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EDITORIAL

Cardiorenal Syndrome: A Glimpse Into Some Intricate Interactions

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KEY WORDS: *renal insufficiency; heart failure; cardiorenal syndrome; renocardiac syndrome; cardiovascular disease; chronic kidney disease; cardiac biomarkers; renal biomarkers*

ABBREVIATIONS
ACE = angiotensin converting enzyme
ADM = adrenomedullin
ADMA = asymmetric dimethylarginine
ANP = atrial natriuretic peptide
ARB = angiotensin receptor blocker
AVP = arginine vasopressin
BNP = B-type natriuretic peptide
BUN = blood urea nitrogen
CMR = cardiac magnetic resonance
CRS = cardiorenal syndrome
FABPs = fatty acid-binding proteins
GFR = glomerular filtration rate
IL = interleukin
KIM = kidney injury molecule
MPO = myeloperoxidase
NAG = N-acetyl-beta-D-glucosaminidase
NGAL = neutrophil gelatinase-associated lipocalin
NO = nitric oxide
RAAS = renin angiotensin aldosterone system
SNS = sympathetic nervous system
TNF = tumor necrosis factor

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ABSTRACT

It is well known that heart and kidney functions are interdependent; primary disorders of one organ have been shown to affect the other organ (organ cross-talk). Over the last decade, growing interest and attention has been drawn to this interaction; the term cardiorenal syndrome (CRS) has been coined and 5 types of CRS have been recognized, whereby a vicious cycle is proposed of acute or chronic dysfunction of either the kidney or the heart which can trigger and aggravate dysfunction of the other organ. This interrelation in which one system negatively influences the other system calls for a closer examination of its pathophysiology, a more systematic approach for the diagnosis and treatment of this syndrome, and more intensive investigation for potential preventive measures. An overview of these complex interactions is herein attempted.

INTRODUCTION

The prevalence of heart failure is estimated at 1–2% of the adult population in developed countries, rising to ≥10% among individuals ≥70 years of age.[1] Kidney function is adversely affected in most patients with heart failure, especially if advanced, and is an important predictor of clinical outcome. It is reported that 25–30% of patients with decompensated heart failure develop worsening kidney function, a condition termed cardiorenal syndrome (CRS), which constitutes a real clinical challenge.[2-4] It has become abundantly clear that renal dysfunction has been associated with poorer outcomes in patients with heart failure with higher in-hospital, post-discharge and long-term mortality and prolonged duration of hospitalization.[5] Higher annual mortality rates (~40%) are reported in patients with any impairment of renal function, reaching at even higher levels (~50%) in those with moderate to severe renal dysfunction, as compared with the mortality rates (~25%) in patients without renal dysfunction.[6] It should be noted that impaired renal function is independently associated with increased risk for death and hospitalization in heart failure patients both in those with preserved as well as in those with reduced left ventricular ejection fraction.[7]

On the other hand, according with the US statistics, the prevalence of any stage of chronic kidney disease has been estimated at 13%.[8] Hence, chronic kidney disease has emerged as an important and independent predictor of cardiovascular disease, includ-

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ing coronary artery disease, left ventricular hypertrophy, and heart failure. This has led to the recognition of a significant overlap and intricate pathophysiological interactions between cardiovascular and kidney disease. Indeed, cardiovascular disease may account for greater than 50% of all deaths in patients with chronic kidney disease, with mortality rates noted to be 10- to 20-fold higher than in an age-matched population devoid of kidney disease.

PATHOPHYSIOLOGY

In patients with heart failure who are developing worsening renal function, there are mutual intricate interactions between the two organs (organ cross talk), with dire consequences. Either the pathophysiological mechanisms underlying heart failure, plus various comorbidities, and/or the administered therapies affect renal circulation and function leading to the development of concomitant renal failure (Fig. 1). Depending on several etiological and chronological interactions, CRS was recently classified into several types, including acute or chronic types, cardiorenal or renocardiac types, and primary or secondary types, all detailed below. The mechanisms underlying the CRS are multifactorial, including structural damage from atherosclerosis, hemodynamic alterations, neurohormonal effects, and inflammatory components.[9-13]

