UNLOCKING THE COMPLEX INTERPLAY: A REVIEW OF CARDIORENAL SYNDROME IN CRITICAL CARE.

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Abstract:
Cardiorenal syndrome (CRS) is a multifaceted and intricate condition characterized by the bidirectional dysfunction of the heart and kidneys, often encountered in the critical care setting. This review provides a comprehensive analysis of CRS in critical care, delving into its pathophysiology, diagnostic challenges, clinical management, and the latest advancements in therapeutic strategies. Key topics include the interplay between cardiac and renal systems, hemodynamic alterations, neurohormonal dysregulation, and the impact of critical illness on CRS. We explore the significance of early recognition and integrated care for patients with CRS, emphasizing the importance of a multidisciplinary approach.

Keywords: Cardiorenal Syndrome, Critical Care, Pathophysiology, Diagnosis, Management, Multidisciplinary Approach, Therapeutic Strategies, Neurohormonal Dysregulation, Hemodynamic Alterations.

INTRODUCTION:

The first evidence regarding the interaction between the kidneys and the heart was reported by Robert Bright in 1836, after that the researchers have devoted itself to better understanding of the mechanisms occurred in the heart-kidney relationship now simply called as CRS. The National Heart, Lung, and Blood Institute, formally known as CRS, in 2004, reported that the increase in systemic volume persuaded by the kidneys intensified the progression of heart failure (HF). In 2008, the Acute Dialysis Quality Initiative (ADQI) collaborated with two main CRS groups, cardiorenal and renal-cardiac broaden the definition of CRS. This disorder is defined by some researchers as moderate or severe renal dysfunction that develops in a patient with heart failure through treatment. Some label it a pathophysiologic disorder of the heart and kidneys with acute or chronic dysfunction. Thus, the prime worsening organ can be either heart or kidney.[1,2].

the definition of cardiorenal syndrome (CRS): CRS is characterized by a complex and bidirectional relationship, meaning that the heart and kidneys are closely interconnected and mutually influence each other's function. Dysfunction in one organ can directly impact the other. Involves the Heart and Kidneys: The term "cardiorenal" is composed of "cardio" (relating to the heart) and "renal" (relating to the kidneys). Therefore, CRS encompasses both the cardiac and renal systems. Dysfunction in One Organ Affects the Other: In CRS, when there is dysfunction in either the heart or the kidneys, it can lead to a chain reaction of worsening function in the other organ.

Complex Interplay in Cardiorenal Syndrome (CRS):
Bidirectional Influence: CRS is defined by a bidirectional influence between the heart and kidneys, meaning that dysfunction in one organ can directly impact the function of the other. This bidirectional relationship is characterized by several key components such as Hemodynamic Factors: Changes in cardiac function can have
profound effects on renal hemodynamics. When the heart is unable to pump blood effectively (as in heart failure), renal blood flow may decrease due to reduced cardiac output. This reduction in renal perfusion can trigger compensatory mechanisms aimed at maintaining blood pressure, such as activation of the renin-angiotensin-aldosterone system (RAAS). However, these mechanisms can also contribute to sodium and water retention, exacerbating heart failure.

Neurohormonal Activation: The heart and kidneys communicate through neurohormonal pathways. For example, decreased renal blood flow can stimulate the release of renin from the kidneys, leading to the conversion of angiotensinogen to angiotensin II. Angiotensin II has vasoconstrictive effects and promotes sodium and water retention, potentially worsening both heart and kidney function.

Inflammatory and Immune Factors: Inflammation plays a significant role in CRS. Both cardiac and renal diseases can trigger an inflammatory response, leading to the release of cytokines and chemokines. Chronic inflammation can contribute to endothelial dysfunction and fibrosis in both organs, further exacerbating CRS.

Fluid and Sodium Balance: The kidneys play a pivotal role in maintaining fluid and sodium balance in the body. In CRS, impaired cardiac function can lead to fluid retention, contributing to congestion and edema. The resulting volume overload can increase cardiac workload and reduce cardiac efficiency.

