ABSTRACT:
The term “Cardiorenal syndrome” has gained wide attention of physicians in recent times specially due to the increasing presentations of patients with dual organ dysfunction resulting from a web of pathophysiological causation, the proper understanding of which might have important bearings on management and outcome of these patients. This web of causation, though poorly understood has been termed the cardio-renal connection and in nutshell includes the Renin-Angiotensin-Aldosterone System (RAAS), Sympathetic Nervous system (SNS), Nitric Oxide, inflammatory cytokines etc. Recently in the World Congress of Nephrology the bi-directional nature of the Cardiorenal syndrome was emphasized and a classification based on pathophysiology was proposed. Till now the management of the syndrome has met with little success and no specific treatment strategy has been established definitively. Diuretics, inotropes, vasodilators, renal replacement therapy and others have all been tried with variable success. More research and definitive clinical trials are required to further understand the pathophysiology and devise effective management strategies for the syndrome.

Key Words: Cardiorenal syndrome, RAAS, heart failure

Concomitant cardiac and renal dysfunction is the most simplistic view of cardio-renal syndrome. However the definition is ambiguous as it lacks a direction of pathogenesis of the disease process. In fact the general view holds that renal injury occurs secondary to a diseased heart and in the presence of a normal cardiac function the same kidneys would perform normally (c.f Hepato-renal syndrome). However it is a known fact that primary disorder of one of these two organs often causes secondary dysfunction of the other. Hence a more comprehensive definition that encompasses the complete patho-physiology linking the two organs is required.

CARDIO-RENAL SYNDROME: DEFINITION

The cardio-renal syndrome includes a variety of acute or chronic disorders where the primary failing organ can be either the heart or the kidney leading to the secondary dysfunction of the other. Thus according to the chronology of events the cardio-renal syndrome can be subdivided into 5 sub-types, namely:

1. CRS type 1: Acute cardio-renal syndrome
2. CRS type 2: Chronic cardio-renal syndrome
3. CRS type 3: Acute reno-cardiac syndrome
4. CRS type 4: Chronic reno-cardiac syndrome
5. CRS type 5: Secondary cardio-renal syndrome

CRS type 1: Acute cardio-renal syndrome is defined as acute cardiac failure leading to worsening of renal function. Within this is a spectrum of disorders involving the heart and the blood vessels leading to acute heart failure which further causes Acute kidney injury through multiple mechanisms. These mechanisms include:

1. Acute hypo perfusion leading to decreased GFR
2. Decreased Oxygen delivery

CRS type 5: Secondary cardio-renal syndrome

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Table 1: Lists important biomarkers for the early detection of AKI.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Associated Injury</th>
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<tbody>
<tr>
<td>Cystatin C</td>
<td>Proximal tubule injury</td>
</tr>
<tr>
<td>KIM-1</td>
<td>Ischemia and nephrotoxins</td>
</tr>
<tr>
<td>NGAL</td>
<td>Ischemia and nephrotoxins</td>
</tr>
<tr>
<td>NHE3</td>
<td>Ischemia, pre-renal, post-renal AKI</td>
</tr>
<tr>
<td>α-GST</td>
<td>Proximal Tubular injury, Acute rejection</td>
</tr>
<tr>
<td>β-GST</td>
<td>Distal Tubular injury, Acute rejection</td>
</tr>
<tr>
<td>L-FABP</td>
<td>Ischemia and nephrotoxins</td>
</tr>
<tr>
<td>Cy61</td>
<td>Ischemic ATN</td>
</tr>
<tr>
<td>Netrin-1</td>
<td>Ischemia and nephrotoxins, sepsis</td>
</tr>
</tbody>
</table>

GST = glutathione S-transferase; IL = interleukin; KIM = kidney injury molecule; L-FABP = L-type fatty acid binding protein; NGAL = neutrophil gelatinase-associated lipocalin; NHE = sodium-hydrogen exchanger; Cy61 = Cysteine rich protein 61.

3. Resistance to ANP/BNP

4. Cell Necrosis/apoptosis

In fact AKI tends to be more severe in patients with impaired Left Ventricular ejection fraction, being >70% in patients with cardiogenic shock.

