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Review Article

Rediscovering the cardiorenal syndrome: from theory to practice

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ABSTRACT

Cardiorenal syndrome (CRS) is a state of advanced involvement that occurs between the heart and the kidneys, with both organs being affected by multiple causes, either secondary to a systemic pathology, or the dysfunction of one of these organs causing dysfunction on the other, acutely or chronically. Typically, there are five different types with different pathophysiology, but with the same purpose: cardiac and renal involvement. Epidemiological data from meta-analysis carried out around the world indicate that it is a very common pathology, yet commonly missed by clinicians. In patients with kidney or heart disease, which places them in a position to develop the syndrome, the first contact doctor must actively search for the diagnosis. In hospitalized patients, especially among those with previous cardiac or renal pathology, this syndrome has an important relevance, since its incidence is very high and early diagnosis is extremely important for an adequate treatment and thus avoid the perpetuation of damage to both organs. An early diagnosis can reduce the mortality rate, since it has been estimated that it increases by approximately 15% for every 10 ml / min reduction in GFR.

Keywords: Cardiorenal syndrome, Heart failure, Renal failure, Neurohumoral blockade

INTRODUCTION

Heart failure (HF) leading to kidney dysfunction and vice versa, termed cardiorenal syndrome (CRS), has been increasingly identified as a marker of increased morbidity and mortality. To date, there are limited data available regarding the clinical profile, associated risk factors, and outcome of CRS in the population. Several studies of patients with HF have reported an association between impaired kidney function and unfavorable outcomes. The change in kidney function during hospitalization for HF may also be of prognostic significance. Krumholz et al in a study of Medicare beneficiaries with HF, it showed that deterioration of renal function, defined as an increase in serum creatinine of 0.3 mg/dl during hospitalization, occurred frequently (incidence 28%) and it was associated with specific clinical characteristics present on admission.[1] Furthermore, patients with impaired renal function had a longer hospital stay, higher hospital costs, higher hospital mortality, and a higher likelihood of readmission. This systematic review is carried out with the objective of showing the prevalence, risk factors, and outcome of CRS and its types, as well as the impact that early diagnosis and adequate treatment can have on patients.

THEORETICAL FRAMEWORK

Definition

This syndrome, also known as cardiorenal anemia syndrome, is an advanced state of dysregulation that occurs between the heart and the kidneys with the involvement of both organs due to multiple causes, which induces one of the two organs to fail with the consequent dysfunction of the other. The dysfunction that occurs in

this entity causes the physiological functions of the heart-kidney relationship to be altered, causing one of the two organs to use a compensation mechanism that will have a significant impact on the other (Table 1).

Table 1: Types of cardiorenal syndrome.

Type	Denomination	Description
1	Acute cardiorenal	Acute heart failure leading to acute kidney failure
2	Chronic cardiorenal	Chronic heart failure leading to chronic kidney failure
3	Acute renocardiac	Acute kidney failure leading to acute heart failure
4	Chronic renocardiac	Chronic kidney failure that conditions chronic heart failure
5	Secondary	Systemic condition that simultaneously causes kidney and heart failure

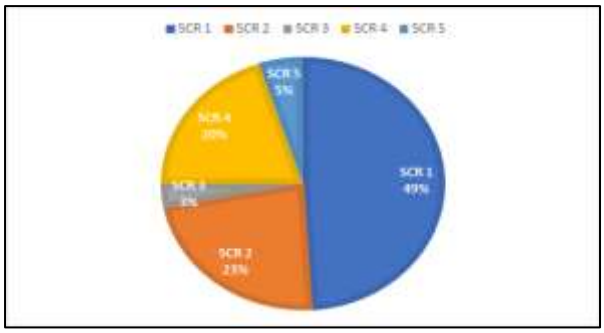

Figure 1: Prevalence of each RCS subtype.

In a simplified way, cardiorenal syndrome must have three fundamental characteristics:

Equal relevance between both systems, since many times it is not clear where the damage began. The dysfunction can be acute or chronic and also functional or structural. The interaction is bidirectional, that is, there are characteristics that lead to a negative vicious circle that results in the decompensation of the entire circulatory system.[2]

Epidemiology

The incidence of CRS depends on the subtype, but it is estimated that about 20-35% of patients with acute heart failure also have kidney failure. Regarding type 1 CRS, it is usually the most frequent in patients with heart failure between 27-45% and 9-54% in patients with acute myocardial infarction. According to data published in 2020 by Prothasis et al. (3), the prevalence of each type of cardiorenal syndrome was estimated, which is shown in Figure 1.

