CHAPTER 115

Cardiorenal Syndrome Type 5

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OBJECTIVES

The chapter will:

1. Describe epidemiology, pathophysiology, diagnosis, and main clinical features of cardiorenal syndrome type 5 (CRS-5).
2. Review main clinical disease leading to CRS-5 development.
3. Identify widespread treatment guidelines in CRS-5 patients.

The cardiorenal syndromes (CRS) recently have been defined systematically as disorders of heart or kidney whereby one organ dysfunction leads to dysfunction of another. Five types of CRS are defined.[1] The first four types describe acute or chronic cardiorenal or renocardiac syndromes. Type 5 CRS (CRS-5) refers to secondary cardiorenal syndrome or cardiorenal involvement in systemic conditions. It is a clinical and pathophysiologic entity to describe the concomitant presence of renal and cardiovascular dysfunction. CRS-5 can be acute or chronic (Table 115.1), and it does not satisfy strictly the definition of CRS. However, it encompasses many conditions in which combined heart and kidney dysfunction is observed. Because this entity was described recently, there is limited information about the epidemiology, clinical course, and treatment of this condition.

All vital organs of the body share biologic information, also termed as organ cross-talk. The normal physiologic functions of the body depend on this normal network. One organ dysfunction can result in dysfunction of another. The interaction between the heart and the kidney is fairly

common. Heart and kidney dysfunction can be observed in many hospitalized patients, especially in the intensive care unit. Over the last decade, many intensivists, cardiologists, and nephrologists have shown keen interest in pathophysiology of this organ cross-talk between the heart and kidney. Many terms for this organ cross-talk have been suggested, such as cardiorenal anemia syndrome, cardiorenal syndrome, and renocardiac syndrome. Until recently CRS was not defined. Ronco et al. have proposed the definition and subdivision of CRS into five subtypes. Irrespective of the first insult (heart failure causing kidney injury or renal failure causing heart disease), CRS portends increased mortality and morbidity. CRS-5 is a recently defined clinical syndrome, and complete epidemiologic data on this entity are still incomplete.

TABLE 115.1

Conditions Causing Acute and Chronic Cardiorenal Syndrome Type 5

ACUTE CRS-5	CHRONIC CRS-5
Sepsis	Diabetes mellitus
Infections (malaria, leptospira, HIV, parvovirus b19, cytomegalovirus, coxsackievirus, toxoplasmosis)	Hypertension
Connective tissue disorders	Tuberculosis
Electric shock	Sarcoidosis
Drugs (cocaine, heroin, calcium channel blockers, cisplatin, methotrexate, mitomycin)	Fabry disease
Thrombotic microangiopathy	SLE (systemic lupus erythematosus)
Toxins (arsenic, snake bite, scorpion bite)	Chronic liver disease
Wegener granulomatosis	Sickle cell disease
Pheochromocytoma	Multiple myeloma
Burkitt lymphoma	Amyloidosis

CRS, Cardiorenal syndrome.

PATHOGENESIS OF CARDIORENAL SYNDROME TYPE 5

Cardiorenal Syndrome Type 5 and Sepsis

Inflammation and microvasculature alterations form a basis to the pathogenesis for involvement of the kidneys and cardiovascular system during sepsis, leading to cell ultrastructural alterations and organ dysfunction.[2,3] The cardiovascular system frequently is involved in sepsis and always is affected by septic shock. Cardiovascular dysfunction in sepsis is associated with a significantly increased mortality rate of 70% to 90% compared with 20% in patients without cardiovascular impairment.[4] Myocardial dysfunction in sepsis has been the focus of intense research. Many mediators and pathways (Fig. 115.1) have been implicated in pathogenesis of septic myocardial depression; however, the precise etiopathogenesis is unclear.[5] Calvin et al. were the first to demonstrate myocardial dysfunction in adequately volume-resuscitated septic patients with decreased ejection fraction and increased end-diastolic volume index.[4] Echocardiographic studies have demonstrated impaired left ventricular systolic and diastolic function in septic patients.[6,7] Many other studies have confirmed decreased contractility and impaired myocardial compliance in sepsis.[8–11]

Septic cardiac dysfunction is multifactorial. Like septic AKI, ischemia and inflammatory mediators are the chief culprits. Global myocardial ischemia was postulated initially as a the main mechanism of cardiac dysfunction, but later septic patients have been shown to have high coronary blood flow and diminished coronary artery–coronary sinus oxygen difference.[12] Further experiments suggested a possibility of myocardial hypoxia resulting from alterations in coronary blood flow and myocardial metabolism as a possible mechanism of cardiac dysfunction.[13] In patients with underlying coronary artery disease, myocardial ischemia is aggravated.[14]

Inflammatory mediators also play a key role in the pathogenesis of cardiac dysfunction. Tumor necrosis factor (TNF) and interleukin-1 (IL-1) are the principal culprits.[15,16] Elevated levels of prostanoids such as thromboxane and prostacyclin, which may alter coronary autoregulation and

