The Cardiorenal Syndrome: A Mutual Approach to Concomitant Cardiac and Renal Failure

Jeremy Ben-Shoshan MD PhD[1,2], Michal Entin-Meer PhD[1], Hanan Guzner-Gur MD[2] and Gad Keren MD[1]

Departments of [1]Cardiology and [2]Internal Medicine B, Tel Aviv Sourasky Medical Center, Tel Aviv, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: Heart failure (HF) accompanied by renal failure, termed cardiorenal syndrome (CRS), encompasses both the development and worsening of renal insufficiency secondary to HF as well as the harmful effects of impaired renal function on the cardiovascular system, and remains a universal clinical challenge. CRS was recently classified into subtypes depending on the etiologic and chronologic interactions between cardiac and renal dysfunctions. The mechanisms underlying the CRS are multifactorial, including hemodynamic alterations, neurohormonal effects, and inflammatory components. However, despite enhanced understanding and awareness of CRS, further elucidation of the mechanisms involved and the appropriate treatment approaches are clearly warranted. CRS is a difficult condition to manage, as treatment to relieve congestive symptoms of HF is limited by a further decline in renal functions, itself a major independent predictor of long-term cardiac morbidity. In order to perform a proper clinical investigation and implement appropriate treatment that will minimize subsequent progression of heart and kidney injury, a comprehensive approach to these two pathologies is crucial. In the present review we discuss current theories behind the mechanistic evolution of the CRS as well as therapeutic issues regarding this multifaceted condition.

IMAJ 2012; 14: 570-576

KEY WORDS: cardiorenal syndrome (CRS), heart failure (HF), renal failure (RF), myocardial dysfunction, creatinine

The pathopysiologic interface between heart failure and renal failure, and its crucial clinical importance, have gained growing attention. According to previous studies, renal insufficiency is present in more than one-third of patients with acute decompensated HF or with symptoms referred to as New York Heart Association class III and class IV [1]. This fact may be attributed both to the natural course of HF and to the adverse effects of fluid overload management of HF patients. Therefore, the main cause of mortality among patients with end-stage renal disease is cardiovascular events [2]. Even mild renal disease is considered a major risk factor for cardiovascular complications after myocardial infarction. On initiation of dialysis therapy, one-third of RF patients suffer from chronic HF, while one-quarter of them will develop HF during the dialysis course [3]. Conversely, among the majority of patients with end-stage renal diseases the mean left ventricular ejection fraction will markedly rise following renal transplantation [4]. These findings mirror the tight interaction between heart and kidney function and, as a consequence, the necessity to address cardiac and renal injuries concurrently. Such an approach may pave the way to a prudent clinical management of HF and RF patients, as well as patients already presenting with simultaneous cardiac and renal impairment.

DEFINITION OF THE CARDIORENAL SYNDROME

The cardiorenal syndrome covers several distinct conditions with different evolvement following renal and cardiac dysfunctions. Ronco et al. [5] recently subtyped the CRS based on the chronology and pathophysiology of the renal and cardiac insults. Accordingly, type 1 CRS, acute cardiorenal syndrome, is distinguished as an acute cardiac dysfunction, as seen in cardiogenic shock or decompensated congestive HF, inducing a concomitant abrupt RF, defined by Forman et al. [6] as a 0.3–0.5 mg/dl rise in serum creatinine, or a 9–15 ml/min decrease in glomerular filtration rate at admission with acute HF. Type 2 CRS, chronic cardiorenal syndrome, is defined as chronic HF leading to chronic RF, due to microvascular and macrovascular kidney disease combined with hemodynamic compromise. Type 3 CRS, acute renocardiac syndrome, comprises acute deteriorating kidney function, as seen in volume depletion, acute glomerulonephritis or bilateral renal artery stenosis, which cause acute cardiac injury, manifested by HF, arrhythmia or ischemia. The abrupt cardiac deterioration in type 3 CRS may be induced by fluid overload, electrolyte disturbances, acute metabolic acidosis, and the overall uremic milieu. Type 4 CRS, chronic renocardiac syndrome, describes chronic RF contributing to continual decreased cardiac function, cardiac hypertrophy, and predisposition to adverse cardiovascular events. The various effects of chronic

HF = heart failure

RF = renal failure
CRS = cardiorenal syndrome

renal dysfunction on cardiac function include, among others, hemodynamic imbalance, chronic inflammation, and progressive atherosclerosis. Type 5 CRS, secondary CRS, is provoked by systemic diseases affecting both cardiac and renal function, such as diabetes mellitus, autoimmune diseases, sepsis, or disseminated intravascular coagulation.