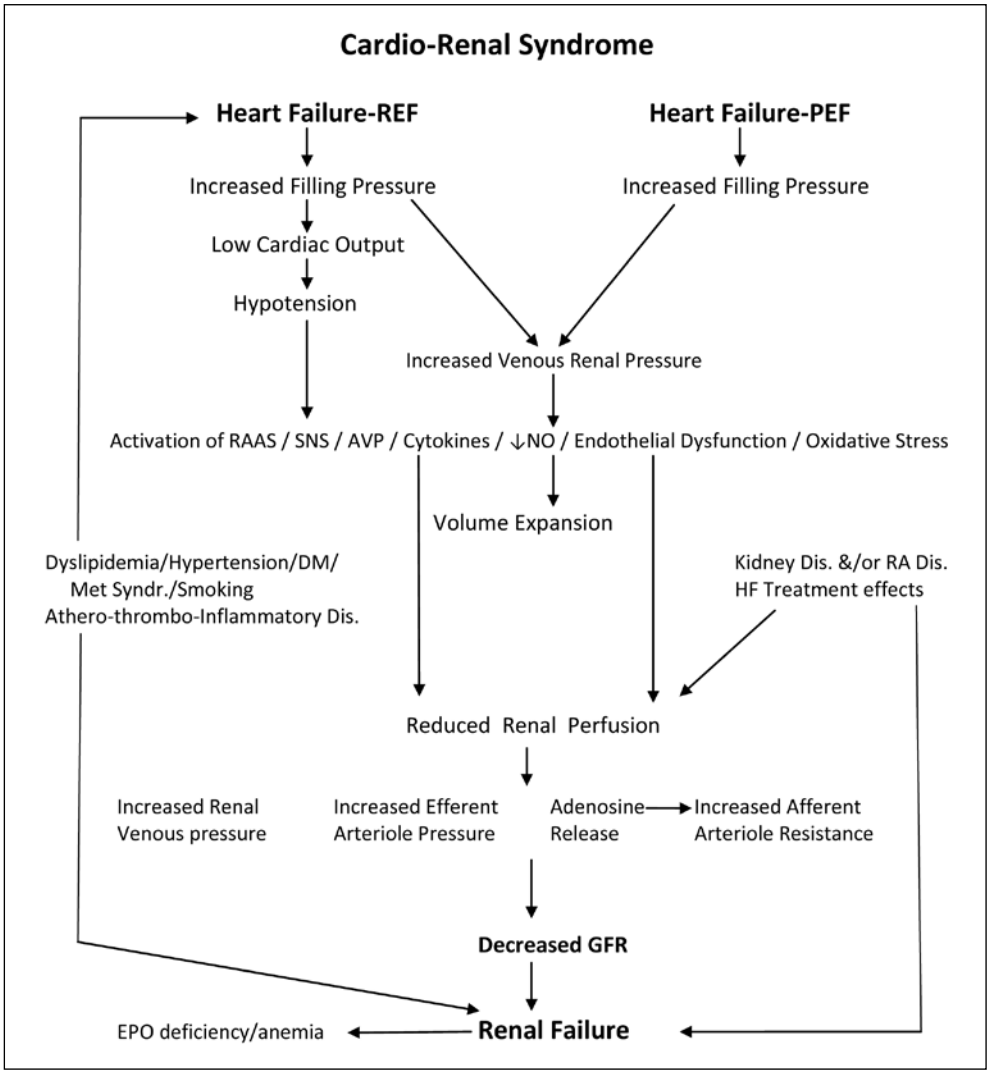

FIGURE 1. Mechanisms of Cardio-Renal Syndrome. AVP = arginine vasopressin; Dis. = disease; DM = diabetes mellitus; EPO= erythropoietin; GFR = glomerular filtration rate; HF = heart failure; HF-PEF = heart failure with preserved ejection fraction; HF-REF = heart failure with reduced ejection fraction; NO = nitric oxide; RA = renal artery; RAAS = renin angiotensin aldosterone system; SNS = sympathetic nervous system; Syndr. = syndrome

In the setting of CRS, these cardiac and renal interactions involve several major contributors, including the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), the arginine-vasopresin (AVP) system, endothelial dysfunction with nitric oxide (NO) inhibition and endothelin production.[9-13] Venous congestion and volume overload play a significant role in the pathogenesis of worsening renal function in heart failure, particularly when perfusion is also impaired.[12,14]

Renal failure is usually ascribed to pre-renal, renal and post-renal causes. Traditionally, in patients with heart failure, the etiology of renal failure has been considered pre-renal. However, a post-hoc examination of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial indicated that impaired baseline renal function, but not worsening renal function, was strongly associated with poor outcome in patients with decompensated heart failure.[15] Thus, compromised flow during heart failure may not be solely responsible for the development of renal insufficiency or renal function deterioration in these patients. In other words, a prerenal etiology on the basis of low forward flow, overdiuresis, or excessive vasodilation is not the mere primary cause of worsening renal function. The trial indicated that that biventricular failure rather than isolated left ventricular failure may be a marker of more advanced cardiac disease and thus may contribute to the development of renal insufficiency in these patients. Other likely explanations for the increased incidence of renal dysfunction in patients with advanced heart failure include older age and the higher prevalence of comorbidities in these patients, such as hypertension and diabetes, which may be responsible for both native renal disease and heart failure. Furthermore, comorbidities, such as hypertension, disrupt the mechanism of renal blood flow autoregulation, rendering the kidney more susceptible to injury during heart failure treatment. Importantly, baroreceptor dysfunction and neurohormonal activation, as already alluded to, lead to increased vasoconstriction of the pre-glomerular afferent arterioles, which further compromises renal blood flow and glomerular filtration rate (GFR). Thus, improving only the hemodynamics, without concomitantly influencing the neurohormonal milieu, apparently may not ameliorate renal function or long-term outcomes.[15]

In addition, inflammation seems to play an important role in both acute and chronic cardiac and kidney disease; it is speculated that circulating mediators of inflammation may function in this organ cross-talk.[12] Thus, it may be even possible to develop anti-inflammatory strategies that might decrease the morbidity and mortality associated with these conditions. However, the preliminary results of anti-TNF strategies in heart failure patients have been disappointing, which renders these approaches more complex than initially considered.[12, 13] Finally, regardless of etiology, the presence or development of renal dysfunction in patients with heart failure is deemed a grave comorbid condition which confers increased mortality, approaching 50% at 1 year.[3,6]

In patients with heart failure with preserved ejection fraction, the pathogenesis of the cardiorenal syndrome has been attributed to similar mechanisms. Among them, main role is ascribed to an elevated intra-abdominal and central venous pressure; activation of the renin-angiotensin system; sympathetic overactivity; oxidative injury and endothelial dysfunction.[16] Furthermore, infections and drugs (e.g. nonsteroidal inflammatory agents) have been considered as precipitating factors. Among patients with heart failure with preserved ejection fraction, CRS is more common in older female patients with hypertension and/or diabetes mellitus. In this setting, CRS may be underdiagnosed more often than in patients with low ejection fraction, whereas the therapeutic options may be even more challenging in an effort to reduce the filling pressure while maintaining adequate volume status.

On the other hand, chronic kidney disease has been noted to accelerate the risk for and development of cardiovascular disease (renocardiac disease).[8] The pathophysiological mechanisms implicated may comprise hyperhomocysteinemia, elevated lipoprotein (a), oxidative stress, endothelial dysfunction, chronic inflammation, vascular remodelling, changes in platelet aggregation, neurohormonal activation, volume overload, reduced parenchymal mass, and hormone deficiency (e.g., vitamin D and erythropoietin). Another important factor to consider is that patients with chronic kidney disease, under the perception of a less favorable response or concern for treatment intolerance, risk or toxicity, have often been excluded from and thus deprived of risk-modifying interventions and/or cardioprotective therapies (such as revascularization, aspirin, beta-blockers, and angiotensin-converting inhibitors). Thus, as cardiac disease directly contributes to renal disease, renal disease clearly confers an increased risk of cardiac disease (heart-kidney crosstalk).