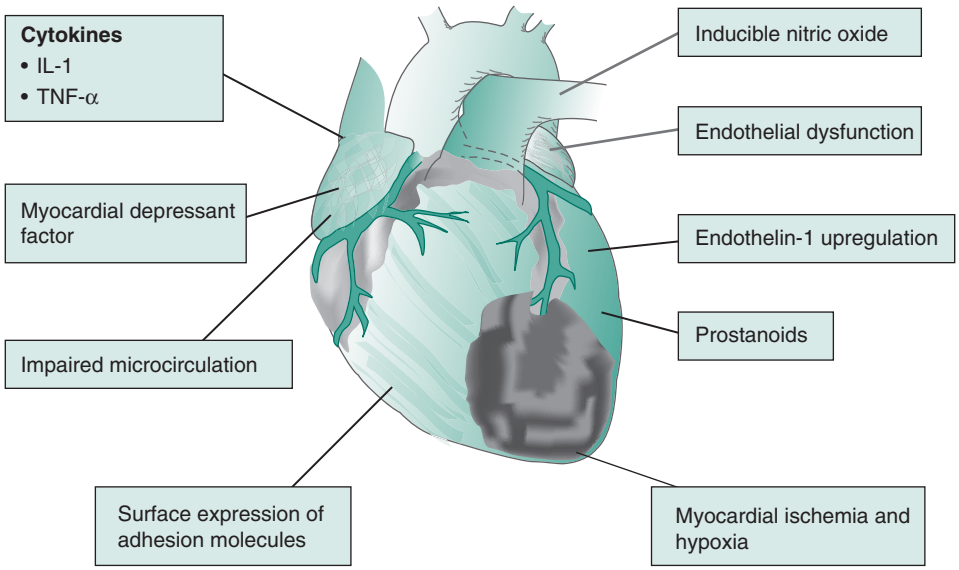

FIGURE 115.1 Pathogenesis of cardiac dysfunction in sepsis.

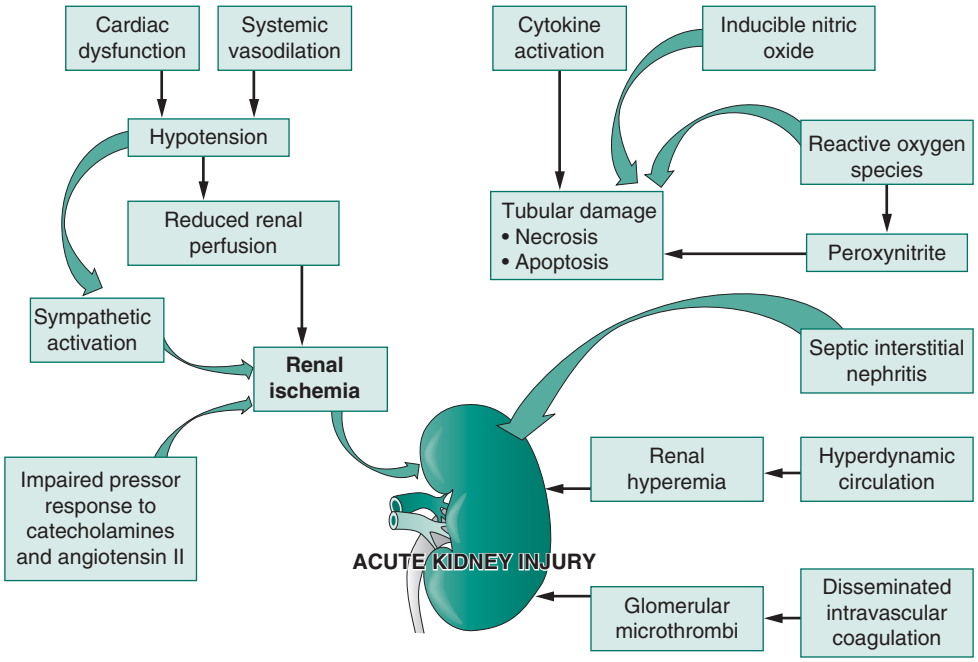

FIGURE 115.2 Pathogenesis of acute kidney injury in sepsis.

endothelial function also have been demonstrated in septic patients.[17] One of these cytokines also may act as a myocardial depressant factor.

Nitric oxide (NO) has important biologic role in cardiovascular system. Higher dose of NO has been demonstrated to induce myocardial dysfunction by depressing energy generation.[18] Sepsis leads to the expression of inducible NOS (iNOS) in the myocardium, which in turn importantly leads to myocardial dysfunction.[19,20]

Acute kidney injury (AKI) is a common complication of patients with sepsis and carries poor prognosis. AKI occurs in 20% of critically ill patients and in 51% of patients with septic shock and with positive blood cultures.[21] The mortality rate of sepsis-induced AKI is high, at approximately 70%, whereas the mortality of AKI alone is 40% to 45%.[22,23] Although the presence of multiple organ dysfunction and other comorbidities contributes to high mortality, AKI independently increases morbidity and mortality.[24] Sepsis is characterized by a generalized inflammatory response and by activation of coagulation and fibrinolytic system, resulting in endothelial injury.[25,26] Current opinion suggests that pathogenesis of septic AKI relies on hemodynamic factors and inflammatory mediators (Fig. 115.2). AKI in sepsis earlier was considered to be secondary to renal ischemia because of septic shock. Experimental studies of septic AKI have reported conflicting results.[27] On one hand, some studies showed that global renal blood flow (RBF) declines after induction of sepsis or endotoxemia, leading to acute tubular necrosis, reduction in glomerular filtration, and severe AKI.[28,29] On the other hand, Ravikant demonstrated renal vasodilation with increased RBF.[30] A meta-analysis of 160 experimental sepsis studies found preserved or increased RBF in about 30% those studies.[31] Changes in intrarenal hemodynamics also play a role in the pathogenesis of septic AKI. The RBF may be redistributed preferentially to the cortex, causing a relative hypoxia of medulla.[32]

