Cardiorenal Syndrome: An Overview

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It is well established that a large number of patients with acute decompensated heart failure present with various degrees of heart and kidney dysfunction usually primary disease of heart or kidney often involve dysfunction or injury to the other. The term cardiorenal syndrome increasingly had been used without a consistent or well-accepted definition. To include the vast array of interrelated derangements and to stress the bidirectional nature of heart-kidney interactions, a new classification of the cardiorenal syndrome with 5 subtypes that reflect the pathophysiology, the time frame, and the nature of concomitant cardiac and renal dysfunction was proposed. Cardiorenal syndrome can generally be defined as a pathophysiological disorder of the heart and kidneys, in which acute or chronic dysfunction of one organ may induce acute or chronic dysfunction to the other. Although cardiorenal syndrome was usually referred to as acute kidney dysfunction following acute cardiac disease, it is now clearly established that impaired kidney function can have an adverse impact on cardiac function.

Key Words: Cardiorenal syndrome (CRS), Risk factors, Diagnosis, Outcomes and treatment

DEFINITION OF CARDIORENAL SYNDROME

An effective classification of cardiorenal syndrome (CRS) has been proposed in a Consensus Conference by the Acute Dialysis Quality Group[1,2] in 2008 (Table 1). This classification essentially divides CRS in 2 main groups, cardiorenal and renocardiac CRS, based on the *primum movens* of disease (cardiac or renal). Both cardiorenal and renocardiac CRS are then divided into acute and chronic types according to the onset and duration of the underlying organ dysfunction. CRS type 5 (CRS-5) integrates all cardiorenal involvements induced by systemic disease.

CARDIORENAL AXIS

The interactions and feedback mechanisms involved in heart and kidney failure are more complex than previously thought. The classic understanding of kidney dysfunction in heart failure was that low renal plasma flow signals the kidneys to retain sodium and water leading to refilling and improved perfusion to vital organs.[3] However, now it is becoming clear that hemodynamic adaptations of the kidney and related pathophysiological mechanisms can be independent of cardiac hemodynamics (Fig 1). The renal hemodynamic response to chronic heart failure is initially characterized by low renal plasma flow and relative preservation of the glomerular filtration rate (GFR) resulting in an increased filtration fraction. The GFR is preserved until cardiac function is severely impaired because of an increase in efferent arteriolar resistance and glomerular capillary hydrostatic pressure.[3] In addition to these changes in GFR, enhanced sodium reabsorption in the loop of Henle also appears to play a significant role in the CRS together with multiple neurohormonal factors as represented by activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). Neurohormonal activation, increased arginine vasopressin release, and endothelin release result in systemic vasoconstriction, preservation of GFR, and salt and water retention.[3] This is an initial compensatory response to preserve or optimize cardiac output, arterial blood pressure, and GFR.[3]

In patients with heart failure, however, because of neurohormonal response, a congestive state with peripheral edema develops. Inappropriate activation of the RAAS also leads to activation of nicotinamide adenine dinucleotide phosphate (reduced) oxidase by angiotensin II, leading to the formation of reactive oxygen species (ROS).[4,5] The critical role that RAAS plays in the CRS suggests the possibility of a treatment paradox: angiotensin-converting enzyme (ACE) inhibitor therapy in patients with chronic heart failure and CKD is associated with long-term benefits, but hypothetically may acutely exacerbate the CRS. However, this is not necessarily true in clinical practice. ACE inhibitors are not associated with worsening kidney function in patients hospitalized for management of heart failure, and the mild worsening of kidney function because of the CRS does not constitute an indication to stop ACE inhibitor therapy in patients already on ACE inhibitor treatment.[6] Nitric oxide (NO) system activation represents a major issue in the pathophysiology of the CRS because it is involved in vasodilation, natriuresis, and desensitization of the tubuloglomerular feedback mechanism.[4,5] It also inhibits several components of atherogenesis and smooth muscle cell proliferation, and increases angiogenesis by ensuring delivery of vascular endothelial growth factor.[4,5] Therefore, NO system activation inhibits platelet aggregation, endothelial adhesion molecule expression, and leukocyte-endothelial cell interaction.[4,5] In kidney failure, the balance between NO and ROS is shifted because a relative deficiency of NO is observed. Decreased NO and increased oxidative stress in patients with kidney failure lead to increased risk for cardiac events also because of accelerated atherosclerosis.[4,6] C-reactive protein (CRP) has numerous proinflammatory

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and proatherogenic effects and is thought to have a role in the pathogenesis of atherosclerosis in cardiorenal patients.[7] It is increased in ESRD and probably has a synergistic role in the progression of renal and cardiovascular disease.[7] The SNS stimulates the release of renin by sympathetic neurons. Catecholamines produce hemodynamic changes in the glomerulus similar to those of angiotensin II (increased systemic vascular resistance and sodium retention).[8] Peripheral sympathetic nerve activity increases in ESRD, but corrects when the diseased kidneys are removed.[8] The complex interactions involved in acute renal disease eventually lead to a compensatory response that involves several natriuretic factors, such as atrial natriuretic factor, brain natriuretic factor, and urodilatin.[9]

CARDIORENAL SYNDROME TYPE 1 (ACUTE CARDIORENAL SYNDROME)

CRS type 1 (CRS-1) (acute cardiorenal) is characterized by acute worsening of cardiac function leading to acute kidney injury (AKI). CRS-1 usually presents in the setting of an acute cardiac disease such as acute decompensated heart failure (ADHF), often after an ischemic (acute coronary syndrome, cardiac surgery complications) or nonischemic heart disease (valvular disease, pulmonary embolism).

