Review

Cardiorenal Syndrome or Renocardiac Syndrome

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Cardiorenal syndrome is a complex physiological, biochemical, and hormonal disorder of the heart and kidneys, whereby acute or chronic dysfunction in one organ may lead to acute or chronic dysfunction in the other, has been under focus for a long time. In this review we aim to define the interaction between the kidneys and the heart and different components to characterize the pathophysiological syndromes and discuss new approaches for the management of this entity.

Keywords: Cardiorenal syndrome; Child; Acute Kidney Injury; Chronic Kidney Diseases; Heart Failure.

Running Title: Cardiorenal Syndrome or Renocardiac Syndrome

Introduction

Heart failure is an important health care concern for children and adults worldwide. More than 5 million American adults live with this condition, but there are limited data regarding prevalence in children [1, 2]. Renal dysfunction is a common phenomenon in heart failure and is one of the most potent prognostic indicators in these patients [3]. This mutual interaction share the common name of "cardiorenal syndrome" [4] and this phrase has been used since 2004 [5], but still there are many unanswered key questions. What is the true prevalence? What is the exact pathophysiology? What is the long term prognosis?

Epidemiology

The report of the Acute Decompensated Heart Failure National Registry (ADHERE) of more than 105000 individuals admitted for acute decompensated cardiac failure, showed that 30% had a history of renal failure, 21% had serum creatinine concentration more than 2.0

mg/dl, and 9% had creatinine concentration above 3.0 mg/dl [6].

In a survey of outpatients with congestive cardiac failure, Mc Alister found that 39% of patients in New York Heart Association (NYHA) class 4 and 31% of patients in NYHA class 3 had severely impaired renal function (creatinine clearance less than 30 ml/min)[7]. It was estimated that about 44% of deaths in patients with end stage renal failure are due to cardiovascular disease. Therefore it is obvious that basic renal function, likewise the ejection fraction and NYHA functional class are important prognostic markers [8].

Definition

Cardiorenal syndrome (CRS) describes disorders of the heart and kidneys where acute or chronic dysfunction in one organ may lead to acute or chronic dysfunction of the other. The current definition has been expanded into five subtypes that are classified into primary and secondary pathology, the time frame, and simultaneous cardiac and renal co-dysfunction secondary to

systemic disease :1) CRS type 1 would occur in the setting of acute myocardial dysfunction leading to acute renal failure(acute kidney injury AKI). (e.g. acute myocardial injury, acute decompensated heart failure (ADHF); 2) CRS type 2 describes chronic myocardial dysfunction resulting in chronic renal failure (chronic kidney disease CKD) (e.g., chronic heart failure); 3) CRS type 3 is characterized by an acute change in kidney function leading to acute cardiac dysfunction (e.g., AKI from acute glomerular nephritis); 4) CRS type 4 refers to chronic kidney disease (CKD) resulting in myocardial dysfunction (chronic glomerular impairment) and; 5) CRS type 5 defines the presence of cardiac and kidney dysfunction due to systemic disorders(sepsis) [9].

Pathophysiology
The etiology of decreased renal function in patients with heart failure has been proposed to be due to reduced renal flow and decreased cardiac output for a long time [10].

The hypothesis was thought to be inadequate renal afferent flow activated the renin–angiotensin-aldosterone system (RAAS) leading to fluid retention, increased preload and therefore worsening cardiac output. However, new reports suggest that, though correct, this is a very narrow and incomplete explanation.

The report of The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial [11] assessed pulmonary artery catheter guided management of over 400 patients admitted with acute decompensated heart failure. It found no correlation between baseline renal function and cardiac index, and improving of the latter was not associated with increased renal function. There are also studies that showed improved cardiac index or reduced wedge pressure during pulmonary artery catheter-guided management could not predict improvement in renal function [12, 13].

Additionally increasing in renal function has been demonstrated in acute decompensated heart failure patients despite normal systolic function (ejection fraction), and thus, the presumably, renal blood flow. In combination, these data suggest more than simply reduced renal blood flow as an explanation for CRS.

Renin angiotensin aldosterone system (RAAS) upregulation in heart failure is a maladaptive response to altered hemodynamics and sympathetic signaling. Moreover, neurohormonal factors are more stimulated in the presence of reduced renal function [14, 15] and in the presence of congestion. Renin, angiotensin II and aldosterone cause both systemic and renal vasoconstriction and therefore reduce renal blood flow and increase tubular sodium reabsorption.