Nonhemodynamic kidney injury is mediated by various inflammatory mediators such as cytokines, arachidonate metabolites, and vasoactive and thrombogenic agents. These various mediators are involved in the pathogenesis of organ dysfunction in sepsis.[33] Among the variety of mediators TNF seems to have the predominant role in septic AKI.[34] Apoptosis seems to be an important pathway of cell dysfunction in sepsis than necrosis. All in all, there is a recent paradigm shift in understanding about the pathogenesis of septic AKI from ischemia and vasoconstriction to hyperemia and vasodilation and from acute tubular necrosis to acute tubular apoptosis.

Cardiorenal Syndrome Type 5 and Amyloidosis

The systemic amyloidoses are an uncommon group of disorders characterized by the extracellular deposition of amyloid in one or more organs. Cardiac and renal deposition leading to restrictive cardiomyopathy and proteinuric renal disease is a common feature of amyloidosis. Importantly, presence and severity of CRS drives the prognosis of systemic amyloidosis.

Among many types of amyloidoses, AL (primary) and AA (secondary) amyloidosis are the types most frequently encountered in clinical practice. AL amyloidosis, in which amyloid is derived from monoclonal light chains, is associated with clinical cardiac involvement in about 50% of all cases.[35] Subclinical cardiac involvement at autopsy or on endomyocardial biopsy may be detected in almost all patients. Renal involvement occurs in 30% to 40% of all AL cases.[36] On the contrary, AA type is characterized by predominant renal involvement in 60% to 100% of all cases.[37-40] Cardiac involvement is less frequent and varies from 0 to 39.5%.[37–40]

In amyloidosis, the heart demonstrates thickening of all four chambers, with biatrial dilation, mildly dilation of right ventricle with normal or small left ventricular cavity. Myocardial cells are separated by amyloid deposits with infiltration of intramyocardial vessels. Occasionally epicardial coronary vessels also are involved, leading to myocardial ischemia.[41] The conduction system is involved frequently. The predominant manifestation of amyloid heart

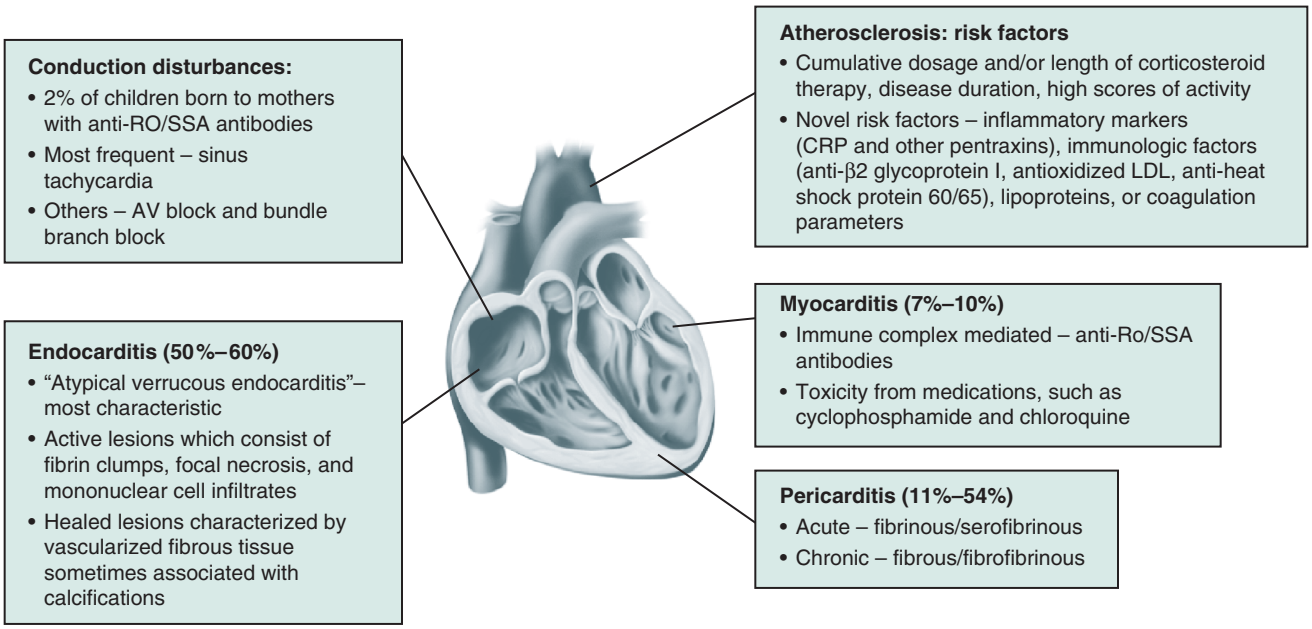

FIGURE 115.3 Pathogenesis and manifestation of cardiac dysfunction in systemic lupus erythematosus.

