

Cardio Renal Syndrome

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Abstract

Cardiorenal syndrome is an umbrella term referring to all conditions where an acute or chronic dysfunction of heart or kidney may cause acute or chronic dysfunction of other organ. The purpose of this review is to give a brief overlook of this important clinical syndrome.

Keywords: Cardiorenal syndrome; Heart; Heart failure; Neurohormonal; Haemodynamic

Introduction

Heart is responsible for blood supply to organs of the body including the kidneys. Kidneys play a major role in regulating salt and water balance of the body. So it is no surprise that dysfunction of one organ will have deleterious effect on the other. This interdependence is termed as “Cardiorenal syndrome” (CRS). This umbrella term has been in use since 2004 but it is yet to permeate day to day clinical practice. The purpose of this review is to provide a brief overview of this important clinical syndrome.

Definition

In 2004, a working group of investigators at the National Heart, Lung, and Blood Institute defined the CRS as a state in which therapy to relieve heart failure (HF) symptoms is limited by further worsening renal function. This was the first attempt to define CRS. Since then a number of definitions are available. Commonly accepted definition is from a consensus conference held at Venice (Italy) in September 2008 under the auspices of the Acute Dialysis Quality Initiative (ADQI). The ADQI work group defined CRS as “disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other [1]. In 2010, Bock et defined cardiorenal syndrome as “each dysfunctional organ has the ability to initiate and perpetuate disease in the other organ through common haemodynamic, neurohormonal, and immunological and/or biochemical feedback pathways” [2].

Problem statement

CRS type 1 has been described in 27-45% of hospitalized AHF patients and in 9-54% of ACS patients [3-10]. In a survey of outpatients with congestive cardiac failure, 39% patients in New York Heart Association (NYHA) class 4 and 31% of patients in NYHA class 3 had severely impaired renal function (creatinine clearance < 30 ml/min) [11]. Elevated serum creatinine on admission to hospital with ADHF and worsening renal function during admission for ADHF have both been shown to predict prolonged hospitalisation and increased mortality [12,13]. There is no good quality data on incidence of type 3 CRS. In an Indian study of 100 patients, 29% of patients admitted with AKI had type 3 CRS [14]. In a study at Madrid over a period of 9 months, of 748 cases of AKI and death were studied. 32 Heart diseases was the reported cause of death in 15% of AKI patients [15]. Almost 44% of deaths in patients with end-stage renal disease (ESRD) are due to cardiovascular diseases [16]. Approximately 50% patients commencing hemodialysis will suffer a myocardial infarction within the following two years [17].

Classification

Ronco et al. have classified CRS into following subtypes (1):

- Acute CRS (Type 1)

- Acute worsening of cardiac function leading to renal dysfunction
- Chronic CRS (Type 2)
- Chronic abnormalities in cardiac function leading to renal dysfunction
- Acute Renocardiac Syndrome (Type 3)
- Acute worsening of renal function causing cardiac dysfunction
- Chronic Renocardiac Syndrome (Type 4)
- Chronic abnormalities in renal function leading to cardiac disease
- Secondary CRS (Type 5)
- Systemic conditions causing simultaneous dysfunction of the heart and kidney

Table 1 summaries the current knowledge on the subject.

Pathophysiology

As the understanding of pathophysiology improves one starts realizing that the interaction between heart and kidneys are much more complex than what was previously believed. The age old concept of low flow hypothesis is no longer accepted. Let us look into certain aspects (Table 2):

Low flow hypothesis: for decades it was believed that as cardiac output decreases there is reduced perfusion of kidneys. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial found no correlation between baseline renal function and cardiac index, and improvement of the latter did not result in improved renal function [18].

The Renin-Angiotensin-Aldosterone System (RAAS) and Sympathetic Nervous System (SNS): Activation of the RAAS and NS by reduced perfusion pressure is a protective mechanism. But, when chronically stimulated-as in both heart and renal failure-the pathophysiological consequences are severe and deleteriously affect function of both organ systems.

