Review Article

# Cardiorenal Syndromes

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## Introduction

Cardiovascular diseases are the commonest cause of morbidity and mortality worldwide. In USA, about one third of population has some form of cardiovascular disease, i.e., hypertension, coronary heart disease (CHD), heart failure (HF), stroke, peripheral vascular disease (PVD) (1). Chronic kidney disease (CKD) affects about 13% of population in USA (2). There is a close relationship between cardiac and kidney diseases, as patients with cardiac disease often develop kidney dysfunction and the most common cause of mortality in patients with kidney disease is cardiovascular (3). Patients with CKD have 10–20 times high chances of cardiovascular disease as compared to age-matched non-CKD population (4). Similarly patients with acute cardiac dysfunction like acute HF or acute coronary syndrome (ACS) may develop acute kidney injury (AKI) and vice versa (5). However, despite this knowledge, the relationship between cardiac and kidney diseases has not been well defined till now, resulting in difficulty in managing these patients. The term cardiorenal syndrome (CRS) is used to define this heart and kidney interaction, and has been in use for sometime now, but a proper identification and classification system was lacking (6). Recently in 2008, the acute dialysis quality initiative (ADQI) group organized a consensus conference in Venice, Italy to discuss this issue, comprising of opinion leaders and experts from nephrology, critical care, cardiology, cardiac surgery and epidemiology (7). The group came out with consensus definition and classification of CRSs.

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The following definitions were proposed:

Term CRS was defined as *disorder of heart or kidneys, whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other organ* (8).

Five subtypes of CRS were defined as follows:

- Acute CRS (Type 1) – an acute worsening of cardiac function leading to renal dysfunction
- Chronic CRS (Type 2) – chronic abnormality of cardiac function leading to renal dysfunction
- Acute renocardiac syndrome (Type 3) – acute worsening of renal function, leading to cardiac dysfunction
- Chronic renocardiac syndrome (Type 4) – chronic abnormality of renal function, leading to cardiac dysfunction
- Secondary CRSs (Type 5) – systemic conditions leading to both cardiac and renal dysfunction; these include amyloidosis, diabetes mellitus, sepsis and systemic lupus erythematous (SLE), etc.

The ADQI group recognized that many patients might migrate to different groups during the course of their illness and so the classification is not fixed.

### Acute cardiorenal syndrome (Type 1)

This is a condition characterized by acute worsening of heart function, i.e., acute decompensated heart failure (ADHF), ACS and cardiac surgery associated low cardiac output, which leads to AKI (9).

Many studies have used the term worsening renal failure (WRF) to define AKI and the incidence of WRF in patients with ADHF and ACS is found to be between 24–45% and 9–19%, respectively. This wide range in incidence is due to different definitions of WRF and heterogeneity of these studies (10-13). Various studies have defined various levels of rise in serum creatinine as criteria of renal dysfunction, from increase of 0.3 mg or 0.5 mg to >25% decrease in glomerular filtration rate

(GFR) (10–15). Newly validated Risk, Injury, Failure, Loss, ESKD (RIFLE) and Acute Kidney Injury Network (AKIN) criteria for AKI take into account a rise in creatinine of >0.3 mg/dL or >25% decrease in GFR, apart from decrease in urine output of <0.5 mL/kg/h for 6 h (16).

Most of this kidney dysfunction due to ADHF/ACS occurs early after admission; however, it can occur any time after hospitalization. The ADQI suggests that AKI associated with ADHF/ACS should be considered within 1 week of hospitalizations, as >90% of patients develop AKI within this duration (17). Patients admitted with ACS/ADHF who develop AKI have higher chances of all cause and cardiovascular mortality, prolonged hospitalization, recurrent admissions and higher chances of progression to advanced CKD stages (12–15).

The acute decompensated heart failure national registry (ADHERE) examined >105,000 patients with ADHF and found that preexisting renal insufficiency was present in 30% of cases and 21% had serum creatinine levels >2 mg/dL. The study also found that the best single predictor of inpatient mortality was high levels of blood urea nitrogen and serum creatinine levels (>43 and 2.75 mg/dL, respectively) at admission (18).