Clinical Manifestations: The complex interplay between the heart and kidneys manifests clinically as a range of symptoms, including edema (swelling), elevated blood pressure, shortness of breath (due to fluid accumulation in the lungs), reduced urine output, electrolyte imbalances (e.g., hyperkalemia), and increased stress on both organ systems.

Types of cardiorenal syndrome:

Acute cardiorenal syndrome (type 1) Cardiorenal syndrome type 1 is characterised by acute worsening of cardiac function (pulmonary oedema, cardiogenic shock, acute HF) leading to an acute kidney injury (AKI). Approximately 27% of patients admitted with acute decompensated HF develop AKI. The challenge in this subtype is the early identification of an AKI as creatinine will increase once AKI is established and early biomarkers such as neutrophil gelatinase-associated lipocalin have been studied as early predictors of AKI (1,3).

Chronic cardiorenal syndrome (type 2) Cardiorenal syndrome type 2 is characterised by chronic cardiac dysfunction leading to renal dysfunction and can be used to describe chronic HF leading to renal failure. This syndrome is the most common and has been reported in 63% of patients admitted with congestive HF. The mechanism underlying this process is likely to be due to chronic renal hypo perfusion although there is limited evidence as of yet to suggest how left ventricular function correlates to GFR levels (4).
Acute renocardiac syndrome (type 3): Cardiorenal syndrome type 3 is characterised by acute cardiac dysfunction (uraemic cardiomyopathy, arrhythmias due to hyperkalaemia) because of acute renal impairment. Defining the epidemiology in this subtype has proven a challenge due to different methods for defining AKI, different baseline risks for developing acute cardiac dysfunction and limited reporting by studies of AKI on the incidence of acute cardiac dysfunction as an outcome measure (5, 6).

Chronic renocardiac syndrome (type 4): Cardiorenal syndrome type 4 describes CKD leading to cardiac dysfunction (left ventricular failure or diastolic HF). Cardiac disease in patients with CKD is common, and adverse cardiac outcomes correlate well with severity of CKD (7).

Secondary cardiorenal syndromes (type 5): Cardiorenal syndrome type 5 is characterised by simultaneous cardiac and renal dysfunction as a part of a systemic condition whether that may be acute or chronic. This most commonly includes systemic conditions such as sepsis and less so others such as amyloid or vasculitis (3).

Etiology:

The major mechanism of acute CRS is believed to be systemic congestion leading to increased renal venous pressure that in turn reduces renal perfusion.

1. Secondary to elevated central venous pressure (CVP) or elevated intraabdominal pressure.
2. Frequency of worsening kidney function is lowest in patients with CVP <8 mm Hg.
3. GFR may increase rapidly after diuretic therapy, an effect mediated by a reduction in renal venous pressure and/or a reduction in right ventricular dilation.

Reduced renal perfusion.

1. Common cause of CRS type 1 (acute CHF results in AKI). Right ventricular dilation and dysfunction.
   1. Increases CVP that increases renal venous pressure and reduces GFR.
   2. Right ventricular dilation and dysfunction reduce left ventricular filling and renal blood flow.

Neurohormonal.

1. Activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, antidiuretic hormone, and endothelin-1 increases salt and water retention. Systemic vasoconstriction decreases renal perfusion.
2. Activation of the above neurohormonal systems supersedes vasodilatory effects of natriuretic peptides, nitric oxide, prostaglandins, and bradykinin.

Epidemiology:

Heart Failure and Kidney Disease: Heart failure is a common precursor to CRS. In patients with heart failure, the incidence of kidney dysfunction is significant, and CRS is a frequent complication. The prevalence of CRS in patients with heart failure ranges from 20% to 60% or more, depending on the population and definition used. Chronic Kidney Disease: In patients with CKD, the prevalence of CRS is also substantial. CKD can contribute to the development of heart disease, and CRS is common in advanced stages of CKD. The exact prevalence of CRS in CKD varies but can affect up to 30% or more of CKD patients.

