CHAPTER 110

Classification of Cardiorenal Syndrome

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OBJECTIVES

The chapter will:
1. Provide an overview of cardiorenal syndrome (CRS) classification.
2. Briefly review cardiorenal syndromes definitions and clinical implications.
3. Focus on main pathophysiologic features of each CRS.

Large numbers of hospitalized patients have various degrees of heart and kidney dysfunction[1]; primary disease of the heart or kidney often involves dysfunction of or injury to the other.[2] Based on this organ cross-talk, the term *cardiorenal syndrome (CRS)* was proposed.[3] Although CRS usually was referred to as an interruption of kidney function after heart injury,[4] it is now clearly established that it can describe negative effects of an impaired renal function on the heart and circulation.[5,6]

DEFINITION OF CARDIORENAL SYNDROME

According to the recent definition proposed by the consensus conference of the Acute Dialysis Quality Initiative Group,[7] the term *cardiorenal syndrome* has been used to define different clinical conditions in which heart and kidney dysfunction overlap. The heart and kidney are involved in basic physiology, and their functions are linked closely. Although the heart provides nourishing and oxygen-rich fluids to all body areas, the kidney is accountable for providing fluid, electrolytes, and acid-base homeostasis together

with neurohormonal activity (erythropoietin synthesis and vitamin D activation).

A clear classification of CRS is crucial as its correct application is required, offering an exciting challenge for nephrologists and cardiologists, who have to contaminate their own fields of applications. An effective classification of CRS has been proposed in a consensus conference by the Acute Dialysis Quality Group[7] in 2008 (Table 110.1). This classification essentially divides CRS in two main groups, cardiorenal and renocardiac CRS, on the basis of primum movens of disease (cardiac or renal). Cardiorenal and renocardiac CRS then are divided into acute and chronic, according to disease's onset. Type – 5 CRS integrates all cardiorenal involvement induced by systemic disease.

CARDIORENAL SYNDROME TYPE – 1 (ACUTE CARDIORENAL SYNDROME)

Type – 1 CRS (acute cardiorenal, CRS-1) is characterized by acute worsening of cardiac function leading to acute kidney injury (AKI).[8,9] Type – 1 CRS usually occurs in the setting of an acute cardiac disease such as acute decompensated heart failure (ADHF) often after an ischemic (acute coronary syndrome, cardiac surgery complications) or nonischemic heart disease (valvular disease, pulmonary embolism) (Fig. 110.1).

Type – 1 CRS occurs in about 25% of patients hospitalized for ADHF[10,11]; among these patients a preexistent chronic kidney disease is common and contributes to AKI in 60% of all cases studied. AKI can be considered an independent mortality risk factor in acute ADHF patients, including those with ST myocardial infarction and/or reduced left ventricular ejection fraction.[12]

AKI is a well-known complication in patients hospitalized for ADHF; up to 45% patients require more complex management because of higher mortality rates. Preliminary observations point out the importance of timing in the development of AKI and its early diagnosis.

Hemodynamic mechanisms play a major role in type – 1 CRS in the presence of ADHF leading to decreased renal arterial flow and glomerular filtration rate (GFR) decline. Different hemodynamic profiles have been proposed[13]: in "cold" pattern patients, reduction in effective circulation fluid volume (ECFV) represents the main hemodynamic change, although there is a marked increase in central venous pressure (CVP) in "wet" pattern patients.

"Cold" patients also have a decrease in renal blood flow related to the renin-angiotensin-aldosterone system (RAAS) and systemic nervous system activation, causing afferent vasoconstriction, decreased renal blood flow, and effective glomerular perfusion pressure. Patients who have a "wet" hemodynamic profile display increased pulmonary and/or systemic congestion. In these patients, high CVP directly affects renal vein and kidney perfusion pressure.[14,15] A CVP increase also results in increased interstitial pressure with tubular collapse and progressive decline in GFR.[16]

Nonhemodynamic mechanisms also were proposed as involved in type – 1 CRS, including sympathetic nervous system (SNS) and RAAS activation, chronic inflammation, and imbalance in the proportion of reactive oxygen species (ROS) to nitric oxide (NO) production. Several pathophysiologic processes contribute to perpetuating AKI, including endothelial and epithelial cell death with a primary role for apoptotic mechanisms resulting from renal ischemia and toxic injury.[17]

TABLE 110.1

Classification of Cardiorenal Syndrome

TYPE1	DENOMINATION	DESCRIPTION	EXAMPLE
1	Acute cardiorenal	Heart failure leading to AKD	Acute coronary syndrome leading to acute heart and kidney failure
2	Chronic cardiorenal	Chronic heart failure leading to kidney failure	Chronic heart failure
3	Acute nephrocardiac	AKD leading to acute heart failure	Uremic cardiomyopathy AKD-related
4	Chronic nephrocardiac	Chronic kidney disease leading to heart failure	Left ventricular hypertrophy and diastolic heart failure resulting from kidney failure
5	Secondary	Systemic disease leading to heart and kidney failure	Sepsis, vasculitis, diabetes mellitus

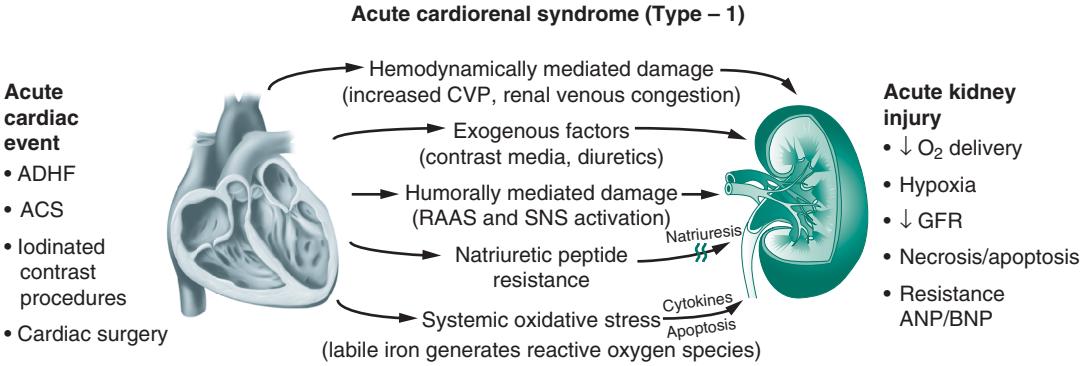

FIGURE 110.1 Pathophysiology of type – 1 cardiorenal syndrome.

