Review Article

A REVIEW ON CARDIORENAL SYNDROME

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Abstract

Cardio-renal syndrome is a blanket term which is used to denote clinical conditions where there is coexistence of cardiac & renal deteriorations. Considering the multitude of articles written about this topic, still the underlying pathophysiological mechanisms continue to be puzzled and implications for management continue to be debated. A classification for CRS has been proposed in 2008 which is being used in clinical practice. There is also need for cardio-renal interdisciplinary team for early identification of decompensated cardio-renal syndrome and their appropriate management. Here we review the epidemiology, classification of CRS, the pathological mechanisms proposed & then focus on management strategies. In this review article, we try to summarize the results from MEDLINE, PubMed, Cochrane Library, Google and Google Scholar search (last article updated till 2019) on the current understanding Cardio-renal syndrome.

Keywords: Decompensated Heart Failure, Nephropathy, Frusemide, Cystatin C

INTRODUCTION

The refined relationship between the kidney and the heart was first described in 1836 by Robert Bright[1]. From then onwards, numerous researches & trials were made to explain the cardio-renal link in terms of the phenotypes, pathophysiological mechanisms, treatment and prognosis.

Definition

The very first attempt of defining CRS has been put-forward by the National Heart, Lung, and Blood Institute in 2004, were CRS has been described as an interaction between the kidneys and other circulatory compartments that increase circulating volume, which in-turn exacerbates the symptoms of cardiac failure and progression of the syndrome[2].

The first official definition of CRS was formed at a consensus conference of the Acute Dialysis Quality Initiative in 2008[3]. It defined Cardio-renal syndrome as disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. We can broadly divide it into 2 major groups, Cardio-renal and Reno-cardiac syndrome[4,5]. On the basis of sequential organ involvement this was further grouped into 5 subtypes. The main goal for defining this syndrome was to categorize the clinical presentation, to develop new diagnostic markers and apt management of CRS.

EPIDEMIOLOGY

The Acute Decompensated Heart failure National Registry showed that 30% of patients admitted with acute decompensated HF had chronic renal disorder (CKD).[3] It is difficult to get accurate epidemiological data, but it's estimated that 25% to 63% of patients with cardiac failure have some sort of Cardio-renal syndrome.[4]

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Editor's Comment

* Cardiorenal syndrome is a common, but often missed clinical entity.
* Vascular inflammation, Oxidative stress and accelerated fibrosis are potent factors in the pathophysiology of this condition
* Both cardiac and renal biomarkers are to be used for diagnosis of the condition
* Diuretics remain the mainstay of therapy but braking phenomenon can limit its utility
* Further trials are needed for deciding on the use of valsartan/sacubitril or nesiritde in cardiorenal syndrome

As per the study by Forman et al, irrespective of cardiac failure, with or without preserved ejection fraction, an increased serum creatinine on admission and worsening renal dysfunction during admission in the hospital, both were associated with long duration of inpatient stay and an increase in mortality. [5]

CLASSIFICATION

Acute Cardio-renal syndrome (type 1)

Type 1 Cardio-renal syndrome is characterized by acute worsening of cardiac function resulting in an acute kidney injury (AKI). There are 4 subtypes for Acute Heart failure: Hypertensive pulmonary edema with preserved left ventricular systolic function, acutely decompensated chronic HF, shock, & predominant right ventricular failure.

Chronic Cardio-renal syndrome (type 2)

Type 2 Cardio-renal syndrome is characterized by chronic cardiac dysfunction resulting in renal dysfunction. It is the most common and has been reported in 63% of patients admitted with congestive HF.[6] The mechanism is probably because of chronic renal hypo-perfusion.

Acute Reno-cardiac syndrome (type 3)

Type 3 Cardio-renal syndrome is characterized by acute cardiac dysfunction due to acute renal dysfunction. The exact incidence and prevalence of type 3 CRS is unknown but from multiple case studies it shows that, in acute kidney

injury, there is cardiac dysfunction. The rise of newer biomarkers and the researches for prevention and management strategies in Acute kidney following radiocontrast or cardiac surgery can also give an insight regarding our knowledge of how Acute kidney injury can induce changes in cardiac function.

