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Review

Pathophysiology of the cardio-renal syndromes types 1–5: An uptodate

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ABSTRACT

According to the recent definition proposed by the Consensus conference on Acute Dialysis Quality Initiative Group, the term cardio-renal syndrome (CRS) has been used to define different clinical conditions in which heart and kidney dysfunction overlap.

Type 1 CRS (acute cardio- renal syndrome) is characterized by acute worsening of cardiac function leading to AKI (5, 6) in the setting of active cardiac disease such as ADHF, while type – 2 CRS occurs in a setting of chronic heart disease.

Type 3 CRS is closely link to acute kidney injury (AKI), while type 4 represent cardiovascular involvement in chronic kidney disese (CKD) patients.

Type 5 CRS represent cardiac and renal involvement in several diseases such as sepsis, hepato – renal syndrome and immune – mediated diseases.

Contents

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1. Background

According to the recent definition proposed by the Consensus conference on Acute Dialysis Quality Initiative Group,[1] the term cardio-renal syndrome (CRS) has been used to define different clinical conditions in which heart and kidney dysfunction overlap. RS complexity needs to be explained starting by its pathogenesis and this is the aim of the following chapter.

The classification of CRS proposed in the Consensus Conference by the Acute Dialysis Quality Group essentially divides CRS in two main groups, cardio-renal and reno-cardiac CRS, on the basis of the *primum movens* of disease (cardiac or renal).Both cardio-renal and reno- cardiac CRS are then divided into acute and chronic, according to disease's acuity of onset. Type 5 of CRS integrates simultaneous cardio- renal involvement induced by systemic disease (Table 1). In the following chapters it will be pointed up all novel approaches on CRS pathophysiological pathways mainly focused on immunologic and biometabolic new findings.

2. Type 1 cardio renal syndrome

Type 1 CRS occurs in about 25% of patients hospitalized for acute decompensated heart failure (ADHF).[2,3] Among these patients, underlying chronic kidney disease (CKD) is quite common and contributes to acute kidney injury (AKI) in 60% of all cases studied. AKI is an independent mortality risk factor in acute decompensated heart failure patients, including those with acute myocardial infarction (AMI) and/or reduced left ventricular ejection fraction.[4]

2.1. Pathophysiology

Type 1 CRS (acute cardio- renal syndrome) is characterized by acute worsening of cardiac function leading to AKI[5,6] in the setting of active cardiac disease such as ADHF. Preliminary observations highlight the importance of timing in the development of AKI and its early diagnosis (Fig. 1).

Hemodynamic mechanisms play a major role in type 1 CRS in presence of ADHF leading to decreased renal arterial flow and a consequent fall in glomerular filtration rate(GFR). Once hemodynamics have been restored, renal and cardiac parameters come back to normal.[7] Different hemodynamic profiles have been proposed[8]: in "cold" pattern patients, reduction in effective circulation fluid volume (ECFV) represents the main hemodynamic change, while there is a marked increase in central venous pressure (CVP) in "wet" pattern patients.

"Cold" patients also present with decrease in renal blood flow related to the renin angiotensin-aldosterone system (RAAS) and systemic nervous system activation causing afferent vasoconstriction, decreased renal blood flow and decreased effective glomerular perfusion pressure. Patients who present with a "wet" hemodynamic profile display increased pulmonary and/or systemic congestion. In these patients, high CVP directly affects renal vein and kidney perfusion pressure[9,10]; CVP increase also results in increased interstitial pressure with tubular' collapse and progressive decline in GFR.[11]

"Warm and wet" patients represent the most frequent profile in acute and chronic advanced heart failure.[12,13] Mechanisms of increased CVP are quite similar to "cold" profile patients, but renal perfusion pressure is less affected because of higher arterial blood pressures.[9]

Non-hemodynamic mechanisms were also proposed as involved in type 1 CRS including sympathetic nervous system (SNS) and RAAS activation, chronic inflammation and imbalance in the proportion of reactive oxygen species (ROS)/nitric oxide (NO) production (Fig. 2). Patients with ADHF show more frequently defective regulation of monocyte apoptosis and activation of inflammatory pathways compared with healthy subjects.[14,15]

Several pathophysiological processes contribute to perpetuating AKI, including endothelial and epithelial cell death, and a primary role for apoptotic mechanisms due to renal ischemia, toxic injury, radiation and ureteral obstruction have been suggested in experimental models.[16]

Renal tubular epithelium is particularly vulnerable to ischemic injury resulting in cell death by apoptosis and necrosis with consequent loss of r epithelial cell structure and function.[17] Renal tubular cells represent major site of cell damage during AKI with strong association between intra-renal inflammatory activity and renal cell apoptosis.[18]

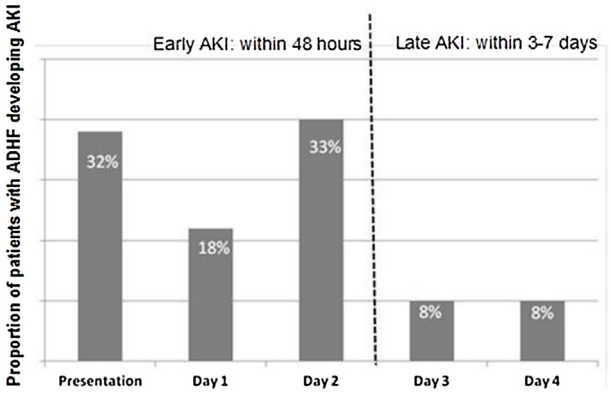

Fig. 1. Timing of acute kidney injury in the setting of acute decompensated heart failure.

Table 1
Classification of cardio-renal syndrome.

Type	Denomination	Description	Example
1	Acute cardiorenal	Heart failure leading to AKI	Acute coronary syndrome leading to acute heart and kidney failure
2	Chronic cardiorenal	Chronic heart failure leading to CKD	Chronic heart failure
3	Acute nephrocardiac	AKD leading to acute heart failure	AKI related uremic
4	Chronic nephrocardiac	CKD leading to heart failure	Left ventricular hypertrophy and diastolic heart failure due to CKD
5	Secondary	Systemic disease leading to heart and kidney failure	Sepsis, vasculitis, diabetes mellitus, amyloidosis