Cardiorenal Syndrome

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Introduction

The Organ talk show between heart and kidney is gaining increased attention from clinicians all over the world. This is because, their coexistence is frequently observed in clinical practice and carries bad prognosis. A diseased heart has many negative effects on kidney, at the same time; a diseased kidney significantly impairs cardiac function. (1) Their coexistence is referred to as Cardiorenal Syndrome. Claudio Ronco et al first proposed the classification of Cardiorenal syndrome in 2008.(2)

Though the classification has become established, the definitive guidelines for treatment for particular class are not yet standardized. This review will discuss the Cardiorenal syndrome in terms of definition, classification, newer insights into the Pathophysiology and treatment from recent clinical trials.

Definition

Cardiorenal syndrome describes a pathophysiological disorder of the heart and kidneys in which acute or chronic dysfunction in one organ induces dysfunction in the other.

Classification

The classification given by Ronco et al (2) is as follows. CRS is a clinical spectrum occurring over a period of time. There is frequent overlap between all five categories and patient may shift from one type to other. (Table 1)

Table 1

Cardiorenal syndrome type	Name	Description
1	Acute cardiorenal	Acute cardiac dysfunction leading to acute kidney injury
2	Chronic cardiorenal	Chronic heart failure leading to renal dysfunction
3	Acute renocardiac	Acute kidney injury leading to acute cardiac dysfunction
4	Chronic renocardiac	Chronic renal failure leading to cardiac dysfunction
5	Secondary	Systemic condition causing cardiac and renal dysfunction

Prevalence- In the Acute Decompensated Heart Failure National Registry (ADHERE) of >105 000 individuals admitted for acute decompensated HF, 30% had a history of renal insufficiency- 21% had serum creatinine concentrations >2.0 mg/dL, and 9% had creatinine concentrations >3.0 mg/dL.(3) In meta analysis of 16 studies of more than 80,000 patients of heart failure, moderate to severe kidney impairment was present in 29 %.(4) More than 50% of deaths in end stage renal disease cohort are attributed to cardiovascular disease. In addition, patients with severe forms of chronic kidney disease have 10 to 20 fold increased risk of cardiac death compared to the general population. (5)

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Pathophysiology

The late Arthur Guyton first extensively described normal physiological interactions between the control of extracellular fluid volume by the kidney and the systemic circulation by heart.(6).However the pathophysiological mechanisms underlying the interactions between heart and kidneys is still ambiguous.The following possible mechanisms are proposed to define interactions between heart failure and renal failure.(7,8)

1 **The Low-output-State Hypothesis**The general understanding of cardiorenal syndrome is that low output state causes decreased renal perfusion which leads to activation of renin angiotensin aldesterone axis. This causes sodium and water retention, peripheral vasoconstriction, leading to both increase in preload and afterload worsening the

heart failure. This logical explanation was said to be too simple to explain all the effects and types of cardiorenal syndrome. This concept of low output state was studied in ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial.(9) They found no correlation between the cardiac index or pulmonary artery wedge pressure and renal function. The improvement in cardiac index did not lead to improvement in renal function. Thus the low output state may not be the only explanation for Cardiorenal syndrome.

2 **Renin-Angiotensin-Aldosterone Axis and Renal Dysfunction-**

Renin is produced in the juxtaglomerular apparatus of the kidneys and catalyses the conversion of angiotensinogen I to angiotensinogen II, which is subsequently turned into angiotensin II by angiotensin-converting enzyme (ACE). In the initial phase the activation of renin angiotensin aldesterone axis helps in restoring the blood flow to vital organs like brain and heart, thus it is protective; but in chronically activated state it has detrimental effect on both heart and kidney. The angiotensin II causes peripheral vasoconstriction which increases afterload increasing myocardial oxygen demand, further decompensating the heart. Also the angiotensin II increases production of IL-6, TNF □, and reactive oxygen species, thus it accelerates the atherosclerosis. Angiotensin-II directly contributes to kidney damage by upregulating the cytokines transforming growth factor-β, tumor necrosis factor-α, nuclear factor-κB, and interleukin-6 and that stimulates fibroblasts, resulting in cell growth, inflammation, and fibrotic damage in the renal parenchyma.(7,8)

