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Cardiorenal syndrome: a review

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Abstract. Objective: The objective is to synthetize the current knowledge regarding cardiorenal syndrome.
Key Words: heart failure, renal failure, prognostic markers.

Introduction. The heart and kidney are connected through hemodynamic and regulation functions (Brenner 2008). In a human weighting 70 kg, each kidney receives a blood flow of 400 mL min^{-1}, which represents about 20-25% of total heart output, which assures a proper irrigation that is necessary for a glomerular ultrafiltration through approximately 1 million nephrons. Although the use of oxygen is low, the kidney necessitates about 8% of total oxygen body consumption. It is a well-known fact that the kidney has a central role regarding electrolytes balance, adjustment of volumes and arterial tension.

Over the last years, medicine has been confronting with an increase of acute or chronic cases of heart failure associated with renal failure. So, a new entity named cardiorenal syndrome has appeared. In order to better the understanding and systematizing, the syndrome was divided into 5 subtypes: cardiorenal syndrome type 1, in which acute heart failure leads to acute renal disease; cardiorenal syndrome type 2 includes chronic anomalies of heart function that leads to chronic kidney disease; cardiorenal syndrome type 3 is characterized by acute renal failure followed by acute heart failure; cardiorenal syndrome type 4, in which chronic kidney disease leads to chronic deterioration of myocardial function; cardiorenal syndrome type 5 describes the situation in which a systemic disease determines concomitantly renal and heart lesions (Mebazaa et al 2008).

Cardiorenal syndrome type 1. In this entity are included situations in which a fast worsening of heart function leads to acute kidney damage. Acute heart failure can be divided into 4 groups: acute pulmonary edema with left ventricle ejection fraction preserved and arterial hypertension, acute decompensation of a chronic heart failure, cardiogenic shock and right heart failure (Ronco et al 2008).

Physiopathology. The physiological mechanisms are multiple and under-defined (Wilson & Mullens 2009). Hemodynamic, neurohumoral and inflammatory factors are implicated. From hemodynamic changes we should consider venous congestion; increase in intra-abdominal pressure; atrial filling and renal perfusion interact with complex neurohumoral mechanisms. Venous congestion was described by an experimental model, when hypervolemia and an increase of pressure in renal vein led to renal failure, independently of cardiac or renal blood flow. Recent studies showed that an increase of central venous pressure (CVP) is associated with a decrease of glomerular filtration rate (GFR) in patients with pulmonary hypertension or in those with low renal blood flow and cardiovascular disease (Damman et al 2009).

Other mechanisms are similar to those existing in liver stasis, namely increased venous pressure that is transmitted in a retrograde fashion and leads to an increase in

interstitial pressure that determines secondary ischemia in renal parenchyma. The increasing of venous pressure may determine secondary stimulation of angiotensin II (AG II), which leads to the increase of sympathetic tonus and to the decrease of GFR. When these hemodynamic and neurohumoral alterations combine, it leads to self-deterioration of renal function.

The increase of intra-abdominal pressure manifests by a fullness sensation, but ascites is rarely present. In surgical literature it is described the abdominal compartment syndrome (abdominal pressure is higher than 15-20 mmHg; normal value is between 5 and 7 mmHg), which progressively compromises the kidney when surgical catastrophes occurs. In patients with heart failure, the prevalence of high abdominal pressure can be up to 60%, without any abdominal symptomatology (Mullens et al 2008). Amelioration of renal function, through intensive medical care, was associated with a decrease of abdominal pressure in patients with a favorable evolution, while in patients with high intra-abdominal pressure, renal function continued to deteriorate independently of the rest of hemodynamical parameters.

Atrial filling and renal perfusion. Traditionally the deterioration of renal function was attributed to kidney's hypoperfusion. These modifications lead to an increase of sodium and water reabsorption through stimulation of sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS) and of vasopressin secretion. These facts cover only partially the physiopathology of renal failure that appears in acute heart failure. The proportion of patients that present a low cardiac output and renal hypoperfusion is relatively small, as ADHERE (Acute Decompensated Heart Failure National Registry) study reports (Adams et al 2005; Yancy et al 2006).

The neurohumoral factors that act in association with hemodynamic ones are: RAAS, nitric oxide, arginine vasopressin, prostaglandins, natriuretic peptides, endothelin, adenosine, oxidative stress and sympathetic hyperactivity (Pokhrel et al 2008).

When cardiac output is decreased or kidney failure is present, the activation of RAAS takes place and it determines vasoconstriction and sodium retention which lead to the increase of pre and afterload. Another negative effect is the activation of NADPH oxidase by AG II, which determines the appearance of active oxygen species. Otherwise, in the myocardium of patients with terminal heart failure the activity of NADPH oxidase is increased (Heymes et al 2003).

