



BMH Medical Journal 2014;1(4):72-76 **Review Article**

Cardio Renal Syndrome

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Key Words: cardiorenal syndrome

For a long time, physicians have recognized that the kidney and the heart are related especially when there is severe dysfunction of either of them. Dysfunction of one of these organs seldom occurs in isolation. [1]. Of late the cardio renal syndrome is assuming significance because of its increasing incidence, awareness and complications. There is no definite definition of the cardio renal syndrome. However, an attempted definition states that it is a "decline in renal function in the setting of advanced heart failure". This definition does not cover the whole gamut of the cardio renal syndrome. Cardiac diseases are associated independently with a decrease in renal function and progression of existing renal disease. Chronic Kidney disease (CKD) is an independent risk factor for cardiovascular events and outcome. This bidirectional nature of cardiac and renal interaction is called Cardio Renal Syndrome (CRS).

In the Acute Decompensated Heart Failure National Registry (ADHERE) comprising of more than 1,05,000 patients admitted for acute decompensated heart failure, 30% had a history of renal insufficiency, 21% had serum creatinine concentration of > 2.0 mg/ dL and 9% had creatinine concentration of >3.0 g/dL. [2]

Pathophysiology

The decrease in cardiac output in cardiac diseases reduces renal perfusion. The Renin Angiotensin Aldosterone System (RAAS) produces vasoconstriction, sodium overload and water retention causing an increasing in preload and afterload. The effects of endothelin which is produced in excess consequent to these pathophysiological changes are vasoconstriction, increased secretion of adrenaline and nor adrenaline. These cause hypertrophy of the cardiomyocytes in a chronic setting. The effect of arginine vasopressin which is also increased is to cause fluid retention, myocyte hypertrophy and potentiation of the effects of angiotensin II and noradrenaline. Increased activity of the Sympathetic Nervous system (SNS) causes cardiomyocyte apoptosis, focal myocardial necrosis and myocyte hypertrophy. This is increased by the fact that in heart failure with advanced renal insufficiency there is reduced clearance of catecholamines by the kidney. [3]

The CRS has been classified into five types depending on the pathophysiology. They are as follows: [4]

1. **CRS type 1 (Acute Cardio renal syndrome)**. It is acute worsening of cardiac function (e.g. Acute

decompensated heart failure or acute coronary syndrome) leading to an acute kidney injury.

2. **CRS type 2 (Chronic Cardio renal syndrome)**. A chronic cardiac dysfunction (e.g. chronic heart failure or congenital heart disease) leads to a progressive and potentially permanent chronic kidney disease.

3. **CRS type 3 (Acute Reno Cardiac syndrome)**. Acute kidney injury (e.g. Acute tubular necrosis or interstitial or glomerular diseases) leads to acute cardiac dysfunction (e.g. Acute heart failure, arrhythmia or ischemia)

4. **CRS type 4. (Chronic Reno Cardiac syndrome)**. Chronic kidney disease (e.g. Chronic glomerular or interstitial disease) leads to progressive cardiac dysfunction.

5. **CRS type 5. (Secondary Cardio renal syndrome)**. Systemic conditions (e.g. Sepsis, Amyloidosis, Vasculitis or Diabetes mellitus) causing simultaneous cardiac and renal dysfunction.

Risk Factors for the Cardio Renal Syndrome

A few risk factors increase the propensity of a patient to develop the CRS. These are:

1. Old age increases the chances of developing CRS.
2. Other co morbid conditions like diabetes mellitus, uncontrolled hypertension and anemia are factors which contribute to the development of CRS.
3. Drugs like anti-inflammatory agents, diuretics (thiazides, loop diuretics), angiotensin converting enzyme inhibitors (ACEI) and angiotensin Receptor blockers (ARB) and aldosterone receptor antagonists can accelerate the development of CRS.
4. In the heart, a history of heart failure or impaired left ventricular ejection fraction, prior myocardial infarction, poor functional class and elevated cardiac troponin contribute to the development of CRS.
5. In the kidney, chronic kidney disease with reduced glomerular filtration rate (GFR), elevated blood urea nitrogen and elevated creatinine and cystatin contribute to the development of CRS.