## MECHANISMS INVOLVED IN THE CRS

THE EFFECTS OF HEART FAILURE ON RENAL FUNCTION

Type 1 and 2 CRS represent a renal injury precipitated by acute/chronic HF, which can occur as the result of several mechanisms [1]. The low-flow state hypothesis ascribes the decrease in renal filtration capacity that accompanies HF to hypoperfusion of the kidney due to low-output failure or hypotension [7]. Accordingly, low-flow states, sensed by baroreceptors and the ascending limb of the loop of Henle, induce renin secretion by granular cells in the juxtaglomerular apparatus. Renin release activates the renin-angiotensin-aldosterone system, which eventually causes vasoconstriction and sodium reabsorption. Additionally, RAAS activation promotes adverse cardiac remodeling through induction of pro-fibrotic factors, such as tumor necrosis factor-alpha or transforming growth factor-beta. Persistent hypoperfusion may also lead to renal parenchymal ischemia and subsequent infarction. This traditional concept was repeatedly challenged by studies that failed to show an improvement in renal function following increase in cardiac output or decrease in pulmonary capillary wedge pressure [8]. The Acute Decompensated HF National Registry (ADHER) has demonstrated that the occurrence of worsening renal function was comparable among HF patients with reduced or preserved systolic function [1]. Actually, most patients with acute HF present with elevated, rather than low systemic blood pressure. Yet, impaired renal blood flow apparently contributes to renal deterioration, as patients with progressive HF or cardiogenic shock frequently develop acute RF that is correctable with advanced support or renal replacement therapy.

Recent studies have suggested that the elevated intraabdominal pressure, which is frequent among HF patients, and the ensuing increased renal venous pressure [8], rather than elevated arterial pressure, might play a role in progressive renal dysfunction. It was previously shown that temporary renal vein compression results in reduced sodium excretion, elevated renal interstitial pressure and reduced GFR [9]. In HF patients with deteriorating renal function, central venous

> **Coexistent heart and renal failure, the cardiorenal syndrome, is strongly associated with a poor prognosis and constitutes a tremendous burden on health economics worldwide**

RAAS = renin-angiotensin-aldosterone system
GFR = glomerular filtration rate

Figure 1. Cardiorenal syndrome hemodynamics
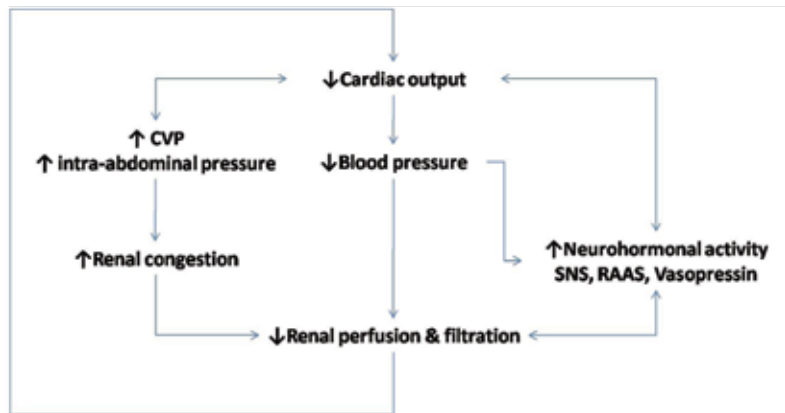
CVP = central venous pressure, RAAS = renin-angiotensin-aldosterone system, SNS = sympathetic nervous system, IVC = Inferior vena cava

pressure is markedly raised compared to patients with minor or no renal injury [8]. In summary, cardiac dysfunction may affect renal function through several related mechanisms, including kidney hypoperfusion, RAAS activation, and increased intraabdominal pressure.

