Cardiorenal Syndrome

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Very often, physicians confront with patients who have concomitant heart and kidney failure. The coexistence of kidney and heart failure carries an extremely bad prognosis. The exact cause of deterioration of kidney function and the mechanism underlying this interaction are complex, multifactorial in nature, and still not completely understood. Both the heart and the kidney act in tandem to regulate blood pressure, vascular tone, diuresis, natriuresis, etc. An extension to the Guytonian model of volume and blood pressure control is proposed called cardiorenal connection. Regulating actions of Guyton’s model were coupled to their extended actions on structure and function of the heart and the kidney changes in the rennin-angiotensin-aldosterone system, the imbalance between nitric oxide and reactive oxygen species, the sympathetic nervous system, and inflammation are the cardiorenal connectors to develop cardiorenal syndrome. Imbalance in this closed complex will often lead to deterioration of both cardiac and kidney function. The World Congress of Nephrology emphasized vast interrelated derangements that can occur in cardiorenal syndrome and proposed that the recent definition of cardiorenal syndrome be modified into categories whose labels reflect the likely primary and secondary pathology and time frame. For management, drugs that impair kidney function are undesirable, particularly in a population with already compromised or at risk of kidney function. In severe volume-loaded patients who are refractory to diuretics, management of cardiorenal dysfunction is challenging. In the absence of definitive clinical trials, treatment decision must be based on a combination of patient’s condition and understanding of individual treatment options.

INTRODUCTION

Very often a physician is confronted with patients who have concomitant heart as well as kidney failure. Cardiovascular disease is the leading cause of death consisting of 43.6% of all deaths in patients with end-stage renal disease (ESRD).¹ Both decrease in glomerular filtration rate (GFR) and proteinuria are independent risk factors for the development of cardiovascular disease.² Some patients with severe renal artery stenosis clinically manifest as acute congestive heart failure due to volume and pressure overload.³ On the other hand, there has been a tremendous increase in the incidence of kidney dysfunction while on treatment for cardiac failure with angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and diuretics to reverse congestion in patients who are have fluid overload.⁴ Further, acute decompensated...
heart failure, cardiac ischemia, and arrhythmia may lead to acute impairment of kidney function through renal arterial under filling and a drop in renal blood flow secondary to low cardiac output. Investigative and therapeutic procedures such as percutaneous coronary intervention, coronary artery bypass surgery, or fibrinolytic therapy can also lead to impaired kidney function.\textsuperscript{5-7} The coexistence of kidney and heart failure in a same individual carries an extremely bad prognosis.\textsuperscript{8-10} The exact cause of deterioration of kidney function and the mechanism underlying the initiation and maintenance of this interaction are complex, multifactorial in nature, and still not completely understood.\textsuperscript{11}

CARDIORENOAL CONNECTION

Fundamentally, the heart and the kidneys are the organs which are richly vascular (the kidneys are more vascular than the heart). In addition, both organs are supplied by sympathetic and parasympathetic innervations. These two organs are acting in tandem to regulate blood pressure, vascular tone, diuresis, natriuresis, intravascular volume homeostasis, peripheral tissue perfusion, and oxygenation. They have endocrine functions with interdependent physiological hormonal actions regulated by arterial natriuretic peptide, a vasodilator secreted from the heart, and rennin-angiotensin-aldosterone system (RAAS). Also, vitamin D3, erythropoietin, and renalase are all secreted from the kidneys and are capable of cellular and humoral signaling. Dysfunction of either of the two organs can cause dysfunction of the other. Changes in the RAAS, the imbalance between nitric oxide (NO) and reactive oxygen species (ROS), the sympathetic nervous system, and inflammation are the cardiorenal connectors to develop cardiorenal syndrome.\textsuperscript{12} These connectors together decrease the sensitivity of erythropoietin and are responsible for renal anemia that also aggravates the clinical conditions of cardiac failure (Figure 1).\textsuperscript{13} Cardiorenal syndrome, a poorly understood clinical entity, needs more widely accepted definition and pathogenesis, and its challenging management needs to be looked into. Yet it has remained a source of debate.

WHAT IS CARDIORENOAL SYNDROME?

