Update on type 2 cardiorenal syndrome

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Abstract

Background: Cardiorenal syndrome type 2 is an "umbrella" term used to describe clinical conditions in which chronic cardiac failure through a chronological and causal relationship leads to renal dysfunction. The syndrome is associated with a significant morbidity and mortality, that is why it has recently become a matter of growing debate related to pathogenesis, diagnosis, treatment effectiveness and safety. Our aim was to review epidemiological and pathological mechanisms underlying cardiorenal syndrome, to focus on up-to-date diagnosis and treatment strategies. We performed literature search in the Pubmed database in July 2015. The 1st key word used for search was "cardiorenal syndrome type 2"; and the 2nd key word was "cardiorenal syndrome in heart failure".

Conclusions: Over the last decade, a significant advance in the understanding of the cardiorenal syndrome has been achieved. However, precise pathways remain to be clarified. Clinical management of these patients include diuretics, vasodilatators, ultrafiltration, all these modalities promise more rapid volume removal, but their ultimate impact on survival and renal function is unknown. Future research is necessary to improve diagnosis, severity grading, to differentiate type 2 and type 4 cardiorenal syndrome and to determine efficient treatment strategies. Because of the syndrome's complexity and poor outcome, it is important that cardiologists, nephrologists and internists work together for a unique goal – protecting the patient with cardiorenal syndrome.
Key words: cardiorenal syndrome type 2, heart failure, biomarkers.

Introduction

Many organ systems are tightly connected. In normal state, this connection helps maintain optimal homeostasis and function of the human body. In pathology, however, an affected organ may initiate and perpetuate structural and functional dysfunction in other connected organs [1, 2]. Thus, acute or chronic heart and kidney diseases often coexist in the same patient. Observational studies and clinical trials have proven that acute / chronic heart disease can directly contribute to acute / chronic kidney disease worsening and vice versa. Considering the close and bidirectional relationship between these two organs, Acute Dialysis Quality Initiative recently proposed a consensus definition and classification. The term cardiorenal syndrome (CRS) is used to identify cardiac and renal disorders as "a complex pathophysiological condition in which acute or chronic dysfunction in one organ can cause acute or chronic dysfunction in the other" [1].

The prevalence of both heart failure and chronic kidney disease in Europe is continuously increasing [2,4,5]. In any case / any genesis the association of heart and kidney dysfunction is accompanied by an increased risk of morbidity and mortality [4,5].

Classification [1]

Acute cardiorenal syndrome (type 1)

Acute worsening of heart function leading to kidney dysfunction and /or damage. This type of injury occurs more frequently as a complication of acute heart failure and / or acute coronary syndrome. It occurs in 27-40% of patients hospitalized with acute heart failure and 70% of patients with cardiogenic shock. In these patients morbidity, length of stay and mortality increases.

Chronic cardiorenal syndrome (type 2)

Chronic heart disease leading to renal dysfunction or injury. This syndrome is frequently encountered, occurs in 63% of hospitalized patients with congestive heart failure. A meta-analytic study focused on the heart failure (IC) - renal dysfunction interrelationship reported a prevalence of 63% mild and 20% moderate renal impairment. In addition, there was a 7% increase in mortality for every decrease in glomerular filtration rate (GFR) of 10 mL / min [4].

Acute renocardiac syndrome (type 3)

Acute worsening of renal function leading to cardiac dysfunction or damage. The incidence is 10-53%.

Chronic renocardiac syndrome (type 4)

Chronic kidney disease (CKD) leading to heart dysfunction, injury and/or disease, dysfunction or heart damage. The

incidence is unknown and difficult to appreciate (depending on primary renal disease incidence), but was noted an increases by 50% in cardiovascular (CV) mortality.

Secondary cardiorenal syndrome (type 5)

Systemic diseases leading simultaneously to renal and cardiac dysfunction/damage (ex. sepsis, diabetes, lupus erythematosus). The incidence and severity depend on systemic disease incidence and severity.