Furthermore, high levels of angiotensin II directly damages intrinsic kidney parenchyma since angiotensin II upregulates cytokines transforming growth factor –β, tumor necrosis factor-α, nuclear factor–kB, and interleukin-6 and stimulates fibroblasts, resulting in cell growth, inflammation, and fibrotic damage in the renal parenchyma [17,18].

RAAS inhibitors have well established long-term major clinical benefits in heart failure and have beneficial effects on renal function. Indeed a recent meta-analysis established the greater benefit of RAAS inhibitors on survival in heart failure patients who develop worsening renal function versus those who do not. There is a greater stimulation of RAAS in the presence of reduced renal function, and this can confer greater potential for improvement when RAAS is adequately blocked.

Overactivation of the sympathetic nervous system (SNS) leads to heart failure and reduce renal function. Renal sympathetic overdrive in renal dysfunction goes through RAAS upregulation, mechano and chemoreflex activation and endothelial malfunction with low bioavailability of nitric oxide (NO) [18]. Sympathetic overactivity leads to direct renal afferent and efferent arteriolar vasoconstriction and renin release, and both lead to decreasing renal blood flow and ultimately GFR. Sympathetic overactivity leads to reduction in beta-adrenoreceptor density within the myocardium and also reduce adrenoreceptor sensitivity in both renal and cardiac failure [19,20]. Cathecolamines are also thought to induce left ventricular hypertrophy in some patients. SNS activation leads to increased cardiomyocyte apoptosis [21] and increases the release of the neurohormone Neuropeptide Y (NPY). NPY is a vascular growth promoter leading to neointimal formation (and thus atherosclerosis) [22], induces vasoconstriction, and also interferes with normal immune system function [23].

Beta–Blockers may counteract the negative effects of chronic renal sympathetic nervous system activation [24]. The CIBIS-II trial [25] and MERIT –HF [26] trial clearly demonstrated the advantage of beta blockers in patients with heart failure and renal dysfunction.

Oxidative injury is one of the common links

between progressive cardiac and renal dysfunction. Neurohormones are strong participants and mediators of an oxidative injury cascade that leads to widespread endothelial dysfunction, inflammation and cell death in the heart and the kidneys.

Angiotensin II activates NADPH and NADH oxidase within smooth muscle cells, cardiac myocytes and renal tubular epithelial cells, generating superoxide, areactive oxygen species [27]. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers can increase the availability of nitric oxide, an important factor in endothelial function [28].

Heart failure is marked by an increase in central venous pressure which reduces the perfusion gradient across the renal capillary bed. Rising renal venous pressures could reduce or even inhibit urine production [29] and rising renal venous pressure is more important than falling arterial (perfusion) pressure in this setting. Extrinsic compression on renal veins also has shown compromise renal function [30]. Patients with baseline renal dysfunction or increasing renal dysfunction have significantly elevated central venous pressure after admission in comparison with those with less or no renal dysfunction [31]. Elevated jugular venous pressure on physical examination is also associated with higher baseline serum creatinine and increased risk of hospitalization due to ADHF and death due to pump failure [32].

The Cardiorenal Anemia Syndrome (CRAS) was defined by Silverberg et al. as a vicious cycle of deterioration that leads to poor outcomes, including faster progression of end stage renal failure and further progression of congestive heart failure [33]. Anemia occurs in over one-third of CRS patients [34]. The Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality (CHARM) study proposed that anemia is an independent adverse prognostic factor in congestive cardiac failure patients. Iron deficiency plays a prominent role in patients with congestive heart failure and chronic kidney disease.

The Ferinject Assessment in patients with Iron deficiency and chronic Heart Failure (FAIR-HF) study assessed intravenous iron therapy in 459 symptomatic patients with iron deficiency. It demonstrated that the treatment group had improvement in heart failure symptoms, exercise capacity and quality of life.

Erythropoietin levels are reduced in renal failure but frequently elevated in heart failure. Early studies demonstrated that erythropoietin protects cardiomyocytes from apoptosis which may cause a decrease in oxidative stress as well as increase in hemoglobin as an anti- oxidant [4, 35].

The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoietin Beta (CREATE) trial found that correcting anemia early in patients with renal failure does not reduce their risk of cardiovascular complications [36].