Chronic Reno-cardiac syndrome (type 4)

Type 4 Cardio-renal syndrome describes Chronic kidney disease leading to cardiac dysfunction (left ventricular failure or diastolic Heart failure). In one of the recent meta-analysis, it described an exponential relation between the severity of renal dysfunction and the risk for all-cause, comparing with a 'normal' glomerular filtration.[7]

Secondary Cardio-renal syndromes (type 5)

Type 5 Cardio-renal syndrome is characterized by simultaneous cardiac and renal dysfunction due to a systemic condition whether it will be acute or chronic. The importance is to permit future investigations to know the frequency of combined acute kidney and heart dysfunction in patients with these secondary causes.

PATHOPHYSIOLOGICAL MECHANISMS REVISITED

Neuro-humeral mechanisms

For many years the reason for kidney dysfunction in cardiac failure patients was mainly thought to be due to renal hypoperfusion which was secondary to decrease cardiac output.[8] From the ESCAPE Trial (Evaluation Study of Congestive Heart failure and Pulmonary Artery Catheterization Effectiveness) (9),it could not find a correlation between renal and cardiac functional index, and improvement of cardiac function didn't improve renal function. Results from other similar studies also found that there was no role in improving renal function, when there was an improved cardiac functional index or reduced pulmonary wedge pressure.[10,11] In addition, even in patients with normal ejection fraction, worsening of renal function was also found to occur.[12] From all these evidences, mechanisms other than simple renal hypoperfusion should be considered in cardio-renal syndrome.

The Renin-Angiotensin-Aldosterone System & Vascular inflammation

RAAS activation is a mechanism to prevent reduced perfusion. But as concluded by Pueyo et al, Angiotensin II also has adverse effects on the circulatory system especially in heart failure patients, which can increase myocardial oxygen needs. But one among the foremost advances recently discovered is the role of vascular inflammation[13]. The Nicotinamide adenine dinucleotide

Renal Biomarkers in CRS

Markers of Glomerular Filtration and Integrity

Biomarkers	Source	Diagnostic Value	Prognostic Value
Serum Creatinine	Skeletal muscle	AKI, CRS	HF, CRS
Cystatin C	All nucleated cells	CRS	CRS
Albuminuria	Marker of glomerular integrity	CRS	CRS

Markers of Renal Tubular Injury

Biomarkers	Source	Diagnostic Value	Prognostic Value
Serum NGAL	Neutrophils, myocardium, renal tubules, activated immune cells	AKI	CRS
Urine NGAL	Loop of Henle, collecting ducts	AKI,CRS	CRS
NAG	Proximal convoluted tubule	CRS, AKI	CRS
KIM-1	Type 1 cell membrane glycoprotein expressed in regenerating PCT epithelium	AKI	CRS
IL-18	Cytokine mediating inflammation and AKI through the nuclear factor-κB pathway	AKI	CRS
H-FABP	Cardiomyocytes , distal tubule	HF,CRS	--
Urine angiotensinogen	--	AKI,CRS	CRS

AKI, acute kidney injury; CKD, chronic kidney disease; CRS, cardiorenal syndrome; cTn, cardiac troponin; CysC, cystatin C; ellipses (...), data not available or reported.; HF, heart failure; H-FABP, heart-type fatty acidbinding protein; IL, interleukin; KIM-1, kidney injury molecule-1; NAG, N-acetyl-κ-d-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; PCT, proximal convoluted tubules. (22-26,50)

Biomarkers	Origin	Diagnostic Value	Prognostic Value
BNP, NT Pro BNP	Marker of myocardial stretch	HF, CRS	HF, CRS
sST2	IL-1 family of receptors	(--)	HF, CRS
Galectin-3	β- Galactoside binding lectin	(--)	HF,CRS