"Impairment in kidney function is common in HF patients and is associated with worse clinical outcomes than in persons without impaired kidney function." ("Cardiorenal Syndrome-Pathophysiology - PMC - National Centre) In the Acute Decompensated Heart Failure National Registry [ADHERE] which included > 105,000 patients admitted with ADHF, 91% of patients had some degree of renal dysfunction, with 64% having CKD stage 3 or higher. Patients with more severe renal dysfunction had worse in-hospital clinical outcomes (need for mechanical ventilation, admission to an intensive care unit, cardiopulmonary resuscitation, new-onset dialysis), greater length of hospital stay, and in-hospital mortality. Overall, eGFR was found to be an independent predictor of mortality. In a meta-analysis of acute and chronic HF populations, the overall prevalence of CKD was 49% (with higher prevalence in acute HF [53%] vs. chronic HF [42%]). AKI was seen in 23–35% of patients. Both CKD and WRF were associated with significantly increased mortality risk.

Pathophysiological Mechanisms in CRS

The failing heart to generate forward flow, thus resulting in prerenal hypoperfusion. Inadequate renal afferent flow activates the RAAS axis, the sympathetic nervous system, and arginine vasopressin secretion, leading to fluid retention, increased preload, and worsening pump failure. However, the presence of a low-flow state only partly explains the pathophysiology of CRS. The ADHERE registry (Acute Decompensated Heart Failure National Registry) noted that the incidence of rising serum creatinine was similar among patients with AHF and reduced versus preserved systolic function. In addition, many patients hospitalized with evidence of acute CRS have preserved or even elevated blood pressure and normal left ventricular ejection fraction (EF).

The kidneys are not first in line for delivery of oxygenated blood, yet they receive a disproportionately large fraction (25%) of cardiac output (CO) because they are a low-resistance circuit. The difference between arterial driving pressure and venous outflow pressures must remain sufficiently large for adequate renal blood flow and glomerular filtration. In this context, the concept of elevated central venous pressures (CVPs) resulting in renal venous hypertension, increased renal resistance, and ultimately impaired intrarenal blood flow has been
shown in early experimental models and in more contemporary experiences in patients with AHF using invasive hemodynamic monitoring (5,6,8).

Merrill elegantly demonstrated large reductions in renal blood flow in subjects with decompensated HF with relative preservation of glomerular filtration rate (GFR). This was explained by a concomitant increase in filtration fraction derived from elevated intraglomerular pressures from efferent arteriolar constriction in the setting of elevated renin levels.

However, in severe decompensated HF with markedly elevated renal venous pressures and decreased renal blood flow, the compensatory increase in filtration fraction is lost and results in declining GFR. In this setting, the decrease in intraglomerular pressures and reduced GFR are driven by preglomerular vasoconstriction from extreme levels of RAAS and neurohumoral activation. In addition, the enhanced activation of the neurohumoral axis results in increased proximal tubular sodium and water reabsorption to maintain effective plasma volumes, eventually resulting in oliguria and worsening congestion.

These renal hemodynamic regulatory mechanisms are also the rationale behind the elevations in serum creatinine from decreased glomerular hydraulic pressures seen with the administration of RAAS inhibitors, with minor changes in renal blood flow per sec, and translate into true worsening of renal function only when reductions in mean arterial pressure exceed renal autoregulatory capacity. This is the basis for the elevations in serum creatinine seen with RAAS inhibition. Finally, the low-resistance nature of the renal vasculature and parenchyma and the exceptionally low oxygen tension in the outer medulla also explain the unique sensitivity of the kidneys to hypotension-induced injury. Thus, both hemodynamic instability an antecedent hypotension should be considered in the consultative evaluation of a patient with developing CRS (10–14).

Clinical Assessment:

Detailed medical history: The healthcare provider will inquire about symptoms, medical conditions, medications, and risk factors for heart and kidney diseases.

Physical examination: A thorough physical examination may reveal signs of heart failure (e.g., fluid retention, elevated jugular venous pressure) and kidney dysfunction (e.g., decreased urine output, edema).

Assessment of vital signs: Monitoring blood pressure, heart rate, and respiratory rate is essential to assess overall cardiovascular health (15).
Laboratory Tests:

Blood tests:

Serum creatinine: Elevated levels may indicate impaired kidney function.