### Chronic cardiorenal syndrome (Type 2)

Chronic CRS is defined as chronic cardiac abnormality leading to CKD. The chronic cardiac abnormalities include congenital heart diseases (CHD), chronic HF, atrial fibrillation, constrictive pericarditis and chronic ischemic heart diseases (17). Sometimes preexisting CKD is present and it is not always possible to distinguish between type 2 and type 4 CRS (9). The prevalence of kidney dysfunction in patients with chronic cardiac diseases is estimated between 45% and 63% in various studies. There is higher morbidity and mortality in patients with CHF and CKD as compared to patients without kidney disease (19–23).

One of the typical examples of type 2 CRS is CHD, in which long-standing cardiac disease results in alteration in renal perfusion and neurohormonal activation resulting in CKD. In a study of 1102 patients with CHD, over 50% had evidence of kidney dysfunction and 9% had GFR <60 mL/min, and these patients had three-fold higher mortality as compared to other patients (23).

Another evidence of type 2 CRS is provided by Atherosclerosis Risk in Community and Cardiovascular Health (24). In this study, 12.9% of study population had cardiovascular disease at baseline. These patients had a mean baseline serum creatinine of 0.9 mg/dL and estimated glomerular filtration rate (eGFR) 86.2 mL/min/1.73 m$^2$. After a mean follow-up of 9.3 years, 7.2% of CVD patients had reduced kidney function when defined as a serum creatinine increase of ≥0.4 mg/dL and 34% when defined as a decrease in eGFR >15 mL/min/1.73 m$^2$. During the observational period, 2.3% and 5.6% developed new kidney disease, respectively. By multivariable analysis, baseline CVD was independently associated with both decline in kidney function and development of new CKD.

### Pathophysiology of cardiorenal syndrome (Figures 1 and 2)

The exact mechanism of renal dysfunction in HF is

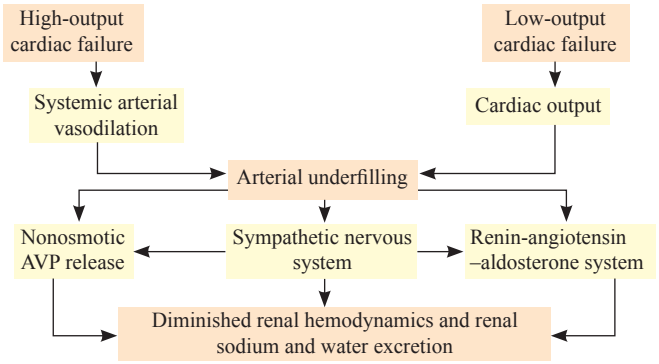


**Figure 1.** Pathophysiology of acute decompensated heart failure.

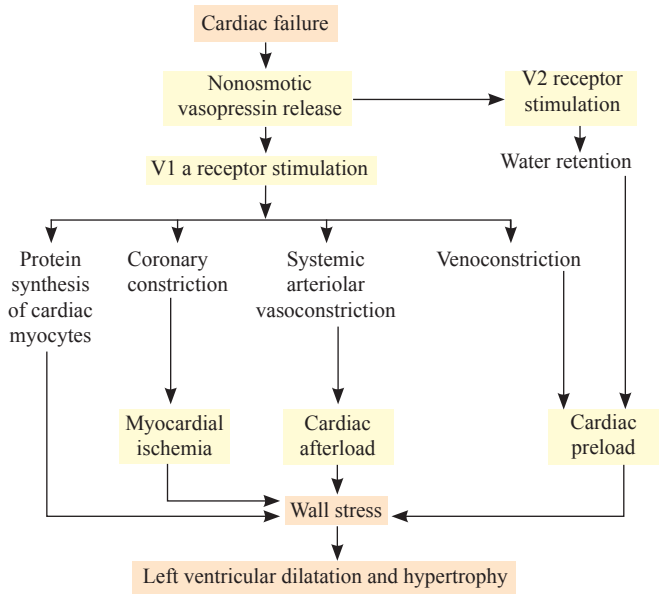


**Figure 2**. Vasopressin stimulation of V2 and V1a receptors can contribute to events that worsen cardiac function

not well-understood. The most common explanation has been that decrease in cardiac output as a result of poor cardiac function results in reduced renal perfusion leading to kidney dysfunction (25–27).