CRS-1 occurs in about 25% of patients hospitalized for ADHF[10,11]; among these patients, pre-existent CKD is common and contributes to AKI in 60% of all cases studied. AKI can be considered an independent mortality risk factor in patients with ADHF, including those with ST-segment elevation myocardial infarction and/or reduced left ventricular ejection fraction.[12]

CLINICAL SUMMARY

- Definition of cardiorenal syndrome.
- Meaning of heart and kidney cross-talk.
- Exploring the role of the newest risk factors for cardiorenal interactions.
- Summarizing therapeutic approaches to cardiorenal syndrome patients.

An acute heart failure syndrome (AHFS) may be defined as heart failure with a relatively rapid onset of signs and symptoms, resulting in hospitalization, or emergency room or unplanned office visits. AHFS can result from a variety of different pathophysiological conditions, although approximately 70% of cases result from worsening of chronic heart failure. Other causes of AHFS include new-onset heart failure caused by an acute coronary event such as a myocardial infarction and end-stage or refractory heart failure not responsive to therapy. Clinical presentation may vary, encompassing worsening congestion, worsening chronic heart failure, pulmonary edema, hypertensive crisis, or cardiogenic shock.[13] In all forms of heart failure, the kidney responds in a similar manner, retaining sodium and water despite expansion of the extracellular fluid volume.[13]

Obesity and metabolic syndrome can also contribute to both heart and kidney disease. In obesity, growth of adipocytes and increase in fatty acid content can be involved in vascular inflammation as it occurs in the epicardial coronary arteries.[13] Obesity-related glomerulopathy has been described as a condition of hyperfiltration in obese individuals without diabetes mellitus that leads to CKD and predisposes to CRS-1.[13] Combined disorders of heart and kidney are also likely to develop in the presence of some degree of cachexia and sarcopenia.[13]

Hemodynamic mechanisms play a major role in CRS-1 in the presence of ADHF leading to decreased renal arterial flow and GFR decline (Fig 2). Four different hemodynamic profiles have been proposed in patients with acute heart failure: cold/warm and dry/wet.[14] In "cold" pattern patients, a reduction in extracellular fluid volume represents the main hemodynamic change together with a decrease in renal blood flow related to the RAAS and systemic nervous system activation causing efferent vasoconstriction. Patients who present with a "wet" hemodynamic profile display increased pulmonary and/or systemic congestion. In these patients, high central venous pressure directly affects renal vein and kidney perfusion pressure.[15,16] Increase in central venous pressure also results in increased interstitial pressure with tubular collapse and progressive decline in the GFR.[17]

As previously mentioned, nonhemodynamic mechanisms involve SNS, RAAS activation, chronic inflammation, and imbalance in the proportion of ROS/NO production.[4]

Diagnosis of CRS-1 focuses on clinical and laboratory findings, ultrasonography, and other radiological tests. Early diagnosis of AKI in CRS-1 (such as in type 3) still remains a challenge[18]; classic biomarkers, such as creatinine levels, which increase when kidney injury is already established and prevention fails. New frontiers are represented by novel biomarkers such as serum and urinary neutrophil gelatinase–associated lipocalin, cystatin –C, kidney injury molecule 1, interleukin 18 (IL-18), and liver-type fatty acid-binding protein.[19,20]

Ultrasonography can provide further useful information for diagnosis of CRS-1. Typical findings on echocardiography reveal abnormal myocardial kinetics (indicating an ischemic condition) and left ventricular hypertrophy, valvular stenosis, and/or regurgitation (particularly in case of rapid deterioration, such as valvular endocarditis or valvular rupture), pericardial effusions, normal inspiratory collapse of the inferior vena cava (excluding severe hypervolemia), and aortic aneurysms or dissection.[21]

Ultrasound evaluation of the kidney usually shows normal or large-sized kidneys with preserved cortical-medullary ratio; color Doppler evaluation shows regular intraparenchymal blood flow, often associated with increased resistance index (>0.8 cm/s).[21]

CARDIORENAL SYNDROME TYPE 2 (CHRONIC CARDIORENAL SYNDROME)

CRS type 2 (CRS-2) is characterized by chronic abnormalities in cardiac function leading to kidney injury or