Cardiorenal syndrome (CRS) can be acute, chronic or secondary, of cardiac or renal genesis. However, the classification is not static, it is generally accepted that patients suffer various types of CRS during disease (ex. 1↔2; 3↔4; 2,4↔5) [3] and all types are associated with increased mortality and morbidity, having a significant impact on health care costs [2, 3].

Epidemiology

CRS syndrome (type 2) occurs when a chronic heart condition leads to chronic renal dysfunction. There are several observational studies describing the coexistence of chronic heart failure (CHF) and chronic kidney disease (CKD), but usually, studies enroll subjects based on the presence of a disease (ex.: HF) and describe the prevalence of the other (ex.: CKD) [2, 4].

A meta-analytic study focused on the heart failure (IC) - renal dysfunction interrelationship reported a prevalence of 63% mild and 20% moderate renal impairment. In addition, there was a 7% increase in mortality for every decrease in glomerular filtration rate (GFR) of 10 mL / min [1,2,4]. These types of studies are not able to identify which was the primary pathology in order to classify properly the CRS. In such cases, the use of the term SCR type 2/4 was suggested [5]. Another study focused on congestive heart failure outpatients, established severe renal impairment (creatinine clearance < 30 ml / min) in 39% of the HF patients with functional class (FC) IV and 31% of the HF patients with FC III NYHA [5].

A comparative analysis of studies focused on the renal dysfunctions prevalence in HF patients shows the following data:

- The SOLVD study conducted in 2000, on a cohort of 2161 patients with ejection fraction of 35.7%, recorded 24.7% cases of renal impairment (GFR <60 mL / min) [13];
- The PRIME II study conducted in 2000, on a cohort of 1906 patients with ejection fraction of 49%, recorded 26.2% cases of renal impairment (GFR <58ml / min) [13];
- The ANCHOR study conducted in 2006, on a cohort of 59 772 patients, reported 39.2% renal impairment cases (GFR 60 mL / min) [14];
- The JCARE-CARD study conducted in 2009, on a cohort of 2013 patients with ejection fraction of 70.3%, reported 44.8% cases with renal impairment (GFR 60 mL / min) [13,15];

In the recent years, the global prevalence of the moderate-severe renal dysfunction gradually increased, up to an epidemic state [9.13]. The HF "epidemic" is also increasing due to aging and post-myocardial infarction survival improvement [8.10]. The risk of CKD occurrence in heart failure is not well-established, but kidney dysfunction is very often encountered in HF patients and it is associated with a poor prognosis [5,13].

Renal function is a prognostic marker as important as ejection fraction and NYHA functional class [5.13].

Pathogenesis

In HF patients who develop renal dysfunction, there are intrinsic interactions between these two organs (organic cross