Risk factors

Multiple risk factors have been identified for the development of cardiorenal syndrome, among which are age older than 60 years, male sex (possibly because cardiovascular and kidney disorders are more prevalent in the male population), increased body mass index, type 2 diabetes mellitus and systemic arterial hypertension (the most important risk factor). The most frequent risk factors for type 1, 2 and 4 CRS were coronary artery disease, for type 3 it was hypertension and sepsis, and finally, for type 5 it was sepsis.[3]

Types of cardiorenal syndrome

In order to differentiate the origin of cardiorenal syndrome, a classification has been made based on the pathophysiology that caused the condition. The different types of SCR are described below.

Type 1 (or acute cardiorenal syndrome)

It is a rapid compromise of cardiac function that generates acute kidney injury. In turn, it can be subdivided into three subgroups based on the patient's symptoms: hypertensive pulmonary edema with preserved left ventricular ejection fraction (LVEF), acute decompensated heart failure, and right ventricular HF with cardiogenic shock. The basic principle in this CRS is an acute kidney injury due to hypoperfusion caused by a low cardiac output with a consequent increase in venous pressure that causes renal congestion.

Type 2 (or chronic cardiorenal syndrome)

It is a chronic deterioration of heart function that causes chronic kidney failure (CRF) progressively. This SCR is secondary to chronic cardiovascular abnormalities such as chronic HF, atrial fibrillation, or cardiomyopathies. It is one of the most common forms of presentation, with reports of up to 63% of hospitalized patients.[4]

Type 3 (or acute renocardiac syndrome)

It is an acute deterioration of renal function that conditions a subsequent cardiac dysfunction. The mechanisms involved in renocardiac dysfunction may be due to fluid overload that contributes to the development of pulmonary edema, or to alterations in the metabolism of minerals with high concentrations of calcium and phosphorus, as well as in uremic patients there may be a direct affectation of myocardial contractility.

Type 4 (or chronic renocardiac syndrome)

It is a cardiovascular dysfunction secondary to chronic kidney disease. What is important about this SCR are the

consequences that are produced by chronic kidney disease, such as ventricular hypertrophy, remodeling and favoring of cardiovascular events such as heart or brain infarcts.

Type 5 (or secondary cardiorenal syndrome)

It is the simultaneous presence of both renal and cardiac dysfunction, which can be acute or chronic. Among the main acute causes we have septic shock, severe burn patients, and systemic diseases such as lupus erythematosus, diabetes mellitus, and vasculitis.[5]

Prevalence

HF is usually accompanied by a reduction in the glomerular filtration rate (GFR) through multiple mechanisms. The prevalence of moderate to severe renal failure (defined as a GFR less than 60 ml/min per 1.73 m2) is approximately 30% to 60% in patients with HF according to reports published between 2004 and 2006.[6-8]

In a systematic review of 16 studies of more than 80,000 hospitalized and outpatients with HF, moderate to severe renal failure (defined as an estimated GFR less than 53 ml/minute, a serum creatinine of 1.5 mg/dL, or a cystatin Serum C of 1.56 mg/dl or higher) was present in 29% of patients.[9]

In a 2007 study, data were presented on more than 100,000 HF patients requiring hospitalization, of which approximately 30% had a diagnosis of chronic kidney disease (defined as serum creatinine greater than 2.0 mg / dL). The estimated mean GFR was 55 ml / min per m2, and only 9% had a normal estimated GFR.[10]

Patients undergoing treatment for acute or chronic heart failure frequently develop an increase in serum creatinine, which meets the criteria for type 1 or type 2 CRS.[11,12] In different series, approximately 20 to 30% of patients developed an increase in serum creatinine of more than 0.3 mg/dl and, in one report, up to 24% of patients had an increase of 0.5 mg/dl. dL or more.[13,14]

Risk factors for worsening renal function during admission for heart failure include a history of heart failure or type 2 diabetes mellitus, a serum creatinine on admission of 1.5 mg/dl or higher, and uncontrolled hypertension.[15] The increase in serum creatinine usually occurs in the first three to five days of hospitalization.[16]

Prognosis and importance of an early diagnosis

A reduced baseline GFR is generally associated with a worse prognosis in patients with HF. However, the prognostic significance of WRF worsening renal function probably depends on its cause.