Sera from type – 1 CRS patients show high levels of proinflammatory cytokines and proapoptotic agents.[18] Fragmentation of renal tubular cells' genomic DNA represents a biochemical hallmark of apoptosis, an irreversible process leading to cell death.[19] The final pathway of apoptotic process is characterized by phagocytosis of apoptotic bodies.[19]

Oxidative stress is a hallmark of type – 1 CRS, as evidenced by a significant increase in circulating ROS and reactive nitrogen species (RNS) coupled with increased expression of interleukin-6 (IL-6).[20]

Gut underperfusion and endotoxin release in patients with ADHF also have been proposed as pathophysiologic mechanisms accelerating the progression of heart failure (HF) and CRS.[21]

Diagnosis of type – 1 CRS focuses on laboratory findings and ultrasonography and/or second level radiologic assays. Early diagnosis of AKI in type – 1 (such as in type – 3) CRS still remains a challenge[22]; classic biomarkers, such as creatinine levels, increase when kidney injury already is established and prevention fails. New frontiers are represented by novel biomarkers such as serum and urinary neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), and liver-type fatty acid binding protein (L-FABP).[23,24]

Together with laboratory diagnosis, type – 1 CRS can be diagnosed also by bioelectrical devices, especially concerning fluid assessment in those patients. Several clinical studies showed an association between decreased impedance values (increased body fluid volume) and adverse events such as rehospitalization and death; bioimpedance measurement also allows clinicians to distinguish cardiogenic dyspnea from noncardiogenic.[25,26] High sensitivity and specificity of reduced bioimpedance's values were confirmed by radiographic findings consistent with pulmonary edema.[27]

Ultrasonography can provide further elements for type – 1 CRS diagnosis; echocardiographic typical findings are represented by abnormal myocardial kinetics (indicating an ischemic condition) and left ventricular hypertrophy, valvular stenosis, and/or regurgitation (particularly in the case of rapid deterioration, such as valvular endocarditis or valvular rupture), pericardial effusions, normal inspiratory collapse of the inferior vena cava (excluding severe hypervolemia), aortic aneurysms, or dissection.[28]

The kidneys' ultrasonographic evaluation usually shows normal or larger dimensions with preserved cortical-medullary ratio; color Doppler evaluation shows regular intraparenchymal blood flow, often associated with raised resistance index (>0.8 cm/sec).[28]

Renal function often improves in response to standard therapy aimed to reduce filling pressures with loop diuretics and nitrates in warm and wet ADHF patients with AKI at presentation. Usually, angiotensin-converting enzyme (ACE) inhibitors are titrated upward slowly during the course of hospitalization. The hemodynamic effect of ACE inhibitors and its associated drop in filtration pressure, as well as "prerenal" kidney dysfunction resulting from the reduction in ECFV associated with intensified therapy with loop diuretics, may be the primary mechanisms underlying AKI development during hospitalization.[29]

CARDIORENAL SYNDROME TYPE – 2 (CHRONIC CARDIORENAL SYNDROME)

Cardiorenal syndrome type – 2 (CRS-2) is characterized by chronic abnormalities in cardiac function leading to kidney injury or dysfunction; the temporal relationship between heart and kidney disease is an epidemiologic and pathophysiologic aspect of the definition. Literature data show that chronic heart and kidney disease often coexist, but large cohort studies assess the onset of one disease (e.g., chronic HF) subsequently describing the prevalence of the other (chronic kidney disease [CKD]).[30,31] It is difficult to establish which of the two diseases is primary versus secondary. CKD has been observed in 45% to 63% of CHF patients,[30–32] but it is unclear how to classify these patients, often including those shifting from a clinical condition of type – 1 CRS. At the same time it is not easy to recognize these patients from type – 4 CRS.[32]

Worsening of renal function is different in acute or chronic HF patients: chronic heart failure is characterized mainly by renal hypoperfusion resulting from vascular (micro- and macro-) disease. At the present time there seems to be no clear relationship between measured glomerular filtration rate (GFR) and left ventricular ejection fraction (LVEF), although patients with low estimated GFR show lower LVEF.[33] Concerning pathophysiology of type – 2 CRS, renal congestion and hypoperfusion together with increased right atrial pressure represent some of the cornerstones in renal dysfunction of chronic heart failure patients[34] (Fig. 110.2). More recently, there is an increasing interest in the role of erythropoietin deficiency contributing to more pronounced anemia's degree than renal dysfunction could explain.[35] Erythropoiesis-stimulating agents (ESA) therapy in patients with HF, CKD, and anemia lead to improved cardiac function with reduction in left ventricle size and volume, whereas diuretic therapy improves fluid retention and patients' New York Heart Association (NYHA) scores.[36]

CARDIORENAL SYNDROME TYPE – 3 (ACUTE RENOCARDIAC SYNDROME)

Type – 3 CRS or acute renocardiac CRS occurs when AKI contributes to and/or precipitates development of acute cardiac injury. AKI may produce directly or indirectly an acute cardiac event, and it can be associated to volume overload, metabolic acidosis, and electrolytes disorders (i.e., hyperkalemia and/or hypocalcemia); coronary artery disease, left ventricular dysfunction, and fibrosis also have been described in patients with AKI with direct negative effects on cardiac outcomes.[37,38] A wide spectrum of cardiac dysfunction includes ADHF, acute coronary syndrome (ACS), arrhythmias as defined by RIFLE (risk, injury, failure, loss, end-stage kidney disease), and AKIN (Acute Kidney Injury Network) criteria.[39,40]

Defining incidence and prevalence of type – 3 CRS is difficult because of the lack of epidemiologic data at the present time, although it is possible to collect data derived from single population studies; among them a 2147 per million population AKI incidence was reported in a northern Scotland population-based study.[41]

In a more recent retrospective study following traumatic disease, cardiac arrest was reported as a cause of death in 20% of patients. Other causes of death include cerebrovascular accidents (46%), sepsis (17%), multiple organ dysfunction syndrome (7.3%), and respiratory insufficiency (3.2%).[42]

Cardiac failure is certainly the most common cause of death in end-stage renal disease patients[43] with a higher incidence than hepatic failure, massive transfusion, older age (>60 years), and respiratory and neurologic failure.[44]