Poor perfusion to kidneys leads to activation of neurohormonal system, resulting in activation of arterial baroreceptors and intrarenal sensors. These lead to activation of renin angiotensin aldosterone system (RAAS), sympathetic nervous system and also arginine vasopressin system. The activation of RAAS results in increase in angiotensin II and aldosterone; the binding of angiotensin II to AT1 receptor leads to vasoconstriction and aldosterone secretion. Aldosterone promotes reabsorption of sodium in distal tubules leading to water and salt retention and worsening of pulmonary vascular congestion. Another mediator which is increased in this condition is endothelin I, which leads to afferent arteriolar constriction, further reducing the renal perfusion and exacerbating renal injury. Blockage of endothelin receptors in animal models has shown to improve GFR and blood flow (26).

In addition to the above effects, RAAS activation causes activation of NADPH oxidase, which results in the formation of reactive oxygen species (ROS); this increase in oxidative stress leads to production of proinflammatory cytokines, like interleukin-1, interleukin-6, C-reactive protein (CRP) and tumor necrosis factor (TNF). These cytokines have negative inotropic effects, assist in cardiac remodeling and cause thrombotic complications (27). Arginine vasopressin (AVP) causes fluid retention and enhances actions of angiotensin II and norepinephrine.

However, recent data suggests that there may be other mechanisms of CRS. Evaluation Study of Congestive heart failure And Pulmonary artery catheterization Effectiveness (ESCAPE) randomized 433 HF patients to receive therapy guided by pulmonary artery catheterization or by clinical assessment alone (28). The result in 193 patients treated with pulmonary catheter showed that there was no correlation between serum creatinine or GFR and pulmonary capillary pressure, cardiac index or systemic vascular resistance. And even increasing their cardiac index (1.9–2.4 mL/m$^2$) did not improve the renal dysfunction. A significant correlation between right atrial pressure with serum creatinine or GFR was observed, suggesting a role of high central venous pressure in renal dysfunction. In a study of 145 patients with HF, patients with higher central venous pressure had higher risk of renal function deterioration and a reduction in central venous pressure to <8 cm resulted in improvement in renal function (29). The change in cardiac index did not change GFR during hospitalization. This is explained by high venous pressure which leads to reduction in perfusion pressure across glomeruli resulting in reduction in GFR (29,30).

### Acute renocardiac syndrome (Type 3)

Acute renocardiac syndrome is seen in patients with AKI, which can lead to acute cardiac dysfunction, for example, ACS or cardiac arrhythmia. This is supposed to be caused by accumulation of uremic toxins, fluid and salt retention, accelerated hypertension and electrolyte disturbances, etc. Various diseases incriminated are postinfectious glomerulonephritis, rhabdomyolysis, and drug-induced AKI. AKI after contrast agents or cardiac surgery can also lead to cardiac dysfunction and included in type 3 CRS (9,17). Contrast nephropathy is common after use of contrast agents, and most patients recover renal functions; however, a small percentage of these patients (0.2–1.1%) do not recover kidney function and require long-term renal replacement therapy and these patients can develop secondary cardiac dysfunction due to renal failure (31,32). The risk factors are older age, preexisting CKD, DM, CAD, PVD and higher volume of contrast medium. However, the exact incidence and epidemiology of this syndrome is not clear because of different definitions used and variable risk factors (17).