3 **Sympathetic Overactivity**

As left ventricular systolic failure progresses, diminished renal blood flow and perfusion pressure (whether from arterial underfilling or renal venous congestion) lead to baroreceptor-mediated renal vasoconstriction, activation of the renal sympathetic nerves, and release of catecholaminergic hormones. This problem is compounded in patients with HF with advanced renal insufficiency because there is reduced clearance of catecholamines by the kidneys. Thus the sympathetic over activity of heart failure causes more renal injury. The catheter based renal sympathetic denervation in patients with resistant hypertension had been shown to improve GFR in 24% of patients of resistant hypertension.(10) Bilateral renal nerve ablation has also been shown to reduce renal norepinephrine spill over, renin activity, and systemic blood pressure 12 months later.(11) The results of these two studies have shown that sympathetic over activity has detrimental effect on renal function, causes progression of both heart failure and worsening of renal function.

4 **Oxidative Injury and Endothelial Dysfunction -**

Neurohormones are strong precipitants and mediators of an oxidative injury cascade that leads to widespread endothelial dysfunction, inflammation, and cell death in the CRS. AT-II causes activation of NADPH oxidase and NADH oxidase in vascular smooth muscle cells, cardiac myocytes, and renal tubular epithelial cells, generating superoxide, a reactive oxygen species.(12) Reactive oxygen species contribute to the processes of aging, inflammation, and progressive organ dysfunction. The oxidative injury is a common link between progressive cardiac and renal dysfunction.(13) Because both primary cardiac failure and primary renal failure lead to activation of the RAAS, activation of oxidases by angiotensin II in one organ leads to progressive dysfunction in the secondary organ through reactive oxygen species generation.

The superoxide and other reactive oxygen species cause inactivation of nitric oxide. The decreased nitric oxide causes endothelial dysfunction in vascular smooth muscle and abnormal contractile response in cardiac myocyte further deteriorating the heart failure.

5 **Intra-abdominal and Central Venous Pressure Elevation**

The blood flow across the organ depends upon the arteriovenous pressure gradient across the particular organ. Reduced cardiac output is traditionally believed to be the main determinant of

worsening of renal function in patients with acute decompensated heart failure. Mullens et al in their study of 145 patients found that venous congestion is the most important hemodynamic factor causing worsening of renal function in decompensated patients with advanced heart failure. (14) Heart failure is associated with an elevation in central venous pressure, which attenuates the gradient across the glomerular capillary network. The higher central venous pressure is associated with lower GFR. The concept that venous congestion is an important mediator of cardiorenal failure is supported by the findings of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, which had shown that only baseline right atrial pressure correlated with baseline serum creatinine and neither pulmonary capillary wedge pressure nor cardiac index.(9) The other hemodynamic parameter which correlated with GFR and creatinine were raised Jugular venous pressure on physical examination, presence of tricuspid regurgitation by echocardiography and intra-abdominal pressure by invasive monitoring.(15,16)

Clinical presentation

There is frequent overlap between one types with the other. It may be difficult to classify particular patient in one or other type. If symptoms, signs and suggestive investigation of one organ precede the other then diagnosis is easy. But if such preceding events, history or proper documentation is not available then diagnosis becomes difficult. In cardiorenal syndromes there are two important aspects: the first is the sequence of organ involvement and the second is the bidirectionality of signaling leading to a vicious cycle. Another is time frame in which the derangements occur (chronic or acute). (17)

1 **Type 1 cardiorenal syndrome**

The type I cardiorenal syndrome typically occurs in the setting of acute heart failure occurring due to accelerated hypertension, acute coronary syndrome, acute myocarditis, arrhythmias like atrial fibrillation. The acute heart failure is diagnosed by raised N terminal brain natriuretic peptide and echocardiography. The recent deterioration in renal function over the baseline normal function can be diagnosed by blood urea, serum creatinine, and more early and specifically by NGAL and serum Cystatin C level.