TYPES OF CARDIO RENAL SYNDROME (TABLE 1)[17-26]

Type 1 CRS relates to *acute cardiorenal syndrome*, observed in acute heart failure, including cardiogenic shock or decompensated congestive heart failure, inducing a concomitant abrupt renal injury, defined as a 0.3–0.5 mg/dl rise in serum creatinine, or a 9–15 ml/min decrease in glomerular filtration rate (GFR).[20,21] **Type 2 CRS** relates to *chronic cardiorenal syndrome*, defined as chronic heart failure leading to chronic renal disease, due to microvascular and macrovascular kidney injury complicated by hemodynamic compromise.[22] **Type 3 CRS** relates to *acute renocardiac syndrome*, when acutely compromised renal function, as seen in volume depletion, acute glomerulonephritis or bilateral renal artery stenosis, causes acute cardiac injury and deterioration, induced by

TABLE 1. Types of Cardiorenal Syndome.[17-26]

- **Type 1**: Acute Cardio-Renal Syndrome with acute worsening of cardiac function leading to renal dysfunction
- **Type 2**: Chronic Cardio-Renal Syndrome with chronic abnormalities in cardiac function leading to renal dysfunction
- **Type 3**: Acute Reno-Cardiac Syndrome with an acute worsening of renal function causing cardiac dysfunction
- **Type 4**: Chronic Reno-Cardiac Syndrome with chronic abnormalities in renal function leading to cardiac disease
- **Type 5**: Secondary Cardio-Renal Syndromes with systemic conditions causing simultaneous dysfunction of the heart and kidney (e.g. sepsis, systemic lupus erythematosus, amyloidosis, diabetes mellitus, hypertension).

fluid overload, electrolyte and metabolic imbalance, and uremia, manifested by heart failure, arrhythmia or ischemia.[23] **Type 4 CRS**, *chronic renocardiac syndrome*, describes chronic renal disease contributing to continual compromised cardiac function, cardiac hypertrophy, and predisposition to adverse cardiovascular events with hemodynamic consequences, chronic inflammatory processes and progressive atherosclerosis. Indeed, chronic kidney disease, defined as a reduction of glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 and/or the presence of renal injury lasting for >3 months, is increasing in incidence and prevalence worldwide, and constitutes a significant risk for cardiovascular events independent of conventional risk factors. Even the very early marker of mild renal function disturbance, manifesting as microalbuminuria, is associated with an increased incidence of cardiovascular disease. Higher than expected rates of coronary events, congestive heart failure, left ventricular hypertrophy, cardiac arrhythmias, and sudden death plague all stages of chronic kidney disease, increasing sharply as renal function declines. The pathophysiology of type 4 CRS is multifactorial, progressive, and bidirectional between kidney and renal dysfunction.[24] It appears that, in the absence of acute ischemia, chronic kidney disease can lead to adverse cardiac remodeling and fibrosis, diastolic dysfunction, left ventricular dilatation and finally heart failure with reduced ejection fraction.[25] **Type 5 CRS** relates to *secondary CRS* caused by drugs or systemic disorders affecting both cardiac and renal function, such as diabetes mellitus, hypertension, autoimmune diseases, sepsis, amyloidosis, disseminated intravascular coagulation.[26] These disorders may cause acute (e.g. drugs or sepsis) or chronic CRS (e.g. diabetes). Treatment of the basic underlying disease is the mainstay of therapy.

DIAGNOSIS

IMAGING[27]

Although a *chest X-ray* is the initial imaging study that all patients with heart failure are submitted to, and all physicians are familiar with, and remains an invaluable tool to evaluate for pulmonary congestion and volume overload and assess the severity of heart failure, most or all of them proceed to have further imaging studies which give more detailed and targeted information regarding the heart and kidney anatomy and function.

Echocardiography. Echocardiography provides valuable information about cardiac anatomy and function. Assessment of both systolic and diastolic left ventricular function can thus be made with this cardinal imaging technique and patients can be categorized into those with heart failure with low ejection fraction and those with preserved ejection fraction. The simple transthoracic approach usually suffices for routine diagnostic assessment, unless there are technical limitations in finding a window for the ultrasound beam or specific situations exist, such as mitral valve disease and prosthetic valves, which necessitate the use of transesophageal echocardiography.

Stress Echocardiography/ Single Photon Emission Computed Tomography (SPECT) / Positron Emission Tomography (PET). Exercise or pharmacological stress echocardiography and thallium scintigraphy are tests which are used to identify the presence and extent of myocardial ischemia or viability. Positron emission tomography may offer some advantages in testing for ischemia and/or viability, but due to its cost has currently a limited use.

Coronary Angiography. Coronary angiography is the ultimate test and remains the gold standard as an imaging technique for assessing coronary anatomy and for guiding the performance of percutaneous coronary angioplasty and stenting. Caution should be exercised and measures taken to avoid or minimize the consequences of contrast-induced nephropathy, particularly in patients with diabetes or renal insufficiency, by providing adequate hydration and limiting the dose of the contrast agent used.

Ultrasonography. In addition to echocardiography, ultrasound techniques, including renal ultrasound, and ultrasonography of the inferior vena cava and chest, can be extremely helpful in establishing a diagnosis and correctly classifying CRS. Transthoracic echocardiography allows evaluation of ventricular diastolic and systolic functions, investigates pulmonary congestion and pericardial effusion, and describes volume overload. Renal ultrasound helps clinicians to distinguish between acute and chronic renal failure, and exclude urinary tract dilation or pathological bladder repletion, and provides crucial information regarding kidney volume or echogenicity.[28]

Computed Tomography (CT) / Renal Scanning. Computed tomography (CT) coronary angiography has been used for specific cases to evaluate coronary anatomy, but conventional coronary angiography still remains the gold standard for assessing coronary anatomy and for guiding percutaneous coronary interventions. CT urography has supplanted intravenous urograms for the diagnosis of renal stones and neoplasms.