disease is congestive heart failure. In patients with small vessel involvement and minimal or no myocardial infiltration, the presenting complaint may be angina. In addition, atrial arrhythmias are seen frequently.[35]

Renal amyloid is characterized by deposits in the glomerular basement membrane, the subendothelial area, and the extracellular mesangial system. Occasionally tubular deposits are seen. The majority of patients with renal amyloidosis present with proteinuria, which can vary from minimal asymptomatic proteinuria to nephrotic syndrome. Hematuria is present in about one third of patients. Chronic renal insufficiency with little proteinuria also can be seen in patients with extensive vascular deposits.[42] In patients with tubular deposits, tubular dysfunction can be seen.

Cardiorenal Syndrome Type 5 and Systemic Lupus Erythematosus

The heart is involved very commonly in SLE. Any cardiac structure, including pericardium, myocardium, endocardium, conduction tissue, and even coronary arteries are involved in SLE.

The spectrum of cardiac complications in SLE is as shown in Fig. 115.3. Pericarditis is the most frequent cardiac manifestation of SLE, and pericardial involvement is seen in 11% to 54% of patients on echocardiographic studies.[43] Pericarditis also is included in the ARA/ACR classification criteria of SLE.[44] Direct immunofluorescence shows the granular deposition of immunoglobulin and C3. It indicates the role of immune complexes in the pathogenesis. Acute or chronic inflammatory changes are seen in pericardium. Acute pericarditis can be fibrinous or serofibrinous, and chronic pericarditis can be fibrous or fibrofibrinous. Pericarditis generally manifests at the start of the disease or during relapses and rarely leads to cardiac tamponade, constrictive pericarditis, or purulent pericarditis. Myocardial involvement was seen in 40% of SLE cases in postmortem examination[45] and in 20% of cases on echocardiography.[46] However, overt myocardial involvement is seen in only 7% to 10% of patients.[47] Immune-complex and complement deposition is seen on direct immunofluorescence, whereas association with anti-Ro/SSA antibodies also is proposed.[48] The patient may have acute illness or a chronic course with development of cardiomyopathy, but left ventricular failure rarely is seen.[49] Myocardial dysfunction in SLE also may be due to renal failure and hypertension, coronary artery disease (CAD), valvular infection, or toxic effects of medications used for treatment of SLE.

Libman-Sacks endocarditis, also known as atypical verrucous endocarditis, is the most typical presentation of endocardial involvement in SLE. These vulvular abnormalities are detected in 40% to 50% of cases with transthoracic echocardiography (TTE) and 50% to 60% with transesophageal echocardiography (TEE). Antiphospholipid (aPL) antibodies bind to endothelial cells and activate them. This leads to platelet aggregation and thrombus formation.[50] Immune-complex and complement deposition also has been reported to have association with valvular involvement. Libman-Sacks endocarditis is clinically silent in the majority of patients and rarely leads to the development of cardiac murmur. Verrucae develop near the edge of the valve, and even if they become large they do not deform the closing line of the valves.[51] Endocardial involvement may lead to valvular insufficiencies, most commonly of the mitral or aortic valves. Although complications are rare, embolic events do occur and stroke, peripheral embolism, has been reported in 13% of cases.[51] Infectious endocarditis has been reported in 7% of cases, and risk of endocarditis is increased by dental treatments. Antibiotic therapy should be considered for patients with valvular abnormalities because SLE patients may receive immunosuppressant therapy for their primary disease. Because patients with SLE live longer because of improved therapies and preventive measures, death and disability from cardiovascular events are increasing. SLE patients are four to eight times more likely to suffer from CAD than patients without SLE, and CAD is diagnosed in 6% to 10% of SLE patients.[52] Women are at a 50 times greater risk of CAD.[53] Atherosclerosis, hypertension, arteritis, thrombotic event, embolism resulting from endocarditis, and vasospasm are the risk factors for development of CAD.[54]

Hypertension, sedentary lifestyle, hyperlipidemia, and hyperhomocysteinemia may lead to atherosclerosis in

SLE patients.[55] Steroid therapy in these patients increases the lipoprotein and homocysteine levels.[56] Inflammation plays an important role in development of atherosclerotic plaque. Atherosclerotic lesions begin with the recruitment of inflammatory cells such as monocytes and T cells to the endothelial wall. Recently CRP and pentraxines are considered to be inflammatory markers in patients with SLE.[57] Autoantibodies and immune complexes also play a major role for atherosclerosis. Circulating antibodies to OxLDL (anti-OxLDL) have been described, although their relationship to the development and progression of atherosclerosis is unclear. Svenungsson et al. have demonstrated that autoantibodies to OxLDL are more common in SLE patients who have a history of cardiovascular disease than in SLE controls or healthy subjects.[58]