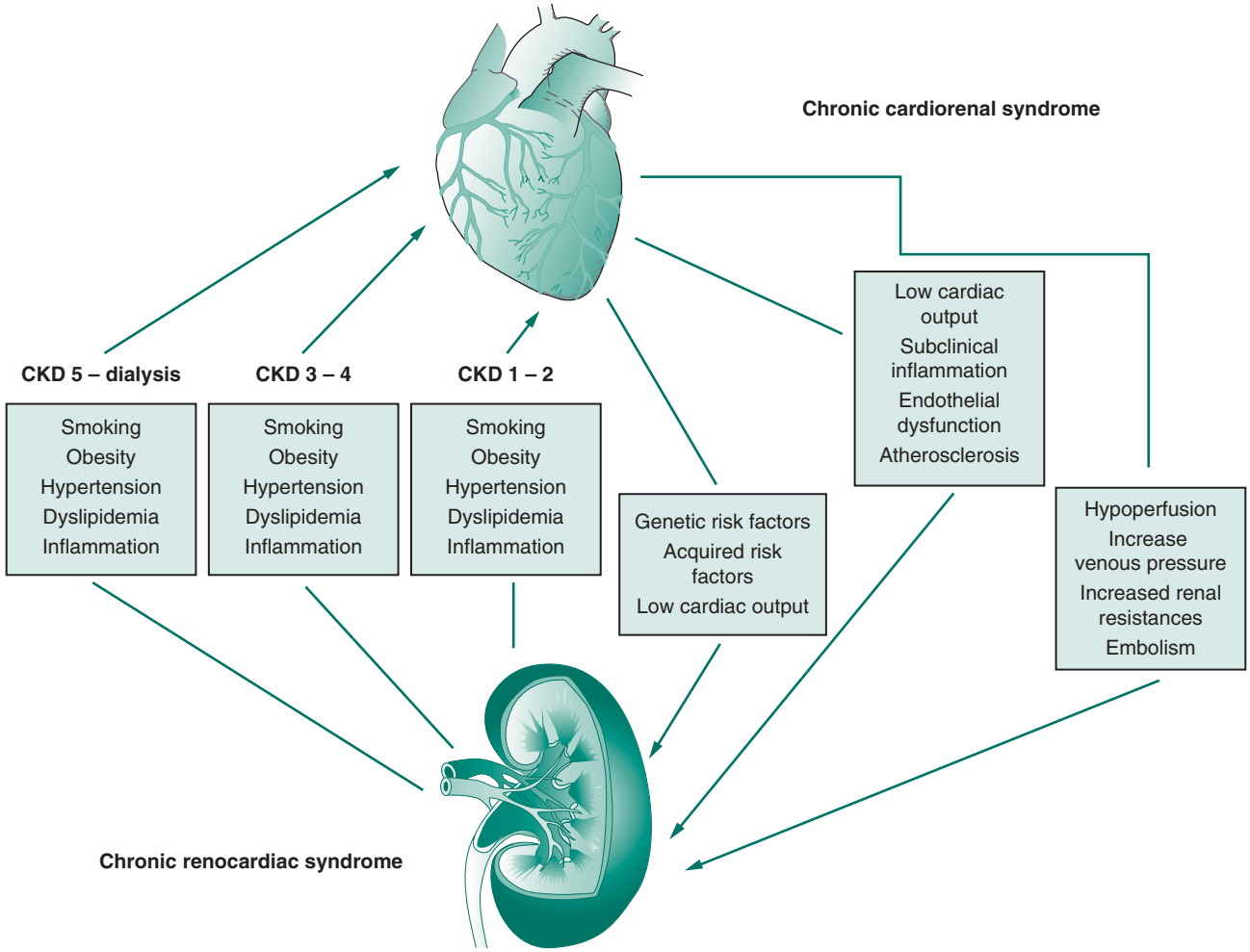

FIGURE 110.2 Pathophysiology of type – 2 cardiorenal syndrome.

Pathophysiologic interactions between the kidney and heart during AKI have been referred to as "cardiorenal connectors,"[45] like activation of immune (i.e., pro- and antiinflammatory cytokines and chemokines release) and sympathetic nervous systems, hyperactivity of RAAS, and coagulation cascade. Oliguria can lead to sodium and water retention with consequent fluid overload and development of edema, cardiac overload, hypertension, pulmonary edema, and myocardial injury. Electrolytes imbalance (hyperkalemia primarily) can contribute to risk of fatal arrhythmias and sudden death, whereas uremia-related metabolic acidosis can affect myocytes' metabolism, and it can be accountable for pulmonary vasoconstriction, increased right ventricular afterload, and negative inotropic effect[46] (Fig. 110.3).

Ultrasound evaluation of type – 3 CRS patients shows several patterns on kidney and heart examination. Kidney size and echogenicity provide primary features to discern between acute and chronic nephropathies.[47,48] A hyperechogenic renal cortex with low corticomedullary ratio is predictive of chronic nephropathy.[47,48] At the same time cortical hyperechogenicity also can occur in acute tubular necrosis or systemic lupus erythematosus nephritis.[47,48] Echocardiographic pattern is not diagnostic, showing an increase in atrial volumes or areas as indices of volume overload or pleural or pericardial effusion; it often is associated with lung comets evidence on thoracic ultrasound.[28] Especially during the last 5 to 10 years, a large amount of potential biomarkers have been proposed for the diagnosis of type – 3 CRS. Among AKI novel biomarkers (each with pros and cons), some of them seem to be particularly interesting, such as NGAL, KIM-1, IL-18, IL-6, cystatin C (CysC), N-acetyl-β-d-glucosamide, L-FABP, Netrin-1, Klotho, and Midkine.

On the other hand, several cardiac biomarkers are employed routinely in clinical practice: biomarkers of myocardial necrosis, such as troponins T (cTnT) and I (cTnI) and markers of heart failure such as B-type natriuretic peptide (BNP) and its inactive N-terminal fragment (NT-proBNP).[49]

The therapeutic approach is focused on treating comorbidities until to renal replacement therapies for nonresponding patients.

CARDIORENAL SYNDROME TYPE – 4 (CHRONIC RENOCARDIAC SYNDROME)

Type – 4 CRS, also defined as chronic renocardiac syndrome, defines cardiovascular involvement in chronic kidney disease patients according to the National Kidney Foundation (NKF) classification. The type – 4 CRS definition necessitates the existence of kidney disease before the development of heart failure.

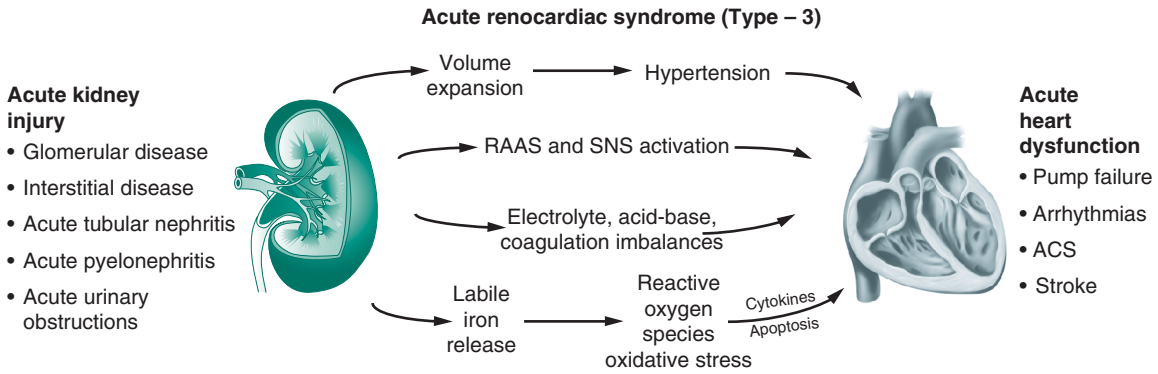

FIGURE 110.3 Pathophysiology of type – 3 cardiorenal syndrome.