Contrast-enhanced CT can evaluate renal veins and arteries, renal parenchyma and the collecting system. Caution should be exercised to prevent contrast-induced nephropathy. Technetium-based renal scanning for radionuclide imaging of the kidney can be employed for the differential diagnosis of acute and chronic renal failure and evaluation of the renal function.

Magnetic Resonance Imaging (MRI). Cardiac magnetic resonance (CMR) is a non-invasive technique that provides information about cardiac anatomy and function, but this is already available from echocardiography, which is simpler and less expensive. Thus, this imaging technique is reserved for some other more specific assessments or when the echocardiogram is non-diagnostic. CMR is a better method to assess volumes, mass, and wall motion. CMR is particularly useful in identifying inflammatory and infiltrative diseases of the myocardium, such as myocarditis, sarcoidosis, amyloidosis, etc. and most valuable in patients with complex congenital heart disease. MRI is also useful for the study of the genitourinary tract, particularly in staging of malignancies. Magnetic resonance angiography can be used to assess renal arteries, but its use is limited due to the risk of nephrogenic systemic fibrosis.

CARDIAC BIOMARKERS (TABLE 2)

Natriuretic Peptides. Brain-type natriuretic peptide (***BNP***) and N-terminal pro BNP (***NT-proBNP***) are secreted from the ventricular myocardium in response to increased wall stress and their levels have now an established role in the diagnosis of acute decompensated heart failure and represent independent predictors of cardiovascular morbidity and mortality. Natriuretic peptides are elevated in patients with CRS in whom acute renal dusfunction occurs as a consequence of acute heart failure, whether new or decompensated. According with the most recent heart failure guidelines,[1] in the acute setting, levels of BNP ≥100 pg/mL or NT-proBNP ≥300 pg/mL are consistent with heart failure, while in the chronic setting the recommended levels are ≥35 pg/mL and ≥125 pg/mL, respectively. Mid regional pro-atrial natriuretic peptide (***MR-proANP)*** is an emerging biomarker with high diagnostic accuracy for heart failure in patients presenting with dyspnea.[29,30] Thus, in the acute setting MR-proANP can be used for diagnosis of heart failure with a cut-off point of >120 pmol/L.[1]

Cardiac Troponins. Cardiac troponins (I or T) have now supplanted creatine kinase as specific markers for ischemic myocardial injury. Now with the availability of high-sensitivity assays,[31,32] the sensitivity of diagnosing small myocardial infarctions has increased, but at the cost of a lower specificity, since moderate elevations of cardiac troponins are common in chronic renal failure patients and a plethora of other conditions without significant myocardial damage. Furthermore, heart failure per se is known to be associated with elevated levels of cardiac troponins in the absence of acute myocardial ischemia or infarction. Thus, when the two conditions coincide, troponins

TABLE 2. Biomarkers of Cardio-Renal Syndrome (see text for discussion)

	RENAL			
CARDIAC	**Functional (GFR)**	**Glomerular Permeability**	**Tubulointerstitial Damage**	**OTHER**
Natriuretic Peptides	Creatinine	Albuminuria	NAG	C- reactive protein
BNP	BUN		KIM-1	Procalcitonin
NT-proBNP	Cystatin C		NGAL	ADM / MR-proADM
MR-proANP			IL-18	Copeptin
Cardiac Troponins (I/T)			FABPs	ADMA
Cytokines			Klotho (deficiency)	
TNF-α				
IL-1				
IL-6				
Myeloperoxidase				

ADM = adrenomedullin; ADMA = asymmetric dimethylarginine; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; FABPs = fatty acid-binding proteins; IL = interleukin; KIM-1 = kidney injury molecule 1; MR-proADM = mid-regional-proADM; MR-proANP = mid regional pro-atrial natriuretic peptide; NAG = N-acetyl-beta-D-glucosaminidase; NGAL = neutrophil gelatinase-associated lipocalin; NT-proBNP = N-terminal pro BNP; TNF = tumor necrosis factor

may certainly be elevated and therefore, the sensitivity and specificity of this biomarker is compromised in these patients.

Cytokines. Pro-inflammatory cytokines, such as tumor-necrosis factor alpha (TNF-α), interleukin (IL)-1 and IL-6, may be overproduced and released in myocardial injury or dysfunction; however, these markers also suffer from specificity and practical applicability.

Myeloperoxidase. Myeloperoxidase (MPO) is an enzyme associated with the inflammatory process involved in rupture of atherosclerotic plaques.[33] In addition to acute coronary syndromes, MPO levels have been shown to correlate with BNP values and independently predict heart failure mortality. Due to its association with a wide range of pathology including inflammation and oxidative stress, MPO has been proposed as a potential biomarker in both cardiovascular and renal disease, but further studies are needed for its value in CRS.

RENAL BIOMARKERS (TABLE 2)

The filtration ability of the kidney, expressed as the glomerular filtration rate (GFR), has been classically estimated by serum creatinine and other formulas mainly based on creatinine. However, GFR does not cover the whole function of the kidney, which also involves glomerular permeability and tubular function, and additionally includes vitamin D metabolism and erythropoietin production. Thus, several markers other than creatinine have been employed to estimate kidney function.[5,33-36]

Glomerular Filtration Rate (GFR)

Serum Creatinine / Creatinine Clearance. Creatinine, filtered through the glomerulus and thus excreted in the urine, comes from the breakdown of creatine phosphate of skeletal muscles, but is also secreted by the tubules and thus overestimates GFR. Muscle wasting in heart failure or obesity also interfere with creatinine production, filtration and secretion and thus pose problems in determining GFR. Several correction formulas have been proposed, which include age, gender, or weight, race, blood urea nitrogen (BUN) and albumin. The most common formulas include the Cockcroft-Gault equation, as an estimate of creatinine clearance, and the (simplified) Modification of Diet in Renal Disease (sMDRD/MDRD) formulas (estimated GFR) (Table 3). However, all these formulas still overestimate GFR in the lower levels of true GFR and underestimate GFR in the higher levels of true GFR. Recently, to account for the poor performance of the MDRD equation in the (near) normal and higher ranges of GFR, a new equation, the CKD-EPI equation was developed. This formula resembles the MDRD but has creatinine-dependent gender differences and produces higher estimated GFR at lower creatinine levels; however, this equation has still to be validated in heart failure.[34]

