cardiovascular dysfunction in patients with acute renal failure increases in-hospital mortality rates.
3. Elevation in levels of circulating proinflammatory cytokines is viewed as the pathophysiologic mechanism for cardiovascular dysfunction in acute renal failure.
4. Proinflammatory cytokines exert distinct cardiodepressant effects.
5. Acute renal failure may lead to an increase in pulmonary vascular permeability, most likely mediated by proinflammatory cytokines.
6. Hemodialysis treatment itself may contribute to cardiovascular stress in AKI patients by inducing hypoxia and hypoperfusion in vulnerable organs such as the heart, brain, gut and kidney.

Key References

6. McIntyre C, Crowley L. Dying to Feel Better: The Central Role of Dialysis–Induced Tissue Hypoxia. *Clin J Am Soc Nephrol*. 2016;11:549-551.
7. Burton JO, Jefferies HJ, Selby NM, et al. Hemodialysis induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol*. 2009;4:1925-1931.
12. Faubel S, Shah PB. Immediate consequences of acute kidney injury: the impact of traditional and nontraditional complications on mortality in acute kidney injury. *Adv Chronic Kidney Dis*. 2016;23:170-185.
17. Kingma JG, Simard D, Rouleau JR. Renocardiac syndromes: physiopathology and treatment stratagems. *Can J Kidney Health Dis*. 2015;2:41.
34. Faubel S, Edelstein CL. Mechanisms and mediators of lung injury after acute kidney injury. *Nat Rev Nephrol*. 2016;12:48-60.

Full references for this chapter can be found on www.expertconsult.com.

References

1. Clementi A, Virzi GM, Brocca A, et al. Advances in the pathogenesis of cardiorenal syndrome type 3. *Oxid Med Cell Longev*. 2015.
2. Chuasuwan A, Kellum JA. Cardio-renal syndrome type 3: epidemiology, pathophysiology, and treatment. *Semin Nephrol*. 2012;32:31-39.
3. Yoshino M, Kuhlmann MK, Kotanko P, et al. International differences in dialysis mortality reflect background general population atherosclerotic cardiovascular mortality. *J Am Soc Nephrol*. 2006;17:3510-3519.
4. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296-1305.
5. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285-1295.
6. McIntyre C, Crowley L. Dying to Feel Better: The Central Role of Dialysis–Induced Tissue Hypoxia. *Clin J Am Soc Nephrol*. 2016;11:549-551.
7. Burton JO, Jefferies HJ, Selby NM, et al. Hemodialysisinduced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol*. 2009;4:1925-1931.
8. Clermont G, Acker CG, Angus DC, et al. Renal failure in the ICU: comparison of the impact of acute renal failure and end-stage renal disease on ICU outcomes. *Kidney Int*. 2002;62:986-996.
9. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. *JAMA*. 1996;275:1489-1494.
10. Behrend T, Miller SB. Acute renal failure in the cardiac unit: etiologies, outcomes, and prognostic factors. *Kidney Int*. 1999;56:238-243.
11. Metnitz PGH. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit Care Med*. 2002;30:2051-2058.
12. Faubel S, Shah PB. Immediate consequences of acute kidney injury: the impact of traditional and nontraditional complications on mortality in acute kidney injury. *Adv Chronic Kidney Dis*. 2016;23:170-185.
13. Butcher BW, Liu KD. Fluid overload in AKI: epiphenomenon or putative effect on mortality? *Curr Opin Crit Care*. 2012;18:593-598.
14. Chawla LS, Amdur RL, Shaw AD, et al. Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. *Clin J Am Soc Nephrol*. 2014;9:448-456.
15. Doi K, Rabb H. Impact of acute kidney injury on distant organ function: recent findings and potential therapeutic targets. *Kidney Int*. 2016;89:555-564.
16. Bongartz LG, Cramer MJ, Doevendans PA, et al. The severe cardiorenal syndrome: 'Guyton revisited'. *Eur Heart J*. 2005;26:11-17.
17. Kingma JG, Simard D, Rouleau JR. Renocardiac syndromes: physiopathology and treatment stratagems. *Can J Kidney Health Dis*. 2015;2:41.
18. Braam B. Renal endothelial and macula densa NOS: integrated response to changes in extracellular fluid volume. *Am J Physiol*. 1999;276:R1551-R1561.
19. Yates MS, Bowmer CJ, Brown GM. Cardiovascular responses in spontaneously hypertensive rats with acute renal failure. *J Pharm Pharmacol*. 1984;36:192-194.
20. Blake P, Hasegawa Y, Khosla MC, et al. Isolation of "myocardial depressant factor(s)" from the ultrafiltrate of heart failure patients with acute renal failure. *ASAIO J*. 1996;42:M911-M915.
21. Horl WH, Riegel W. Cardiac depressant factors in renal disease. *Circulation*. 1993;87(5 suppl):IV77-IV82.
22. Simmons EM, Himmelfarb J, Sezer MT, et al; for the PICARD Study Group. Plasma cytokine levels predict mortality in patients with acute renal failure. *Kidney Int*. 2004;65:1357-1365.
23. Gormley SM, McBride WT, Armstrong MA, et al. Plasma and urinary cytokine homeostasis and renal function during cardiac surgery without cardiopulmonary bypass. *Cytokine*. 2002;17:61-65.
24. Andres-Hernando A, Dursun B, Altmann C, et al. Cytokine production increases and cytokine clearance decreases in mice with bilateral nephrectomy. *Nephrol Dial Transplant*. 2012;27:4339-4347.
25. Silverberg DS, Wexler D, Iaina A, et al. The interaction between heart failure and other heart diseases, renal failure, and anemia. *Semin Nephrol*. 2006;26:296-306.
26. Faubel S. Acute kidney injury and multiple organ dysfunction syndrome. *Minerva Urol Nefrol*. 2009;61:171-188.
27. Prabhu SD. Cytokine-induced modulation of cardiac function. *Circ Res*. 2004;95:1140-1145.
28. Ognibene FP, Rosenberg SA, Lotze M, et al. Interleukin-2 administration causes reversible hemodynamic changes and left ventricular dysfunction similar to those seen in septic shock. *Chest*. 1988;94:750-754.
29. Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol*. 2003;14:1549-1558.
30. Kingma JG Jr, Vincent C, Rouleau JR, et al. Influence of acute renal failure on coronary vasoregulation in dogs. *J Am Soc Nephrol*. 2006;17:1316-1324.
31. Uchino S, Kellum JA, Bellomo R, et al. Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) investigators: acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. 2005;294:813-818.
32. Rabb H, Chamoun F, Hotchkiss J. Molecular mechanisms underlying combined kidney-lung dysfunction during acute renal failure. *Contrib Nephrol*. 2001;132:41-52.
33. Kramer AA, Postler G, Salhab KF, et al. Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. *Kidney Int*. 1999;55:2362-2367.
34. Faubel S, Edelstein CL. Mechanisms and mediators of lung injury after acute kidney injury. *Nat Rev Nephrol*. 2016;12:48-60.
35. Rabb H, Wang Z, Nemoto T, et al. Acute renal failure leads to dysregulation of lung salt and water channels. *Kidney Int*. 2003;63:600-606.