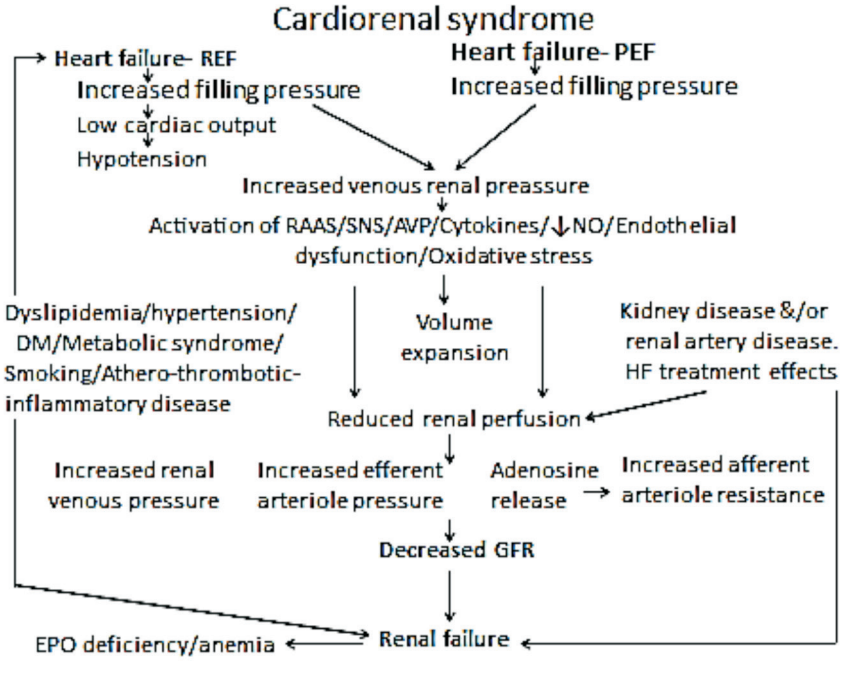

Fig. 1. Cardiorenal syndrome mechanisms.

talk) that could lead to severe complications [1,2,4]. Any HF underlying mechanisms, plus existing comorbidities, and / or their treatment affect renal function with subsequent renal failure development (fig. 1) [1,2,17].

The CRS pathogenesis is multifactorial including structural lesions caused by atherosclerosis, hemodynamic changes, neurohormonal and inflammatory components effects [1,5,17].

The hypothesis of low cardiac output. Over the past decade, progressive worsening of renal function in HF is considered as a direct result of the renal flow reduction caused by decreased cardiac output. Inadequate afferent renal flow activates RAAS - leading to volemic retention, increased preload and impaired pump function [17]. Recent studies state that, although it is correct, this mechanism does not fully explain the CRS features. The ESCAPE Study (Evaluation Study of Congestive The Failure and Pulmonary Artery Catheterization Heart Effectiveness) evaluated management through guided pulmonary artery catheterization in 400 patients; no correlations were found between renal function and cardiac index; and, at cardiac index improvement renal function has not changed [18], moreover, impaired renal function was proven despite the preserved ejection fraction.

The renin-angiotensin-aldosterone system (RAAS) activation - RAAS activation at renal perfusion depression is a protective mechanism in dangerous situations (ex. hemorrhage). The chronic stimulation - in heart or renal failure, has adverse consequences on both, heart or kidney. Angiotensin II has multiple negative effects on the cardiovascular system in HF patients, increases both pre- and afterload with a subsequent increase in myocardial oxygen demand [1.18]. Angiotensin II activates NADPH oxidase in endothelial cells, renal tubules and cardiomyocytes, releasing free radicals responsible for aging, inflammation and progressive organ dysfunction [1].

Sympathetic nervous system activation (SNS) – SNS activation has initially a protective character, overactivation, however, reduces the myocardial beta-adrenoreceptors density and adrenoreceptors sensitivity both in heart and renal failure [17,26]. SNS induces cardiomyocyte apoptosis and increases the neuropeptide Y release, which is a promoter of vascular growth, accelerates atherosclerosis, induces vasoconstriction and interferes with the normal immune system functions.

Intra-abdominal hypertension. HF patients have increased central venous pressure, which reduces the renal capillary perfusion gradient. It was established that HF patients with renal changes had higher central venous pressure than those without impaired renal function [17]; also, both high venous pressure and jugular pressure correlated with increased creatinine levels [16].

Cardiorenal syndrome anemic. Anemia occurs frequently in patients with HF and in 30% patients with CRS, being caused by renal and heart failure progression, but also by iron deficiency as pointed out the authors of the FAIR-HF study (Ferinject Assesmentin Patients with Iron deficiency and chronic Heart Failure) [26]. At this time the role and treatment of CRS anemia remains controversial.

