Review Article

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CARDIO-RENAL SYNDROME: A SNAPSHOT

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ABSTRACT Cardiorenal syndrome encompasses a spectrum of disorders involving both the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. It represents the confluence of heart-kidney interactions across several interfaces. These include the hemodynamic cross-talk between the failing heart and the response of the kidneys and vice versa, as well as alterations in neurohormonal markers and inflammatory molecular signatures characteristic of its clinical phenotypes. Understanding the relationship between these two organs during each organ's impairment has significant clinical implications that are relevant for therapy in both chronic and acute conditions. The mission of this review is to describe the epidemiology, definition, classification, pathophysiology, therapy, and outcome of each form of cardiorenal syndrome.

KEYWORDS : Cardiorenal Syndrome, Heart Failure ,CKD,

INTRODUCTION

Cardiorenal syndrome (CRS) is characterized by the coexistence of acute or chronic dysfunction of heart and kidneys resulting in a cascade of feedback mechanisms causing damage to both organs. It refers to the complex interplay between cardiovascular and renal diseases, where dysfunction in one organ can lead to dysfunction in the other. It represents a bidirectional relationship, with each organ impacting the function and prognosis of the other. The significance of cardio-renal syndrome in clinical practice lies in its high prevalence, detrimental effects on patient outcomes, and the challenges it poses for diagnosis and management.[1]

Epidemiology And Phenotype.

It is challenging to determine the precise incidence and prevalence of CRS due to variations in definitions and study populations. However, CRS is considered to be a relatively common condition, especially among individuals with cardiovascular and renal diseases. Estimates suggest that the prevalence of CRS ranges from 25% to 45% in patients with heart failure and from 20% to 40% in patients with chronic kidney disease. The incidence of acute CRS (type 1 and type 3) in hospitalized patients can range from 10% to 60%, depending on the specific population and setting.[2]

The cardiorenal syndrome has been grouped into five subcategories that describe the etiology, pathophysiology, duration, and pattern of cardiac and renal dysfunction. This classification reflects the large spectrum of interrelated dysfunctions and underlines the bidirectional nature of heart-kidney interactions.[3]

Table-1 Clinico-pathophysiological Mechanisms In CRS

Phenotype	Nomenclature	Description	Clinical Examples
Type 1 CRS	Acute CRS	HF resulting in AKI	ACS resulting in cardiogenic shock and AKI, AHF resulting in AKI
Type 2 CRS	Chronic CRS	Chronic HF resulting in CKD	Chronic HF
Type 3 CRS	Acute renocardic syndrome	AKI resulting in AHF	HF in the setting of AKI from volume overload, inflammatory surge, and metabolic disturbances in uraemia
Type 4 CRS	Chronic Reno cardiac syndrome	CKD resulting in chronic HF	LVH and HF from CKD-associated cardiomyopathy
Type 5 CRS	Secondary CRS	Systemic process resulting in HF and kidney failure	Amyloidosis, sepsis, cirrhosis

The pathophysiology of cardio-renal syndrome involves a complex interplay between various mechanisms and pathways, including hemodynamic factors, neurohormonal activation, inflammation, and oxidative stress.

1. Hemodynamic Factors

Reduced Cardiac Output: Decreased cardiac output, often seen in heart failure or acute cardiac events, leads to decreased renal perfusion and glomerular filtration rate (GFR). The resulting renal hypoperfusion can trigger compensatory mechanisms that exacerbate cardiac dysfunction.

Venous Congestion: Venous congestion, commonly observed in heart failure, increases hydrostatic pressure in the renal veins and interstitial space. This congestion impairs renal blood flow, promotes fluid leakage into interstitial compartments, and compromises renal function.[4]

2. Neurohormonal Activation

Renin-Angiotensin-Aldosterone System (RAAS): Reduced renal blood flow and activation of sympathetic nervous system in heart failure trigger the release of renin, leading to increased levels of angiotensin II and aldosterone. These hormones cause vasoconstriction, sodium and water retention, and promote renal inflammation and fibrosis.

Natriuretic Peptides: In response to increased ventricular wall stress, natriuretic peptides (e.g., atrial natriuretic peptide, brain natriuretic peptide) are released. While initially exerting natriuretic and diuretic effects, prolonged activation of natriuretic peptide systems can lead to desensitization, neurohormonal imbalance, and adverse remodelling.[5]

3. Inflammation

Systemic Inflammation: In cardio-renal syndrome, systemic inflammation can be triggered by various factors, including cardiac ischemia, oxidative stress, and endothelial dysfunction. Inflammatory mediators (e.g., cytokines, chemokines) propagate inflammation, leading to vascular dysfunction, endothelial activation, and tissue damage in both the heart and kidneys.