The National Heart, Lung, and Blood Institute constituted a working group of investigators in August 2004 to examine the current state of knowledge regarding the spiral interplay between the cardiovascular system and the kidneys.\textsuperscript{14} The current definition of cardiorenal syndrome arisen from the work carried out by the above group is “a state in which therapy to relieve congestive heart failure symptoms is limited by further worsening renal function.” More broadly it is described as “moderate or greater renal dysfunction exists or develops in a patient with decompensated heart failure during treatment.”\textsuperscript{15} Moderate kidney

\begin{figure}
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\includegraphics[width=\textwidth]{cardiorenal_diagram.png}
\caption{Cardiorenal connection and its effect on erythropoietin. Imbalance between nitric oxide and reactive oxygen species, by increased inflammation, increased activity of the rennin-angiotensin system, and increased activity of the sympathetic nervous system, causes cardiorenal syndrome. Together, these “cardiorenal connectors” decrease sensitivity to erythropoietin. NO-ROS indicates nitric oxide-reactive oxygen species.}
\end{figure}
dysfunction is defined, in turn, as a glomerular filtration rate of less than 60 mL/min/m². Thus, worsening kidney function as determined by a decline in creatinine clearance in patients with decompensated heart failure is an identifier of this syndrome. However, there is currently no common agreement on what degree of change in serum creatinine is needed for the diagnosis of cardiorenal syndrome.

Recently in the World Congress of Nephrology, Ronco and colleagues did emphasize the bidirectional nature of the heart-kidney interaction and the vast interrelated derangements that can take place in cardiorenal syndrome, and hence, proposed that the recent definition of cardiorenal syndrome be modified into categories whose labels reflect the likely primary and secondary pathology and time frame (Table). Emerging biomarkers may be used for early recognition and intervention because of this interrelation of these two organs. Accordingly the definition was proposed as “a pathophysiological disorder of the heart and kidney in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.” This classification further needs to be looked into, and hence, this review is focused on the more widely accepted definition of cardiorenal syndrome—manifestation of deteriorating kidney function in the presence of heart failure.

PREVALENCE

For predicting adverse outcomes in the hospitalized patients with decompensated cardiac failure, worsening of kidney function is more important than the baseline kidney function. Further, it is at least as powerful adverse prognostic factor as most clinical variables, including ejection fraction. Retrospective analyses of the studies of left ventricular dysfunction (SOLVD) treatment and prevention trials by Dries and colleagues revealed that estimated GFR was an important determinant of survival. Reviewing the second prospective randomized study of ibopamine on mortality and efficacy (PRIME-II trial), Hillege and coworkers also observed that estimated GFR was the most powerful predictor of mortality as ejection fraction.

The Acute Decompensated Heart Failure National Registry database (namely the ADHERE) was the largest database to study the management and outcome of patients with acute decompensated heart failure. The ADHERE enrolled more than 100 000 discrete patient admissions to 270 hospitals in the United States due to heart failure. Analyses of this database showed that the mean estimated GFR was 48.9 mL/min/m² for men and 35.0 mL/min/m² for women. Thus, a typical patient admitted for acute decompensated heart failure had stage 3 (moderate) kidney dysfunction. Among women, fewer than 10% had a normal GFR or only mild kidney dysfunction, and 46.8% had severe dysfunction or frank kidney failure. These figures were only slightly better in men; over 60% had moderate to severe kidney dysfunction. Thus, kidney disease, albeit uncommon in patients enrolled in clinical trials, is observed in most patients with acute decompensated heart failure. According to the ADHERE database, an increase of 25% or greater...