Blood Urea Nitrogen (BUN). BUN is a varying and relatively unreliable marker of renal function compared with creatinine and relevant formulas, but it holds a value as a marker for the effectiveness of dialysis, but also as a predictor of morbidity and mortality in patients with heart failure.[37]

TABLE 3. Most Commonly Used Formulas for GFR Measurement

I. Cockcroft-Gault equation (estimated creatinine clearance rate)

$$\text{Creatinine Clearance (ml/min)} = \frac{(140 - \text{Age}) \times \text{Body mass (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72} \times \text{GF}$$

GF = gender correction factor; 0.85 in women, 1.00 in men

Normal values for Creatinine Clearance: 75-115 in women; 95-145 in men

II. Modification of Diet in Renal Disease (MDRD) formula (estimated GFR)

For Creatinine in mg/dL, simplified "4-variable MDRD":

eGFR = 186 x *Serum Creatinine*$^{-1.154}$ x *Age*-0.203 *x* [1.212 *if Black*] *x* [0.742 *if Female*]

The normal range of GFR, adjusted for body surface area, is similar in men and women, and is in the range of 100-130 ml/min/1.73m^2. In children, GFR measured by inulin clearance remains close to about 110 ml/min/1.73m^2 down to about 2 years of age in both sexes, and then it progressively decreases. After age 40, GFR decreases progressively with age, by about 0.4 - 1.2 mL/min per year (http://en.wikipedia.org/wiki/Renal_function).

Cystatin C. Cystatin C is freely filtered through the glomerulus and completely reabsorbed and degraded in the tubulus. Its level in the circulation is therefore an ideal marker of GFR.[34, 35] Cystatin C has been shown to be superior to serum creatinine as an estimate of GFR. However, in heart failure, no data exist on the reliability of cystatin C to accurately estimate GFR. Nevertheless, cystatin C appears to have a strong impact on prognosis of the CRS and the potential to assess the effect of mild renal dysfunction on cardiovascular outcomes; particularly, it has been shown to predict cardiovascular events and disease progression of heart failure and renal insufficiency in elderly patients at risk.[38]

Glomerular Permeability

Albuminuria. In patients with diabetes, hypertension, and chronic renal dysfunction, microalbuminuria (30–300 mg/24h) and macroalbuminuria (>300 mg/24h) are commonly observed. Albuminuria has been proposed as an important therapeutic target in patients with chronic renal insufficiency. Furthermore, albuminuria may serve as marker of prognosis in patients with heart failure and as a predictor of heart failure in patients without myocardial dysfunction, even when GFR is normal.[34]

Tubulointerstitial Injury

N-acetyl-beta-D-glucosaminidase (NAG). NAG, a lysoso-

mal enzyme formed in the proximal tubule and appearing in the urine in response to tubular injury, is a sensitive marker of proximal tubular damage and the occurrence of acute kidney injury or worsening renal function.[34] In congestive heart failure, urinary NAG levels are significantly elevated compared with controls and associated with poorer clinical outcome, independent of GFR. However, higher levels of NAG are also encountered in other conditions, such as urinary tract infections, which may limit their specificity.

Kidney Injury Molecule 1 (KIM-1). KIM-1 is a transmembrane protein found in urine only after proximal tubular epithelial cell injury, and thus may predict those patients that are at increased risk for deteriorating renal function. Urinary KIM-1 levels decrease after anti-hypertensive therapy. However, clinical data on KIM-1 expression in chronic heart failure are limited and again this molecule also lacks specificity.[34]

Neutrophil Gelatinase-Associated Lipocalin (NGAL). NGAL is a protein of small molecular weight, normally detectable in serum in low levels, being secreted in lung, kidney, trachea, stomach, and colon, but freely filtered through the glomerulus and completely reabsorbed in the tubules. Thus, plasma NGAL levels are less specific for renal disease, as increased secretion occurs in inflammation, sepsis, or cancer; however, urine levels are more specific, since the NGAL that appears in the urine is secreted only from the tubules (plasma NGAL is filtered and totally reabsorbed). In acute kidney injury, both plasma and urine NGAL rise significantly, with very high concentrations of NGAL expressed in urine, which mostly comes from production in the distal nephron (loop of Henley and collecting ducts), although high levels of NGAL have also been observed during proximal tubular injury. Thus, NGAL measurements are clinically useful as predictors of acute kidney injury or worsening renal function. Recently, higher plasma NGAL levels were found to predict the occurrence of worsening renal function in patients admitted with acute heart failure.[35] However, in chronic heart failure, NGAL levels, albeit increased, did not predict outcome, in contrast to both NAG and KIM-1.[34]

Interleukin 18 (IL-18). Among a plethora of cytokines, IL-18 is a proinflammatory cytokine, which is increased in response to acute kidney injury, particularly from an ischemic insult, detectable in urine, preceding the rise in creatinine, but with a slower rise compared to NGAL. However, IL-18 is also increased in inflammatory conditions, such as arthritis and sepsis which limits its specificity. No studies have evaluated the ability of IL-18 to predict acute kidney injury or worsening renal function in the setting of heart failure.[34]

Fatty Acid-Binding Proteins (FABPs). FABPs are proteins that bind selectively to free fatty acids. There are numerous different tissue-specific FABPs. Of these, liver FABP (L-FABP or FABP-1) and heart FABP (H-FABP or FABP-3) have been localized in the proximal or distal tubules, respectively. They are associated with impaired renal function from ischemic injury, deemed sensitive and specific biomarkers of acute kidney injury. FABP-1 may even outperform NGAL and KIM-1 in acute kidney injury. Limited data are available in patients with heart failure.[34]

Klotho. The Klotho protein is a single-pass transmembrane protein expressed mainly in the kidney, the parathyroid gland and the choroid plexus.[39,40] Klotho has pleiotropic regulating functions with an emerging role in cardiorenal disease. It is expressed in areas involved with calcium regulation, predominantly, among other areas, in the renal distal convoluted tubules. Klotho downregulation appears to be an early biomarker for kidney dysfunction and mineral dysregulation. It may play a pathogenetic role in the progression of chronic kidney disease, which has been suggested as a state of klotho deficiency. Klotho is also responsible for vascular calcification, which is one of the principal complications of chronic renal dysfunction. Furthermore, low plasma klotho concentrations have been independently associated with a higher likelihood of having cardiovascular disease. It remains to be seen whether this novel biomarker could be of value in patients with CRS.