### Chronic renocardiac syndrome (Type 4)

Cardiovascular diseases are the leading cause of death in patients with CKD. CKD can cause either reduction in cardiac function (left ventricular hypertrophy or diastolic dysfunction) or cardiovascular disease (HF, MI or stroke) (9,17). Several studies have demonstrated that the risk of CVD mortality is 10–20 times higher in CKD patients as compared to age- and sex-matched population. About 50% of patients of CKD die of cardiovascular diseases (3,4). The risk of CVD increases as the grade of CKD increases and risk is highest in patients on dialysis (33,34). Both traditional risk factors like presence of diabetes, hypertension, increased age, dyslipidemia, etc. and nontraditional risk factors related to uremia, for example, abnormities in calcium phosphorus metabolism, chronic inflammation, endothelial dysfunction, vascular remodeling, and oxidative stress, etc. are responsible for this increased risk (33–35).

### Secondary cardiorenal syndromes (Type 5)

Many systemic diseases can lead to simultaneous involvement of heart and kidney. The exact epidemiology of this syndrome is not known because of different diseases causing it. There is incomplete understanding of pathophysiological mechanism causing this syndrome, whether it is truly bidirectional or concurrent involvement of both organs. The prototype diseases are diabetes, amyloidosis, sepsis, SLE etc. (17).

Sepsis is a common condition which can frequently lead to simultaneous AKI and cardiac dysfunction. Approximately, 11–64% of patients with sepsis develop AKI (36,37). Numerous studies have shown that morbidity and mortality is much higher in patients with sepsis and AKI as compared with sepsis or AKI alone (38,39). Similarly, cardiac dysfunction is very common in patients with sepsis and up to 30–80% of patients with sepsis have elevated cardiac troponin levels and it correlates with reduced left ventricular function (40,41). The mortality in these patients is very high. However, there is a lack of studies that have specifically examined the incidence, risk factors, pathophysiology and outcomes of this syndrome.

## Diagnosis and Biomarkers of Cardiorenal Syndromes

### Biomarkers in cardiorenal syndrome

Biomarkers are routinely used for early diagnosis in patients with ACS or HF, and they have been found to be useful in these conditions. Recently various biomarkers have been proposed for early diagnosis in patients with AKI, especially after CABG; however, they are still not used widely. Some of these biomarkers were proposed for diagnosis of AKI in patients with CRSs during the recent ADQI meeting (7).

### Biomarkers of heart failure

#### *Natriuretic peptide*

B-type natriuretic peptides (NT pro-BNP and BNP) are elevated in patients with ADHF and they are established diagnostic tools. High levels of these peptides are also seen in patients with ACS, stable HF and associated with increased cardiovascular events and mortality in these patients (42,43). Natriuretic peptides are increased in patients with type 1 HRS and can be used as a marker. Patients with CKD have high levels of natriuretic peptides as compared to patients with normal kidney function even in the absence of CHF. However, BNP has been shown to have prognostics utility in patients with various stages of CKD, demonstrating prognostic utility in CRS type 2 and type 4 (44, 45).

### Biomarkers of renal injury

#### *Neutrophil gelatinase associated lipogalin (NGAL)*

NGAL is a protein, expressed at low levels by various human tissues, including kidneys. It is rapidly released by renal tubules after injury and increased in serum as well as urine soon after AKI. It is increased both in nephrotoxic and ischemic AKI (46).

Various studies have shown the diagnostic usefulness of NGAL as a marker of AKI, and it has been extensively studied in post-CABG AKI (47,48), but it can be used as a marker of AKI in patients with acute HF also.

#### *Cystatin C*

Cystatin C has been proposed as an ideal molecule to estimate GFR. In a prospective study, cystatin C and NGAL were measured in urine and serum of patients with AKI; the serum levels were not predictive of AKI within 6 h after surgery, but urinary levels were elevated, suggesting that urinary biomarkers may be superior to serum values in early detection of AKI (49).

#### *Kidney injury molecule-1 (KIM-1)*

KIM-1 is another marker, which increases in patients with ischemic and nephrotoxic AKI. Urinary KIM-1 is highly specific for ischemic AKI and not for CKD, prerenal AKI or contrast nephropathy (50,51).

#### *Interleukin-18 (IL-18)*

IL-18 is a proinflammatory cytokine, which is detected in urine after ischemic proximal tubular injury. It shows good sensitivity and specificity for ischemic AKI (52).