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Mechanism</th>
<th>Clinical Conditions</th>
<th>Markers</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Acute cardiorenal syndrome</td>
<td>Abrupt worsening of kidney function leading to acute kidney injury</td>
<td>Acute cardiogenic shock and acutely decompensated congestive heart failure</td>
<td>ET-1, Troponin, CPK-MB</td>
<td>17</td>
</tr>
<tr>
<td>Type II</td>
<td>Chronic cardiorenal syndrome</td>
<td>Chronic abnormalities in kidney function causing progressive and potentially permanent kidney disease</td>
<td>Chronic congestive heart failure</td>
<td>ET-1, BNP</td>
<td>17, 18</td>
</tr>
<tr>
<td>Type III</td>
<td>Acute renocardiac syndrome</td>
<td>Abrupt worsening of kidney function causing acute cardiac disorder</td>
<td>Acute kidney ischemia and glomerulonephritis</td>
<td>TNF-α, IL-1, IL-6, IL-8</td>
<td>3, 19</td>
</tr>
<tr>
<td>Type IV</td>
<td>Chronic renocardiac syndrome</td>
<td>Chronic kidney disease contributing to decline in cardiac function</td>
<td>Chronic glomerular and Interstitial disease</td>
<td>PTH, CPP product, Cystatin C</td>
<td>16, 20, 21,22</td>
</tr>
<tr>
<td>Type V Secondary cardiorenal syndrome</td>
<td>Systemic condition causing both cardiac and kidney dysfunction</td>
<td>Diabetes mellitus, Sepsis</td>
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in serum creatinine level is a very specific marker for poor prognosis, but it lacks sensitivity.

Not only the worldwide prevalence of ESRD is increasing, but also the number of patients with moderate kidney dysfunction shows as an epidemic. An epidemic of heart failure is also in progress, due to increasing age and better survival after myocardial infarction. The risk of developing chronic kidney disease in heart failure has not been defined clearly, but kidney dysfunction is often observed in patients with heart failure and is associated with adverse prognosis.

PATHOPHYSIOLOGY

The mechanism underlying the interplay of cardiac failure and kidney dysfunction is still not completely understood. Decline in cardiac function causing decrease in tissue perfusion, and thus, adversely affecting renal perfusion is well known and provide an explanation for some aspects of cardiorenal syndrome. Nonetheless, some studies proved worsening of kidney function had no correlation with ejection fraction. Similarly, changes in body weight and diuresis was not significantly related to the development of kidney dysfunction amongst hospitalized patients with heart failure. These observations reflect that the pathophysiology of kidney dysfunction in the context of heart disease is much more complex than simple reduction of cardiac output.

CARDIORENAL CONNECTORS AND SEVERE CARDIORENAL SYNDROME

Bongartz and colleagues recently proposed an extension to the Guytonian model of volume and blood pressure control called “the cardiorenal connection.” Actions of the regulators of Guyton’s model were coupled to their extended actions on structure and function of the heart and the kidney. Thus, it can be stated that “when one of the organs fails, a vicious circle develops in which the RAAS, the NO-ROS balance, the sympathetic nervous system, and inflammation interact and synergize, called the cardiorenal connection” (Figure 2). An imbalance in this closed complex loop will often lead to deterioration of both cardiac and kidney function.

Inappropriate activation of the RAAS in kidney and heart failure causes dysregulation of extracellular fluid volume and vasoconstriction, results in formation of ROS via activation of nicotinamide adenine dinucleotide phosphate oxidase, leads to vascular inflammation via the nuclear factor-kappa B pathway, and increases sympathetic activity. On the other hand, the imbalance between NO and ROS, by increased ROS production, a low antioxidant status, and lower availability of NO may increase activity of preganglionic sympathetic neurons and stimulate
RAAS directly by damaging the renal tubular or interstitial cells or by afferent vasoconstriction with chronic inhibition of NO synthesis. The chronic inflammatory state that is present in both chronic kidney disease and heart failure, in turn, can cause ROS production by activating leukocytes to release their oxidative contents. Finally, the increased sympathetic nervous system activity in both kidney and heart failure may induce inflammation by norepinephrine-mediated cytokine production, and by releasing neuropeptide Y, which can alter cytokine release and immune cell function. In this way, all four cardiorenal connectors can augment each other with their deleterious effects in severe cardiorenal syndrome as a consequence (Figure 3).

**MANAGEMENT**

Unfortunately, there is not enough evidence from clinical trials on heart failure in patients with significant kidney dysfunction as most patients are recruited from the populations with relatively preserved kidney function. Drugs that impair kidney function are undesirable, particularly in a population with already compromised or “at-risk” kidney function. In severe volume-loaded patients who are refractory to diuretics and also have kidney dysfunction, management of cardiorenal dysfunction is challenging, and effective therapy is lacking. In the absence of definitive clinical trials, treatment decision must be based on a combination of individual patient information and understanding of individual treatment options.