THE EFFECTS OF RENAL FAILURE ON CARDIAC FUNCTION

Types 3 and 4 CRS represent a cardiac dysfunction promoted by acute/chronic RF. Renal dysfunction often provokes sodium and fluid retention, which directly contributes to hypertension and increased pre-load, potentially leading to pulmonary congestion and heart failure progression. Left ventricular end-diastolic diameter is increased in advanced RF patients mainly due to elevated stroke volume and cardiac index. Volume overload is partially mediated by atrial natriuretic peptides, whose concentration depends on extracellular fluid volume [10]. Vasopressin and adenosine also mediate water and salt retention; however, blockade of both vasopressin V2 and adenosine A1 receptors failed to show clinical improvement of renal function in patients with HF receiving optimal standard therapy in large-scale clinical trials [11].

Electrolyte disturbance, especially hyperkalemia, may cause severe arrhythmias, including ventricular fibrillation and asystole. Metabolic acidosis secondary to renal failure induces negative inotropic effects and might also evoke arrhythmias. Right heart failure might be exacerbated in the presence of acidemia due to increased pulmonary vasoconstriction. Uremia impairs myocardial contractility and causes pericarditis. During renal failure secondary to renal ischemia, systemic inflammation

and oxidative stress induce myocyte apoptosis and necrosis, which can be partially reversed through TNFα blockade [12].

An additional mechanism by which the kidney affects cardiac function, notably during HF, occurs through continuous sympathetic activity. Impaired renal perfusion pressure promotes baroreceptor-mediated renal vasoconstriction, stimulation of renal sympathetic nerves, and secretion of catecholamines [13]. The renal vessel injury, emanating from permanent sympathetic stimulation, finally affects renal filtration capacity. Of note, recent studies have shown that attenuation of renal sympathetic activity by catheter ablation improved renal function [14]. Prolonged sympathetic status amplifies RAAS activation, which promotes fluid and salt retention leading to worsening of HF. Consequently, inhibition of RAAS has become a mainstay of HF treatment.

We reported previously on the high prevalence of anemia, which typically accompanies RF, in patients hospitalized with HF [15]. Lower baseline hemoglobin correlates with a higher risk of short-term adverse clinical outcomes in HF [16]. In HF patients, the decreased production of erythropoietin and decreased response to erythropoietin during renal dysfunction correlate with a poor prognosis. As a stress-mediated hormone, erythropoietin inhibits apoptosis of cardiomyocytes and renal cells and attenuates oxidative stress [17]. Erythropoietin markedly enhances exercise capacity in patients with chronic HF by improving oxygen delivery from increased hemoglobin concentration. Additional studies are needed to define whether anemia is solely a result of concomitant RF and HF or rather an active factor in CRS development.

Currently, our laboratory is conducting a thorough investigation of the physiological and molecular alterations that characterize the cardiac tissue during RF. Using animal models of the CRS, we performed broad gene chip array analyses of the cardiac tissue and found that CRS-specific genetic alterations are highly related to regulation of liquid surface tension, coagulation homeostasis and extracellular matrix metabolism (unpublished data). Bioinformatics analysis reveals that cardiac hypertrophy development starts even in early stages or RF, involving different pathways than those activated in infarct-related hypertrophy. This tissue remodeling may induce endoplasmic reticulum stress as a response to an increased demand for protein synthesis. The generation of mediators of angiotensin II and arginine vasopressin as well as reactive oxygen species during renal dysfunction have also been shown to induce endoplasmic reticulum stress, leading to cardiomyocyte apoptosis. On the other hand, endoplasmic reticulum stress in

> **Based on current data, the main mechanisms that bind heart and kidney dysfunction include primarily hemodynamic modification, hormonal and inflammatory factors, as well as chronic tissue fibrosis and remodeling**

the kidney may result in renal fibrosis and eventually nephron loss. We believe that the exploration of these crucial cellular determinants may reveal novel mechanisms that contribute to reciprocal cardiac and renal tissue damage.