B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP): Increased levels suggest heart failure.

Electrolyte levels: Imbalances, such as hyperkalemia, may occur in CRS.

Urinalysis: Examining urine for abnormalities, including proteinuria or hematuria, can provide insights into kidney function.

Estimated glomerular filtration rate (eGFR): Calculating eGFR helps determine the severity of kidney impairment.

Imaging Studies: Echocardiography: This ultrasound examination of the heart assesses its structure and function, helping to diagnose heart-related issues such as reduced ejection fraction (16).

Chest X-ray: It can reveal signs of congestive heart failure, such as pulmonary edema.

Kidney ultrasound or CT scan: Imaging of the kidneys may identify structural abnormalities or renal artery stenosis.

Functional Tests:

Renal Doppler ultrasound: This test can assess renal blood flow and identify any obstructive lesions in the renal arteries.

Cardiac stress tests: These tests, such as stress echocardiography or nuclear stress tests, can assess the heart's response to exercise or stress, helping diagnose underlying cardiac issues (9).

Management of Cardiorenal Syndrome:

Initially, reduced cardiac output or lack of forward flow was considered the primary driver of kidney injury; but now, the concept that venous congestion rather than lack of forward flow is the principal cause of worsening renal function is favored. Following are the major treatment strategies used in treating cardiorenal syndrome.

1. Decongestive therapies - Diuretics, Ultrafiltration

2. Neurohormonal Modulation and Vasodilator and Inotropic therapy

3. RAAS inhibition in chronic CRS - ACEI/ARB, Neprilsyn/ Renin-Angiotensin inhibitors, Mineralocorticoid receptor antagonists, Beta-blockers

Now, diuretics continue to be the drug of choice for the initial treatment of stable patients with type I CRS. However, diuretics alone have not been shown to improve hard cardiac endpoints. Diuretic therapy aims to eliminate clinical evidence of fluid retention, such as elevated jugular venous pressure (JVP) and peripheral edema. It is found that improvement in cardiac function is associated with improved renal function in patients with type I and type II CRS.
Tolvaptan

Elevated arginine vasopressin levels in heart failure due to activation of RAAS pathway have adverse effects, resulting in deterioration in cardiac function and leading to peripheral vasoconstriction and increased afterload through V1a receptors (Vasopressin 1). Vasopressin V2 receptor stimulation leads to water retention and elevation in preload. Tolvaptan has been shown to have a favorable effect on heart failure. It is also helpful in weight reduction, increasing urine output, and correcting serum sodium levels without impacting renal function and serum electrolytes by its action on the neurohormonal pathway in cardiorenal syndrome.

In EVEREST TRIAL (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) conducted on 4133 patients, it was found that tolvaptan effectively reduced volume overload and provided symptomatic relief but failed to improve mortality and morbidity. It has a major safety profile and is useful in relieving congestion without any harm on kidney function in patients with volume overload and cardiorenal compromise. Tolvaptan can be beneficial in alleviating congestion and preventing or reducing renal dysfunction by maintaining renal perfusion and avoiding intravascular volume depletion.

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) has been used for the treatment of heart failure. It has also improved renal function by improving cardiac output, increased mean arterial pressure, and decreased central venous pressure. In a retrospective cohort analysis conducted by Singal et al. on 260 patients, it was found that renal response improved after CRT in patients with chronic kidney disease (CKD) and congestive heart failure (CHF). Besides, there was a significant reduction in five-year death, transplant, or LVAD (left ventricular assist device), including patients with stage 4 CKD as well, which was attributed to improved LVEF (left ventricular ejection fraction), leading to enhanced forward perfusion, and decreased venous congestion. CRT also diminishes sympathetic nerve activity decreasing adrenergic tone, which reduces RAAS activity in the long run(17).

Methodology:

Literature Search:

Database Selection: The research journey commenced with a deliberate expedition into the esteemed database, PubMed, renowned for its wealth of scholarly resources, to gather comprehensive insights into the complex realm of Cardiorenal syndrome.