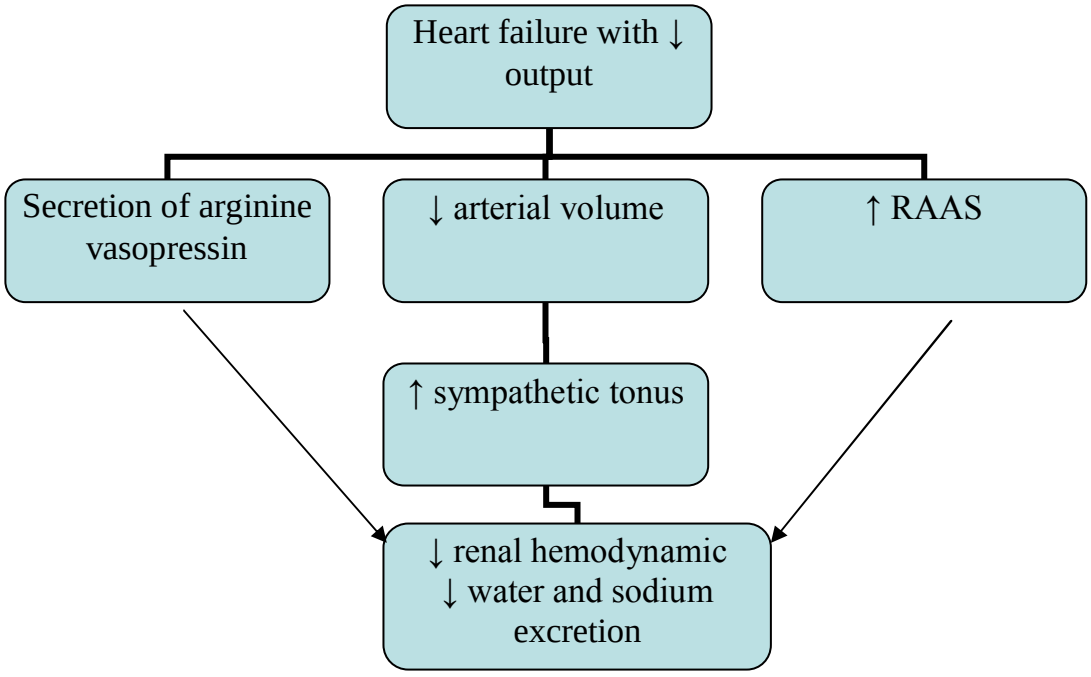

Figure 1. Physiopathology of acute heart failure (Sarraf et al 2009).

Nitric oxide (NO) and reactive oxygen species. In cardiorenal syndrome the equilibrium between these two components is broken in favor of the latter. This leads to an increase of oxidative stress with initiation of an inflammatory response with its consequences (Bongartz et al 2005).

Arginine vasopressin (AVP) has unfavorable effects consisting in augmenting fluid retention and increasing activity of AG II and noradrenaline. Also, it stimulates myocardial hypertrophy (Lee et al 2003). AVP increases the transport of urea through nephron's collector tubes which accentuates nitrogen retention. Brain natriuretic peptide (BNP), released by ventricles, has benefic effects by inhibiting RAAS, endothelin and other vasoconstrictors. Atrial natriuretic peptide (ANP), released by atria, increases glomerular ultrafiltration, water and sodium excretion and inhibits activity of sympathetic nervous system, RAAS and vasopressin. Adenosine may have high blood levels in heart failure and it lowers GFR by dilatation of postglomerular capillaries and/or vasoconstriction of preglomerular capillaries (Sarraf et al 2009).

Sympathetic nervous system is initially activated in heart failure by a baroreceptor reflex in order to provide inotropic support and to preserve cardiac output. In heart failure a decrease of myocardial norepinephrine levels and an increase of blood norepinephrine exists (Kramer et al 1968). This phenomenon is explained by maximal turnover of norepinephrine at myocardial level, as an insufficient heart is not capable to respond to this maximal stimulation. Sympathetic hyperactivity induces hypertrophy and myocardial focal necrosis, as well as cardiomyocyte's apoptosis (Pokhrel et al 2005). At renal level, stimulation of alpha receptors from proximal tube determines reabsorption of sodium and of beta receptors from juxtaglomerular apparatus stimulates RAAS. In addition, in heart failure, pressure in postglomerular capillary decreases and oncotic pressure rises though stimulating the proximal tubular reabsorption (Schrier 2007).

Inflammatory factors appear in response to oxidative stress. Proinflammatory cytokines are synthesized, particularly interleukin-1, interleukin-6, C-reactive protein and tumor necrosis factor-alpha. The compounds have crucial role in pathogenesis of atherosclerosis, have a negative inotrope effect, produce heart remodeling and even lead to thrombotic complications (Arici & Walls 2001; Bongartz et al 2005; Geisberg & Butler 2006).