THERAPEUTIC IMPLICATIONS

GENERAL CONSIDERATIONS

Regardless of the specific type and course of development of the CRS, major clinical dilemmas often arise upon concomitant treatment of established heart and renal failure. The main therapeutic issue focuses on the balance between adequate diuresis required to control HF versus worsening of renal function due to volume loss and consequent impaired perfusion. Clinical predictors of worsening renal function during treatment of decompensated HF include older age, history of ischemic heart disease, advanced NYHA functional class, and comorbidities such as diabetes mellitus, uncontrolled hypertension and anemia. Current use of non-steroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and aldosterone receptor antagonists also predispose the HF patient to renal dysfunction mainly due to their effects on glomerular arteriole tone. These agents should be suspected as a cause of renal injury, especially in patients with adequate systemic blood pressure and normal cardiac output.

Notably, a relatively slight rise in serum creatinine may reflect a significant worsening of renal filtration, especially in elderly, characterized by low muscle mass. A large proportion of HF patients suffer concomitantly from intrinsic renal disease, mainly hypertensive or diabetic nephropathy, which tends to accelerate renal deterioration during HF treatment. Thus, intensive monitoring of renal function is essential during HF therapy. Assessing a combination of biomarkers, such as natriuretic peptides, cystatin C and neutrophil gelatinase-associated lipocalin, will likely provide a more accurate picture during the evaluation of renal function while managing HF patients.

TREATMENT APPROACH ACCORDING TO CRS TYPES
Acute cardiorenal syndrome (CRS type 1)

The inciting event for type 1 CRS is usually acute coronary syndrome, uncontrolled hypertension or non-compliance with pharmacological therapy and sodium intake. The general approach to type 1 CRS should include adequate oxygenation, pain relief, and prompt management of pulmo-

---

TNFα = tumor necrosis factor-alpha

NYHA = New York Heart Association

nary congestion, mainly by vasodilators and loop diuretics, together with treatment of arrhythmias and withdrawal of nephrotoxins. Notably, vasodilators and diuretics may induce electrolyte disorders as well as hypovolemia, reflected by high serum urea and creatinine, and thus their effects should be carefully monitored.

In case of cardiogenic shock, treatment should focus on improving cardiac output and renal perfusion, mainly through optimization of systolic blood pressure. For this purpose, dopamine at low (renal) doses was recently found to be as effective as norepinephrine as first-line vasopressor therapy, yet dopamine administration correlated with more arrhythmic events and higher rate of death [18]. Dobutamine and milrinone have been shown to increase cardiac index and renal blood flow [19]. Vasopressin has also been suggested due to its capability to improve vascular resistance and elevate blood pressure [20]. However, the clinical benefits of these agents, including urine output and overall patient outcome, are still equivocal. Although routine inotropic therapy in HF is not indicated, the selective use of inotropes or other adrenergic stimulating agents for acute decompensated HF might have beneficial effects on renal function. In case of refractory systemic hypotension, intraaortic balloon pump or elective ventilation can be used, with the goal of keeping cardiac index above 2 L/min/m² and mean arterial pressure above 60 mmHg. When the insult is acute cardiac ischemia, prompt coronary revascularization should be performed. Eventually, early use of a left ventricular assist device in patients with deprived renal perfusion may improve renal function. These devices should be considered mainly when recovery from acute decompensation is expected. In patients with persistent worsening of renal function, continuous venovenous ultrafiltration has been suggested as an alternative to volume and sodium reduction without further compromising renal function; however, regular use of ultrafiltration has not shown improved renal outcomes.

Chronic cardiorenal syndrome (CRS type 2)

The treatment of chronic HF is based on NYHA score and is initially subject to a combination of diet (i.e., sodium and fluid restriction), exercise training, and treatment of underlying diseases, mainly hypertension, diabetes mellitus, hyperlipidemia and arrhythmias. Beta-blockers (carvedilol, metoprolol, bisoprolol) improve ejection fraction in the long run and were shown to reduce mortality and rehospitalization [21]. Loop diuretics and thiazides, despite not reducing mortality, may relieve symptoms by decreasing fluid overload and are recommended in patients with overt HF [22]. Aldosterone antagonists reduce mortality in patients