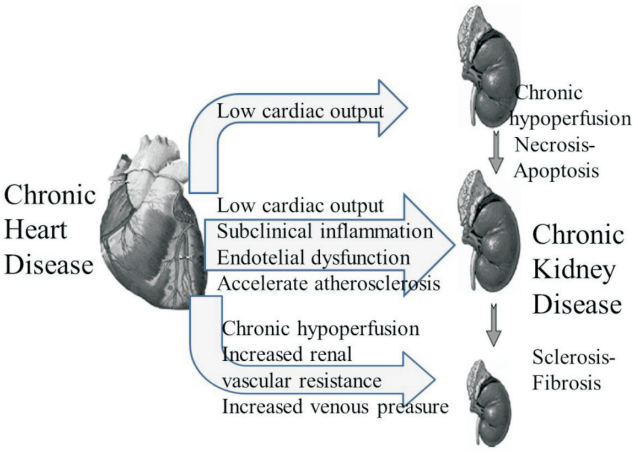

Fig. 2. CRS appearance assumptions. Reproduced from C. Ronco, 2010 [1].

Diagnosis

The prevalence of symptomatic CHF in the European population is 2-3% [8]. The mortality rate increases in concordance with the functional class (CF): 5-10% for CF II, 10-20% and 20-40% for CF III and CF IV respectively [10]. For the ability to evaluate and compare the patients, it is necessary to stratify / divide them by gravity; but because of the CRS complexity, until now there was no severity classification consensus and it is recommended to use specific classifications for HF (NYHA) and CKD (KDOQI). [1].

The diagnosis, prevention and treatment of this syndrome are usually fragmented, focused on a single organ and not on a multidisciplinary approach. In result, the timing and quality of treatment may be affected. In 2010, for the first time the ADQI (Acute Dialysis Quality Initiative) consensus group comes to define and classify the CRS, to provide standardized recommendations for diagnosis (Cystatin C, KIM-1, BNP, NT-proBNP, etc.), prevention and management of disease, and most importantly, they recommended the cardiologists and nephrologists collaboration for the optimization of the proposed outcome [1].

The mere coexistence of HF and chronic kidney disease is not sufficient for diagnosis. According to the working group of the 11th Conference of the Consensus ADQI (2013), to confirm CRS type 2 it is necessary: 1) the coexistence of HF and CKD in a patient; 2) temporal causality (documented or presumed onset of heart failure precedes the onset of kidney damage); and 3) pathophysiological plausibility (the manifestation and the degree of renal impairment could be explained by the preexisting cardiac pathology) [2].

Imaging investigations

Chest X-ray - assesses pulmonary congestion and fluid load for the HF severity assessment [19].

Echocardiography - provides information about the heart function and anatomy, differentiates preserved or reduced ejection fraction HF. Usually echocardiography is sufficient as routine imaging diagnostic [17,19].

Table 1

Proposed definition of CRS2 in stable chronic HF. Reproduced from D. Cruz, 2013 [2]

Chronic HF		EITHER: New onset of CKD
Symptoms typical of HF Signs typical of HF (HF-REF) Reduced LVEF OR: (HF-PEF) Normal or mildly reduced EF and LV not dilated, with relevant structural disease and/or diastolic dysfunction (according to ESC, ACC/AHA)	➡	Albuminuria and/or GFR <60 ml/min/1.73m2 (according to KDIGO/KDOQI) OR: Progression of CKD Sustained ↓ eGFR of >5 ml/min/1.73m2/year, or >10 ml/min/1.73m2/5 years* OR: sustained increase in albuminuria
Plus		
Temporal association: A documented or presumed onset of congestive heart failure precedes the occurrence or progression of CKD		
Plus		
Pathophysiological plausibility: The manifestation and degree of kidney disease is plausibly explained by the underlying heart condition.		

Stress echocardiography / PET CT (positron emission computed tomography) - assesses the ischemic extent and myocardial viability. Limited use because of the high cost [19].

Ultrasonography - assesses renal volume, echogenicity, vena cava; contributes to the proper syndrome classification; differentiates acute renal failure from chronic kidney disease; excludes renal structural pathologies.