The Trial to Reduce Cardiovascular Events with Anaresp Therapy (TREAT) study found that diabetic patients with renal failure and moderate anemia had no benefit from receiving erythropoietin stimulating agents [37]. Finally the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial found that aiming for a higher hemoglobin level in patients with chronic kidney disease and anemia was associated with a higher risk of adverse outcome including death, hospitalization for heart failure, or myocardial infarction [38]. Consequently, the routine use of ESA therapy to increase hemoglobin levels in anemic CCF patients is not based on valid evidence.

Inflammation in Cardiorenal syndrome

The pathophysiological mechanisms associated with heart failure in CRS has evolved from a simple hemodynamic schema focused on changes in cardiac output and local circulation to one that incorporates maladaptive neurohormonal abnormalities, ventricular neo proteins such as myosin and the modeling, and inflammation as interactive factors. In states of heart failure there is increased production and enhanced release of proinflammatory cytokines, activation of complement system, production of auto-antibodies and the β–adrenergic receptor, overexpression of the major histocompatibility complex class II molecules, and activation of vascular cellular adhesion molecules [39,40].

There are at least five potential routes for immune activation:

1. Through direct antigenic stimulation such as in patients with viral myocarditis
2. Secondary to cardiac damage such as when new antigenic peptides are present on the myocardium and trigger an immune response
3. By local or systemic cytokine release
4. Secondary to chronic, ongoing injury such as chronic congestive heart failure
5. Activation secondary to hemodynamic overload [41].

Inflammation in heart failure is not restricted to the heart, these processes and mediators also may induce functional disturbances in extra cardiac

organ systems such as kidney.

Proinflammatory cytokines in heart failure
These mediators include tumor necrosis factor α (TNF α), interleukin (IL)-1-β, IL-2, IL-6, IL-8, IL-10, IL-13 and IL-18, monocyte chemoattractant protein-1, macrophage inflammatory protein-1, and Regulated upon Activation, Normal T-cell Expressed and Secreted (RANTES) [42].

The specific pattern of cytokine levels highly depends on the etiology and severity of heart failure. In patients with chronic heart failure, increased plasma levels of TNF-α and IL-6 correlate with both the severity of disease symptoms and clinical outcomes [43].

Increased levels of TNF-α occur in patients with New York Heart Association class III/IV heart failure [44], in a sub study of the Studies on Left Ventricular Dysfunction, patients who became symptomatic according to heart failure had progressively higher circulating TNF-α levels, TNF –α is secreted in the failing but not in the non-failing heart, and transgenic mice over expressing TNF-α in cardiac tissue develop dilated cardiomyopathy [45].

Levels of IL-6 are considered an important prognostic marker for mortality of patients with heart failure. Levels of IL-6 have been correlated directly with cardiac filling pressures and inversely with cardiac output. The source of IL-6 is thought to be in cardiac myocytes, peripheral immune cells, or immune cells infiltrating the injured myocardium [46].

C-reactive protein may be increased in patients with left ventricular failure. Recent evidence points that CRP has direct effects on modulating endothelial cells. CRP impairs the ability of endothelial progenitor cells to defend themselves against oxidant stresses and upregulates the rate of endothelial progenitor cell apoptosis [47]. This effect may impair endothelial function and increases the chance of development of atherosclerosis.

Adhesion Molecules are cell-surface receptors that are involved in the adhesion of leukocytes to each other, to endothelial cells, or to extracellular matrix. Soluble intracellular adhesion molecule-1 (ICAM-1) has been proposed to be upregulated in patients with chronic heart failure and a significant negative correlation is observed between left ventricular output and soluble ICAM-1 levels [48]. TNF-α induces the expression of adhesion molecules and thus this cytokine, through its effects on adhesion molecule expression, may lead to mononuclear cell infiltration of the myocardium [49].

Some studies have highlighted the high mortality rate associated with acute kidney injury in critically ill patients thought to be caused in part by multiple distant organ dysfunction syndrome [50].

Acute loss of glomerular filtration rate can lead to dysfunction of heart, brain, lung, and other organs. Factors related to distant organ dysfunction include circulating factors such as cytokines and chemokines, activated leukocytes, and adhesion molecules, which lead to immune cell infiltration. Oxidative injury, apoptosis, cellular necrosis, and uremia play a significant role in the final pathway of organ dysfunction. Acute kidney injury induced by bilateral nephrectomies or bilateral ischemia–reperfusion injury lead to an increase in serum levels of IL-1β, IL-6, and granulocyte colony–stimulating factor (GCSF) early in the course of injury [51].