**Diuretics**

Although diuretics are effective in producing short-term symptomatic relief, several studies have found that higher doses of diuretics are independently associated with pump failure and sudden death. In the presence of ACEI therapy, aggressive induction of diuresis can be associated with worsening kidney function. There is long-standing and increasing evidence indicating that diuretic drugs exacerbate neurohumoral activity; deteriorate left ventricular function; and increase systemic vascular resistance, plasma rennin and aldosteron activity, and plasma levels of maladaptive neurohormones such as norepinephrine and arginine vasopressin. These can lead to kidney dysfunction and possibly worsening of heart failure outcomes.

In the absence of definitive data, patients with volume overload and nonhypotension patients should not be restricted from receiving loop diuretics (slow high intravenous doses to minimize ototoxicity) or thiazides to alleviate symptoms.

**Iontropes**

To facilitate diuresis with preservation or
improvement of kidney function, positive inotropic agents (dobutamine, phosphodiesterase inhibitors, and levosimendan) may be used. In both acute and chronic heart failure, inotropic drugs, in comparison to placebo and vasodilators, have been associated with an increased risk of mortality and other adverse cardiac events. Therefore, the role of inotropes in cardiorenal syndrome remains controversial. Until more data are available, inotropic therapy should be reserved for patients with clinical evidence of severe low cardiac output, in which vasodilator therapy is not possible because of reduced systemic pressure or low systemic vascular resistance.

**Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers**

Inhibitors of the RAAS are the cornerstone for management of patients with left ventricular systolic dysfunction. They also prevent progressive kidney dysfunction in diabetic nephropathy and other forms of chronic kidney disease. It was also observed that discontinuation of ACEIs because of kidney dysfunction identified a patient group with heart failure who had a high mortality risk. The effect of ACEIs in patients with heart failure and renal insufficiency is not easy to determine because: (1) exclusions in the clinical trials are based on serum creatinine levels rather than estimated GFR, and (2) only a small proportion of patients included in these trials have serum creatinine levels greater than 2.0 mg/dL. Proteinuria is a widely accepted surrogate marker for renoprotection. In patients with advanced renal insufficiency, ACEI therapy is associated with significant long-term benefits. To reduce the incidence of kidney dysfunction, patients should be started on the lowest dose of an ACEI, but avoid dehydration and concomitant use of nonsteroidal anti-inflammatory drugs. It is therefore wise to refrain from administering ACEIs or angiotensin receptor blockers if serum creatinine concentration is approximately 6 mg/dL, the estimated GFR is less than 20 mL/min, or any other clinical contraindication situation exists. It can be continued as long as kidney dysfunction does not steadily deteriorate and severe hyperkalemia does not develop.

**Vasodilators and Natriuretic Peptide**

In some nonhypotensive patients with low cardiac output, cold extremities and increased peripheral vascular resistance due to excessive vasoconstriction often favorably responds to vasodilation. Renal insufficiency is not a contraindication to the use of vasodilators. It is important to bear in mind that these agents were not specifically developed for treatment of acute decompensated heart failure, nor were they studied in robust and properly powered clinical trials on acute decompensated heart failure. Thus, their usage in acute decompensated heart failure and cardiorenal syndrome is subject to further study.