Sinus tachycardia is the most frequent rhythm disturbance observed in SLE patients. Atrioventricular block and bundle branch block are seen in children of mothers with anti-Ro/SSA antibodies and rarely in adults.[59] These patients are mostly asymptomatic, or it may lead to fatigue and palpitations. Syncope is seen in very rare cases.[60] Sinus tachycardia in SLE patients may be due to pericarditis, myocarditis, or chloroquine use.[44] Renal involvement remains a major cause of morbidity in patients with SLE. Abnormalities of immune regulation lead to autoantibody production in SLE. Antibodies directed against nuclear antigens (ANA) and specifically against the DNA (anti-dsDNA) are considered diagnostic of SLE. Among these anti-Sm antibodies have significant association with lupus nephritis (LN). The initiating event may be the local binding of nuclear or other antigens to glomerular sites followed by in situ immune complex deposition. Immune complexes made up of DNA-anti-DNA along with some other aggregates (nucleosomes, ribosomes, chromatin, C1q, laminin, Sm, La [SS-B], Ro [SS-A], and ubiquitin) cause glomerular injury. Previously T cells were considered only as helping factor for B cells to produce autoantibodies. However, recent studies support the significant role of T cells for progression of renal disease in SLE. In addition, deposition of immune complex leads to release of chemokines such as mitochondrial complementing protein (MCP-1) and RANTES in glomeruli. These chemokines cause proliferation of mesangium, which results into acute glomerular nephritis characterized by mesangial expansion and cellular infiltration. With the progression of disease, acute glomerulonephritis turns into chronic glomerulonephritis characterized by glomerulosclerosis, interstitial fibrosis, and tubular atrophy. Recent studies have been done on Toll-like receptors (TLR), and TLR expression on renal cells causes activation of end organ response and renal injury.

Females are affected more commonly by SLE, but clinical manifestations are similar in both the genders, adults, and children. SLE is a multisystem disease, and any organ system can be involved in SLE. Kidneys are affected from the start of SLE or at any stage and follow a protracted course of remissions and exacerbations. Clinical renal involvement correlates well with degree of glomerular involvement.[61] Clinical features of renal involvement may be correlated with histologic findings seen on renal biopsy and classified by International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 (Table 115.2).[62]

Patients of class I having only mesangial involvement often have no or, at the most, mild evidence of clinical renal disease. Patients of class II have proteinuria of less than 1 g/day. But these patients have high anti-DNA antibody titer and low serum complement. Hypertension is seen infrequently and serum creatinine and GFR are in the normal ranges. In class III patients, proteinuria is often more than 1 g/day, and many patients have nephrotic range proteinuria. Most of the patients suffer from hypertension and have elevated creatinine at the presentation. Serologic tests usually indicate active lupus disease at this stage. Patients with diffuse lupus nephritis (class IV) have extensive clinical features. Almost all patients have proteinuria, and half of these patients fall in nephritic range. Hypertension is very common and renal dysfunction is typical. These patients have very high titers of anti-DNA antibody and low complement levels. Patients with membranous lupus nephritis (class V) usually have proteinuria, edema, and other typical nephrotic syndrome features. Of these, 40% of patients have less than 3 g/day proteinuria, and up to 60% of patients will have elevated anti-DNA antibody titers and low serum complement levels. Usually these patients have hypertension and renal dysfunction. Patients of this class are likely to develop thrombotic complications, as seen in idiopathic membranous nephropathy. Patients end up in class VI after long periods of flares alternating with periods of inactivity. Patients have inactive sclerotic and fibrotic lesions. Almost all patients have hypertension and renal dysfunction. However, anti-DNA antibody titers and serum complement levels may be normalized by the time patients reach this stage.[62]

TABLE 115.2

International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis

Class 1	Minimal mesangial lupus nephritis
Class 2	Mesangial proliferative lupus nephritis
Class 3	Focal lupus nephritis[a]
Class 4	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis[b]
Class 5	Membranous lupus nephritis[c]
Class 6	Advanced sclerosing lupus nephritis

[a]Indicates the proportion of glomeruli with active and with sclerotic lesions.
[b]Indicates the proportion of glomeruli with fibrinoid necrosis and cellular crescents.
[c]Class V may occur in combination with class III or IV in which case both will be diagnosed.

CRS-5 and Fabry Disease

Fabry disease (FD) is responsible for a CRS-5 with insidious onset, in which the kidney and cardiac dysfunction may develop slowly until a "point of decompensation." It also can be chronic, acute, or acute-on-chronic CRS-5. Mechanisms in acute and chronic CRS-5 are different: the nature, severity, and duration of organ dysfunction also are influenced by the management interventions. In most cases of CRS-5 there is usually a precipitating event that brings the condition to attention (e.g., Fabry's crises), precipitated by fever, exercise, fatigue, stress, and rapid changes in temperature.[63,64] Being a systemic disease, FD starts with an specific effect(s), involving kidney and/or heart, contributing for the bilateral organ cross-talk for the development of CRS-5.