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| Syndromes | Acute cardio-renal (type 1) | Chronic cardio-renal (type 2) | Acute reno-cardiac (type 3) | Chronic reno-cardiac (type 4) | Secondary CRS (type 5) |
|---------------------------|---|--|---|--|---|
| Definition | Acute worsening of heart function (AHF–ACS) leading to kidney injury and/or dysfunction | Chronic abnormalities in heart function (CHF-CHD) leading to kidney injury or dysfunction | Acute worsening of kidney function (AKI) leading to heart injury and/or dysfunction | Chronic kidney disease (CKD) leading to heart injury, disease and/or dysfunction | Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney |
| Primary events | Acute heart failure (AHF) or acute coronary syndrome (ACS) or cardiogenic shock | Chronic heart disease (LV remodelling and dysfunction, diastolic dysfunction, chronic abnormalities in cardiac function, cardiomyopathy) | AKI | CKD | Systemic disease (sepsis, amyloidosis, etc.) |
| Secondary events | AKI | CKD | AHF, ACS, arrhythmias, shock | CHD (LV remodelling and dysfunction, diastolic dysfunction, abnormalities in cardiac function), AHF, ACS | AHF, ACS, AKI, CHD, CKD |
| Cardiac biomarkers | Troponin, CK-MB, BNP, NT-proBNP, MPO, IMA | BNP, NT-proBNP, C-reactive protein | BNP, NT-proBNP | BNP, NT-proBNP, C-reactive protein | C-reactive protein, procalcitonin, BNP |
| Renal biomarkers | Serum cystatin C, creatinine, NGAL. Urinary KIM-1, IL-18, NGAL, NAG | Serum creatinine, cystatin C, urea, uric acid, C-reactive protein, decreased GFR | Serum creatinine, cystatin C, NGAL. Urinary KIM-1, IL-18, NGAL, NAG | Serum creatinine, cystatin C, urea, uric acid | Creatinine, NGAL, IL-18, KIM-1, NAG |

AKI, acute kidney injury; CKD, chronic kidney disease; NGAL, neutrophil gelatinase-associated lipocalin; NAG, N-acetyl-β-(D)glucosaminidase; CK-MB, creatine phosphokinase; MPO, Myeloperoxidase; BNP, Brain Natriuretic Peptide; KIM, kidney injury molecule; IL, interleukin

Table 1: summary of CRS (classification, definition, cardiac and renal biomarkers).

| | |
|-----------------------------|---|
| Type 1 cardiorenal syndrome | Specific treatment directed towards the precipitating event. General supportive measures: maintain oxygenation, relieve pain and pulmonary congestion, treat arrhythmias appropriately, differentiate left from right heart failure, treat low cardiac output or congestion; avoid nephrotoxins and closely monitor kidney function. |
| Type 2 cardiorenal syndrome | Treat CHF according to guidelines Exclude precipitating pre-renal AKI factors (hypovolaemia and/or hypotension), Adjust therapy accordingly and avoid nephrotoxins, while monitoring renal function and electrolytes Extracorporeal ultrafiltration and dialysis may be required in cases which do not respond to above measures. |
| Type 3 cardiorenal syndrome | Specific management for underlying aetiology. Early renal replacement therapy should be considered especially if diuretic resistant. |
| Type 4 cardiorenal syndrome | Look for reversible causes like hypovolemia and use of Nephrotoxic drugs. Follow KDOQI guidelines for CKD management. Treat heart failure according to guidelines. Consider early renal replacement support |
| Type 5 cardiorenal syndrome | Specific treatment according to etiology. |

Table 2: Summarizes the management of cardiorenal syndrome.

Intra-abdominal hypertension: Heart failure is marked by an elevation in central venous pressure which reduces the perfusion gradient across the renal capillary bed. A study of 40 patients admitted with ADHF found that 24 had an (Intra-abdominal pressure) IAP >8 mmHg though none had abdominal symptoms. The degree of reduction of IAP with diuretic treatment correlated with an improvement in renal function [19]. The ESCAPE trial found that baseline right atrial pressure, but not arterial blood flow, correlated with baseline serum creatinine.