Clinical and lab parameters. Renal failure. The following factors are correlated with worsening of renal function defined as an increase of serum creatinine with 0.3 mg dL^{-1} (Knight et al 1999):

1. Advanced age
2. Decreased ejection fraction
3. High levels of creatinine in the moment of admission
4. Systolic arterial hypotension
5. Diabetes mellitus
6. Arterial hypertension
7. Treatment with antiaggregants, diuretics or beta blockers

It appears that the most important factor is the modification of renal function during hospitalization, respectively a small increase of creatinine level (0.1 mg dL^{-1}) leads to an unfavorable evolution (Sarraf et al 2009). Forman et al (2004) showed that those with altered renal function had a longer hospitalization period, with higher costs and morbidity and frequent readmissions. Altered renal function was associated with severe heart failure in elderly (Macarie et al 2009). A GFR under 60 ml/min/1.73 m^2 was correlated with a 40% higher risk of mortality in those with left ventricle dysfunction (Dries et al 2000). In ADHERE study, beside the factors mention from SOLVD study, several parameters emerged as predictors of renal failure in patients with decompensated heart failure: anemia, medication (NAIDs, ACE inhibitors, AG II receptor blockers, aldosterone antagonists), history of acute myocardial infarction, elevated cardiac troponins, NYHA class and basal renal dysfunction (Gottlieb et al 2002).

Smith et al (2005, 2006) found similar correlation to dose-effect between serum creatinine and mortality. So, the risk rises by 33% for every elevation by 1 mg dL^{-1} of serum creatinine or by 7% for every drop of GFR by 10 mL min^{-1}.

Arterial pressure. ADHERE and OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) studies showed that, in majority of patients with decompensated heart failure, systolic arterial pressure was frequently over 140 mmHg (Gheorghiade et al 2006; Fonarow et al 2007). Also, it was pointed that an inverse correlation exists between mortality and value of systolic arterial pressure. The risk of mortality was enhanced by a systolic pressure lower than 160 mmHg. With every 10 mmHg drop in arterial pressure the mortality risk rose by 21%.

Ischemic cardiopathy. Clinical trials showed that majority of patients with heart failure have a diagnostic of ischemic cardiopathy (Peacock et al 2008). The worsening of renal function during hospitalization for an acute myocardial infarction with ST elevation (STEMI) is a powerful and independent predictor for intrahospital and one-year mortality (Goldberg et al 2005; Jose et al 2006). In patients that had undergone cardiac surgery or PTCA (percutaneous transluminal coronary angioplasty), even an increase of 0.3 mg dL^{-1} in serum creatinine it is associated with prolongation of hospitalization and increased mortality (Lassnigg et al 2008; Roghi et al 2008). The increase of creatinine is not just a simple marker of severity of kidney disease, renal failure being an accelerator factor of cardiovascular damage through neurohumoral and inflammatory mechanism (Berl & Heinrich 2006; Tokuyama et al 2007).

Anemia. The presence of anemia is common in patients with heart failure, even in the absence of renal disease. Multiple mechanisms are known in the etiology of anemia: hemodilution, deficit of erythropoietin, inflammatory syndrome inhibiting bone marrow, nutritional and vitaminic deficiency.

From the analysis of SOLVD study arise the fact that for each decrease of hematocrit by 1%, the rate of mortality increases by 2.7% (Al-Ahmad et al 2001). Other studies did not found a decrease of mortality rate and hospitalization number in those treated with erythropoietin (Singh et al 2006).

Level of serum urea. In ADHERE study it was highlighted that the level of serum urea at admission (over 43 mg dL^{-1}), is the best indicator of in-hospital mortality (Fonarow et al 2005). Other studies showed the importance of modification of urea levels during hospitalization (Klein et al 2008). Patients that had the highest urea values had also a lower arterial tension, hyponatremia, high CVP and unfavorable evolution.

BNP. The value of BNP has prognostic importance (Harrison et al 2002). Patients with heart failure with BNP over 480 pg mL^{-1} had a 51% chance for death, readmission or emergency room visit over the next six months, while for those with BNP under 30 pg mL^{-1} the probability was of 2.5%.

Troponin. Cardiac troponins I and T are highly sensitive and specific markers for myocardial injury. In ADHERE study a strong association between elevation of troponins and mortality (Peacock et al 2009). Those with positive troponins had systolic arterial tension lower at admission, lower ejection fraction and higher in-hospital mortality (8% vs. 2.7%), compared to patients with negative troponins.

Hyponatremia. Hyponatremia (Na < 135 mmol L^{-1}) is usually met in patients with decompensated heart failure. In 1986 it was demonstrated that hyponatremia is associated with increased mortality in people with chronic heart failure (Lee et al 1986).

Table 1

Proteic biomarker for early screening of renal injury

Biomarker	*Associated lesion*
Cystatin C	Proximal tube
KIM-1	Ischemia and nephrotoxins
NGAL (lipocalin)	Ischemia and nephrotoxins
NHE3	Pre and post renal failure
Cytokine (IL-6; IL-8; IL-18)	Toxins, transplant reject
Actin-actin depolymerization	Ischemia, transplant reject
α-GST	Proximal tube, acute transplant reject
Π-GST	Distal tube , acute transplant reject
L-FABP	Ischemia and nephrotoxins
Netrin-1	Ischemia and nephrotoxins
Keratin chemokine	Ischemia, transplant reject

It seems that the evolution is towards a panel of biomarkers from serum and urine, which associated give an optimal sensibility and sensitivity.

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