Pathology of Renal Involvement

The natural course of Fabry nephropathy in children or adolescent patients is still largely not understood. Like

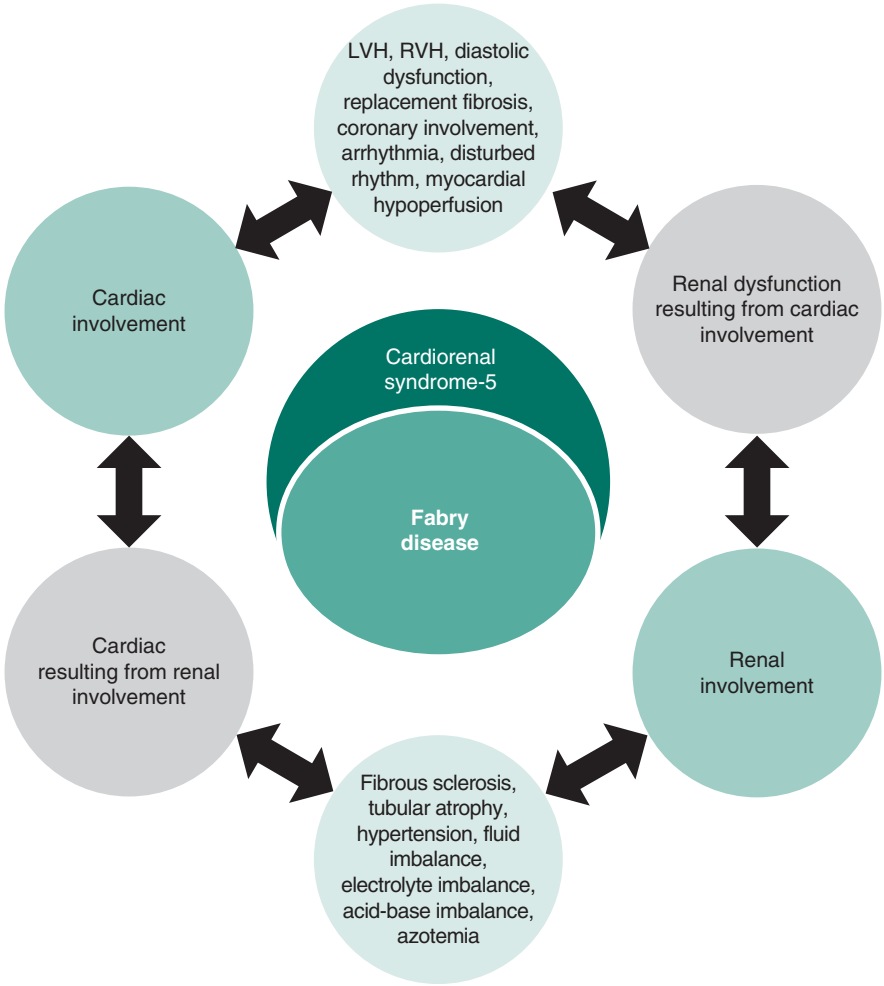

FIGURE 115.4 Fabry disease pathophysiology.

most aspects of the disease, renal pathology increases in severity with age. In classically affected patients with FD, renal lesions result from Gb3 deposition in the glomerular endothelial, mesangial, interstitial cells, and in podocytes, which are terminally differentiated epithelial cells that accumulate numerous myelin-like inclusions in their lysosomes. Podocyte foot process effacement has been described, and it represents the histologic counterpart of proteinuria. Glycosphingolipid storage also occurs in the epithelium of the loop of Henle and the distal tubules, and in the endothelial and smooth muscle cells of the renal arterioles.[64,65] Histologic, potentially irreversible changes to glomeruli, interstitial tubules, and vascular structures before the first appearance of signs can be observed in renal biopsy specimens from children[66] (Fig. 115.4). The glomerular podocytes are swollen and finely vacuolated in light microscopy examination, such as epithelial cells of distal tubules (Fig. 115.5); lamellated lipid inclusions (zebra bodies) in podocytes' cytoplasm also can be seen on electron microscopy.

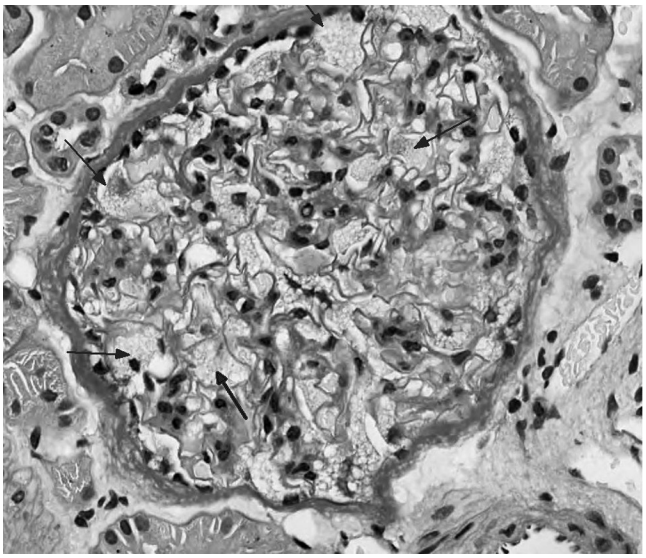

FIGURE 115.5 Light microscopy. The glomerular podocytes are swollen and finely vacuolated *(arrows)* in a patient with Fabry nephropathy disease.