Nesiritide is a synthetic form of b-type natriuretic peptide that was approved by the Food and Drug Administration for treatment of acute decompensated heart failure. Administration of nesiritide results in venous, arterial, and coronary vasodilatation, reducing cardiac the pre- and after-load, which increases cardiac output without direct inotropic effects. Nesiritide is currently used in the treatment of acute decompensated heart failure, where it has been shown to decrease pulmonary capillary wedge pressure, pulmonary artery pressure, right atrial pressure, and systemic vascular resistance, as well as increasing cardiac and stroke volume indexes. In addition, nesiritide has long been known to attenuate neurohormonal activity, and no surprisingly, it increases GFR and filtration fraction, suppresses the RAAS, and enhances diuresis and natriuresis. However creatinine clearance did not show any improvement in those patients who showed natriuresis and diuresis. In the context of cardiorenal dysfunction, renal effects of nesiritide was first addressed by Wang and colleagues. They found that nesiritide had no effect on GFR, renal plasma flow, urine output, or sodium excretion. The serial infusion of nesiritide (FUSION-II) trial, which was completed recently, was a study designed to look at intermittent infusion of nesiritide in patients with severe heart failure. Infusions were given either once weekly or twice weekly over 12 weeks. At the recent Heart Failure Society of America Meeting, an analysis of the patients with renal insufficiency was presented; 600 of the 900 patients had a GFR less than 60 mL/min and were included in the analysis. The FUSION-II study demonstrated no significant effect on outcome or quality of life, but there was an effect on the kidney—an increasing serum creatinine level of more than 0.5 mg/dL.
was favorably influenced by nesiritide. Out of 911 patients, the primary endpoint was time to all-cause death or cardiovascular or renal hospitalization at 12 weeks as 36.8% and 36.7% of the placebo and nesiritide groups, respectively.

Ultrapfiltration
Currently, ultrafiltration is reserved for patients with chronic volume overload resistant to therapy. Renal replacement therapy (ultrafiltration or dialysis) improves renal responsiveness and cardiac hemodynamics, but is usually used as a palliative option in the end stages of cardiorenal syndrome and does not provide a long-term solution.

FUTURE TARGETS
A number of investigational drugs are currently under investigation for the treatment of acute decompensated heart failure, several targeting neurohormonal blockade, specifically endothelin and vasopressin pathways. Further studies are warranted to fully elucidate the safety and therapeutic benefits of these agents. Levosimendan belongs to a promising new class of inotropic agents called “calcium sensitizers.” A randomized trial showed a moderate or marked improvement in the patient’s global assessment of patients treated with levosimendan. Tezosentan, an endothelin receptor blocker, has recently emerged as a promising therapeutic agent. Tolvaptan, a V2 receptor antagonist, has been shown in preliminary studies to increase urine output in patients with heart failure. Early studies have indicated that adenosine A1 receptor antagonists show promising diuretic properties in patients with acute decompensated heart failure. Finally, it appears that regular use of erythropoietin in anemic patients with diminished kidney function improves cardiac performance and delays progression of kidney disease. It is not yet clear whether erythropoietin modulates inflammation, NO-ROS balance, sympathetic nervous system, or RAAS in a greater or lesser degree.

CONCLUSIONS
Cardiorenal syndrome is an interdependent involvement of both the heart and the kidney in a spiral fashion leading to volume overload, diuretic resistance, and further involvement of all systems in which clinical condition will likely worsen before they get better. Decrease in GFR or creatinine clearance in patients with decompensated heart failure involves longer hospital stay and more utilization of hospital resources, but still the prognosis is grave. Although the exact underlying pathogenesis is not clear, the cardiorenal connections are the co-involvement of balance between NO and ROS, RAAS, inflammation, and the sympathetic nervous system, in which oxidative stress is the factor being strongly implicated.

Earlier use of slow high-dose intravenous diuretics, dialysis with ultrafiltration for treatment of congestion, ionotropes, and left ventricular assistant device to stabilize the hemodynamics and maintenance of the renal perfusion is the vital component for a short period of time which is a clinical challenge of initial management. In the present scenario, potential rewarding pharmacological management is lacking. However, treatment with nesiritide, selective adenosine A1 receptor blocker, and vasopressin antagonists which have different effects on generalized hemodynamics and tubular functions may have some response. Studies on nesiritide demonstrated either a neutral effect or favorable effect of nesiritide on kidney function, but were disappointing in the sense that the use of nesiritide did not result in improvement of survival or quality of life. There is no selective pharmacological therapy available to directly influence the four cardiorenal connection (balance between NO and ROS, RAAS, inflammation, and the sympathetic nervous system), other than ACEI and aldosterone inhibitors to block the RAAS and inhibit oxidative stress and inflammation. Postulation to intervene all these connectors may stop the cascade of cardiorenal connection to prevent severe cardiorenal (newly delineated clinical) syndrome.

CONFLICT OF INTEREST
None declared.

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