Pediatric Cardiorenal Syndromes

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Cardiorenal syndrome (CRS) is defined as a disorder resulting from the abnormal interaction between the heart and kidney, in which acute or chronic dysfunction of one organ may lead to acute and/or chronic dysfunction of the other. The functional interplay between the heart and kidney is characterized by a complex bidirectional symbiotic interaction, regulated by a wide array of both genetic and environmental mechanisms. There are at least five known subtypes of CRS, based on the severity of clinical features and the degree of heart/renal failure. The fourth subtype (cardiorenal syndrome type 4 (CRS4)) is characterized by a primary chronic kidney disease (CKD), which in turn leads to a decreased cardiac function. Impairment of renal function is among the most important pathophysiological factors contributing to heart failure (HF) in the pediatric age group, and cardiovascular complications could be one of the most important causes of mortality in pediatric patients with advanced CKD. In this context, a loss of glomerular filtration rate directly correlates with both the progression of cardiovascular complications in CRS and the risk of HF.

Keywords: cardiorenal syndrome ; pathophysiology ; chronic kidney disease ; pediatric age ; heart failure ; renal function ; child ; kidney injury ; treatment ; management

1. Introduction

In 2004, the Working Group of the National Heart, Lung, and Blood Institute proposed the first definition of CRS. CRS was described as a consequence of abnormal functional connections between the kidneys and other circulatory compartments, leading to increased circulating blood volume and exacerbating the symptoms of heart failure (HF) and CVD progression. This initial definition was extremely cardiocentric, thus not explaining the real complexity underlying the interplay between the two organ systems. In 2008, the Acute Dialysis Quality Group proposed a new classification in a Consensus Conference. This classification divided CRS into two key sets, cardiorenal and renocardiac CRS, according to the primum movens of disease (cardiac or renal). Both cardiorenal and renocardiac CRS were then subsequently organized into five subtypes based on disease acuity and according to the beginning and duration of the organ dysfunction (**Table 1**). The new classification overcame some of the initial ambiguity in defining CRS and helped clinicians to aim for a personalized approach, in both diagnosis and treatment, for each patient. However, in clinical practice, it can be challenging to identify the initial pathophysiological events of CRS [1].

Table 1. CRS Classification.

CRS Type	Denomination	Description
Type 1	**Acute cardiorenal**	**Heart failure leading to acute kidney disease**
Type 2	**Chronic cardiorenal**	**Chronic heart failure leading to acute kidney disease**
Type 3	**Acute renocardiac**	**Acute kidney disease leading to acute heart failure**
Type 4	**Chronic renocardiac**	**Chronic kidney disease leading to heart failure**
Type 5	**Secondary**	**Systemic disease leading to heart and kidney failure**

2. CRS Classification

CRS includes all the disorders involved in the bidirectional interactions between the heart and kidneys, in which the dysfunction of one organ can significantly impair the function of the other. CRS is divided into two main categories based on the initial insult and into five subcategories according to the direction of the effect and the acuity of the initiating insult (acute or chronic) [2][3] **Table 1**. CRS type 1 reflects an acute worsening of cardiac function affecting the kidneys, type 2 encompasses chronic cardiac disorders worsening the kidney's function, type 3 comprises acute renal abnormalities

causing acute heart failure, type 4 reflects a chronic kidney disorder leading to decreased cardiac function and heart failure, and, finally, type 5 describes a systemic insult leading to cardiorenal dysfunction.

2.1. CRS Type 1

CRS type 1 (acute cardiorenal) is characterized by the fast deterioration of cardiac function, which leads to acute renal injury (AKI). Type 1 CRS is relatively prevalent. It is usually present in the setting of acute decompensated heart failure (ADHF), often after an ischemic (acute coronary syndrome, cardiac surgery complications) or nonischemic heart disease (valvular disease, pulmonary embolism), which may be divided into four subtypes: hypertensive pulmonary edema with preserved left ventricular systolic function, acutely decompensated chronic HF, cardiogenic shock, and predominant right ventricular failure.

Pathophysiology. *Hemodynamic mechanisms*. In the presence of ADHF, hemodynamic processes play a prominent role in CRS type 1, resulting in decreased renal artery flow and, as a result, a decrease in GFR. Different hemodynamic profiles have been proposed: in “cold” pattern patients, the predominant hemodynamic change is a drop in effective circulating fluid volume, whereas in “wet” pattern patients, there is a significant increase in central venous pressure. *Nonhemodynamic mechanisms*. CRS type 1 has been linked to SNS and RAAS activation, chronic inflammation, and an imbalance in the percentage of reactive oxygen species (ROS)/nitric oxide (NO) generation. The beginning of AKI has an impact on the prognosis of HF in CRS type 1, but early detection of AKI is difficult [4]. The preservation of both cardiac and renal function should be prioritized.