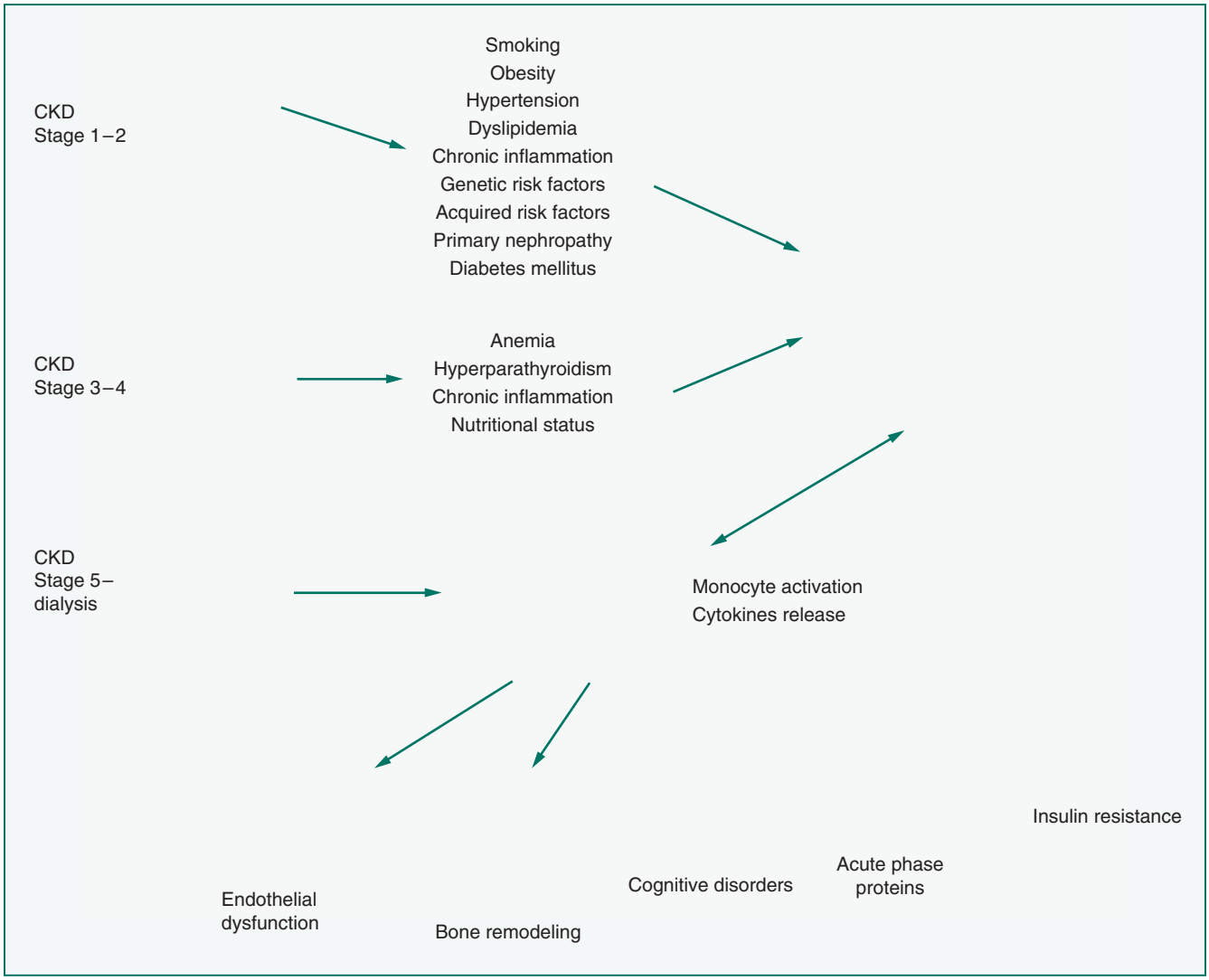

FIGURE 110.4 Pathophysiology of type – 4 cardiorenal syndrome.

It now should be clear that there is a close relationship between CKD and the increased risk for cardiovascular disease: major cardiac events actually represent almost 50% of the causes of death in CKD patients resulting from the aging population, and higher rates in diabetic, dyslipidemic, and hypertensive patients[10] (Fig. 110.4). The HEMO study clearly demonstrated high prevalence (about 80%) of cardiovascular disease in hemodialysis patients in relation with age, prevalence of diabetes, and dialysis duration,[50] whereas Tonelli et al. conducted a meta-analysis on 1.4 million patients and found higher mortality rates for all causes.[51] The largest epidemiologic study was performed by Go et al.:[52] they screened more than 1 million people, identifying cardiovascular events (hospitalization for

coronary disease, heart failure, stroke, or peripheral artery disease) and all-cause mortality hazard ratio increases according to each declining interval of GFR. The conclusion was that the GFR is a strong, independent factor of cardiovascular morbidity and mortality.[52] Therefore it was highlighted that cardiovascular risk is particularly evident in CKD patients with stage IIIb to IV (according to KDIGO CKD classification) and in those who underwent renal replacement therapy (RRT, hemodialysis, peritoneal dialysis, and transplant).[53] Finally, in the Chronic Renal Insufficiency Cohort (CRIC) study investigators focused their attention on 190 CKD patients with a GFR less than 60 mL/min and performed serial echocardiographic evaluations: in a 2-year evaluation period during which patients shifted from stage V to end-stage renal disease, ejection fraction (EF) dropped from 53% to 50%.[54]

Concerning type – 4 CRS pathophysiology, Figs. 110.2 and 110.3 show close interactions between CKD and cardiovascular involvement. Chronic kidney disease can contribute indirectly (exacerbating ischemic heart disease) and directly (pressure and volume overload leading to left ventricular hypertrophy) to heart disease.[55] Hyperphosphatemia and secondary hyperparathyroidism (also described as CKD-mineral and bone disorder, or CKD-MBD) can induce the ossification of cardiac vessels and valves through "osteoblastic" transformation of vascular smooth muscle cells.[56] Hypertension also can contribute to vascular calcification and consequent pressure overload.