Despite good sensitivity and specificity of these markers, there are some limitations, like NGAL may be affected by preexisting renal diseases as well as infections. KIM-1 is specific for ischemic and nephrotoxic AKI and may not be useful for other causes of renal injury. IL-18 peaks at 4–6 h and more specific for ischemic injury and finally, cystatin C is not specific for ischemic AKI and increases in serum much later that other markers.

Another problem with these biomarkers is that these are not well-studied in patients with HF; most of data

is with post-CABG AKI. These need validation in these patients before some recommendations can be made (7).

## Bio-impedance Vector Analysis

Bio-impedance vector analysis gives better idea about hydration of patient with CRS and it can be used in combination with natriuretic peptide to guide the therapy in these patients.

## Role of Imaging in Cardiorenal Syndrome

Imaging techniques have a major role in patients with CRS. These patients have high risk of deterioration in kidney functions if iodinated contrast media are used. So whenever possible, noninvasive techniques like stress echo or stress myocardial perfusion (SPECT, PET) should be used to diagnose ischemia along with cardiac enzymes (7).

## Prevention of Cardiorenal Syndrome

The prevention of CRS is important because once CRS is set up, it is very difficult to interrupt, is not completely reversible always and is associated with serious adverse outcomes including need of hospitalization, dialysis and sometimes death (53). The pathophysiology of this disease is complex, so the preventive approaches should also be different in each syndrome.

### Type I cardiorenal syndrome

The principal causes of type 1 CRS are ADHF and ACS leading to AKI. Of the patients who present with type 1 CRS, one-third are de novo cases, caused by pneumonia, hypertension, atrial fibrillation and acute ischemic events, etc. The remaining two-third of cases are patients with established HF, and CRS is precipitated by noncompliance with diet and medications of HF (54,55). Prevention can be achieved by proper use of angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers, aldosterone receptor antagonists, adequate control of blood pressure, prevention of ACS via CAD risk modification and volume control by help of dietary restrictions and diuretics (7,53). A number of clinical trials have shown that HF can be prevented by patient's education, weight monitoring and proper adherence to diet and medicines (56,57). A meta-analysis of 29 trials involving more than 5000 patients found that active intervention was associated with 26% less hospitalizations for HF as compared to controls (58). Once patient is admitted with HF then prompt treatment of underlying condition might prevent development of CRS type 1.

### Chronic cardiorenal syndrome (Type 2)

Therapies to prevent type 2 CRS include proper use of ACEI/ARBs, aldosterone receptor antagonists, beta-blockers, vasodilators and cardiac resynchronization therapy (59,60). One of the most important preventive maneuvers is to control volume overload by fluid restriction, low salt diet and use of diuretics. Many studies have shown that the lowest doses of diuretics should be used to control symptoms and patients who require high doses of diuretics have the highest chances of developing CRS and have high mortality (61,62). In patients with low-output HF, anemia might cause decompensation and correction of anemia with erythropoietin has been shown to improve oxygen carrying capacity, left ventricular hypertrophy and ejection fraction in patients with CHF and CKD without survival benefits (63,64).

Lastly, use of nephrotoxic drugs like NSAIDs, aminoglycosides and contrast agents should be avoided in these patients (65).

### Acute renocardiac syndrome (Type 3)

Acute renocardiac syndrome is caused by AKI leading to acute cardiac dysfunction. It usually occurs after sudden volume overload or accelerated hypertension or hyperkalemia caused by AKI. It can be prevented by salt and fluid restriction and adequate use of renal replacement therapy including ultrafiltration whenever necessary (53). Sometimes AKI after contrast media and post cardiac surgery can also lead to type 3 CRS by causing AKI, which in turn would precipitate HF or arrhythmias. Adequate preventive strategies like hydration with saline or soda bicarbonate should be used before any contrast study, especially in patients with underlying CKD, elderly and other high-risk patients (66,67).