Early diagnosis of kidney injury in CRS 1 and also CRS 3 (discussed later) is important, but still remains difficult as serum creatinine rises when the AKI is already established. Recently, novel biomarkers which rise within first few hours of onset of AKI have been discovered. Of these Neutrophil Gelatinase Associated Lipocalin (NGAL) is one of the earliest and highly sensitive marker of ischemic/nephrotoxic kidney injury detected in the blood/urine. Similarly Kidney Injury Molecule is a highly specific marker for ischemic AKI. Table 1 lists important biomarkers for the early detection of AKI.

Thus by using a combination of assay of these biomarkers Type 1 CRS can be diagnosed early with timely intervention to prevent ongoing renal damage.

Management: While diuretics, both loop and thiazides have been useful in volume overloaded non-hypotensive patients, there overzealous use is associated with worsening of renal function. Also diuretic therapy exacerbates neurohormonal activity, activates the RAAS, increases systemic vascular resistance and worsens left ventricular function. Besides, inotropes like dobutamine, dopamine, milrinone may be judiciously used in patients with impaired cardiac output although their role is still controversial as they have been associated with increased mortality and cardiac events. Vasodilators like Nesiritide have been used favourably in the treatment of Acute Decompensated Heart Failure where a non hypotensive, low cardiac output state is combined with cold extremities and increased peripheral vascular resistance due to excessive vasoconstriction. In fact Nesiritide has been shown to reduce both systemic and pulmonary pressures and increase the cardiac and stroke volume indices. However in the context of cardiorenal dysfunction Wang and colleagues found that nesiritide had no effect on GFR, renal plasma flow, urine output, or sodium excretion.

Patients who have diuretic resistant volume overload may still respond to ultrafiltration.

Newer promising approaches in the management include the Arginine Vassopressin Receptor antagonists like Tolvapatan (EVEREST trial) and Adenosine A, receptor antagonists.

CRS type 2: Chronic cardio-renal syndrome involves Chronic Congestive cardiac failure causing progressive kidney dysfunction set on a background of chronically reduced renal perfusion and chronic renal venous congestion. The prevalence of renal dysfunction in chronic HF has been reported to be approximately 25% In fact the pathophysiology of renal dysfunction in this syndrome is poorly understood. The ESCAPE study found no link between pulmonary artery catheter measured hemodynamic variables and serum creatinine. The different putative mechanisms include low cardiac output causing activation of RAAS and sympathetic nervous system, subclinical inflammation, endothelial dysfunction, increased renal vascular resistance and accelerated atherosclerosis. Recently it has been found that these patients have relative/absolute erythropoietin deficiency causing more severe anaemia than can be accounted for by renal failure alone. In fact erythropoietin receptor activation in the heart may reduce the risk of apoptosis, inflammation and fibrosis.

Management: Although diuretics are helpful in managing a volume expanded state, the key drugs in treating left ventricular systolic dysfunction are the Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers. They by blocking the RAAS not only affect cardiac remodeling and cause reduction of LVH but also retard proteinuria and progression of CKD. Due to the presence of excessive vasoconstrictor mediators in chronic heart failure, vasodilators might be of use in reducing the congestion and improving renal perfusion.

CRS type 3: Acute renocardiac syndrome is Acute Kidney injury leading to acute cardiac dysfunction through different pathophysiological mechanisms involving three main systems: the RAAS, Nitric Oxide-Reactive oxygen species and the sympathetic nervous system. Fluid overload and accelerated hypertension can lead to acute pulmonary edema. Hyperkalemia can lead to life threatening cardiac arrhythmias and sudden cardiac arrest. Metabolic acidosis can affect cardiac inotropy and cause pulmonary vaso-constriction leading to right sided heart failure. Acute uremia may cause depression of myocardial contractility while uremic pericarditis may act as a mechanical hindrance for the same. Myocardial ischemia frequently complicates AKI which is due to a reduced coronary reserve which fails to meet increases in myocardial oxygen demand. Renal ischemia also induces a Systemic inflammatory response syndrome producing a number of pro-inflammatory cytokines leading to a delayed cardiodepressant response.