Biomarkers for the Detection of Kidney and Heart Injury

Various biomarkers have been identified for the detection of Kidney and Cardiac injury in CRS. Cystatin-C, Neutrophil Gelatinase Associated Lipocalin (NGAL), L-type fatty acid binding protein (L-FABP), Glutathione S-Transferase (GST) and Interleukin are some of the common protein biomarkers which can be used in the early detection of Acute Kidney Injury [5],[6],[7].

The biomarkers identified for the detection of cardiac injury are Troponin I, Myoglobin, B-Natriuretic Peptide (BNP) Ischemia Modified Albumin, S-Amyloid Protein A and the C - reactive protein (CRP).

Renal Failure - Cardiac Effects

The cardiac effects of chronic renal failure are multiple. The left ventricle shows hypertrophy which subsequently leads to 'diastolic heart failure' or 'heart failure with preserved ejection fraction'. There is development of early and progressive atherosclerotic coronary artery disease. High levels of inflammation and oxidative stress cause negative inotropic and vascular effects. When the patient goes for a dialysis program, the arteriovenous fistula created may contribute to a high output state and high output heart failure subsequently.

In acute renal failure, the main cardiac problems are due to a volume overload and electrolyte disturbances. Increased volume overload may stress the left ventricle to cause acute left ventricular failure presenting as acute pulmonary edema. The commonest electrolyte disturbance seen is hyperkalemia which can lead to various arrhythmias which may be fatal.

The GFR and Cardiac Output

There is no linear correlation between the serum creatinine and the Glomerular Filtration Rate. Approximately two-thirds of patients with heart failure have a low GFR. In these the serum creatinine may be normal. The GFR affects the prognosis in patients with congestive heart failure. The cardiac output is also not a very reliable indicator to assess the severity of CRS. The cardiac output may be normal in patients with CRS.

Diuretic Resistance in CRS

Patients with CRS may develop resistance to diuretics and hence may not respond to adequate therapeutic doses of diuretics. This may be due to various factors. There may be a delayed intestinal absorption of drugs. The GFR decrease along with a decreased renal perfusion. There is also a decreased diuretic excretion in urine. Inadequate diuretic dose, concomitant use of NSAID's and hypoalbuminemia may also contribute to the diuretic resistance. There may be increased re-absorption of sodium due to distal tubular hypertrophy causing a phenomenon of diuretic "braking" [8].

Treatment of diuretic resistance or refractoriness may be by many methods. A continuous infusion of frusemide or torsemide rather than bolus injections may be effective in many. An infusion of frusemide in a dose of 5 - 10 mg /hour is given. Metazolone may increase the response of other diuretics. An oral dose of 5 - 10 mg per day often is beneficial. A change from oral to intravenous diuretics also helps in many patients. If the patient is resistant to frusemide, bumetanide or torsemide may be tried as they are better absorbed from the intestines.

Management of Cardio Renal Syndrome - Heart Failure

The management of CRS caused by heart failure centers mainly on the use of oral or intravenous diuretics in adequate therapeutic doses. Low dose infusion of dopamine may be useful in some patients both to improve the renal perfusion and improve myocardial function [9]. Other inotropes like milrinone, levosimendan and dobutamine have been used with variable results. If the serum creatinine is less than 2.5 mg/dL, ACEI or ARB's may be used. Ultrafiltration (aquapheresis) or other renal replacement strategies may be employed in patients who need them [10]. Vasopressin antagonists like conivaptan or tolvaptan have recently been used in patients with heart failure with salutary results [11].

Management of Reno Cardiac Syndrome - Acute and Chronic Renal Failure

The management of reno cardiac syndrome mainly revolves around managing the fluid and electrolyte balance. Volume overload may be tackled by restricting fluid intake and employing renal replacement therapy when needed. The management of electrolyte disturbance is mainly the management of hyperkalemia with sodium bicarbonate, intravenous calcium and when needed renal replacement. Other electrolytes like sodium also need to be addressed. In addition, one has to look for factors which precipitate CRS like, hypertension, infections and anemia.