### Chronic renocardiac syndrome (Type 4)

This is the most common type of CRS, as it is associated with CKD. The prevention of this syndrome lies in adequate control of diabetes, hypertension, etc., which cause CKD. It is seen in various studies that use of ACEI/ARB is beneficial in slowing the progression of diabetic nephropathy and proteinuric kidney diseases

and slowing the progression of CKD (68). These agents can also reduce the incidence of cardiovascular disease in these patients. However, they are underused in CKD. Patients with CKD stage 5 on dialysis might develop recurrent ischemia and it has been seen that patients who have chronically high levels of cardiac biomarkers like troponins and NT pro-BNP have high chances of developing cardiac events, so these patients should be optimally managed with medications and revascularization (69,70). Fluctuation in volume status should be minimized, as this might lead to increased risk of cardiac systolic and diastolic dysfunction (71).

### Type 5 cardiorenal syndrome

General approach includes adequate treatment of systemic condition causing cardiac and renal dysfunction, which improves function of both the organs (53).

## Management of Cardiorenal Syndrome

Guidelines exist for management of HF and kidney disease separately; however, there are no guidelines to treat CRS. Recently ADQI group has reviewed the management based on available evidences (72).

### Type 1 CRS

Initial management of patients with acute HF includes oxygen therapy to keep saturation above 90%, and noninvasive ventilation and morphine to relieve stress, anxiety and pain occasionally. Patients should be assessed clinically to see whether they have predominantly congestive symptoms or poor cardiac output or both (72). Treatment depends on underlying condition causing it, i.e., cardiac arrhythmias, myocardial infarction, hypertension, etc. In patients with ADHF, loop diuretic in higher doses are required mostly. Intravenous infusions are more effective than loading doses. Loop diuretics provide symptomatic relief, but overdiuresis and volume depletion can cause electrolyte imbalance like hypokalemia and reduce intravascular volume which lead to neurohormonal activation and further deterioration in kidney functions (73,74). So their doses should be adjusted accordingly.

Vasodilators like nitroglycerine and nesiritide are important agents to reduce congestion and preload (75). Nesiritide is a recombinant human B-type natriuretic peptide, which has vasodilator as well as mild diuretic property. In a small study, high-dose nesiritide was found to be useful in reducing pulmonary capillary wedge pressure (PCWP) and symptoms of HF in 57% of patients (76). However, in another study, regular and low doses of nesiritide (<0.03 to 0.015 µg/kg/min) were associated with worsening renal parameters in patients with ADHF. In a meta-analysis of five randomized trials, there was no difference in renal parameters when low-dose nesiritide was compared with standard treatment of diuretics and other vasodilators (77). Based on these data, nesiritide might be useful to improve symptoms in patients with HF, but worsening renal dysfunction is a concern and potential use of nesiritide is still under investigation (77,78).

Another class of drugs useful in ADHF is vasopressin receptor antagonist – vaptans. These agents improve hyponatremia by increasing free water excretion (72). Effect of tolvaptan – a V2 receptor antagonist – was studied in a prospective randomized trial (ACTIV) in 319 patients hospitalized with HF. Three doses of tolvaptan were used, i.e., 30, 60 and 90 mg/day and compared with placebo. It was seen that patients on tolvaptan 90 mg had significant reduction in weight, – 2.5 kg as compared to -0.6 kg within 24 h after randomization – but there was no difference in serum creatinine at discharge (79). In EVEREST trial, which was a larger study with >4000 patients, oral tolvaptan 30 mg/day was compared to placebo in patients with HF and serum creatinine >3.5 mg; results showed that there was a significant reduction in weight (-1.76 kg vs 0.97 kg) and improvement in dyspnea with tolvaptans. Serum sodium levels also increased significantly by 6 meq/L in tolvaptan group. However, there was no effect on mortality after a follow-up of 10 months (80).

Endothelin receptors blockers are not found to be useful in patients with HF and trials are ongoing for adenosine receptor blockers (81).

Patients who are resistant to diuretics, ultrafiltration might be required to reduce congestion. Ultrafiltration versus intravenous diuretics for the treatment of patients hospitalized for ADHF trial (UNLOAD) was a multicentric prospective randomized trial, which randomized 200 patients with ADHF and compared ultrafiltration with standard intravenous diuretic therapy (82). The primary outcomes were reduction in weight and dyspnea symptoms. After 90 days, the ultrafiltration group had less rehospitalization and greater net fluid loss (4.6 L as compared to 3.3 L with diuretics). There was no significant difference between serum creatinine and dyspnea score in two groups.