BNP, B-type natriuretic peptide; ST2, soluble suppressor of tumorigenicity; HF Heart failure;ellipses (--), data not available or reported(27-29,50)

phosphate oxidase (NADPH) enzyme is activated by Angiotensin II, which result in reactive oxygen species formation. Research evidences suggests that these reactive oxygen species radicles are liable for inflammatory processes and can result in early organ dysfunction (14). Oxidative stress also increase the production of pro-inflammatory mediators such as IL-1, 6 & TNF alpha (interleukin-1, interleukin-6, and tumor necrosis factor alpha)[15]. Among these Interleukin-6 can stimulates fibroblasts can result in both cardiac & renal fibrosis.

The role of Sympathetic Nervous System in CRS.

The activation of SNS is also a protective mechanism in CCF patients, akin to RAAS activation. SNS over activity results in reduced adrenoceptor sensitivity in both renal and cardiac failure[16]. It can also result in increased apoptosis of myocytes & release of neuro-hormone, mainly Neuropeptide Y. This may act as a vascular growth promoter resulting in neo-intimal atherosclerosis formation [17,18] & can cause vasoconstriction.

The Emergence of Cardio-renal Anemia Syndrome (CRAS)

Silverberg et al. first described Cardio-renal anemia syndrome[19]. They suggested anemia as a condition caused by dysfunction of either heart or kidney dysfunction but which can also exacerbate dysfunction of either of these organs.[20] Evidence from CHARM study (Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality) suggested that anemia was an independent adverse prognostic indicator in CCF patients[24]. However, we discover that, for CRAS, there's a scarcity of consensus over the exact definition followed by management of these patients & there's a vital need for large-scale RCTs.

Newer update-Role of Fibrosis in Cardio-renal Syndrome

Travers et al concluded after a cardiac insult, myocardial remodeling occurs when myo-fibroblasts secrete extracellular matrix proteins, but this can result in cardiac fibrosis & subsequent heart failure. In the kidney, the tubule interstitial cells differentiates & can synthesis extra cellular matrix & result in fibrosis[21]. Thus fibrosis can be considered as a newer pathophysiological mechanism for Cardio-renal Syndrome, which should be focused intimately through future trials.

AHA Scientific statement- A New dimension in the diagnostic algorithm of CRS

Early diagnosis of CRS, allows early intervention strategies which might hopefully prevent further clinical deterioration. Therefore, the novel biomarkers for Cardio-renal syndrome, as included in AHA statement 2019, becomes promising.

A REVIEW ON CURRENT MANAGEMENT OF CARDIORENAL SYNDROME

Medical management of patients with Cardio-renal syndrome remains challenging at times as evidence for treatment in heart failure from most of trials have excluded patients with renal impairement, apart from this 5 different subtypes of CRS, by itself throws unique challenges in management.

The New definition for Renal failure in Cardiorenal syndrome

Besides the typical threshold changes in serum creatinine or eGFR, the new definition require a deterioration in heart failure status not leading to hospitalization (chronic heart failure) or deterioration in heart failure status in which it fails to improve or there is a need for inotropes, ultrafiltration, or renal replacement therapy (acute heart failure). This new definition enable better detection of true worsening renal function.[30]

Diuretics

Diuretics always remains the mainstay of management in fluid overload in cardio-renal syndrome. But there's limited data from large trials proving mortality benefit for diuretics in CRS. According to data from the ADHERE registry 81% of decompensated heart failure patients were using long-term diuretics[31]. Studies have shown that, Furosemide may decrease GFR & can also stimulate fibrosis.[30,32] There's unfortunately a scarcity of high-quality trial to support or refute the utilization of diuretics in patients with cardio-renal syndrome. So until there is a definitive report that diuretics is harmful in patients with heart failure, diuretics can be given in fluid overload in CRS patients. This also supported by a Cochrane review[34] in which continuous IV Furosemide decreased mortality rate & reduced the admission days.