Oxidative injury and endothelial dysfunction: Neurohormones are strong mediators of an oxidative injury cascade that leads to widespread endothelial dysfunction, inflammation, and cell death in the CRS.

Cardiorenal-anemia syndrome: Anemia is common in individuals with chronic kidney disease and HF and may contribute to the abnormal renal oxidative state; hemoglobin is an antioxidant. Although anemia should induce increased erythropoietin, there is evidence that decreased concentrations in patients with CRS may directly exacerbate the renal abnormalities. Therefore, the combination of anemia and decreased erythropoietin may exacerbate the underlying factors causing CRS.

Management

General Principles

Improving cardiac function: In patients with type 1 and type 2 CRS, use of cardiac resynchronization and left ventricular assist devices can improve renal function [20,21].

Diuretics: These are first line therapy to manage fluid overload. According to 2013 American College of Cardiology/American Heart Association HF guidelines the goal of diuretic therapy is to eliminate clinical evidence of fluid retention such as an elevated jugular venous pressure and peripheral edema [22].

Renin-angiotensin-aldosterone-system antagonism: Angiotensin inhibition with an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) should be a part of the therapy of HF with reduced ejection fraction. Their use was associated with symptomatic improvement, reduced hospitalization for HF, and increased survival. While these drugs have clinical benefit in HF among patients with CKD, the risk of adverse events like hyperkalemia and worsening renal function is higher than in patients without CKD.

Vasodilators: Nitrates and nesiritide are intravenous vasodilators which are used in the treatment of acute decompensated HF.

Inotropic drugs: Intravenous administration of inotropic drugs, such as dobutamine, dopamine, and milrinone, has a role in the treatment of cardiogenic shock in a subset of patients with acute decompensated heart failure.

Mechanical ultrafiltration: Use of diuretics is associated with electrolyte imbalance. By removing isotonic fluid, ultrafiltration tends to maintain physiologic electrolyte balance. In HF patients, ultrafiltration is considered in patients with acute decompensated HF and diuretic resistance and impaired renal function. Despite above benefits, the available evidence does not establish ultrafiltration as first line therapy for AHDF or as an effective therapy for CRS. The 2009 American Heart Association/American College of Cardiology guidelines state that ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy [23-25].

Investigational therapies: Vasopressin receptor antagonist and adenosine A1 receptor antagonists are two classes of drugs which may be of utility in future.

Tolvaptan, a selective vasopressin 2 receptor antagonist, produces a water diuresis, not a salt diuresis. The EVEREST Outcome trial looked into the effect of tolvaptan on cardiovascular outcomes and decongestion in patients with acute HF. Tolvaptan had no effect on the co-primary end points of all-cause mortality or HF hospitalization. However, there were significant benefits in secondary end points including an increase in urine output, resulting in reduced dyspnea and edema and an increase in serum sodium. Further trials evaluating the role of tolvaptan for the management of the CRS should help in defining the use of these drugs [26].

Selective adenosine A1 receptor antagonist like rolofylline can increase GFR and promote a diuresis by inhibiting the action of adenosine of afferent arteriole. In the PROTECT trial, 2033 patients hospitalized with HF and impaired renal function were randomly assigned to the rolofylline or to placebo [27]. During the study period, there was no difference between the groups in cardiovascular outcomes or in the rate of persistent worsening of renal function. Rolofoylline therapy was associated with a higher rate of neurologic events (seizure and stroke). Given the results of this trial, the role of rolofylline is yet undetermined.

Conclusion

Acute or chronic dysfunction of heart or kidney may cause acute or chronic dysfunction of other organ. Based on the rapidity of onset and the primary organ which triggers the dysfunction, CRS can be classified into 5 types. Various biomarkers are available which can be used in conjunction with clinical evaluation to classify CRS.

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