with advanced HF or post-MI patients with adequate renal function [23]. ACE inhibitors are included early in HF treatment and were shown to reduce mortality, recurrent MI and HF-related rehospitaization rate [24]. ARB might be added to ACE inhibitors in symptomatic patients with decreased EF or as an alternative in patients who cannot tolerate ACE inhibitors [25]. Nitrates and hydralazyne, although inferior to ACE inhibitors, were shown to reduce mortality compared to placebo and are mainly recommended in patients who cannot tolerate ACE inhibitors/ARB or in Blacks with NYHA III/IV [26]. Digoxin was proved to lessen HF-related hospitalizations without reducing mortality [27]. In fact, digoxin therapy has been associated with an increased risk of all-cause mortality among women, but not men, with HF and reduced LVEF.

Chronic HF symptoms, namely orthopnea, paroxysmal nocturnal dyspnea and peripheral edema, result mainly from volume overload due to high filling pressures. Therefore, one of the key goals of chronic HF management is to reduce fluid accumulation without compromising cardiac output. Diuretics are a well-established component of HF therapy, mostly directed to deplete sodium and fluid excess while relying on refilling from extravascular sources [22]. Insistent intravenous loop diuretic treatment tailored to decrease venous congestion and optimize urine flow and effective volume loss can improve hemodynamic parameters, ameliorate HF symptoms and preserve renal function in most patients. However, in order to keep an adequate renal perfusion, a subtle equilibrium should be watchfully maintained while restoring intravascular volume removed by loop diuretics. Additionally, increasing serum creatinine, azotemia and metabolic contraction alkalosis tend to limit diuresis. Furosemide may induce nonspecific tissue fibrosis by stimulation of RAAS, resulting in both heart and kidney damage. In parallel, diuretic resistance, often indicated by refractory hyponatremia, may reflect the kidneys' failure to compensate for the volume expansion regardless of cardiac output. Eventually, the ongoing Dose Optimization Strategy Evaluation (DOSE) trial recently showed that in relatively mild RF patients (serum creatinine < 3 mg/dl) high dose furosemide is associated with greater relief of HF symptoms, with no significant differences in rates of death or rehospitalization compared to low doses (http://clinicaltrials.gov/ct2/show/NCT01132846). In this study, a more aggressive loop diuretic treatment correlated with only

> **Management of CRS is multifaceted and must therefore be methodological, focusing mainly on fluid and blood pressure homeostasis, together with correction of precipitating accompanying factors**

MI = myocardial infarction
ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blockers
EF = ejection fraction
LVEF = left ventricular ejection fraction

a mild increase in creatinine levels, suggesting it was as safe as a conservative approach.

Vasodilators remain pivotal agents in the treatment of patients with poor cardiac output and high blood pressure levels. ACE inhibitors are one of the milestones of HF treatment and their use is noticeably associated with a better prognosis [24]. However, ACE inhibitors and ARB may reduce GFR, especially in the presence of diuretics and mainly in patients with chronic RF or renal artery stenosis. Additionally, ACE inhibitor treatment should be accompanied by careful watching for impending azotemia and hyperkalemia, especially in patients with concomitant renal dysfunction. Yet, previous studies have demonstrated improved prognosis in HF patients treated with ACE inhibitors even in the presence of increased serum creatinine levels [28]. It is thus reasonable to allow a certain elevation of creatinine levels during ACE inhibitors or ARB treatment, even if reduction of diuretic therapy is needed. According to the European Society of Cardiology guidelines for HF, a 50% increase in serum creatinine or absolute levels of 3 mg/dl should be accepted, while a creatinine rise of 3–3.5 mg/dl requires a 50% dose reduction [29]. Apparently, with careful monitoring of renal function and serum potassium, the potential benefits of RAAS blockade eventually outweigh their risks in CRS patients.