Clinical Renal Involvement

Signs indicative of early, insidiously progressing renal damage include microalbuminuria and proteinuria

developing as early as in the second decade of life, which, as in diabetic nephropathy, are believed to contribute directly to the progression of the Fabry nephropathy. With advancing age, proteinuria worsens.[67] Isosthenuria accompanied by alterations in tubular reabsorption, secretion, and excretion develop. Initially, glomerular compensation (hyperfiltration) may mask impairment of renal function, but, once a critical number of nephrons have been damaged, renal function will decline progressively. Gradual deterioration of renal function and development of azotemia usually occur in the third to fifth decades of life.[68] At this stage, fibrosis, sclerosis, and tubular atrophy dominate the disease activity, portending end-stage renal disease that generally occurs in males in the fourth to fifth decade of life. The nephrologic aspects of FD are major contributors to the morbidity and mortality associated with the disorder. Progression to end-stage renal failure is the primary cause of death in male patients with untreated FD, and death most often results from uremia, unless chronic hemodialysis or renal transplantation is undertaken (see Fig. 115.4).

Pathology of Cardiac Involvement

Storage of globotriaosylceramide (Gb3) is found in various cells of the heart, including cardiomyocytes, conduction system cells, valvular fibroblasts, endothelial cells within all types of vessels, and vascular smooth muscle cells.[69] Gb3 storage by itself, however, is unable to explain the observed level of cardiac manifestations. Autopsy of an individual with FD who had an extremely hypertrophied heart revealed a relatively limited contribution (1%–2%) of the stored material to the enormous increase in cardiac mass. It appears that storage induces progressive lysosomal and cellular malfunctioning that, in turn, activates common signaling pathways. Energy depletion recently was proposed as the common denominator in multiple metabolic and even sarcomeric hypertrophic cardiomyopathies[70] (Fig. 115.6). Energy depletion also may occur in FD, as suggested by the impairment in energy handling seen in skin fibroblasts. This may be supported further by the observation of a decreased ratio of ATP to inorganic orthophosphate, as has been shown by magnetic resonance imaging (MRI) studies in patients with sarcomeric hypertrophic cardiomyopathies[71] (see Fig. 115.4).

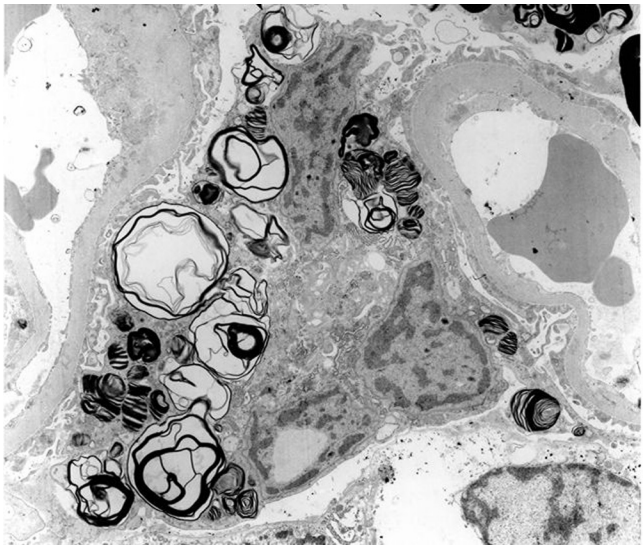

FIGURE 115.6 Electron microscopy. Lamellated lipid inclusions (zebra bodies) in a podocyte cytoplasma.

Clinical Cardiac Involvement

Cardiac symptoms, including left ventricular hypertrophy, arrhythmia, angina, and dyspnea, are reported in approximately 40% to 60% of patients with FD.[72] Arrhythmias and impaired heart rate variability arise from involvement of the sinus node, conduction system, and imbalance between sympathetic and parasympathetic tone. Diastolic dysfunction and concentric left ventricular hypertrophy, which is typically nonobstructive, are important features, with men generally more severely affected than women. Myocardial ischemia and infarction may result from compromised function of the coronary vascular bed.[73] With age, progressive myocardial fibrosis develops with interstitial and replacement fibrosis.[74] Replacement fibrosis almost always starts in the posterior-lateral wall and in the mid-myocardium. In end-stage patients, transmural replacement fibrosis gradually reduces cardiac function to the stage of congestive heart failure.[75] Malignant arrhythmias are responsible for a number of cardiac deaths in patients affected with FD.[76] The cardiomyopathy of FD is characterized by reduced myocardial contraction and relaxation tissue Doppler velocities are sometimes detectable even before development of left ventricular hypertrophy (LVH). Right ventricular hypertrophy (RVH) with normal chamber size and preserved systolic but impaired diastolic function represents the typical right ventricular (RV) structural change in FD. The myocardial perfusion reserve was found to be reduced significantly in patients affected with FD. Patients with FD have abnormal coronary microvascular function. FD is associated with an increased risk of developing aortic root dilatation in male patients.[77] Aortic root dilation was detected in 24% of 71 hemizygous male patients and was associated statistically with the presence of a dolicho-ectatic basilar artery ($P = .008$).[77]

DIAGNOSIS OF CARDIORENAL SYNDROME TYPE 5

For whom to concern diagnostic approach to sepsis, prototype of CRS-5, initial emphasis has to be on setting of severe sepsis and septic shock, then on heart and kidney assessment and risk evaluation to start an appropriate treatment.