Prevention of Cardio Renal Syndrome

The prevention of CRS varies depending on the type of CRS that the patient is suffering from.

Type 1 CRS

In type 1 CRS acute decompensated heart failure or acute coronary syndrome leads to decrease in left ventricular function and subsequently to acute renal failure. The mainstay in preventing acute

renal failure in this setting is the adequate treatment of the acute left ventricular failure and acute coronary syndrome. Prompt treatment of the precipitating factors like infections, drugs, atrial fibrillation and hypertension is absolutely essential in the prevention of CRS. When acute coronary syndrome is associated with shock, prompt revascularization, using intra-aortic balloon pump and inotropic agents are needed to get adequate results.

Type 2 CRS

In chronic congestive heart failure the strategies to prevent CRS are those that will improve the congestive heart failure. Drugs like ACEI, ARB, or a combination of nitrate with hydralazine are useful in reducing the afterload and improving left ventricular function. Optimal management of sodium and fluid volume is mandatory in controlling the symptoms of chronic heart failure. To maintain adequate hemodynamics the lowest dose of loop diuretics that give the best results are used. Anemia, if present should be corrected. Added insults to the kidney like contrast agents, NSAIDs and nephrotoxic agents are to be avoided. In extreme cases, ultrafiltration or other forms of renal replacement therapy may be resorted to. Those patients who may benefit from Cardiac resynchronization therapy may benefit from the increase in cardiac output that follows.

Type 3 CRS

In the acute reno cardiac syndrome due to acute renal failure, cardiac decompensation may be prevented by aggressive avoidance of hypervolemia. Electrolyte imbalance like hyperkalemia need to be addressed immediately. Contrast induced acute kidney injury also needs to be prevented by the judicious use of contrast when and if needed along with adequate hydration and n-acetyl cysteine.

Type 4 CRS

Chronic reno cardiac syndrome where cardiac complications follow chronic kidney disease (CKD) may be prevented by adequate management of CKD. Reducing the rate of progression of CKD delays cardiac complications. Patients during hemodialysis may develop acute cardiac ischemia with chest pain, ECG changes and increase in cardiac biomarkers. It has been found that cooling of the dialysate solution can reduce the transient left ventricular dysfunction that may occur during dialysis. Both overdosing and under dosing of cardiac drugs are to be avoided in patients with CKD. Drugs should be prescribed based on the calculated GFR and not on serum creatinine alone. In addition treatment of other cardiac risk factors like dyslipidemia, diabetes mellitus, hypertension and life style factors have to be addressed in the prevention of type 4 CRS.

Type 5 CRS

Secondary CRS is caused by a disease that causes both cardiac and renal complications. Hence the important preventive measure in them is to adequately treat the primary illness which could be sepsis, diabetes mellitus, amyloidosis, hemorrhagic shock etc. If the primary disease is adequately treated, the renal and cardiac complications can be postponed though in many cases cannot be totally prevented.

Lacune in the Knowledge of CRS

In spite of the large volume of literature available regarding the CRS, there are still lacunae in our knowledge regarding this syndrome. Some of these are just listed below and the future may hold the answers to these questions.

- It is not known as to what is the optimal target blood pressure needed to prevent CRS.
- What methods and technology can be developed to assess the intra / extra vascular sodium content?
- What is the ideal timing and mode of renal replacement therapy to achieve optimal results?

- Will the treatment of other responses in CKD like hyperparathyroidism, renal bone disease and hyperphosphatemia change the development and progression of CRS?

Concluding, the cardio renal syndrome is an interdependent involvement of both the kidney and the heart, one leading to the dysfunction of the other. Considering the pathophysiology and the ubiquitous nature of the disorder, prevention of the syndrome is of the utmost importance in patients who have cardiac or renal disease, especially in an acute setting. Many questions remain unanswered and are still out there. The future probably will hold the answers to these and the treatment of CRS may be more crystallized in future.

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