2.2. CRS Type 2

Chronic anomalies in heart function (e.g., chronic congestive HF) contribute to progressive kidney failure in CRS type 2 (chronic cardiorenal syndrome).

Pathophysiology. Hemodynamic mechanism. The most important pathophysiological processes of CRS type 2 are renal hypoperfusion and persistent elevations in renal venous pressure. *Nonhemodynamic mechanisms*: Maladaptive activation of the RAAS axis and the SNS, as well as a chronic inflammatory state, are important pathophysiological causes of renal disease progression. Structure injury, such as glomerulosclerosis and tubulointerstitial fibrosis, is precipitated by intrarenal oxidative stress and proinflammatory signaling. Chronic HF and renal illness can coexist for a long time, making it difficult to determine which of the two disease states is predominant (or secondary). Even a small drop in glomerular filtration rate (GFR) results in a markedly poor prognosis, increasing the mortality rate in these individuals, and it can be used as a marker of cardiovascular disease severity [5]. Diabetes mellitus, advanced age, hypertension, and acute and coronary syndrome are also other useful indicators of a poor prognosis [6].

2.3. CRS Type 3

When AKI leads to the development of acute HF, CRS type 3 (acute renocardiac syndrome) ensues. It is less prevalent than type 1 CRS and has not been thoroughly researched in the literature. AKI can impact the heart directly or indirectly, and through numerous distinct pathways, it can cause an abrupt cardiac event [7].

Pathophysiology. Hemodynamic mechanisms. Renal dysfunction can cause severe pathophysiological derangement, which can lead to heart damage. Oliguria can cause sodium and water retention, resulting in fluid overload and the development of hypertension, pulmonary edema, and myocardial injury. *Nonhemodynamic mechanisms*. Electrolyte abnormalities that cause arrhythmias and cardiac arrest, metabolic acidosis that causes vasoconstriction, coronary artery disease, and left ventricular dysfunction can be also associated with CRS type 3. Renal ischemia can cause myocardial inflammation and apoptosis on its own [8]. Furthermore, baroreceptor and intrarenal chemoreceptor activation is triggered by changes in systemic and renal hemodynamics. These conditions have a negative impact on cardiac outcomes.

2.4. CRS Type 5

CRS type 5 (secondary CRS) is characterized by the presence of cardiac and renal dysfunction in the same patient, and it can occur in a variety of clinical settings as a result of acute or chronic systemic illnesses (e.g., sepsis, hepatorenal syndrome, and Fabry’s disease). Type 5 CRS has a scarcity of information in the literature. It is obvious that some systemic diseases affect both organs at the same time, and that the malfunction of one might have an impact on the other. The most common cause of CRS type 5 is sepsis, which causes cell ultrastructural changes and organ failure. Sepsis can cause AKI and severe cardiac depression at the same time. Many mediators and pathways have been implicated in the pathogenesis of sepsis-induced cardiac depression; however, the exact etiopathogenetic mechanism remains unknown.

Pathophysiology. *Hemodynamic mechanisms*. Pathophysiological abnormalities in sepsis-related CRS type 5 are influenced by the sepsis's systemic effects and direct cross-talk between the injured heart and kidney. Despite good systemic hemodynamics, microcirculation is frequently involved in the early stages of sepsis. With dilatation and decreased ejection fraction, both the left and right ventricles can be affected in septic cardiomyopathy. There are obvious changes in intraparenchymal blood flow in sepsis-associated AKI, independent of systemic hemodynamic abnormalities due to the septic process. *Nonhemodynamic mechanisms*. The pathophysiology of septic cardiomyopathy does not appear to include myocardial blood flow or oxygen consumption. The role of proinflammatory mediators and complement factors in the development of cardiac involvement during sepsis has been suggested. Sepsis can influence the autonomic nervous system (ANS), the RAAS, and the hypothalamus–pituitary–adrenal axis (HPA) independently, affecting cardiac and/or renal function in numerous, separate processes. Several physiological and molecular alterations occur in both tissues with combined heart and kidney dysfunction, as in sepsis. Activation and elevation of cytokines (TNF-a and IL-6), as well as leukocytes (macrophages, neutrophils, and lymphocytes) in the heart and kidney during sepsis, has been well documented.

3. Conclusions

CRS patients have a higher risk of death and morbidity than those with each disease entity alone. The heart and kidneys interact bidirectionally and interdependently through several mechanisms. A better understanding of the interactions between these organs is important for his practical clinical implications. Patients with CKD have the highest cardiovascular risk of any pediatric demographic, and dialysis is a primary factor linked to poor outcomes in children with ESRD. These data suggest that long-term dialysis should be avoided in these patients, with preemptive transplantation as the best management strategy when feasible. When compared to long-term dialysis, successful transplantation can considerably alleviate uremia-related risk factors and, most importantly, enhance life expectancy by 20–30 years. More research is needed to better understand the pathogenetic process and best therapies in this pediatric population

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