Systemic inflammation, like sepsis, has to be suspected when body temperature is less than 36°C (96.8°F) or greater 38°C (100.4°F), heart rate is greater than 90 beats/min, and tachypnea is already present (more than 20 breaths/min). White blood cells count can be less than 4×100 cells/L or greater than 12×100 cells/L.

A recent review pointed out some characteristic biomarkers whose elevation is typical during septic process: lipopolysaccharide binding protein, procalcitonin, C-reactive protein, and proinflammatory cytokines (IL-6, transforming growth factor-β [TGF-β]).[78]

Assessment of cardiac function in CRS-5 is similar to other clinical situations in which myocardial dysfunction is present. Natriuretic peptides and troponins levels assays provide informations about cardiac chambers (especially left cardiac chambers) and myocardial cells damage.

Leukocytosis and C-reactive protein are not specific for myocardial injury diagnosis, and imaging devices are preferred by clinicians.

Sepsis cardiomyopathy present a complex clinical picture, and its pathophysiology is not well understood. In early stages of septic process there is a low output myocardial involvement. After starting fluid therapy clinical pictures shift to typical distributive shock characterized by increased cardiac output and systemic vasodilatation.[79] Echocardiographic assays confirm high-output cardiomyopathy with abnormalities in left ventricular regional contractility together with dilation of left heart chambers.[80]

Diagnosis of kidney involvement in sepsis-related CRS-5 is overlapping to other forms of AKI with acute changes in serum creatinine levels according to RIFLE, AKIN, and KDIGO criteria.[81]

Several other biomarkers are proposed, such as cystatin C (the only new biomarker approved in the United States), KIM-1, NGAL, and NAG, but RIFLE, KDIGO, and AKIN criteria still recommend serum creatinine levels and urine output for diagnosis and monitoring of AKI in CRS-5.

MANAGEMENT OF CARDIORENAL SYNDROME TYPE 5

Once the diagnosis of CRS-5 is made, every organ and tissue involved must be investigated to pay attention to the at-risk prediction and protect from further and irreversible alterations in organ function. Preliminary data (not published at present time) seem to indicate that biomarkers of cell cycle regulation may predict patients will develop severe AKI in few days. Regarding cardiac risk, patients who survive septic shock had lower ejection fractions and higher left ventricular end-diastolic volumes to suggest a myocardial depression protective role.[82]

Treatment of CRS-5 is based primarily on underlying disease management and on kidney and heart complications. First of all, maintaining hemodynamic stability and guarantee tissue perfusion are key points to prevent CRS-5 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.[83]

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 techniques using convection, high-volume hemofiltration, and high-permeability membranes.[84] Best results were obtained with high-permeability membranes and absorption.[85]

A therapeutic alternative is provided by hit cellular elements accountable for apoptosis and neutrophil activation and remove them by polymyxin filters or citrate anticoagulant-based selective cytopheretic device.[86]

To manage heart complications, especially in the hyperacute stage, a multifaceted approach is required to maintain filling pressures with fluid therapy together with vasopressors, vasodilators, and inotropes; vasopressors should be employed carefully because of depressive effects on cardiac output (increased afterload), especially with concomitant hypovolemia. Vasodilators increase cardiac output, especially in ischemic patients, whereas phosphodiesterase inhibitors have inotropic and vasodilatory effects, but they provide less increase of myocardial oxygen requirements.

Vasopressin increases arterial pressure, but it has negative effects on cardiac output; more recently levosimendan has been proven to provide benefits in decompensated heart failure to increase ejection fraction and diuresis; levosimendan efficacy is still to be proven in prevention of CRS-5.[87]

Renal support includes removal of any nephrotoxic drug and media, maintenance of adequate perfusion pressure, and, if indicated, early intervention with dialysis therapy.[88]

There is no role for dopamine for improving renal hemodynamics,[89] and there are limited studies with fenoldopam.[90] Norepinephrine decreases renal perfusion in normal conditions but increases systemic blood pressure in septic patients,[89] whereas vasopressin increases diuresis and GFR in septic patients.[91]

Diuretics have a limited role in managing heart and kidney involvement in septic patients,[92] and renal replacement therapy with continuous renal replacement therapy (CRRT) should be started promptly[89]; early ultrafiltration seems to improve renal outcomes in septic shock patients, but these data have to be confirmed in further clinical trials.

Key Points

1. Cardiorenal syndrome type 5 (CRS-5) refers to secondary cardiorenal syndrome or cardiorenal involvement in systemic conditions. It is a clinical and pathophysiologic entity to describe the concomitant presence of renal and cardiovascular dysfunction, and it can develop with an acute or chronic onset.
2. Sepsis, systemic lupus erythematosus, amyloidosis, and Fabry disease patients can develop CRS-5.
3. Diagnosis of CRS-5 is closely dependent on clinical onset (acute or chronic) and underlying disease.
4. Management has to be focused on general support cares and specific treatment of underlying disease.

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