OTHER MARKERS (TABLE 2)

C-Reactive Protein. High-sensitivity C-reactive protein (hs-CRP) is an important biomarker of inflammation, useful for predicting short- and long-term outcome in patients with cardiovascular disease. Similarly, chronic kidney disease belongs to chronic inflammatory diseases, and CRP has been useful in predicting mortality. However, despite the suggestion that the risk is lowered in patients with cardiovascular disease and elevated CRP who received statin therapy, this has not been consistently corroborated in patients with chronic kidney disease,[41] indicating the complexity of this inter-relationship. Furthermore, there is some suggestion that CRP may not be a mere marker of inflammation, but it may be directly affecting endothelial function.[12]

Procalcitonin. Procalcitonin is a marker for coincidental infection in patients with heart or renal failure. Procalcitonin may be more sensitive than C-reactive protein (CRP) in severe inflammatory processes, such as in cardiogenic shock. [35] As patients with cardiac and/or renal disease are frequently complicated by infection and/or sepsis, this marker is useful to aid the diagnosis of concomitant infection with additional prognostic capability. It can also be combined with other markers, e.g. MR-proANP, to differentiate patients with acute heart failure and superimposed pneumonia.[35]

Adrenomedullin (ADM) / MR-proADM. Adrenomedullin (ADM) is expressed in endothelial cells and is a strong prognostic marker for cardiovascular disease. However, due to its short half-life, assays have been technically difficult. Recently, the midregional-proADM (MR-proADM) peptide has been discovered and used as a more stable product and important prognostic marker of cardiovascular events in patients with heart failure or myocardial infarction.[35]

Copeptin. Copeptin, the C-terminal part of the prohormone of vasopressin, is secreted from the posterior pituitary in response to hypovolemia and parallels the secretion of antidiuretic hormone (arginine vasopressin-AVP), being also a more stable counterpart of AVP. Studies have indicated that copeptin is a strong prognostic biomarker in patients with heart failure. It also appears to be a marker for albuminuria and renal failure as well. Thus, copeptin, a surrogate marker for AVP, may be a potential predictor of CRS.[35]

Asymmetric Dimethylarginine. The amino acid asymmetric dimethylarginine (ADMA) acts as a potent endogenous inhibitor of the enzyme NO synthase, which can lead to endothelial dysfunction, deemed as the initiator of the atherosclerotic process. Furthermore, the enzyme that metabolizes ADMA is located, along with NO synthase, in glomerular endothelial and tubular epithelial cells. Thus, NO availability can be locally compromised in the kidney and result in progressive damage. Consequently, ADMA can serve as a marker of chronic kidney disease progression; however, plasma ADMA is increased in several conditions associated with endothelial dysfunction (atherosclerosis, diabetes, hypertension, heart failure) and this lack of specificity has limited its use as a reliable biomarker in CRS.[33]

THERAPEUTIC IMPLICATIONS

Due to a paucity of data with regards to treatment of heart failure in the setting of renal dysfunction or vice-versa, patient management in this grim setting remains empirical.

DIURETICS

Hypervolemia remains the main feature of CRS of various types. Targeting volume status can be effected by dietary sodium restriction and fluid removal with use of diuretics, and/or the combination of these two therapeutic maneuvers; in severe heart failure, hyponatremia can urge for additional fluid restriction.[14] However, the use of aggressive diuresis with a loop diuretic (furosemide), which is often needed in these patients to respond, is prone to be associated with worsening renal function, especially in the presence of ACE inhibitors. Maintaining an optimal balance between the benefits of decongestion and the potential adverse effects of therapies remains a challenge. When faced with resistance to diuretic therapy, which is a common theme in this scenario, either employing higher doses or continuous intravenous infusion of furosemide and/or adding a thiazide diuretic (e.g. metolazone) to the loop agent may occasionally induce a good response. However, under these circumstances, the use of renal replacement therapy emerges. Indeed, renal replacement therapy via extracorporeal techniques for fluid removal with use of ultrafiltration has been proposed as a last resort in patients with severe congestion along with poor cardiac output.

VASODILATORS

The use of venous and/or arterial vasodilators has been considered to improve hemodynamics but not renal function, and, if aggressive, it can worsen renal perfusion. Furthermore, this therapy may promote neurohormonal activation with its attendant consequences. Nevertheless, in the setting of acute heart failure with high systolic arterial blood pressure (>140 mmHg), in addition or concomitantly with the use of loop diuretics, intravenous nitroglycerin or even nitroprusside can alleviate pulmonary congestion, decrease both preload and afterload and stabilize the patient. Caution should be exercised lest the patient becomes hypotensive in which case renal perfusion can be acutely compromised.

POSITIVE INOTROPIC SUPPORT

Intravenous use of dobutamine, dopamine, milrinone and levosimendan has been routinely advocated to improve cardiac and renal hemodynamics, and facilitate diuresis, but without confirmation of any benefit from randomized controlled studies. Nevertheless, inotropic agents are commonly used in hypotensive or low-output states.[1] "Renal" or low-dose (2-3 μg/kg/min) dopamine has been proposed to have a selective renal vasodilatory and natriuretic effect, but this still remains dubious. Periodic (e.g. every 3 months) 24-hour intravenous infusion of levosimendan has served well several patients in our practice with advanced heart failure symptoms and low cardiac output state; concomitant support with intravenous dopamine allows patients with low blood pressure to better tolerate the infusion of levosimendan. Future studies may further define levosimendan's role in CRS patients.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI) / ANGIOTENSIN RECEPTOR ANTAGONISTS (ARBS)

Although ACE inhibitors or ARBs constitute the cornerstone of heart failure therapy,[1] the use of these agents in the presence of renal failure is hindered by a potential further increase in creatinine and worsening renal function. Thus, there should be very close monitoring of renal function parameters when initiating or further increasing the doses of these agents in this setting.