Local Renal Inflammation: Inflammatory processes within the kidneys contribute to renal injury and dysfunction. Inflammatory cells infiltrate the renal interstium releasing cytokines and chemokines that promote fibrosis, apoptosis, and impaired renal function.[6]

4. Oxidative Stress

Increased Reactive Oxygen Species (ROS): In cardio-renal syndrome, increased oxidative stress occurs due to an imbalance between ROS production and antioxidant defence mechanisms. ROS are generated by multiple sources, including activated inflammatory cells, mitochondrial dysfunction, and NADPH oxidase. Excessive ROS can cause cellular damage, inflammation, and impair endothelial and renal function.

Nitric Oxide (NO) Dysregulation: Oxidative stress reduces the bioavailability of nitric oxide, impairing its vasodilatory and protective effects. Decreased NO contributes to endothelial dysfunction, vasoconstriction, and altered renal perfusion.[7]

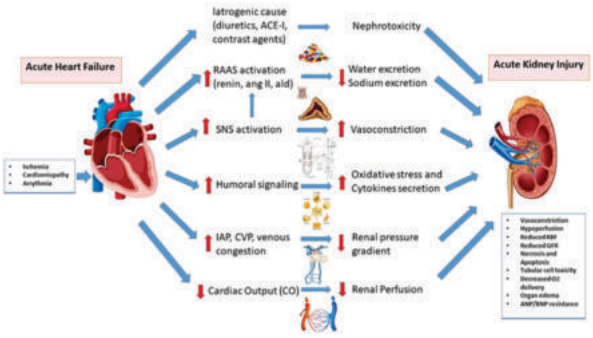

Figure-1

Understanding these underlying mechanisms is crucial for developing therapeutic strategies that target multiple pathways involved in cardio-renal syndrome. By addressing hemodynamic abnormalities, modulating neurohormonal activation, reducing inflammation, and attenuating oxidative stress, clinicians can aim to improve outcomes and prevent further deterioration of both cardiac and renal function.

Diagnostic Strategies In CRS

Several diagnostic tools help establish the structural and functional derangements characteristic of CRS including biomarkers, non-invasive imaging modalities, invasive hemodynamic monitoring, and adjuvant volume measurement techniques.

Biomarkers

Biomarkers of cardiac and kidney injury may provide valuable information when applied to the clinical context of CRS and can serve to indicate early cardiac or renal injury, the repair process, and long-term sequelae. They represent an opportunity to prognosticate CRS, to discriminate between CRS phenotypes, and to serve as markers for targeted therapeutic interventions.[8]

Table -2 Imaging Modalities

Biomarkers of glomerular function	➢ Creatinine ➢ Urea ➢ Cystatin-C ➢ Albumin ➢ Creatinine clearance
Biomarkers of tubular function	➢ KIM-1 ➢ NGAL ➢ L-FABP ➢ Electrolytes
Cardiac biomarkers	➢ cTnT, cTnI ➢ NT-proBNP ➢ MR pro-ANP ➢ MR pro-ADM
Other Biomarkers	➢ PRA ➢ Aldosterone ➢ Il-1β, IL-10 ➢ ET-1

Non-invasive imaging modalities play an important role in establishing markers of venous congestion and impaired forward flow in CRS and are readily accessible clinical tools at the bedside. Echocardiography may help in diagnosing the congestive state by hemodynamic parameters, including CVP, systolic PA pressure, pulmonary capillary wedge pressure/left atrial pressure, and CO. Renal ultrasonography and intrarenal venous flow patterns are emerging tools in identifying renal venous congestion and its clinical significance in CRS.[9]

Volume Status Determination Strategies In CRS

Fluid overload represents a core target for treatment in the process of optimizing the vicious cycle of CRS.

Bioimpedance vector analysis (BIVA) is a non-invasive bedside volume assessment technique based on the electric principle that the body is a circuit with a given resistance (opposition of current flow through intracellular and extracellular solutions) and reactance (the capacitance of cells to store energy). With BIVA, total body water may be measured by placing a pair of electrodes on the dorsum of the wrist and ipsilateral ankle and then applying a 50-kHz current to the body.[10]

Measurement of IAP

In advanced HF, inefficient natriuresis with progressive volume overload may ultimately lead to a state of systemic congestion with increased IAP if the capacitance function of the splanchnic vasculature is insufficient. In 60% of patients admitted with AHF, measurements of IAP are elevated beyond the baseline value range of 5 to 7 mm Hg. Bedside non-invasive measurements of IAP can be obtained with a urinary bladder catheter connected to a transducer.[11]

Implantable Hemodynamic Monitoring Devices

An implantable device (Optivol, Medtronic) has been used to assess transthoracic impedance as a measure of pulmonary fluid status. Direct measurements of intrathoracic impedance with an implanted device have been shown to have prognostic value in HF. However, a reduction in outpatient visits for HF symptoms or hospital admissions with the use of device alerts has not been demonstrated. Specific data on outcomes with CRS using implantable intrathoracic impedance measurements are currently lacking.[12]

Management And Therapeutic Approach.