Computed tomography and magnetic resonance imaging - study the heart function and structure in particular cases (usually echocardiography is sufficient), and examine the renal vessels.

Cardiac biomarkers

B-type natriuretic peptide (BNP) and the N-terminal proBNP (NT-proBNP) are secreted by the heart muscle as response to the parietal stress and play an important role in the fluid and sodium homeostasis. Volemic loading is the most powerful stimulus for the proBNP and BNP secretion [1, 2]. The RedHot study (Rapid Emergency Department Heart Failure Outpatient Trial) in 2004 showed that natriuretic peptides are independent predictors for cardiovascular events and mortality in patients with HF [17]. Moreover, their prognostic role was reported in patients with different stages of renal failure, demonstrating the potential application of these markers in type 2 and type 4 cardiorenal syndrome [1.2].

Cardiac troponins - in HF, there is a progressive loss of myocytes due to necrosis or apoptosis. Proof of myocyte death was obtained by histological studies and, more recently, by testing troponin (Tn) T and I [1, 25]. These markers can identify subclinical myocardial injury. The Vecchis et al. showed an increase of TnI in a group of severe non-ischemic HF patients; furthermore, they observed a decrease in troponin level at HF improvement [3]. Existing studies enrolled relatively small groups of patients and excluded patients with severe CKD, so the troponin clinical significance in patients with HF and severe CKD is not fully clear. Tsutamoto et al. after measuring the troponin level difference between caroticus sinus and basal aorta; assume that the troponin elevation may be caused by glomerular filtration reduction [25].

Highly sensitive troponins - allow HF patients risk stratification. In a cohort of 4053 HF patients TnT was found in 10.4%, while highly sensitive TnT in 92% patients [25].

Renal biomarkers

Most existing randomized clinical trials (Heywood, 2007 ADHERE; Cruz, 2010) have focused on mortality and cardiovascular events, and only few have examined the long-term renal changes occurrence (Capes, 2000; Testani, 2011) by dynamic evaluation of creatinine, GFR and some of inflammatory markers. The prognostic role of renal changes (increased creatinine level and / or decreased GFR) in HF was demonstrated, it is associated with increased hospitalization rate and CV mortality (Jackson, 2009).

Creatinine is an available marker, but may vary up to 5% throughout the day, has a latency of 2-3 days (changes with a delay of 2-3 days), it is influenced by the infections, inflammatory processes, meat intake, weight. Measured glomerular filtration rate (GFR) may decrease up to 50% until the creatinine level reaches the upper limit of normal (i.e. estimated GFR will be within normal range). In the recent period more sensitive and specific renal biomarkers appeared.

Cystatin C - a marker of proximal tubular damage, most commonly used for early detection of CKD [1, 2, 11]. It is freely filtered in the glomerulus, completely reabsorbed and degraded in the tubules, thus its level is considered an ideal marker for glomerular filtration rate assessment [3, 25]. Most studies suggest that cystatin is not influenced by age, sex, muscle mass or diet. It is superior to creatinine in early detection of renal damage, preclinical renal disease detection or in acute conditions. So far, however, the comparative role of cystatin and creatinine in diagnosis / treatment decision making in patients with chronic stable or relatively stable HF is not established.

KIM-1 (Kidney injury molecule 1) - it is detected in proximal tubule epithelial lesions and changes rapidly in acute chronic failure; predictor for patients at risk of renal function rapid deterioration; decreases after antihypertensive

treatment. There is limited evidence about the KIM-1 value in HF patients [1,2].

NAG (N acetyl-beta-D-glucosaminidase) - the enzyme formed in the proximal tubule in response to tubular damage. It is a sensitive marker of acute renal impairment or renal dysfunction worsening. Increases significantly in congestive HF, with an important prognostic role independent from the glomerular filtration rate [2,24,25].