2 **Type 2 cardiorenal syndrome**

The gradual deterioration in renal function diagnosed by deteriorating serum creatinine level, in patients of chronic heart failure is suggestive of type 2 cardiorenal syndrome.

3 **Type 3 cardiorenal syndrome**

Though classified in 2008, this type as clinical entity is only recently appreciated. An example of type 3 CRS could be the development of an acute coronary syndrome, arrhythmia, or acute heart failure after the onset of acute kidney injury or after acute glomerulonephritis or acute cortical necrosis. The acute renal failure associated toxaemia, fluid and sodium retention, neurohormonal mediators, and electrolyte derangements contribute to acute dysfunction of the heart. The biomarkers like NT PRO BNP, Troponin T or I and imaging with echocardiography, cardiac MRI, Nuclear Scan can clinch the cardiac involvement in acute renal failure.

4 **Type 4 cardiorenal syndrome**

The increasing number of cardiovascular deaths amongst chronic kidney disease patients suggests the increasing diagnosis of type 4 cardiorenal syndrome. The non invasive imaging like echocardiography, Computed tomography guided Coronary angiography, Carotid intima media thickness, can diagnose the underlying atherosclerosis and cardiac dysfunction. Thus early diagnosis of associated cardiac disease can help in prevention of secondary cardiac involvement.

5 **Type 5 cardiorenal syndrome**

The secondary involvement of heart and kidney in case of primary disorder like sepsis, systemic lupus erythematosus, diabetes mellitus, amyloidosis, or other chronic inflammatory conditions is type 5 cardiorenal syndrome. These systemic conditions lead to simultaneous injury and/or dysfunction of heart and kidney. Although this subtype does not have primary and/or secondary organ dysfunction, it refers to situations where both organs are

simultaneously affected by systemic illnesses, either acute or chronic.

Current and future treatment of CRS

The therapy for cardiorenal syndrome is directed towards correcting the basic pathophysiological abnormalities with the help of diuretics, Ionotrops, ACEI, ARBs and beta blockers.

a **Diuretics**

Diuretics are the mainstay of treatment for fluid removal in patients of acute or chronic heart failure. However they have been associated with worsening of renal function and decreased survival in these patients. Low dose versus high dose diuretics and bolus versus continuous infusion have been studied in DOSE trial (18), which showed no superiority of one strategy over other. Till the other avenues are available the diuretics will remain mainstay therapy for fluid removal. Out of all the diuretics, Tolvaptan is newer aquauretic. It prevents water reabsorption by blocking vasopressin II receptor at collecting duct without causing significant change in electrolyte balance. The EVEREST trial (19) was negative in terms of mortality, change in body weight and improvement in renal function assessed by creatinine, though the blood urea nitrogen was decreased.

b **Ultrafiltration**

The excessive fluid removal by ultrafiltration with the help of venovenous hemodialysis sounds logical as it removes the isotonic fluid from the venous compartment via filtration of plasma across a semi permeable membrane without disturbing the electrolyte imbalance. With Ultrafiltration, there are no side effects of diuretics. The UNLOAD trial (20) and RAPID-CHF trial (21) which compared the fluid removal by ultrafiltration versus intravenous diuretics were neutral in terms of renal function, but ultrafiltration had caused more body weight loss and decreased the rehospitalisation in short term follow up. In CARESS HF trial (22) weight loss was similar in ultrafiltration and stepped pharmacologic therapy groups, however ultrafiltration therapy caused an increase in serum creatinine and a higher rate of adverse events. So at present, the role of ultrafiltration remains only in cases of acute decompensated heart failure with diuretic resistance and impaired renal function.