The management of CRS patients is a real challenge, considering the complex and heterogeneous pathophysiology of CRS. Furthermore, each patient has his own personal history and risk profile due to combination of comorbidities. It is worth of note that the main causes of CV death in patients with kidney diseases are specific types of cardiomyopathies, atherosclerosis, and CHF related complications.[13]

1. Diuretic And Ultrafiltration Therapy

In patients with acute or chronic HF, central and peripheral congestion is commonly detected, and diuretics represent an important therapeutic tool with or without CRS. However, although diuretics improve HF symptoms, they have no beneficial effects on HF hospitalizations and mortality. Loop diuretics (including furosemide, bumetanide, torsemide and ethacrynic acid) are the diuretics of choice in acute or chronic HF. The use of diuretics may induce worsening of renal function particularly in patients with advanced HF. CRS patients may often develop diuretic resistance, which is associated with renal impairment, increased risk of rehospitalization and mortality in HF patients.[14]

Ultrafiltration is a mechanical process that removes isotonic liquid and low molecular weight molecules from the circulatory system, eliminating the liquid excesses without neurohormonal activation. Ultrafiltration is useful in patients with severe HF with fluid retention and resistance to diuretic treatment.[15]

2. Inotropic Agents And Beta Blockers

In the setting of type 1 CRS, the use of inotropes may contribute to improve cardiac output and reduce venous congestion. Among inotropes, dopamine induces cardiac inotropic effect, systemic vasoconstriction and improves renal blood flow through its effects on the and adrenergic receptors, as well as the renal dopaminergic receptors.[16]

Beta Blockers are included in the first-line therapy of chronic HF, with evidence of the striking improvement of HF prognosis. However, BB are not suggested as the treatment for patients with acute decompensated HF and in CKD patients without HF as well as no direct benefit has been proven in CRS.[17]

3. Renin Angiotensin System Inhibitors

Several clinical trials demonstrated that neuro-hormonal modulation in HF may contribute to reduce HF symptoms, reverse cardiac remodelling, and improve survival. Hence drugs that modulate neuro-hormonal activation in HF are becoming the pillar of the modern pharmacological approach in HF treatment. In HF patients, RAAS inhibitors(i.e., ACEI, ARB or ARNI and MRA) have been shown to improve prognosis , with beneficial effects also on renal function.[18]

4. SGLT2 Inhibitors: An Emerging Therapeutic Tool In CRS

SGLT2i were originally used as antidiabetic drugs, and early clinical trials, including CANVAS, DECLARE-TIMI and EMPA-REG OUTCOME, have demonstrated their efficacy in reducing cardiovascular mortality and HF hospitalizations in diabetic patients with HF. SGLT2is have an excellent diuretic and metabolic effect, as

well as they may exert several other mechanisms, including neurohormonal modulation and reducing oxidative stress, inflammation and cardiovascular remodelling.[19]

5. Novel Therapeutic Strategies

Other therapeutic options have been proposed in CRS patients. Selective antagonists of the V2 receptor of arginine vasopressin have been tested in the treatment of HF with controversial results. In the EVEREST program (Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan), the V2 receptor antagonist tolvaptan did not achieve benefits in term of reduction of cardiovascular death and HF hospitalizations in patients with acute HF and LVEF < 40%.[20]

6. Non-Pharmacological Approaches

Finally, non-pharmacological approaches may also potentially impact on prognosis in patients with HF and CKD in terms of improvement of the cardiorenal status and mortality, although controversial issues exist. Several evidence has suggested that implantable cardiac defibrillators (ICD) are useful not only in HF patients but also in patients with CRS. In these patients ICD is recommended to reduce the risk of sudden death and all-cause mortality in those who have recovered from a ventricular arrhythmia associated with hemodynamic instability and in patients with symptomatic HF and a LVEF 35% despite optimized medical treatment over at least 3 months. Furthermore, cardiac resynchronization therapy (CRT) is recommended if QRS duration on electrocardiogram is >150 ms, particularly if a left bundle branch block is present.[21]

Prognosis and Outcome

Considering the unclear pathophysiology and treatment modality of CRS, these patients have poor prognosis. A rise in serum creatinine or decrease in creatinine clearance in patients with ADHF is associated with a worsened prognosis. The prognosis is even poorer if the increase in serum creatinine or the decrease in creatinine clearance is accompanied by oliguria (less than 50 mL/h), edema, hyponatremia or refractoriness to diuretics.[22] There are multiple mortality and readmission predictor calculators available to predict the individual patient's prognosis further. They use multiple variables to predict in-hospital mortality and readmission rate, including the blood urea nitrogen (BUN), systolic blood pressure, serum creatinine, brain natriuretic peptide, and response to diuretics.[23]

CONCLUSIONS

CRS received much attention in preclinical and clinical studies, since it represents a serious healthcare problem with high morbidity and mortality. A growing body of evidence fostered the understanding of the strict relation between heart and kidney by showing different pathophysiological mechanisms involving various cell mediated signalling pathways Nonetheless, the pathophysiology of acute and chronic CRS types remains incomplete and still under investigation.

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