Diuretic use & Braking Phenomenon in CRS

A recent update in diuretic usage is that it induce, the braking phenomenon within the short term of diuretic therapy and distal tubular hypertrophy within the future. This phenomenon signify decreased diuretic efficacy with serial doses. It is assumed that Sodium loss, during diuretic therapy plays a role in the braking phenomenon[35].

Angiotensin-Converting Enzyme (ACE) Inhibitors

RAAS inhibitors have convincing evidence of benefit on prolonging survival and reducing morbidity in patients with Heart failure, as recommended by both US and European guidelines providing a Class I, LOE (A). The CONSENSUS

(Cooperative North Scandinavian Enalapril Survival), study revealed considerable increase in creatinine levels when started on ACE inhibitors.[36] But in this trial the treatment outcome was better, even when the creatinine was increased. To be on safer side, when used along with diuretics as in case of CRS, an accompanying reduction of diuretic dosage is advisable.

Aldosterone Antagonists

In patients with CRS, similar to ACE inhibitors, aldosterone antagonists also benefits. The RALES and EPHESUS trials demonstrated that, in patients already receiving standard medications for cardiac failure, adding low-dose spironolactone or eplerenone dramatically improved the result[37,38]. During a study of Norwegian HF outpatients with renal dysfunction, in patients treated with spironolactone there was a 2-year improvement in survival compared to the propensity-matched patients not treated with spironolactone. From one of the recent study from the Swedish Heart Failure Registry which reported an interaction between usage of spironolactone and renal function concerning all-cause of mortality, pointing out a relatively more favorable effect of spironolactone in patients with decreased GFR.[39]

As recent advances in Cardio-renal syndrome pathophysiology confirms, Aldosterone can trigger a cascade of mechanisms that typically causes fibrosis within the heart, vessels, and kidneys which will reciprocally evolve into a cardio-renal syndrome, thus proving the utilization of mineralocorticoid receptor antagonists capable of providing organ protective effects in CRS.

From our experience in the management of CRS, we observed a benefit of using high dose spironolactone, but serum potassium levels were monitored. But our observations were from a small group of patients, it needs a standard control group & further research. Nevertheless, we believe that our findings and those from other trials indicate it's time to conduct a RCT regarding the long-term effects of high dose spironolactone in patients with CRS.

Inotropic Support in CRS

Patients with CRS are mostly hypotensive, if it is associated with heart failure frequently, will end in frank cardiogenic shock or severe hypotensive episodes, but low-dose dopamine is understood to extend renal blood flow. Many trials shown improvement of heart function with dobutamine and milrinone in proportion to renal blood flow, however, there was not much mortality benefit. The OPTIME-HF(Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of a Chronic Heart Failure) trial rejected the hypothesis that milrinone would improve overall renal function and survival.[40] The complexity of pathophysiology in CRS, with both heart failure and renal failure, raise the challenge for adequate RCTs to study the role of inotropes. Current ESC guidelines for heart failure state the evidence for using dobutamine as class II a level B, dopamine as class II a level C, milrinone as class II b level B, and levosimendan class II a level B. [41]

Nesiritide

Nesiritide is a brain natriuretic peptide(BNP) analogue, it can induce vasodilation & also increase cardiac output. The primary large randomized trial of nesiritide there was no mortality benefit. In a meta-analysis of seven large RCTs of nesiritide, also there was no mortality benefit during follow up [42]. In one of the pooled analysis of three random trials there was even increase in early mortality when treated with nesiritide [43]. Further the results of ASCEND (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial[44] may also help to know the future of this drug in the management of CRS patients.

Beta-blockers

Beta-blockers are utilized in the management of chronic HF. During a systematic review by Badve et al.,[45] of patients with HF and CKD, it was found that the utilization of beta-blockers decreased the risk of all causes and cardiovascular mortality. However, it has been related to an increase in incidences of bradycardia and hypotension. So we should be cautious in using them in acute decompensated HF as they'll further reduce forward flow and exacerbate renal dysfunction.