BETA BLOCKERS

Beta blockers have an important role in treating chronic heart failure by negating the detrimental effects of the sympathetic system,[1] but their role in CRS is limited due to abnormal hemodynamics. They can be re-started when patients get stabilized, usually at low doses.

STATINS

Due to their pleiotropic effects, in addition to their hypolipidemic actions, statins have been proposed to exert beneficial, cholesterol-lowering-independent effects in pa-

tients with CRS. Specifically, investigators have focused on statin-conferred improvement of endothelial function by an increase in NO availability and/or by their antioxidant effects, and amelioration of vascular inflammation.[42] Furthermore, statins have been shown to reduce coronary atherosclerotic volume, may improve cardiac remodeling and systolic and diastolic function in patients with early-stage cardiac injury, and may reduce the incidence of atrial fibrillation via attenuation of atrial remodeling, all beneficial effects for early treatment of patients with cardiovascular disease. The beneficial effects of statins in reducing cardiovascular events may also be seen in chronic kidney disease, but mostly in patients with mild to moderate disease and not consistently in end-stage disease.[41] Since hyperlipidemia has also been shown to be a risk factor for renal disease, it is also possible that statins might slow the rate of renal injury progression. Among statins, a new agent, pitavastatin, has been suggested as having more cardiovascular and renoprotective effects compared to other statins, associated with stronger pleiotropic effects, particularly the reduction of oxidative stress.[42] Further data are needed to confirm these initial results.

VITAMIN D RECEPTOR AGONISTS

Vitamin D deficiency has been shown to affect a number of organ systems, including the renal and cardiovascular systems. Renal insufficiency in CRS leads to reduced synthesis of calcitriol (active vitamin D) and inadequate clearance of phosphate, thus creating serum mineral imbalance with hypocalcemia and hyperphosphatemia, which have been correlated with increased cardiovascular events. In response, the parathyroid gland increases parathormone (PTH) secretion, which can further lead to parathyroid gland hyperplasia and secondary hyperparathyroidism. Increased PTH will promote vascular calcification and bone remodeling. In addition, decreased vitamin D can stimulate the RAAS, with all its deleterious consequences, further aggravating a vicious cycle of system dysfunction in CRS. On the other hand, vitamin D supplementation may attenuate these issues and improve survival. However, vitamin D also elevates serum levels of calcium and phosphorus, while elective vitamin D receptor agonists provide similar efficacy but a lower increase in calcium and phosphorus. Thus, selective activation of vitamin D receptors may confer cardiorenal protection, offering a novel approach to managing these high-risk patients, as suggested by some preliminary studies, [43,44] albeit refuted by others.[45]

IRON AND ERYTHROPOIETIN THERAPY

Iron deficiency is commonly encountered in both chronic kidney disease and in chronic heart failure, and has been deemed an independent risk factor for increased mortality. Studies of correction of the anemia with intravenous iron in both renal and heart failure have shown an improvement in the anemia and, in some cases, in renal and cardiac function, as well as in exercise capacity and quality of life. If future studies confirm these preliminary results, this will offer a new addition to the therapeutic armamentarium of the cardiorenal syndrome. [46] Before these data regarding iron therapy became available, there preceded an initial enthusiasm about the potential benefit of anemia therapy with use of erythropoietin agents. However, this enthusiasm has been recently curtailed by the results of newer studies and meta-analyses indicating the potential harm, in addition to increased cost, of this therapeutic approach, mainly due to untoward effects of erythropoietin including hypertension, thrombosis and cardiovascular complications and possible increased cancer risk. [47] Furthermore, in a recent meta-analysis, the use of erythropoietins to treat anemia in patients with heart failure was associated with a neutral effect on both mortality and non-fatal heart failure events. [48] Finally, it should be noted that the optimal hemoglobin target remains elusive, since studies have indicated that higher hemoglobin concentration targets $\geq$13 mg/dl are of no benefit and may indeed be harmful.[47]

MINERALOCORTICOID RECEPTOR (MR) ANTAGONISTS

Spironolactone and eplerenone have been used in heart failure patients with beneficial effects,[1] but their use is limited to patients with normal renal function and normokalemia, as they may cause hyperkalemia and worsening renal function, especially in the elderly. On the other hand, small pilot studies using spironolactone in patients with end-stage renal disease on hemodialysis have indicated that it may be safe, without higher hyperkalemia rates, for short-term therapy and if electrolytes are closely monitored.[49]

ULTRAFILTRATION

It is widely recognized that worsening renal function, conferred by various processes, in patients with decompensated heart failure has a negative impact.[50] Among these processes, main contributors comprise the venous congestion, elevated levels of natriuretic peptides, systemic vasoconstriction, and diuretic resistance. In order to overcome this latter situation, extracorporeal ultrafiltration has been heralded as a novel therapy to ameliorate heart failure,[50-52] however, such a potential benefit has not been confirmed by clinical studies. Indeed, the recent results of the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF)[53] refute the efficacy of ultrafiltration. Ultrafiltration resulted in similar weight loss or improved renal function compared with pharmacologic therapy and similar rate of death or rehospitalization for acute heart failure.