A variety of markers of cardiac dysfunction/injury including Cardiac Troponins, NT-Pro BNP, cytokines like TNF α, IL-6 and myeloperoxidase may be utilized for early detection of this
Cardio-Renal Syndrome

Management: Adequate treatment of accelerated hypertension, hyperkalemia and metabolic acidosis reduces the risk of cardiac injury. At the same time hemodialysis can be used in removing the uremic toxins as well as treating the pericarditis effectively. In patients with hemodynamic instability Continuous renal replacement therapies may offer better outcomes.

CRS type 4: Chronic Renocardiac syndrome is characterized by primary chronic kidney disease contributing to the development of cardiac dysfunction resulting in increased cardiovascular morbidity and mortality. While microalbuminuria is known to increase the Cardiovascular risk 2-4 times, declining GFR per se is associated with increasing CV risk as shown in Table 2.

<table>
<thead>
<tr>
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<td>60-89</td>
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Anemia: For every 1g/dl decrease in mean haemoglobin the risk of cardiac failure increases by 25%.

Management: The primary prevention of CRS type 4 consists of cessation of smoking, adequate control of Diabetes and hypertension.

- Correction of anemia using iron supplements and Erythropoietin to maintain a Haemoglobin between 11-12g% and a packed cell volume >36%.
- Control of volume overload and hypertension by using loop diuretics as well as blocking the overactive RAAS by using ACE inhibitors and ARB's. ACE inhibitors and ARB's should be used even if the patient is not hypertensive because they are antiproteinuric and retard the progression of kidney disease.

5. Endothelial Dysfunction: In CKD various factors including inflammation, ADMA, oxidative stress, hypertension result in endothelial dysfunction leading to accelerated atherosclerosis and increased cardiovascular mortality.


7. Hyperhomocysteinemia: The prevalence of hyperhomocysteinemia in ESRD patients exceeds 90%. However their exact relationship with Cardiovascular disease is still not clear.

8. ADMA: A competitive inhibitor of NO synthase, causes decreased NO bioavailability. ADMA is degraded by dimethyl arginine aminohydrolase—an enzyme found in renal tissue. With advancing CKD, ADMA accumulates and leads to endothelial dysfunction and is strongly associated with CV mortality.

**Table 2 : Chronic Kidney Disease and CV Risk**

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- Hyperphosphatemia and secondary hyperparathyroidism have to be controlled and the Calcium * Phosphate ionic product should be kept below 50mmol²/m² by dietary phosphate restriction and use of phosphate binders. Moreover newer non-calcium containing phosphate binders like Sevelamer are known to reduce the progression of coronary and aortic calcification better than the calcium containing phosphate binders.
- CKD patients are high risk cardiovascular individuals, hence syndrome.
Statins should be used to achieve a LDL cholesterol level of less than 100 mg/dl (K/DOQI guidelines). Besides Statins also have modest antiproteinuric effect14. However there use should be judicious in view of recent reports that they may favour development of renal fibrosis15.

- Antioxidants like Vitamin E and acetylcysteine have been shown to have a beneficial effect on cardiovascular events in recent small studies and require further authentication.

**CRS type 5:** It is characterized by cardiac and renal dysfunction due to acute or chronic systemic cause. While in the acute setting sepsis is the most important cause, chronic conditions consist of diabetes, amyloidosis, SLE etc. The acute or chronic inflammatory states acting through various cytokines like TNF-α, IL-1β, IL-6 etc. may affect the functioning of both these organs10. Thereafter the pathophysiological mechanisms of both Type 1 and Type 3 CRS apply in sepsis while those of Type 2 and Type 4 CRS for chronic conditions.

**Management:** Treatment is directed at the prompt identification and treatment of the underlying cause while supporting organ function, both cardiac and renal by judicious use of vasopressors, inotropes and diuretics. In septic patients, preliminary studies suggest that intensive renal replacement therapy may have a role in improving myocardial performance while providing optimal small solute clearance16.

**Conclusion:** Thus the concept of Cardiorenal syndrome is still in its preliminary stages of development with further research needed to clarify its pathophysiology and adequate methods of management. Till then individualization of each patient with judicious use of drugs is the best line of management.

**REFERENCES**

Cardio-Renal Syndrome