NGAL (neutrophil-associated lipocalin gelatinase) is secreted in the lungs, kidney, trachea, stomach and in the colon, thus, it is less specific; it may increase in inflammatory processes, sepsis or cancer. It is freely filtered in the glomerulus and completely reabsorbed in the proximal tubules. NGAL is a marker of renal impairment or acute worsening of renal dysfunction. It increases in HF, without proven prognostic role.

Other markers

Albuminuria- assesses the glomerular permeability.

Interleukin 18 -proinflammatory cytokine, precedes creatinine elevations, but it is secreted less than NGAL. Increases in renal failure, but there are not enough studies to prove its predictive role in renal function worsening in HF.

High sensitive C-reactive protein - prognostic value in cardiovascular disease.

Copeptin- is C-terminal segment of the vasopressin prohormone - important prognostic biomarker in HF, but also in albuminuria and renal failure.

Insulin resistance, leptin, adiponectin, procalcitonin, adrenomodulin, interleukin 6, interleukin 1, tumor necrosis factor α - are markers with questionable role.

Because of high cost and limited access to CRS specific biomarkers; because of the serious damage they cause (increased post-myocardial infarction mortality) occurs the need to highlight predisposing factors (hypertension, diabetes, obesity and metabolic diseases, cachexia, renal disease, preexisting proteinuria, uremia, anemia, chemotherapy, mineral and bone deficiencies, electrolyte and acid-base imbalances, etc.)

Treatment

Treatment is complex and incompletely defined [2]. Accurate HF treatment is essential to reduce or eliminate the causes that led to the appearance / progression of renal dysfunction.

Diuretics

Hypervolaemia is the most pre-eminent CRS manifestation. Normalization of the fluid status may be achieved by sodium reduction or diuretics use. Although for long diuretics were considered the essential strategy in this syndrome, there is little data to confirm their beneficial effect on mortality. ADHERE registry data reported that 81% patients with acute HF, were receiving chronic diuretic treatment at admission. Other studies have shown a decreased glomerular filtration rate due to furosemide [4], and increased cardiovascular mortality [23]. Marker of poor prognosis in patients with HF can be considered diuretic resistance, most likely caused by inadequate doses of diuretics, high sodium intake, slowing diuretics intestinal absorption because of the intestinal mucosa edema, reduced diuretic clearance [25, 26] or concomitant NSAIDs administration by decreasing natriuretic and vasodilating prostaglandin synthesis [4]. In such cases: 1) furosemide dosage should be increased, not the administration frequency; 2) to avoid low absorption and bioavailability, diuretics will be administered intravenous. A Cochrane review article confirms that the diuresis obtained at intravenous continuously with furosemide administration is superior to that obtained at bolus administration; they also noted a reduction in the mortality and length of stay. Other options are thiazides or low salt content albumin supplementation to increase sodium excretion.

Vasodilators. Intravenous nitroglycerin or nesiritide (recombinant human type B atrial natriuretic peptide).

Kidney detrimental effects are lower than those of diuretics are. Vasodilators rapidly decline central venous pressure and decrease myocardial oxygen demand without blood pressure lowering (in small doses), may decrease systemic vascular resistance, left ventricular pressure, and improve cardiac output. Central venous pressure reduction may decrease renal perfusion pressure, but long-term effect on renal function and survival is not known [25].

Angiotensin-converting enzyme (ACE) inhibitors

ACE are known to reduce HF patients' mortality [13], but most of these studies have excluded moderate-severe renal impairment patients [21]. The CONSENSUS study (Cooperative North Scandinavian Enalapril Survival) demonstrated that in patients with moderate renal impairment upon the enalapril initiation creatinine levels substantially increased. Despite initial growth of creatinine in some of these patients improved long term prognosis was noted, therefore ACE should not be excluded, but should be administered with caution and with close renal function monitoring during the treatment initiation and titration[4].