Volume overload is supported mainly by CKD-related secondary anemia together with sodium and water retention; it also can be worsened by the presence of hemodialysis vascular access.[57,58]

Chronic inflammation, insulin resistance, hyperhomocysteinemia, and lipidic dysmetabolism also can contribute to cardiovascular disease in CKD patients. As the GFR decreases, the gradual accumulation of a large number of toxins (β2 microglobulin, guanidines, phenols, indoles, aliphatic amines, furans, polyols, nucleosides, leptin, parathyroid hormone, and erythropoiesis inhibitors) occurs.[59–61]

On the other hand, many other biomarkers' serum levels increase as GFR declines: troponins, asymmetric dimethylarginine (ADMA), plasminogen-activator inhibitor type I, homocysteine, natriuretic peptides, C-reactive protein (CRP), serum amyloid A protein, ischemia-modified albumin, and others.[62–64] All of these are involved in the CKD-related vascular disease development. Impaired heart function leads to renin-angiotensin-aldosterone system (RAAS) and SNS activation with consequent worsening of blood pressure and volume overload[65]; the RAAS and SNS activation also can be responsible for glomerulosclerosis and progressive kidney damage.[66,67]

The diagnosis of type – 4 CRS is based on serologic and instrumental tests. Cardiac function is assessed more widely by NT- proBNP serum levels, whereas eGFR represents the main biochemical test to evaluate kidney function.

Instrumental diagnosis is based mainly on ultrasound examination of the heart and kidneys. The kidneys show features of chronic nephropathy, such as a thin and hyperechogenic cortex with a reduced corticomedullary ratio together with small dilation of the urinary tract; parapyelic and subcortical cysts also are found.[28]

Echocardiography can demonstrate signs of volume overload, left ventricular dysfunction, and right ventricular dysfunction in end-stage renal disease and hemodialysis patients.

Increased atrial volumes or areas, pleural or pericardial effusion, and lung comets' presence confirm volume overload.[28] It is common to observe valvular calcifications (related to secondary hyperparathyroidism)[28] and frequent right heart dysfunction feature, such as high pulmonary artery pressure, low tricuspid annulus plane systolic excursion (TAPSE), or right chamber dilation.[58]

CARDIORENAL SYNDROME TYPE – 5

Type – 5 CRS is a recently defined clinical syndrome, and complete epidemiologic data on this entity are still incomplete. Type – 5 CRS occurs when cardiac and renal injury simultaneously occur, as it happens in several clinical syndromes (i.e., sepsis).[68]

Pathophysiology of CRS-5 depends on the underlying disease (Fig. 110.5). Acute CRS-5 results from systemic processes such as sepsis, infections, drug abuse, toxins, and connective tissue disorders (systemic erythematous lupus, Wegener granulomatosis, sarcoidosis). On the other hand, in patients with cirrhotic liver disease, CRS-5 has a more insidious onset and the kidney and cardiac dysfunction may develop slowly until a crucial point is reached and full decompensation occurs. Acute CRS-5 develops into the five following steps: hyperacute (0–72 hours after diagnosis), acute (3–7 days), subacute (7–30 days), and chronic (more than 30 days). Chronic CRS-5 (i.e., CRS in cirrhotic patients) presents a variable time sequence. Pathophysiologic changes in sepsis-related CRS can depend on systemic effects of sepsis, from sepsis' direct effect to systemic metabolic pathways or, at least, from direct crosstalk between the damaged heart and kidney.

Septic cardiomyopathy represents one of main predictors of mortality in septic patients, and it is diagnosed in almost half of patients.[69] The left and right ventricle can be injured with dilation and decreased ejection fraction often unresponsive to fluid and catecholamine therapy.[70] Sepsis also affects the autonomic nervous system (ANS), RAAS, and hypothalamus-pituitary gland-adrenal gland axis (HPA), which can affect, in several and distinctive steps, cardiac and/or renal function. Sepsis also activates RAAS as an attempt to restore and maintain blood pressure; a blockade of RAAS may be beneficial because RAAS activation also has been involved in endothelial dysfunction and mortality during severe sepsis.[71,72]

Sepsis also is involved in causing severe alteration in HPA, leading to adrenal insufficiency[73] and increased production of proinflammatory biomarkers, free radicals, and prostaglandins. Therefore inhibition of chemotaxis and expression of adhesion molecules can occur; administration of low-dose glucocorticoids can reduce vasopressors' employment and critical care units' hospitalization period.[74]

Together with hemodynamic effects of a decompensated heart on renal blood flow, there are cardiac metabolic changes resulting from reduced fluid removal by kidneys. In an experimental model AKI led to cardiac apoptosis, partially limited by anti-TNF therapy,[75] hypertrophy,[76] and an increase in cardiac macrophages.[77] Activation and induction of cytokines (TNF-α and IL-6) and leukocytes (macrophages, neutrophils, and lymphocytes) are well documented in the heart and kidney during sepsis. Contractile heart function mainly is affected, and muscle protein expression (actin and myosin) is abnormal in sepsis as well as membrane-associated proteins such as dystrophin, normally regulating cell shape.

Concerning diagnostic approach to sepsis, prototype of type – 5 CRS, initial emphasis has to be on the setting of severe sepsis and septic shock (body temperature less than