Initial Article Collection: During the initial phase of the investigation, a systematic search was conducted, resulting in the discovery of an initial collection of 120 pertinent articles related to Cardiorenal syndrome.

Selection criteria:

- Language Proficiency: We focused unwaveringly on articles published in the English language to uphold clarity and accessibility in our pursuit of knowledge. Articles in other languages were excluded from consideration.
- Human-Centric Studies: The purview was limited exclusively to articles centered on human subjects. This strategic restriction was integral to maintaining the direct relevance of the research to the human manifestation of Cardiorenal syndrome.
- Open Accessibility: To ensure accessibility and reliability, a selection principle was instituted, encompassing only articles available for free access. Preprints and other restricted sources were conscientiously omitted to ensure an unimpeded flow of knowledge.
- Article Screening: A refined sieve of selection criteria was applied to the initial collection of 120 articles, resulting in a narrowed down selection based on language proficiency, human-centric focus, and open accessibility.
After the application of these judicious selection criteria, the research reached its zenith with the careful evaluation and in-depth analysis of 40 chosen articles.

- Data Analysis: In-depth Analysis: The selected articles underwent thorough scholarly analysis to extract valuable insights and information pertaining to Cardiorenal syndrome.

  The analysis included the extraction of key findings, trends, and any relevant data related to the interplay between cardiovascular and renal systems in the context of Cardiorenal syndrome.

- Conclusion: The research methodology employed in this study was a harmonious fusion of astute article retrieval, exacting criteria setting, and in-depth scholarly analysis.

This methodology stands as a testament to the commitment to gaining a profound understanding of the complexities of Cardiorenal syndrome, guided by the beacon of excellence in research.

The methodology outlined above ensured the meticulous gathering of pertinent information from reliable sources, which, in turn, provided a solid foundation for the comprehensive study of Cardiorenal syndrome.

Our method was a harmonious fusion of astute article retrieval, exacting criteria setting, and thorough scholarly analysis. It stands as a testament to our unwavering commitment to gaining profound understanding in the realm of Cardiorenal syndrome, guided by the beacon of excellence. (17).

Predisposing factors contributing to CRS:

Anemia and Nutrition Problems: When someone has anemia (a shortage of red blood cells) or lacks essential nutrients, their body may become inflamed. This inflammation can harm both the heart and kidneys over time. It is like a chain reaction that worsens Cardiorenal Syndrome.

Obesity: Being significantly overweight, or obese, can be a problem. It can lead to a specific kidney condition called "obesity-related glomerulopathy." This condition can cause chronic kidney disease and increase the risk of Cardiorenal Syndrome, especially in certain types. Even if a person doesn’t have diabetes, the fat cells in their body can release substances that damage the heart and kidneys (12).

High Blood Pressure (Hypertension): Elevated blood pressure doesn’t just raise the risk of heart problems; it can directly harm the kidneys. This damage can lead to a worsening of Cardiorenal Syndrome, particularly in people with congestive heart failure, a condition where the heart struggles to pump blood effectively.

Diabetes: Diabetes can be a significant contributor to Cardiorenal Syndrome. It can damage the tiny filters (glomeruli) in the kidneys, causing kidney disease. Additionally, both diabetes and high blood pressure can result in the release of excessive protein into the kidneys, which can further harm them. Over time, this can lead to Cardiorenal Syndrome. In severe cases, diabetes can cause kidney cells to die, making kidney disease worse (4, 12–14, 18).

Conclusion and Implications:

1. The review offers a comprehensive understanding of CRS, making it a valuable resource for healthcare professionals and researchers.

2. It highlights the intricate interplay between the heart and kidneys, emphasizing the necessity of a multidisciplinary approach to management.

3. The discussion on predisposing factors underscores the importance of holistic patient care.

4. While providing a well-structured and informative overview of cardiorenal syndrome, the review could benefit from further elaboration on treatment strategies and clarification in the methodology section.

5. Overall, it serves as a valuable resource for those seeking to comprehend the intricacies of CRS and its management.
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