5B APPROACH

The 5B approach has been proposed by Ronco et al, and includes **b**alance of fluids (as reflected by body weight), **b**lood pressure, **b**iomarkers, **b**ioimpedance vector analysis, and **b**lood

volume.[54] To facilitate maintaining fluid **b**alance, volume status assessed by clinical examination, central venous pressure and body weight, monitoring fluid intake and output, measuring (plasma and urine) osmolality, electrolytes and acid-base status, all assist in avoiding dehydration or overhydration. Although **b**lood pressure is not an ideal measure of volume status, as there are many compensatory mechanisms maintaining the blood pressure despite volume changes, when affected, it is still a good indicator of a significant volume disturbance, especially when combined with orthostatic vital sign (blood pressure and heart rate) measurements. Testing for myocardial **b**iomarkers, such as the BNP, provides assistance with the diagnosis, prognosis and course of heart failure and/or response to therapy, although some limitations may apply, particularly in presence of renal insufficiency and obesity, in which cases the BNP cut-off for heart failure may need to be doubled. Renal injury biomarkers, such as the NGAL, may also assist in early diagnosing renal damage and guiding therapy. **B**ioimpedance vector analysis (BIVA) is a bedside noninvasive method for volume assessment which can be performed within minutes, by placing a pair of electrodes on the dorsal surface of the wrist and ipsilateral ankle, and then applying a 50-kHz current to the body. The relative hydration is graphically depicted by BIVA as vector length, which, if short, indicates volume overload, whereas longer vectors represent volume depletion. Combining BIVA with BNP measurement has an additive diagnostic and prognostic value.[54] Finally, monitoring volume status during renal replacement therapy by measuring relative **b**lood volume changes with optical or ultrasound techniques can enhance the assessment of the patient's status and guide fluid removal.

CARDIAC RESYNCHRONIZATION THERAPY

Cardiac resynchronization therapy (CRT), effected via biventricular pacing, has now been established as an important therapy in patients with refractory advanced heart failure, low ejection fraction and left bundle branch block.[1] Recently, the indications have expanded to include patients at earlier stage of heart failure. There are some preliminary results that this electrical therapy may also benefit patients with the cardiorenal syndrome, although there is a known initial risk of contrast-induced nephropathy during the procedure.[55]

MECHANICAL SUPPORT

Finally, when all therapies fail and patients progress to end-stage status, left ventricular assist devices have been used to manage these patients with the hope that they will serve either as a bridge to transplant or as an effective destination therapy, being cognizant of the exuberant cost and risks that this aggressive therapy entails.[1] However, patients having both heart failure and kidney failure are poor candidates for mechanical support, due to increased surgical risk and grim overall prognosis. For patients in cardiogenic shock, temporarizing measures include ventilator and intra-aortic balloon pump support, until more definitive therapies, if applicable, can be employed (e.g. revascularization).

Other Therapies

Vasopressin receptor antagonists (vaptans) have been used to promote aquaresis and increase serum sodium in hyponatremic patients but studies have not confirmed any long-term benefit.[1] Since elevated plasma adenosine levels have been reported in patients with heart failure and implicated in the associated renal dysfunction and diuretic resistance, *adenosine receptor antagonists* have been proposed to ameliorate renal function and promote water and sodium excretion. However, preliminary data have not ascribed any benefit to the use of these agents.[11] Intravenous use of a *recombinant BNP agent, nesiritide*,[1] available in the US, but not in Europe, has been shown to be an effective vasodilator, which improves both natriuresis and diuresis, not suffering from tachyphylaxis as nitroglycerin is. However, early data questioned its efficacy and raised questions regarding its potential to aggravate renal function and increase acute mortality, concerns which have not been fully disproved as yet.

CONCLUSION AND FUTURE PERSPECTIVE

Real challenges have been encountered in the understanding of the pathophysiology, the early diagnosis (e.g. with use of new biomarkers and/or other tools), and effective management of the cardiorenal syndrome, which, when fully developed, confers a grave prognosis in patients with decompensated heart failure. Although CRS has spawned some controversy,[56] it is widely recognized that intricate interactions have been implicated in a cascade of events involving a complex process of poorly unraveled cross-talk between the two vital organs, the heart and the kidney (Fig. 1).[8-14,18-26,57] We are in dire need of new therapeutic strategies to be developed and evaluated in future studies in these patients and of a multidisciplinary approach with close collaboration of the cardiologist, the nephrologist and the internist to prevent and/or effectively manage this difficult and puzzling clinical entity.

Admittedly, there is currently no effective medical treatment to directly improve renal function in patients with CRS, however, therapies aimed at improving cardiac function have been promising in producing an increase in GFR with consequent improvement in clinical outcomes. Although several novel therapies have turned our hope into hype, some more recent data give credence to and offer hope for a more effective approach. For example, *cardiac myosin activators (e.g. omecamtiv mecarbil)*, directly activating the enzymatic pathway within the cardiac myocyte leading to ventricular contraction, are new unique inotropic agents, which have been shown in pre-clinical and clinical studies to be effective and hold

promise as a safer and more effective therapeutic approach for the treatment of systolic heart failure.[58] *Urocortins* are endogenous peptides that belong to the corticotrophin-releasing hormone family, hormones that are secreted in response to stress, and have been shown in pre-clinical studies to have beneficial effects on the cardiovascular, hemodynamic, renal, and neurohormonal systems.[59] *Serelaxin*, a recombinant form of human relaxin-2 (a peptide hormone that increases during pregnancy mediating the maternal physiological cardiovascular and renal adaptations) was recently shown to have potential protective effects against organ damage. In the RELAX-AHF (Relaxin in Acute Heart Failure) study, serelaxin, given early in patients with acute heart failure, had favorable effects on the short-term changes in biomarkers of cardiac (troponin, NT-proBNP), renal (creatinine, cystatin-C), and liver damage (transaminases) and was associated with improved 6-month mortality.[60] Importantly, early recognition of heart failure decompensation, via application of novel methods of detection of pulmonary venous congestion with measurement of *bioimpedance* and *remote monitoring of volume status*, would lead to individualized diuretic or other decongestive regimen to prevent florid venous congestion and abort worsening of renal function.[61] Finally, novel approaches are just emerging with *renal artery denervation* techniques for refractory hypertension and heart failure treatment, which may earn a place in the future management of this complex syndrome.[62]

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