c **Ionotrops**

Ionotrops are supposed to increase the cardiac output without causing significant increase in myocardial oxygen demand and peripheral vasoconstriction. Till date the ideal ionotropic agent is not available. Ionotrops are indicated in setting of acute heart failure with hypotensive low output state. In chronic heart failure the digoxin had been shown to reduce the rehospitalisation. The low dose dopamine infusion helps in improving or preserving renal function in heart failure by increasing the glomerular filtration rate (GFR) in patients with moderate or severe heart failure. Dopamine increased renal blood flow at doses of 2 to 10 mcg/kg/min and this occurs due to dilatation of both large conductance and small resistance renal blood vessels. Dopamine also caused significant increases in cardiac output at doses in the range of 5 to 10 mcg/kg/min.(23) The clinical efficacy and safety of dopamine for preservation of renal function in patients with HF has not been established. Preliminary studies suggest that the combination of low-dose dopamine (eg, 2 or 5 mcg/kg/min) plus a diuretic may reduce the risk of worsening renal function compared to diuretic therapy alone. The DAD-HF trial found that the combination of dopamine 5 mcg/kg/min plus low dose frusemide (5mg/h continuous infusion) resulted in similar urine output as high dose frusemide (20 mg/h) with reduced risk of worsening renal function. (24) Similarly it has been proposed that ionotropic agents such as Dobutamine and Milrinone improve renal function in patients with severe heart failure by increasing renal blood flow and reducing renal venous pressure, but the clinical data is limited. Amongst the devices, left ventricular assist devices HEARTMATE II have been shown to improve renal function. (25)

d **Vasodilators**

The effects of vasodilators like nitroglycerin and Nitroprusside on renal function was never studied. The other vasodilators like endothelin antagonist Tezosentan, a dual action endothelin-1 receptor

inhibitor studies in VERITAS trial)(26), adenosine A 1 receptor antagonist Rolofylline studied in PROTECT- 1 & 2 trial (27), did not improve the renal function in acute heart failure. The Neseritide (ASCEND HF) was not associated with a worsening of renal function, but it was associated with an increase in rates of hypotension. On the basis of ASCEND HF results, Neseritide is not recommended for routine use in the broad population of patients with acute heart failure.(28)

The relaxin neurohormone secreted by placenta during pregnancy in high concentration had been shown to cause 20 percent increase in cardiac output, 42 percent increases the renal blood flow and importantly 30 percent decrease in systemic vascular resistance. Thus it has all the desirable effect on cardiorenal syndrome. Serelaxin is a first-in-class recombinant form of human hormone relaxin 2. Investigators found that relaxin can modulate various important hemodynamic and neurohormonal effects, such as increases in cardiac output and decreases in systemic vascular resistance, pulmonary capillary wedge pressure, and N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP). In PRERELAX AHF and RELAX AHF trials, serlaxin had been shown to have favorable effect on renal function.(29)

e **ACEI OR ARB**

The ACEIs and ARBs are useful in chronic heart failure as they block the action of angiotensin II, cause vasodilation, and reduce cardiac fibrosis. Their use in acute heart failure can be detrimental because their hypotensive effect may further reduce the renal blood flow and precipitate acute renal failure. The Cooperative North Scandinavian Enalapril Survival (CONSENSUS) study revealed that patients with the most severe CCF had a substantial increase in creatinine on initiation of an ACE inhibitor irrespective of baseline creatinine.(30) Inspite of 15 percent increase in serum creatinine over baseline, there was significant improvement in heart failure.

f **BETA BLOCKERS**

The beta blockers have favorable effect on heart failure. Amongst the beta blocker Carvedilol was shown to increase the renal blood flow as well as cause systemic vasodilatation by acting on β1 β2 and α2 blocking action. The use of renal sympathetic denervation and baroreflex device controlled hypertension will define the future treatment.

Conclusion

The improved survivals after myocardial infarction and increase in aging population have increased the number of heart failure patients, of which increasing number will develop the renal dysfunction over time. Once the syndrome begins it is difficult to interrupt, not completely reversible in all cases, and associated with serious adverse outcomes, hence early diagnosis and strategies to prevent other organ involvement can reduce incidence of cardiorenal syndrome. Though systematically classified, there are no definite guidelines for the treatment of these patients. Therefore their treatment depends upon the clinical setting and judgment of treating cardiologist and physician. The conventional drug therapy in heart failure has frequent cardiorenal side effects. The novel drugs and devices may improve the scenario.

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