Implantable cardiac defibrillators are employed as primary prevention in symptomatic patients with EF < 35% or as secondary prevention in HF resulting both from ischemic and non-ischemic etiology and were shown to reduce morbidity and mortality in these patients [30]. In patients with advanced CRS the effectiveness of ICDs decrease considerably, limited by the preponderance of non-arrhythmic death. Cardiac resynchronization therapy was proven to effectively reduce mortality and increase EF in NYHA III-IV patients with EF ≤ 35% and QRS ≥ 120 ms [31]. In patients with NYHA I/II, EF < 30% and a wide QRS, CRT reduces HF without reducing the mortality rate. In these patients, the addition of CRT to ICD and optimal medical therapy reduces rates of death and hospitalization for HF. In patients undergoing CRT, RF is associated with a poor response to CRT and a higher mortality rate [29]. Moreover, in this study, response to CRT correlated with preservation of renal function. Eventually, treatment of cardiac arrythmia, such as catheter ablation or pulmonary vein isolation in atrial fibrillation, improves cardiac function and clinical outcomes. Yet, no mortality benefits were documented by routine strategy of rhythm control versus rate control in patients with atrial fibrillation and HF.

Acute renocardiac syndrome (CRS type 3)
Type 3 CRS is typically caused by acute RF following direct insults such as exposure to toxins, contrast nephropathy, or

cardiac surgery-associated acute kidney injury. To avoid cardiac dysfunction during acute RF it is necessary to treat the underlying cause, optimize hemodynamics, correct electrolyte and coagulation disturbance, and perform urgent dialysis if indicated (i.e., acidemia, uremia, hyperkalemia or excessive volume overload). Hypertension management, provoked by decreased GFR, sodium retention and volume expansion secondary to acute kidney injury, is essential to minimize subsequent cardiovascular impairment. The use of cardiac markers such as troponin, myoglobin, myeloperoxidase and B-natriuretic peptide may assist in early detection of HF development during acute RF.

A critical issue to take into account when assessing the consequential impact of acute renal injury on cardiac function is the common lack of optimal pharmacological therapy, mainly due to concerns regarding worsening of kidney function. In fact, patients with advanced RF are far less likely to be treated with the combination of aspirin, beta-blockers, statins and ACE inhibitors, when presenting with acute coronary syndrome, probably contributing to the increased mortality observed in these patients. The doses of diuretics and ACE inhibitors are often reduced or even eliminated in the presence of mild creatinine elevation, despite their renoprotective role, contributing to acute decompensated HF. Eventually, cardiac dysfunction may ensue during dialysis as a result of hypotension-related ischemia or arrhythmias subsequent to electrolyte disturbance.

Contrast-induced acute RF has become extremely frequent and is likely to occur in patients with chronic kidney disease, diabetes, chronic HF, hypotension, elderly, and when using high contrast volume. Evidence so far points at isotonic fluid as the most effective way to prevent contrast nephropathy, while additional options include N-acetylcysteine or the low osmolar, non-ionic monomer iopamidol [33]. In cases of creatinine baseline levels > 2 mg/dl hemofiltration might be of benefit. Studies show that patients with contrast-induced acute kidney injury are associated with significantly higher rates of death, end-stage renal disease and cardiovascular complications in the year following the contrast exposure, underlining the detrimental effects of type 3 CRS [33].

Chronic renocardiac syndrome (CRS type 4)
Chronic RF may evoke HF in many pathways, including vascular calcification and chronic cardiac fibrosis, anemia and fluid retention. The chronic uremia state associated with chronic kidney disease may result in pericarditis, accelerated atherosclerosis, cardiomyopathy, hypertension and hyperlipidemia. Decreased GFR causes defective sodium secretion and elevated pressure load. Volume overload may also develop due to dietary non-compliance or elevated dialysate sodium and failure to attain target weight during hemodialysis. Treatment of chronic RF should include appropriate

ICD = implantable cardiac defibrillator
CRT = cardiac resynchronization therapy

dietary restriction – including sodium, potassium and protein restriction – as well as strict glycemic control. Blood pressure should be controlled, with a goal of < 130/80 mmHg, using ACE inhibitors and/or beta-blockers due to their cardio-protective effects. Metabolic acidosis should be reversed by sodium bicarbonate or sodium citrate.