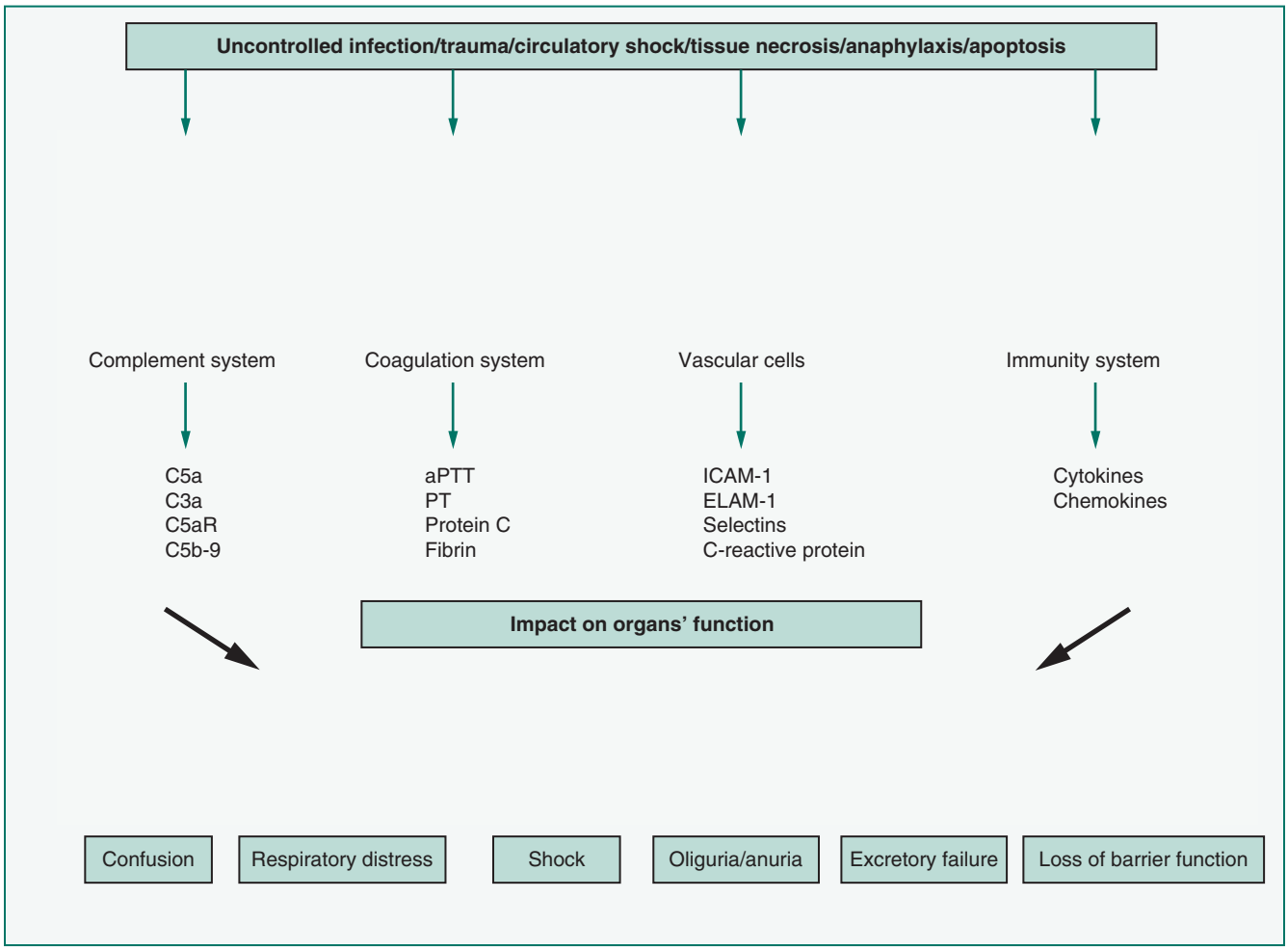

FIGURE 110.5 Pathophysiology of type – 5 cardiorenal syndrome.

36°C [96.8°F] or greater than 38°C [100.4°F], heart rate greater than 90 beats/min, tachypnea, and white blood cell counts less than 4 × 100 cells/L or greater than 12 × 100 cells/L), then on heart and kidney assessment and risk evaluation to start an appropriate treatment. Assessment of cardiac function in type – 5 CRS is similar to other clinical situations in which myocardial dysfunction is present. Echocardiography confirms high-output cardiomyopathy with abnormalities in left ventricular regional contractility together with dilation of left heart chambers.[78]

The diagnosis of kidney involvement in sepsis-related type – 5 CRS is overlapping to other forms of AKI with acute changes in serum creatinine levels according to RIFLE, AKIN, and KDIGO criteria.[79,80] Currently, although several other biomarkers are proposed (cystatin C, KIM-1, NGAL, NAG), RIFLE, KDIGO, and AKIN criteria still recommend serum creatinine levels and urine output for diagnosis and monitoring of AKI in type – 5 CRS.

Treatment of type – 5 CRS is based primarily on underlying disease management and on kidney and heart complications.

First of all, maintaining hemodynamic stability and guaranteeing tissue perfusion are key points to prevent type – 5 CRS in hyperacute phase of sepsis together with fluid control and correct antibiotic treatment. Fluid therapy must be managed carefully to avoid fluid overload and other iatrogenic complications.[81,82]

Because inflammation and immune disorders play an important role in the pathogenesis of sepsis, removal of cytokines and immunomodulation are two approaches based on extracorporeal convection devices, high volume hemofiltration, and high permeability membranes.[83–85] The best results were obtained with high permeability membranes and absorption.[86]

Key Points

1. Cardiorenal syndrome involves a large spectrum of cardiorenal diseases based on heart-kidney cross-talk.
2. The heart and kidney are involved in basic physiology, and their functions are linked closely; whereas the heart provides nourishing and oxygen, the kidney provides fluid, electrolytes, and acid-base homeostasis together with neurohormonal activity.
3. Classification of cardiorenal syndromes allows identification of acute and chronic diseases on the basis of primum movens of the disease.

Key References

3. Ronco C. Cardiorenal and renocardiac syndromes: clinical disorders in search of a systematic definition. *Int J Artif Organs*. 2008;31:1-2.
8. Ronco C. Cardiorenal syndromes: definition and classification. *Contrib Nephrol*. 2010;164:33-38.
28. Di Lullo L, Floccari F, Granata A, et al. Ultrasonography: Ariadne's thread in the diagnosis of cardiorenal syndrome. *Cardiorenal Med*. 2012;2(1):11-17. [Epub 2011 Nov 30].
32. Bagshaw SM, Cruz DN, Aspromonte N, et al. Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference. *Nephrol Dial Transplant*. 2010;25(5):1406-1416.
64. Ronco C, Di Lullo L. Cardiorenal syndrome. *Heart Fail Clin*. 2014;10(2):251-280.

A complete reference list can be found online at ExpertConsult.com.