In acute kidney injury, cytokines may be produced in other tissues and removed by the kidneys. The inability to metabolize or clear cytokines in acute kidney injury may lead to an increase in serum levels that may contribute to systemic effects and negatively affect cardiac function.

In a cohort study of critically ill patients with acute renal failure, TNF- α, IL-1β, IL-6, IL-8, and CRP were increased [52]. Furthermore, an increase in serum IL-10 levels, an anti-inflammatory cytokine, suggests that a compensatory reaction was initiated to decrease the inflammation process.

Immune activation in acute kidney injury has been best studied in a model of ischemia reperfusion injury study. Intact leukocytes, endothelial cells, and epithelial cells contribute to early ischemia–reperfusion injury with final inflammation [53]. In response to hypoxia-reoxygenation, early immune cell infiltration is proposed to initiate processes involved in tissue repair, however, uncontrolled inflammation can be deleterious and lead to further tissue injury.

Resident kidney dendritic cells (DCs) are the dominant resident leukocyte subgroup, and are found in the interstitial extracellular compartment throughout the whole kidney [54].

Management
Medical management of patients with cardiorenal syndrome is often challenging as focus on treatment of one organ may have negative outcome on the other. Multiple therapies for acute decompensated heart failure (ADHF) were investigated in large randomized trials, of which

some included only patients with worsening renal function after initial therapy for ADHF. There are no medical therapies proven to directly increase the GFR (manifested clinically by a decline in serum creatinine) in patients with HF. On the other hand, improving cardiac function can increase GFR, indicating that types 1 and 2 CRS have substantial reversible components.

Clinical trials on decongestion
In essence, all the agents tried to improve renal blood flow, by increasing cardiac output (inotropes, vasodilators) decreasing congestion (diuretics, ultra infiltration) and lowering renal vascular resistance (rolofylline, serelaxin, nesitiride). However, none of the current studied therapeutic strategies have shown beneficial outcomes.
Provisional results on serelaxin and renal denervation therapy are convincing, but need to be confirmed in on-going large trials. Additionally, for the future, it needs to be studied the potential of antioxidative agents in the treatment of the cardiorenal syndrome.

Therapeutic approach for worsening renal function
Current guidelines emphasize that treatment of symptoms of acute decompensated heart failure should be achieved without worsening renal function. When worsening renal function arises during treatment of acute decompensated heart failure, these guidelines recommend different strategies as other diuretic regimens, inotropic support, ultrafiltration, dialysis and vasodilator association [55].
Therapeutic strategies that focus on effectively decongesting the patient, with permissive worsening renal function, have a beneficial impact on mortality compared to persistent fluid overload. Therefore the goal of treatment of acute decompensated heart failure should be effectively reach decongestion, while avoiding significant blood pressure drops and preserve renal blood flow [56].

Diuretics
Used in the treatment of heart failure and cardiorenal syndrome patients, however must be carefully dosed to prevent renal injury. Diuretic resistance is usually a challenge for physicians to overcome which may tackle by changing the dosage, frequency, or adding a second drug [5].
Loop diuretic agents play a key role through their strong diuretic effect on the loop of Henle,

combination therapies with more proximally acting agents like acetazolamide or distal–acting agents like thiazides have shown great outcome.
Furosemide can increase fibrosis by its known stimulation of the renin-angiotensin-aldosterone axis. Furthermore furosemide can also inhibit renal tubular 11-beta hydroxyl steroid dehydrogenase-2, which would permit cortisone to activate the renal mineralocorticoid receptor [57].
The possible adverse effects of diuretics are just beginning to be studied, and better knowledge of how to use them is essential. Nevertheless they remain the mainstay of treatment until other interventions are proven to be safer and more effective.
Worsening serum creatinine, azotemia, and metabolic dehydration alkalosis often limit conventional diuresis in patients with heart failure. Continuous venovenous ultrafiltration is emerging as a possible alternative to pharmacological diuresis in these scenarios and may offer greater ease and efficacy of volume and sodium reduction without further compromising renal function [58].