CRF-related anemia is frequent among type 4 CRS patients and correlates with a poor prognosis [34]. Yet, no clear guidelines have been provided by the American College of Cardiology/American Heart Association or the European Society of Cardiology regarding targeted management of anemia in HF. We have previously shown that correction of anemia by erythropoietin and iron administration in HF patients is associated with improved cardiac function parameters and NYHA class, as well as inhibition of renal deterioration [35]. On the other hand, prompt correction of anemia in RF may provoke major adverse events, including death, MI, stroke and acute HF [36]. The TREAT study (**T**rial to **R**educe cardiovascular **E**vents with **A**ranesp **T**herapy) has shown that hemoglobin values of 11–12 g/dl should be generally sought in chronic RF patients without intentionally exceeding 13 g/dl in order to diminish cardiovascular morbidity [37]. Eventually, in case of hemoglobin level < 10 g/dl iron deficiency should be excluded before applying erythropoiesis-stimulating therapy.

Secondary cardiorenal syndrome (CRS type 5)

Secondary CRS consists of concomitant renal and cardiac injury secondary to either acute chronic or acute systemic illness. The most common acute cause of type 5 CRS is severe sepsis, where cardiac dysfunction and subsequent, nearly inevitable, RF are induced by inflammatory cytokines, lipo-polysaccharide/endotoxins, systemic/intrarenal vasodilation and vascular permeability, hypoxia and deprived perfusion [38]. In this setup, impaired renal function can further affect myocardial function, creating a deleterious vicious cycle. Prompt treatment of systemic hypotension, by fluid resuscitation as well as inotropic and vasopressor support, is imperative. In case of persistent renal impairment, veno-venous hemofiltration may be used to remove cytokines and restore renal function [39,40]. In parallel, treatment should be timely directed to the source of infection. Systemic diseases such as diabetes, vasculitis and amyloidosis may also induce secondary CRS through vascular dysfunction, and treatment should target the background disease.

CONCLUSIONS

Simultaneous cardiac and renal failure presents a complicated biological and clinical condition that challenges the treating clinician. The mechanisms that bind cardiac and kidney dysfunction involve hemodynamic alterations such as organ hypoperfusion and decreased venous return as well as hormonal elements, including oversympathetic activity and RAAS stimulation. Currently, the therapeutic strategies used to treat CRS are mainly based on fluid balance regulation through diuretics and RAAS inhibition. Further investigation is still needed to clarify the different mechanisms that underlie, and potentially reverse, the evolution of CRS.

Corresponding author:
Dr. G. Keren
Dept. of Cardiology, Tel Aviv Sourasky Medical Center, 6 Weizmann St., Tel Aviv 64234, Israel
Fax: (972-3) 546-9832
email: kereng@tasmc.health.gov.il

References

1. Adams KF, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; 149 (2): 209-16.

2. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 1998; 339 (12): 799-805.

3. Harnett JD, Foley RN, Kent GM, et al. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. *Kidney Int* 1995; 47 (3): 884-90.

4. Wali RK, Wang GS, Gottlieb SS, et al. Effect of kidney transplantation on left ventricular systolic dysfunction and congestive heart failure in patients with end-stage renal disease. *J Am Coll Cardiol* 2005; 45 (7): 1051-60.

5. Ronco C, House AA, Haapio M. Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. *Intensive Care Med* 2008; 34 (5): 957-62.

6. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004; 43 (1): 61-7.

7. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med* 1999; 341 (8): 577-85.

8. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 2009; 53 (7): 589-96.

9. Burnett JC, Knox FG. Renal interstitial pressure and sodium excretion during renal vein constriction. *Am J Physiol* 1980; 238 (4): F279-82.

10. Zoccali C, Mallamaci F, Benedetto FA, et al. Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. *J Am Soc Nephrol* 2001; 12 (7): 1508-15.

11. Massie BM, O'Connor CM, Metra M, et al. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med* 2010; 363 (15): 1419-28.

12. Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol* 2003; 14 (6): 1549-58.

13. Grassi G, Quarti-Trevano F, Seravalle G, et al. Early sympathetic activation in the initial clinical stages of chronic renal failure. *Hypertension* 2001; 57 (4): 846-51.

14. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; 373 (9671): 1275-81.

15. Silverberg DS, Wexler D, Blum M, et al. The interaction between heart failure, renal failure and anemia – the cardio-renal anemia syndrome. *Blood Purif* 2004; 22 (3): 277-84.