References

1. Dar O, Cowie MR. Acute heart failure in the intensive care unit: epidemiology. *Crit Care Med*. 2008;36:S3-S8.
2. Schrier RW. Cardiorenal versus renocardiac syndrome: is there a difference? *Nat Clin Pract Nephrol*. 2007;3:637.
3. Ronco C. Cardiorenal and renocardiac syndromes: clinical disorders in search of a systematic definition. *Int J Artif Organs*. 2008;31:1-2.
4. Liang KV, Williams AW, Greene EL, et al. Acute decompensated heart failure and the cardiorenal syndrome. *Crit Care Med*. 2008;36:S75-S88.
5. Ronco C, House AA, Haapio M. Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. *Intensive Care Med*. 2008;34:957-962.
6. Patel J, Heywood JT. Management of the cardiorenal syndrome in heart failure. *Curr Cardiol Rep*. 2006;8:211-216.
7. Ronco C. The cardiorenal syndrome: basis and common ground for a multidisciplinary patient-oriented therapy. *Cardiorenal Med*. 2011;1:3-4.
8. Ronco C. Cardiorenal syndromes: definition and classification. *Contrib Nephrol*. 2010;164:33-38.
9. Eren Z, Ozveren O, Buvukoner E, et al. A Single-Centre Study of Acute Cardiorenal Syndrome: Incidence, Risk Factors and Consequences. *Cardiorenal Med*. 2012;2:168-176.
10. Bargshaw SM, Cruz DM, Aspromonte N, et al; for the Acute Dialysis Quality Initiative (ADQI) Consensus Group. Epidemiology of cardio-renal syndromes: workgroup statements from from the 7th ADQI Consensus Conference. *Nephrol Dial Transplant*. 2010;25:1406-1416.
11. Damman K, Navis G, Voors AA, et al. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. *J Card Fail*. 2007;13:599-608.
12. McCullough PA. Cardiorenal syndromes: pathophysiology to prevention. *Int J Nephrol*. 2010;2010:762590.
13. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA*. 1989;261:884-888.
14. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol*. 2009;53:589-596.
15. Uthoff H, Breidthardt T, Klima T, et al. Central venous pressure and impaired renal function in patients with acute heart failure. *Eur J Heart Fail*. 2011;13:432-439.
16. Braam B, Cupples WA, Joles JA, et al. Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. *Heart Fail Rev*. 2012;17:161-175.
17. Havasi A, Borkan SC. Apoptosis and acute kidney injury. *Kidney Int*. 2011;80:29-40.
18. Elmore S. Apoptosis: a review of programmed cell death. *Toxicol Pathol*. 2007;35:495-516.
19. Pastori S, Virzì GM, Brocca A, et al. Cardiorenal syndrome type 1: activation of dual apoptotic pathways. *Cardiorenal Med*. 2015;5:306-315.
20. Virzì GM, Clementi A, De Cal M, et al. Oxidative stress: dual pathway induction in cardiorenal syndrome type 1 pathogenesis. *Oxid Med Cell Longev*. 2015;2015:Article ID 391790.
21. Kraut EJ, Chen S, Hubbard NE, et al. Tumor necrosis factor depresses myocardial contractility in endotoxemic swine. *J Trauma*. 1999;46:900-906.
22. Han WK, Bonventre JV. Biologic markers for the early detection of acute kidney injury. *Curr Opin Crit Care*. 2004;10:476-482.
23. VandeVoorde RG, Katlman TL, Ma QA, et al. Serum NGAL and cystatin C predictive biomarkers for acute kidney injury. *J Am Soc Nephrol*. 2006;17:404A.
24. Vaidya VS, Ramirez V, Ichimura T, et al. Urinary kidney injury molecule-1: a sensitive quantitative biomarker for early detection of kidney tubular injury. *Am J Physiol Renal Physiol*. 2006;290:F517-F529.
25. Di Somma S, De Berardinis B, Bongiovanni C, et al. Use of BNP and bioimpedance to drive therapy in heart failure patients. *Congest Heart Fail*. 2010;16:S56-S61.
26. Parrinello G, Paterna S, Di Pasquale P, et al. The usefulness of bioelectrical impedance analysis in differentiating dyspnea due to decompensated heart failure. *J Card Fail*. 2008;14:676-686.
27. Milzman D, Napoli A, Hogan C, et al. Thoracic impedance vs chest radiograph to diagnose acute pulmonary edema in the ED. *Am J Emerg Med*. 2009;27:770-775.
28. Di Lullo L, Floccari F, Granata A, et al. Ultrasonography: Ariadne's thread in the diagnosis of cardiorenal syndrome. *Cardiorenal Med*. 2012;2(1):11-17. [Epub 2011 Nov 30].
29. Voors AA, Davison BA, Felker GM, et al. Early drop in systolic blood pressure and worsening renal function in acute heart failure: renal results of Pre-RELAX-AHF. *Eur J Heart Fail*. 2011;13:961-967.
30. Heywood JT, Fonarow GC, Costanzo MR, et al. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail*. 2007;13(6):422-430.
31. Hebert K, Dias A, Delgado MC, et al. Epidemiology and survival of the five stages of chronic kidney disease in a systolic heart failure population. *Eur J Heart Fail*. 2010;12(8):861-865.
32. Bagshaw SM, Cruz DN, Aspromonte N, et al. Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference. *Nephrol Dial Transplant*. 2010;25(5):1406-1416.
33. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med*. 2006;355:260-269.
34. Nohria A, Hasselblad V, Stebbins A, et al. Cardiorenal interactions – insights form. The Escape trial. *J Am Coll Cardiol*. 2007;51:1268-1274.
35. Jie KE, Verhaar MC, Cramer MJ, et al. Erythropoietin and the cardiorenal syndrome: cellular mechanisms on the cardiorenal connectors. *Am J Physiol Renal Physiol*. 2006;291:F932-F944.
36. Palazzuoli A, Silverberg DS, Iovine F, et al. Effects of beta-erythropoietin on left ventricular remodeling, systolic function and B-type natriuretic peptide levels in patients with the cardiorenal anemia syndrome. *Am Heart J*. 2007;154:645.e9-645.e15.
37. Prabhu SD. Cytokine-induced modulation of cardiac function. *Circ Res*. 2004;95(12):1140-1153.
38. 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(5):1316-1324.
39. Bagshaw SM, Cruz DN, Aspromonte N, et al; for the Acute Dialysis Quality Initiative (ADQI) Consensus Group. Epidemiology of cardio-renal syndrome: workgroup statements from the 7th ADQI Consensus Conference. *Nephrol Dial Transplant*. 2010;25:1406-1416.
40. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs. The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8:R204-R212.
41. Ali T, Khan I, Simpson W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol*. 2007;18:1292-1298.
42. De Abreu KLS, Silva Junior GB, Carreto AGC, et al. Acute kidney injury after trauma: prevalence, clinical characteristics and RIFLE classification. *Indian J Crit Care Med*. 2010;14:121-128.
43. Raine A, Margreiter R, Brunner F, et al. Report on management of renal failure in Europe. XXII. *Nephrol Dial Transplant*. 1992;7(suppl 2):7-35.
44. Schwilk B, Wiedeck H, Stein B, et al. Epidemiology of acute renal failure and outcome of haemodiafiltration in intensive care. *Intensive Care Med*. 1997;23:1204-1211.
45. Bongartz LG, Cramer MJ, Doevendans PA, et al. The severe cardiorenal syndrome: 'Guyton revisited'. *Eur Heart J*. 2005;26(1):11-17.
46. Scheuer J, Stezoski W. The effects of uremic compounds on cardiac function and metabolism. *J Mol Cell Cardiol*. 1973;5:287-300.
47. Licurse A, Kim MC, Dziura J, et al. Renal ultrasonography in the evaluation of acute kidney injury: developing a risk stratification framework. *Arch Intern Med*. 2010;170:1900-1907.
48. Ozmen CA, Akin D, Bilek SU, et al. Ultrasound as a diagnostic tool to differentiate acute from chronic renal failure. *Clin Nephrol*. 2010;74:46-52.