Beta blockers

Although they have a role in HF by decreasing sympathetic activity, their use in CRS is limited because of the hemodynamic changes. When the patient is stabilized, it can re-initiate its administration in low doses [17].

Positive inotropic support - controversial

Albeit is known that Milrinone, Levosimendan and Dopamine improve cardiac index and in "renal" (small) doses increase renal perfusion, the OPTIME-HF trial (The Outcome Of A Prospective Trial of Intravenous Milrinone for exacerbations for Chronic Heart Failure) demonstrated their beneficial effects on renal flow and cardiac output, however they do not influence the mortality [4.26].

Statins

Are used for lipid lowering effect, but also for endothelial function improvement by increasing the nitric oxide availability, reducing vascular inflammation and oxidative stress [17].

Vasopressin antagonists

Vasopressin, by coupling to specific receptor V1a (vascular) and V2 (renal), induces vasoconstriction and water absorption. The selective antagonists V2 (Tolvaptan) activates the free water clearance. The EVEREST study (Efficacy of vasopressin antagonist Failure Outcome Study with Tolvaptan Heart) part of the

ACTIV research has confirmed the early beneficial effect in acute HF patients, although on long term there were not significant differences compared to placebo [26].

Adenosine antagonists

There are new agents that promote diuresis by coupling with A1 receptors, it may improve renal blood flow and increase sodium excretion [24, 26]. The efficacy and safety of the medication is being assessed.VVV

Ultrafiltration

It is a method increasingly used in HF patients. The amount of sodium and water removed by ultrafiltration is much higher than that eliminated by forced diuresis, it further decreases the hospitalization length, decreases mortality and rehospitalization rate [4.24]. The ultrafiltration decreases right atrial and pulmonary artery pressure, improves cardiac output and gas exchange. However, aggressive ultrafiltration, can convert a non- oliguric renal dysfunction in oliguric renal insufficiency.

The renal impairment worsening may require calcium, vitamin D agonists, iron or erythropoietin administration.

Unsolved problems

While remarkable progress has been made in the cardiorenal syndrome understanding, it is necessary to implement new biomarkers that would allow early diagnosis before the appearance of kidney irreversible changes, in order to slowdown the cardiorenal complications progression in CHF patients with adverse impact on length and quality of life. Also, there are no criteria for severity and evolution assessment in cardiorenal syndrome; in clinical practice renal impairment severity within cardiorenal syndrome is assessed according to the KDOQI classification and heart failure according to NYHA criteria.

There are multiple studies that assess the coexistence of HF and kidney disease, but there are no clear, objective (other than chronological) criteria that may differentiate type 2 from type 4 cardiorenal syndrome. Usually, such studies enroll patients admitted to a cardiology ward or who address the cardiologist and were conventionally considered as having primary cardiac pathology, i.e. type 2 CRS; if the same patient addressed the nephrologist he could be conventionally considered as having primary renal disease, respectively CRS type 4. Therefore, the study accuracy may be affected. A possible solution would be the start of a long-term prospective project with enrollment and monitoring of HF FC I-II NYHA patients, without other comorbidities or renal function impaired. From our best knowledge up to this moment, there are no such studies; the present studies used only chronological criteria.

CRS treatment involves the use of diuretics, vasodilators, ultrafiltration; all these options provide rapid volemic decline, but until now, their real impact on renal function and survival is not known.

It requires further research to determine effective, safe and cost-efficient therapeutic strategies.

It was determined that when the treatment is fragmented on pathologies, the patient's condition worsens: intensive treatment with loop diuretics for heart failure worsens renal dysfunction; angiotensin converting enzyme, spironolactone or vasodilators treatment, may also aggravate renal dysfunction; on the other hand, renal failure may affect the drugs clearance with the need of dosage review [1, 3]. To achieve a common goal – patient's safety, in clinical practice collaboration of cardiologists, nephrologists and internists is of utmost importance.

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