16. Felker GM, Gattis WA, Leimberger JD, et al. Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure. *Am J Cardiol* 2003; 92 (5): 625-8.

17. Schwartzenberg S, Ben-Shoshan J, Keren G, George J. The role of erythropoietin in myocardial protection: potential mechanisms and applications. *Exp Rev Cardiovasc Ther* 2006; 4 (1): 41-50.

18. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; 362 (9): 779-89.

19. Drexler H, Höing S, Faude F, Just H, et al. Central and regional vascular hemodynamics following intravenous milrinone in the conscious rat: comparison with dobutamine. *J Cardiovasc Pharm* 1987; 9 (5): 563-9.

20. Argenziano M, Choudhri AF, Oz MC, Rose EA, Smith CR, Landry DW. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. *Circulation* 1997; 96 (9 Suppl): II-286-90.

21. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003; 362 (9377): 7-13.

22. Jentzer JC, DeWald TA, Hernandez AF, et al. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol* 2010; 56 (19): 1527-34.

23. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; 341 (10): 709-17.

24. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. Report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee to revise the 1995 guidelines for the evaluation and management of heart failure) developed in collaboration with the International Society for Heart and Lung Transplantation endorsed by the Heart Failure Society of America. *J Am Coll Cardiol* 2011; 38 (7): 2101-13.

25. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; 362 (9386): 772-6.

26. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. *N Engl J Med* 1986; 314 (24): 1547-52.

27. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; 336 (8): 525-33.

28. Ljungman S, Kjekshus J, Swedberg K. Renal function in severe congestive heart failure during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] Trial). *Am J Cardiol* 1992; 70 (4): 479-87.

29. Authors/Task Force members, et al. Focused Update of ESC Guidelines on device therapy in heart failure. *Europace* 2010; 12 (11): 1526.

30. Das M. Indications for ICD and cardiac resynchronization therapy for prevention of sudden cardiac death. *Expert Rev Cardiovasc Ther* 2009; 7 (2): 181-95.

31. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; 352 (15): 1539-49.

32. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. *J Am Coll Cardiol* 2003; 42 (2): 201-8.

33. Marenzi G, Marana I, Lauri G, et al. The prevention of radiocontrast agent-induced nephropathy by hemofiltration. *N Engl J Med* 2003; 349 (14): 1333-40.

34. Sharma R, Francis DP, Pitt B, Poole-Wilson PA, Coats AJ, Anker SD. Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. *Eur Heart J* 2004; 25 (12): 1021-8.

35. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000; 35 (7): 1737-44.

36. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; 355 (20): 2085-98.

37. Locatelli F, Aljama P, Canaud B, et al. Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following publication of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) Study. *Nephrol Dial Transplant* 2010; 25 (9): 2846-50.

38. Abraham E, Singer M. Mechanisms of sepsis-induced organ dysfunction. *Crit Care Med* 2007; 35 (10): 2408-16.

39. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345 (19): 1368-77.

40. Singer P, Cohen JD. The Surviving Sepsis Campaign guidelines: should we follow? *IMAJ Isr Med Assoc J* 2011; 13 (11): 692-3.

Capsule

The dynamics of B effector cell differentiation and homeostasis

In response to an infection, immunological B cells undergo a maturation process that results in the production of immunoglobulin (Ig) that is better able to bind and clear the invading pathogen. This occurs through somatic cell hypermutation and class switch recombination of the Ig gene and requires activation-induced deaminase (AID). Péron and collaborators observed that the 3' cis-regulatory region of the heavy chain locus is transcribed and undergoes AID-mediated mutation and recombination.

The resulting deletion of the Ig heavy gene cluster generates B cells that are no longer able to express Ig on the cell surface. Because cell surface Ig expression is essential for B cell survival, this process is termed "locus suicide recombination" (LSR) and may be important in shaping the dynamics of B effector cell differentiation and homeostasis.

Science 2012; 336: 931

Eitan Israeli

An economist is an expert who will know tomorrow why the things he predicted yesterday didn't happen today

Laurence J. Peter (1919-1990), Canadian educator and "hierarchiologist," best known for the formulation of the Peter Principle: "In a hierarchy every employee tends to rise to his level of incompetence"