Ultrafiltration
Ultrafiltration refers to the removal of isotonic fluid from the venous compartment via filtration of plasma across a semipermeable membrane. Ultrafiltration is most often considered in patients with acute decompensated HF and diuretic resistance and/or impaired renal function. By removing isotonic fluid, ultrafiltration maintains physiologic electrolyte balance, in contrast to diuretic therapy.
Three randomized trials (UNLOAD, RAPID-CHF, and CARESS-HF) compared ultrafiltration to diuretic therapy in patients with acute decompensated HF [58-60]. The mean baseline serum creatinine levels were 1.5, 1.7, and 2.0 mg/dL (133, 150, and 177 μmol/L), respectively. In UNLOAD and RAPID-CHF, ultrafiltration was associated with a significantly greater rate of fluid loss than diuretic therapy but no difference in serum creatinine. In CARESS-HF, ultrafiltration was compared to stepped pharmacologic therapy (including bolus plus high doses of continuous infusion loop diuretics, addition of thiazide diuretic [metolazone], and selected intravenous inotrope and/or vasodilator therapy) in patients with worsening renal function and persistent congestion [58]. Although weight loss was similar in ultrafiltration and stepped pharmacologic therapy groups, ultrafiltration therapy led to an

increase in serum creatinine and a higher rate of adverse events.

Thus, although ultrafiltration may be useful for fluid removal in acute decompensated cardiac failure in patients unresponsive to diuretic therapy, the available evidence does not establish ultrafiltration as first line therapy for AHDF or as an effective therapy for CRS. The 2009 American Heart Association/American College of Cardiology guidelines stated that ultrafiltration is reasonable for patients with resistant congestion not responding to medical therapy [61].

Investigational therapies
Two other classes of drugs have been evaluated in the treatment of HF, with no proven effect on kidney function: Antagonists of the vasopressin receptors, which mediate the antidiuretic response, and antagonists of the adenosine A1 receptor.

Neurohormonal activation in patients with HF result in the nonosmotic release of antidiuretic hormone (arginine vasopressin), which leads to free water retention and hyponatremia that parallels the severity of the HF [62].

Tolvaptan is a selective vasopressin 2 receptor antagonist that produces a water diuresis, not a salt diuresis as induced by conventional diuretics. The effect of tolvaptan on cardiovascular outcomes and decongestion in patients with acute HF was evaluated in the EVEREST Outcome trial [63]. Tolvaptan had no effect on the mortality of any cause, mortality or HF hospitalization, or seven-day patient global assessment. However, there were significant benefits in a number of secondary end points including an increase in urine output, resulting in reduced dyspnea and edema and an increase in serum sodium. There was also a statistically significant, but not clinically significant, greater increase in serum creatinine with tolvaptan (0.08 versus 0.03 mg/dL [7.1 versus 2.7 μmol /L] with placebo). Tolvaptan is approved only for the treatment of hyponatremia in patients with HF. Further trials are ongoing to evaluate the role of vasopressin receptor antagonists for the management of the CRS.

Adenosine, acting on the adenosine-1 receptor, narrows the afferent glomerular arteriole, thereby reducing the GFR, and increases tubular sodium reabsorption [64]. Thus, selective adenosine A1 receptor antagonism can increase GFR and promote a diuresis [65], potentially acting synergistically with loop diuretics.

In the PROTECT trial, 2033 patients hospitalized with HF and impaired renal function (mean creatinine clearance 51 mL/min) were randomly assigned to the experimental selective A1 adenosine antagonist rolofylline or to placebo [66]. During the study period, there was no significant difference between the groups in cardiovascular outcomes or in the rate of persistent worsening of renal function, which was defined as an increase in serum creatinine of 0.3 mg/dL (27 micromol/L). In addition, rolofylline therapy was associated with a higher rate of neurologic events (seizure and stroke).

ACEI, ARB, renin inhibitors, aldosterone inhibitors
The use of ACE inhibitors has long term protective effect on renal and cardiac tissue. However, they should be used with caution in patients with cardiorenal syndrome and renal failure. Although patients with renal failure experience slight deterioration of renal function in the short term, the use of ACE inhibitors is shown to have prognostic benefit over the long term which was shown in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) [67]. Data suggest that some increase in creatinine should be tolerated with using of ACE inhibition, and other interventions (such as decreased diuresis) might be needed to accomplish this. The advantage of ACE inhibitors in delaying progression and death in heart failure is undeniable, and their use should be encouraged unless detrimental effects are clearly proven.

Although a minority of patients have an increase in GFR after initiation of ACE inhibitor or ARB therapy, most have a moderate reduction in GFR that can often be ameliorated by reducing the intensity of diuretic therapy. Compared with low-dose ARB therapy in chronic heart failure, high-dose losartan is associated with sustained reductions in e GFR. Despite this effect, high-dose losartan is associated with improved long-term clinical outcomes [68].