An analysis of the PROTECT trial identified multiple different trajectories in kidney function during hospitalization for acute heart failure. The most common pathways were transient intrahospital increase in serum creatinine (19%), sustained increase (17.6%), and decrease (14.5%). After multivariate adjustment, no path of change was associated with significantly better or worse outcomes, calling into question the prognostic significance of changes in kidney function during acute HF.[17]

In 2006, a review was made of 16 studies that included more than 80,000 patients with HF.[18] Patients were classified as having normal renal function (GFR 90 ml/min or higher), mildly impaired renal function (GFR 53 to 89 ml/min, serum creatinine greater than 1.0 mg/dL, or serum cystatin greater than 1.03 to 1.55 mg/dL), or moderate to severely impaired kidney function (GFR less than 53 mL/min, serum creatinine of 1.5 mg/dL or more, or serum cystatin of 1.56 mg/dL or higher). Serum cystatin C may be a better GFR marker than serum creatinine in certain circumstances because, unlike creatinine production, cystatin C production is less dependent on muscle mass and therefore less influenced by muscle mass. nutritional status.[19]

All patients were monitored for one year with a mortality rate of 24% in those with normal GFR compared to 38% and 51% in patients with mild and moderate to severe reductions in GFR, respectively. Mortality was estimated to increase by approximately 15% for each 10 ml/min reduction in GFR.[20]

Diagnosis

Heart failure, as well as kidney failure, require different tools to establish the damage, both structural and functional, of these two organs. Including biomarkers, non-invasive imaging studies, or invasive hemodynamic monitoring.[21] It is important to make use of the definitions proposed by international organizations to define both heart and kidney failure, with the help of these studies mentioned below:

Biomarkers: Among the most commonly used cardiac damage biomarkers are atrial natriuretic peptide (BNP / NT-proBNP) and troponins. Creatinine and the presence of albuminuria are important to estimate GFR, another parameter that will help us evaluate renal function is nitrogen dioxide.

Imaging studies: Up to 40% of hospitalized patients with heart failure develop renal failure, both cardiac and renal ultrasound is a very high-value tool, important to estimate LVEF and classify the cardiac patient, estimate pulmonary pressures, measure hemodynamic parameters, renal flow patterns, size, echogenicity, and renal corticomedullary relationships give us an overview of this type of patient.

Hemodynamic monitoring: Both invasive and non-invasive can give us information on the cardiovascular

and renovascular status, different types of pressures (central venous pressure, mean arterial pressure, oncotic and osmotic pressure) that guide the doctor in the evaluation of the intravascular volume of the patient, one of the main pillars in the pathophysiology of this syndrome.[8,21]

Treatment

The management of these patients turns out to be very complex and depends to a great extent on the type of CRS that is presented.[18,21] Addressing it extensively is outside the objectives of this work. Some treatment strategies are briefly mentioned below. of the CRS, emphasis is placed on the concept of neurohumoral blockade in these patients, which consists of antagonizing neurohumoral mechanisms that lead to the perpetuation of this syndrome, such as adrenergic discharge, the renin-angiotensin-aldosterone system (RAAS) effectively and antagonize the activity of neprilysin that degrades BNP.

Decongestant therapy: The mainstay of this therapy is diuretic treatment. The main therapeutic objective focuses on the balance between the diuresis necessary for the control of heart failure and avoiding the possible worsening of renal function due to volume loss and impaired perfusion. The most commonly used diuretics are loop diuretics such as furosemide. It must be taken into account that the chronic use of diuretics can result in resistance to them and the need to increase the doses or the type of diuretics to be used.

Ultrafiltration techniques: The use of this type of therapy, such as hemodialysis, allows the decongestion of the patient without the use of diuretics, with the secondary benefit of saving potassium, less activation of the RAAS and less loss of sodium.

Blockade of the renin angiotensin aldosterone system (RAAS): It has been shown that the blockade of the RAAS slows the progression of CRF and in turn contributes to the neurohumoral blockade necessary for an adequate treatment of HF, this type of medication (such as ACEI or ARA) is mostly used in SCR type 2 and 4.

Neprilysin inhibitors: The combination of these inhibitors with drugs that block RAAS (Sacubitril/valsartan) considerably reduces mortality in these patients.

Beta blockers: These reduce the number of hospitalizations, relieve symptoms, and prolong survival. However, tolerance to these drugs is limited by fluid retention, which can complicate the management of acute CRS (type 1 and 3).[22]

CONCLUSION

Although the different pathophysiological mechanisms of CRS are not well elucidated, there is strong evidence that, among hospitalized patients, especially nephropathy or heart disease, there is a strong incidence and a considerable number of patients develop it. We have many tools at the hospital level for the detection, follow-up and proper management of this pathology and it is a diagnosis that we must always keep in mind when approaching patients with risk factors and the aforementioned characteristics, prone to developing this syndrome. As mentioned in the text, the correct and prompt recognition of this pathology reduces the mortality rate by up to 15% for every 10 ml / min in GFR. However, the management these patients receive is also important.

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