Sacubitril/valsartan

It is a first-in-class drug in ARNI. The benefits of this drug has been revealed by The Prospective Comparison of ARNI with ACE inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial randomized 8442 participants with HFrEF to treatment with sacubitril/valsartan or enalapril and was terminated earlier than planned as it showed overwhelming evidence of benefit at a median follow-up duration of 27 months. Similar to this, in PARAGON-HF trial had 4822 participants with HFpEF to compare sacubitril/valsartan with valsartan. Apart from its known benefits in HFrEF and strong potential for benefit in HFpEF, they also have better effects on the kidney. Sacubitril/valsartan also demonstrated to slow the deterioration of kidney function in the PARADIGM-HF and PARAMOUNT trials. Still more trials are needed to know the efficacy of this drug especially in the setting of Cardio-renal syndrome.

Cardiac resynchronization in CRS

In a systematic review by Garg et al[46], Cardiac resynchronization therapy improves the LV function, thus improving the GFR in CKD patients. More studies are needed in the setting of CRS, so that, if accurately used based on CRS subtypes, whether it can help in the reversal of this syndrome.

Role of Implantable Hemodynamic Monitoring Devices in CRS

The CHAMPION trial revealed a lower hospitalization rate and a lower mortality in HFrEF(HF with reduced ejection fraction) monitored with PA pressure guided HF management versus. [47] Intra-thoracic impedence was measured directly by implantable device (Optivol, Medtronic) in Heart failure patients. [48,50] But specific data for outcome and prognosis in CRS is still lacking.

Ultrafiltration (UF)

Those patients who are immune to diuretic therapy may enjoy ultrafiltration (UF). This will help in removal of huge

fluid volumes faster than diuretics, without inducing profound hypotension. The UNLOAD trial revealed that, Ultrafiltration was better than IV diuretic therapy to prevent fluid re-accumulation. However, there are trials which failed to demonstrate an improvement in renal hemodynamics with ultrafiltration.[49] Further trials within the setting of CRS is awaited.

CONCLUSION

The advances till date in this newly emerged branch of Cardio-renal medicine is appreciable & pronounced. However, based on all the major trials & meta-analysis, there is a critical need for new guidelines from the cardio-nephrology societies. A cardio-nephrology multidisciplinary approach is found to be vital in the management of patients with CRS with an emphasis based on Physician priorities. Furthermore, the reversibility of CRS & role of biomarkers for early detection of the syndrome deserves dedicated studies which will resolve today & tomorrow for the patients.

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CARDIO RENAL SYNDROME CRS
TAKE HOME POINTS

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1. Involvement of Kidney in Heart Failure (HF) (Type I and II)
2. Involvement of Heart in Kidney Disease (Type III and IV)
3. Single condition (like DM) producing both heart and kidney diseases(Type V)
4. Worsening renal function (>0.3mg) is a very important bad prognostic marker in HF
5. Creatinine will raise only after 3-5 days of hospitalisation for HF
6. Always estimate creatinine and eGFR on the day of discharge
7. Renal congestion rather than reduced perfusion is the most important cause of CRS
8. Earliest markers of kidney involvement are cystatin and N-GAL
9. Always look for non-traditional risk factors such as abnormal Ca/ PO4 ratio and homocysteine in CRS
10. Treating congestion with diuretic therapy will improve renal and cardiac function.
11. Avoid combination of ACE,ARB and aldosterone inhibitors in CRS
12. Use Hydralazine and nitrates in ACE,ARB intolerant patients.
13. In stabilised patients, reducing diuretics and increasing Carvedilol will help
14. Look for reversible causes like NSAID use, UTI or urinary tract obstruction
15. Keep looking for kidney disease in HF and HF in kidney disease

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