While clinical trials of renin-angiotensin-aldosterone system (RAAS) antagonists in HF have not specifically focused on patients with the CRS, subgroup analyses of patients with and without chronic kidney disease (CKD) as well as cohort studies have demonstrated that the beneficial effect of RAAS antagonism on clinical outcomes is not decreased by concomitant CKD [69-71]. While RAAS antagonists retain their clinical benefit in HF among patients with CKD, the risk of adverse events including hyperkalemia and worsening renal function is higher than patients without CKD

[69, 72, 70, and 71]. Patients with CKD should be monitored closely during periods of drug initiation and titration and should receive periodic monitoring of electrolytes and creatinine throughout the duration of therapy [73].

Among patients with decompensated HF, the best outcomes may occur with aggressive fluid removal even if associated with mild to moderate worsening of renal function. Support for aggressive fluid removal comes from the following studies:

A study of 336 patients with decompensated HF in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial found that hemoconcentration was associated with worsening renal function as well as a lower mortality rate [74]. Hemoconcentration was defined as baseline-to-discharge increases in the top one-third of the group in at least two of the following: hematocrit, serum albumin, and serum total protein. Patients with hemoconcentration were treated with higher doses of loop diuretics and more fluid loss, lost more weight, and had greater reductions in intracardiac filling pressures compared with patients without hemoconcentration. Hemoconcentration was strongly associated with worsening renal function (odds ratio 5.3), but also was associated with a significantly lower 180 day mortality rate (adjusted hazard ratio, 0.16, 95% CI 0.02-0.44). Although the total number of deaths was small (n =29), this study suggests that aggressive decongestion in the face of worsening renal function may favorably affect the survival.

An analysis of data from the EVEREST (Efficacy of Vasopressin Antagonism in heart Failure Outcome Study with Tolvaptan) trial showed that hemoconcentration was associated with greater risk of in hospital worsening renal function, though renal parameters generally returned to baseline within four weeks of discharge [75]. Despite this association, every 5 percent increase in-hospital hematocrit change was associated with a decreased risk of all-cause mortality (hazard ratio 0.81, 95% CI: 0.70-0.95).

Additionally, the timing of hemoconcentration may be important, as a study of 845 consecutive patients with HF found that hemoconcentration achieved late during the hospitalization was associated with improved survival while early hemoconcentration was not associated with improved survival compared to no hemoconcentration [73]. Late hemoconcentration was associated with higher average of daily loop diuretic doses and greater weight loss than early hemoconcentration.

These findings provide support for the recommendation included in the 2013 American College of Cardiology/American Heart Association HF guidelines that the goal of diuretic therapy is to eliminate clinical evidence of fluid retention such as an elevated jugular venous pressure and peripheral edema [70]. The rapidity of diuresis can be slow if the patient develops hypotension or worsening renal function. However, the goal of diuretic therapy is to eliminate fluid retention even if this leads to asymptomatic mild to moderate reductions in blood pressure or renal function.

Inotropes
The role of inotropes in patients with CRS is uncertain and the routine use of inotropes cannot be recommended given their lack of proven efficacy and their association with adverse events when used outside of selected patients with cardiogenic shock or acute decompensated HF.

Dobutamine and milrinone have shown to increase cardiac index and renal blood flow in most studies, and after open heart surgery, the increase in renal blood flow is proportional to the increase in the cardiac index [76]. However, the clinical consequences are not clear, with urine output and outcomes have not shown improvement in many studies [77].

A report from the DAD-HF trial of 60 patients with acute decompensated HF found that the combination of dopamine 5 mcg/kg/min plus low-dose furosemide (5mg/h continuous infusion) produced similar urine output as high-dose furosemide (20 mg/h) with reduced risk of worsening renal function (defined as rise in serum creatinine of more than 0.3 mg/dl from baseline to 24 hours; 7 versus 30 percent) [78].

The Renal Optimization Strategies Evaluation (ROSE) trial also tested the hypothesis of whether low-dose dopamine (2mcg/kg/min) (n= 122) would improve urine output and renal function compared to placebo (n= 119) among patients hospitalized with HF and concomitant renal disease [79]. Low-dose dopamine did not improve decongestion or increase renal function when added to diuretic therapy.