In patients with ACS and cardiogenic shock, inotropic agents are frequently required. Dopamine and dobutamine are usually used in these conditions. Levosimendan belongs to a new class of inotropic drugs called calcium sensitizers. A randomized trial showed moderate to marked improvement in patients treated with levosimendan (83). Sometimes systemic vasoconstrictors like norepinephrine are needed to increase blood pressure. Intra-aortic balloon pump is required sometimes to augment cardiac output. Left ventricular assist device may be used in certain patients as a bridge to cardiac transplantation (84).

### Type 2 CRS

Therapeutic approach to patients with CHF includes treatment of underlying disease, regular medications and adherence to diet and exercise (72).

Pharmacological therapy includes use of ACEI/ARBs and beta-blockers and aldosterone receptor antagonists. These agents significantly reduce morbidity and mortality (85–88). Caution is required when using combination of ACEI/ARB and aldosterone receptor antagonist, as it may cause hyperkalemia. So a dietary advice should always be given along with monitoring of serum potassium and renal function in these patients. The combination of ACEI and ARB has shown to improve outcomes (89) but ONTARGET trial did not show any additional benefit of combining ARBs with ACEI and had higher chances of hyperkalemia (90). Similarly, a combination of all four neuroendocrine blockers (ACEI, ARB, beta-blockers and aldosterone antagonists) is not recommended. Digoxin and diuretics provide symptomatic relief, but they have no survival benefit (91).

Cardiac resynchronization therapy is nowadays recommended to symptomatic patients with NYHA class III and IV HF, poor left ventricular ejection fraction (LVEF) and QRS prolongation (92,93). Implantable defibrillators are useful in survivor of cardiac arrest, patients with recurrent ventricular arrhythmias and also in patients with HF with poor LVEF. In selected patients with no response to these therapies, mechanical assist devices and/or cardiac transplantation may be useful (94).

In patients with right sided HF, the treatment depends on whether it is underfilled or overfilled. Treatment should be directed toward underlying causes of right sided failure.

Patients having concomitant CKD require loop diuretics as thiazides are less effective in these patients. Sometimes a combination of these two agents is required, but it can cause severe electrolyte disturbances like hypokalemia and hyponatremia due to sequential action of these agents. Diuretic infusion is more effective than bolus injections. In patients refractory to these agents, renal replacement therapy may be required. Use of ACEI/ARB can sometimes cause hyperkalemia and renal function deterioration in these patients, so a careful monitoring is required.

Anemia is frequently present in these patients and its correction may improve symptoms without improving survival. Nephrotoxic drugs like NSAIDs and aminoglycosides should be avoided in these patients. The doses of many renally excreted drugs, for example, digoxin and allopurinol, should be reduced accordingly in these patients.

### Chronic renocardiac syndrome (Type 4)

CKD often leads to multiple cardiac problems like chronic volume overload which can lead to HF and accelerated hypertension. So dietary restriction of fluid and salt is required in these patients. Adequate control of blood pressure is another important aspect. Correction of anemia is associated with improvement in symptoms as well as reduction in LVH in some studies without survival benefit. Despite benefit, use of ARB/ACEI and beta-blockers is less in patients with CKD; these agents should be used whenever tolerated (95). Loop diuretics are often necessary.

## Conclusions

CRS is a complex disorder involving both heart and kidneys. The classification of this syndrome in various subgroups would help in better identification and management of problem. The CRS type 1 is most well-known type of cardiorenal disorder in clinical practice; however, the epidemiology of other types of CRSs is not so well defined. There is important role of neuroendocrine system in pathophysiology of this syndrome and similarly agents which block these responses are found to be useful in these syndromes. There is an important role of diet and salt restriction in addition to drugs in management. Novel biomarkers, which have been used to diagnose AKI and HF may be useful in early diagnosis of this syndrome, which might help to prevent the progression of complication.

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