49. Chuasuwan A, Kellum JA. Cardio-renal syndrome type 3: epidemiology, pathophysiology, and treatment. *Semin Nephrol*. 2012;32(1):31-39.
50. Damman K, Navis G, Voors AA, et al. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. *J Card Fail*. 2007;13:599-608.
51. Tonelli M, Wiebe N, Culleton B, et al. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol*. 2006;17(7):2034-2047.
52. 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(13):1296-1305.
53. U.S. Renal Data System, USRDS 2009 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2009.
54. Bansal N, Keane M, Delafontaine P, et al. CRIC Study Investigators. A longitudinal study of left ventricular function and structure from CKD to ESRD: The CRIC study. *Clin J Am Soc Nephrol*. 2013;8(3):355-362.
55. Levin A, Singer J, Thompson CR, et al. Prevalent left ventricular hypertrophy in the predialysis population: Identifying opportunities for intervention. *Am J Kidney Dis*. 1996;27(3):347-354.
56. Olgaard K, Lewin E, Silver J. Calcimimetics, vitamin D and ADVANCE in the management of CKD-MBD. *Nephrol Dial Transplant*. 2011.
57. MacRae JM, Pandeya S, Humen DP, et al. Arteriovenous fistula-associated high-output cardiac failure: A review of mechanisms. *Am J Kidney Dis*. 2004;43(5):e17-e22.
58. Di Lullo L, Floccari F, Polito P. Right ventricular diastolic function in dialysis patients could be affected by vascular access. *Nephron Clin Pract*. 2011;118:c258-c262.
59. Fort J. Chronic renal failure: a cardiovascular risk factor. *Kidney Int Suppl*. 2005;(99):S25-S29.
60. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. *Circulation*. 2007;116(1):85-97.
61. Bologa RM, Levine DM, Parker TS, et al. Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients. *Am J Kidney Dis*. 1998;32(1):107-114.
62. Parikh SV, de Lemos JA. Biomarkers in cardiovascular disease: integrating pathophysiology into clinical practice. *Am J Med Sci*. 2006;332(4):186-197.
63. Austin WJ, Bhalla V, Hernandez-Arce I, et al. Correlation and prognostic utility of B-type natriuretic peptide and its amino-terminal fragment in patients with chronic kidney disease. *Am J Clin Pathol*. 2006;126(4):506-512.
64. Ronco C, Di Lullo L. Cardiorenal syndrome. *Heart Fail Clin*. 2014;10(2):251-280.
65. Cruz DN, Bagshaw SM. Heart-kidney interaction: epidemiology of cardiorenal syndromes. *Int J Nephrol*. 2010;2011:351291.
66. Entin-Meer M, Ben-Shoshan J, Maysel-Auslender S, et al. Accelerated renal fibrosis in cardiorenal syndrome is associated with long-term increase in urine neutrophil gelatinase-associated lipocalin levels. *Am J Nephrol*. 2012;36(2):190-200.
67. Lekawanvijit S, Kompa AR, Zhang Y, et al. Myocardial infarction impairs renal function, induces renal interstitial fibrosis, and increases renal KIM-1 expression: Implications for cardiorenal syndrome. *Am J Physiol Heart Circ Physiol*. 2012;302(9):H1884-H1893.
68. Ronco C, McCullough PA, Anker SD, et al. Cardiorenal syndromes: an executive summary from the consensus conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib Nephrol*. 2010;165:54-67.
69. Jardin F, et al. Sepsis-related cardiogenic shock. *Crit Care Med*. 1990;18(10):1055-1060.
70. Lambermont B, et al. Effects of endotoxic shock on right ventricular systolic function and mechanical efficiency. *Cardiovasc Res*. 2003;59(2):412-418.
71. Doerschug KC, et al. Renin-angiotensin system activation correlates with microvascular dysfunction in a prospective cohort study of clinical sepsis. *Crit Care*. 2010;14(1):R24.
72. Shen L, et al. Losartan prevents sepsis-induced acute lung injury and decreases activation of nuclear factor kappaB and mitogen-activated protein kinases. *Shock*. 2009;31(5):500-506.
73. Soni A, et al. Adrenal insufficiency occurring during septic shock: incidence, outcome, and relationship to peripheral cytokine levels. *Am J Med*. 1995;98(3):266-271.
74. Sligl WI, et al. Safety and efficacy of corticosteroids for the treatment of septic shock: A systematic review and meta-analysis. *Clin Infect Dis*. 2009;49(1):93-101.
75. Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol*. 2003;14(6):1549-1558.
76. Burchill L, et al. Acute kidney injury in the rat causes cardiac remodelling and increases angiotensin-converting enzyme 2 expression. *Exp Physiol*. 2008;93(5):622-630.
77. Tokuyama H, et al. Macrophage infiltration and cellular proliferation in the non-ischemic kidney and heart following prolonged unilateral renal ischemia. *Nephron Physiol*. 2007;106(3):p54-p62.
78. Vignon P, et al. Hand-held echocardiography with Doppler capability for the assessment of critically-ill patients: is it reliable? *Intensive Care Med*. 2004;30(4):718-723.
79. Mehta RL, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31.
80. KDIGO Clinical Practice Guideline for Acute Kidney Injury: Summary of Recommendation Statements. *Kidney Int*. 2012;Suppl. 2(1):8-12.
81. Liu KD, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med*. 2011;39(12):2665-2671.
82. Bellomo R, et al. Fluid management in septic acute kidney injury and cardiorenal syndromes. *Contrib Nephrol*. 2010;165:206-218.
83. De Vriese AS, et al. Cytokine removal during continuous hemofiltration in septic patients. *J Am Soc Nephrol*. 1999;10(4):846-853.
84. Tapia P, et al. Effectiveness of short-term 6-hour high-volume hemofiltration during refractory severe septic shock. *J Trauma Acute Care Surg*. 2012;72(5):1228-1237, discussion 1237-8.
85. Matson J, Zydney A, Honore PM. Blood filtration: new opportunities and the implications of systems biology. *Crit Care Resusc*. 2004;6(3):209-217.
86. Nakamura M, et al. Treatment of severe sepsis and septic shock by CHDF using a PMMA membrane hemofilter as a cytokine modulator. *Contrib Nephrol*. 2010;166:73-82.