The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME) study tested and rejected the routine use of inotropes to permit more effective diuresis and treatment of patients with congestive heart failure [80]. In this study,

the worst renal function, despite poorest outcome, did not show any benefit with milrinone.

Inotropic therapy will continue to be used in patients with worsening renal function presumed to be secondary to decreased cardiac output. Although this treatment regimen still needs to be tested, the routine use of inotropes or other adrenergic stimulating drugs for acute congestive heart failure is not indicated.

Vasodilators

Intravenous vasodilators used in the management of acute decompensated HF include nitrates (eg, nitroglycerin and nitroprusside) and nesiritide, which is recombinant human brain natriuretic peptide.

With respect to effects on the CRS, the Acutely Decompensated Heart Failure National Registry (ADHERE) database of almost 100,000 patients defined worsening renal function as a rise in serum creatinine between admission and discharge of more than 0.5 mg/dL (44 μmol/L) or more than 0.3 mg/dL (27 μmol/L) with a serum creatinine more than 1.5 mg/dL (133 μmol/L) [81]. The rate of worsening renal function was significantly higher when intravenous diuretics were given with the nitroglycerin or nesiritide compared to with intravenous diuretics alone (relative risk 1.20 and 1.44, respectively). However, a causal effect could not be distinguished from patients requiring combination therapy having more severe HF.

Randomized trials have yielded conflicting results on the effect of nesiritide therapy on renal function in the management of acute decompensated HF. The largest trial, ASCEND-HF, found no change in the outcome of worsening renal function with nesiritide therapy (continuous infusion at 0.01 μg/kg/min with an optional initial loading dose of 2 μg/kg) [82, 83]. Similarly, the Renal Optimization Strategies Evaluation (ROSE) trial found that low-dose nesiritide (0.005 μg/kg/min without bolus for 72 h) did not improve decongestion or alter renal function when added to diuretic therapy [79].

Left ventricular assist devices

Evidence suggesting that improvement in cardiac function is associated with increased renal function in patients with types 1 and 2 CRS comes from studies of left ventricular assist devices (LVADs) and cardiac resynchronization therapy:

A study of 4917 patients with continuous-flow LVADs enrolled in the INTERMACS registry demonstrated improvements in serum creatinine and reductions in blood urea nitrogen (BUN) among patients with baseline moderate or severe renal dysfunction. Improvements in estimated GFR (e GFR) were noted within one month of LVAD implantation and persisted over a two-year period of follow-up [84]. However, a separate analysis of data from the INTERMACS registry found early improvements in e GFR with LVAD use were transient and typically only sustained for a period of weeks to months [85].

Analysis of data from an observational study and from the MIRACLE trial found that cardiac resynchronization therapy improved the LV ejection fraction and the e GFR in selected patients with HF and moderately reduced baseline e GFR (e GFR 30 to 59 mL/min) [86, 87].

Conclusion

Renal dysfunction is present in a large group of patients with heart failure, and worsening renal function occurs in 20-30% of patients admitted for acute congestive heart failure. The underlying pathophysiology of worsening renal function is related to an imbalance in interactions of the failing heart, the neurohormonal and inflammatory system, as well as heart failure therapies influencing glomerular filtration.

Fortunately, the importance of the cardiorenal syndrome has been realized recently, and investigations looking at both cause and treatment are ongoing. Nowadays, interventions to treat the renal problems are lacking; no agents have been shown to directly increase renal function in patients with heart failure. Our improved understanding of the mechanism behind cardiorenal syndrome should be considered when evaluating these patients with a poor prognosis and complex dilemmas.

Recommendations

Pediatric patients followed for systolic or diastolic dysfunction or a history of heart failure secondary to myocardial dysfunction should be appropriately screened for kidney disease, including evaluating by a heart failure cardiologist with noninvasive imaging such as echocardiography and appropriate serologic testing including assessment of renal function and BNP.

All pediatric patients followed for chronic kidney disease should be appropriately screened for myocardial disease with noninvasive imaging such as echocardiography and appropriate serologic testing. Pediatric patients with evidence of acute

decompensated heart failure should be monitored for acute kidney injury. Early intervention should be administered in patients with clinical evidence of cardiorenal syndrome based on its potential benefits in specific population. Consultation of pediatric cardiology and pediatric nephrology should be considered to provide a multidisciplinary assessment and approach to patients with evidence of cardiorenal syndrome.

Conflict of Interest
None declared

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