Cardiorenal Syndrome

Himanshu Sekhar Mahapatra,[1] Robert Lalmalsawma,[1]
Narendra Pal Singh,[1] Mahender Kumar,[1] Suresh Chandra Tiwari[2]

[1]Department of Nephrology, Postgraduate Institute of Medical Education & Research, Dr RML Hospital, New Delhi, India
[2]Department of Nephrology, All India Institute of Medical Science, New Delhi, India

Keywords. heart failure, renal insufficiency, hemodynamics

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.

IJKD 2009;3:61-70
www.ijkd.org

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.[5-7] The coexistence of kidney and heart failure in a same individual carries an extremely bad prognosis.[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.[11]

CARDIORENAL 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.[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).[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 CARDIORENAL 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.[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.[11]" Moderate kidney

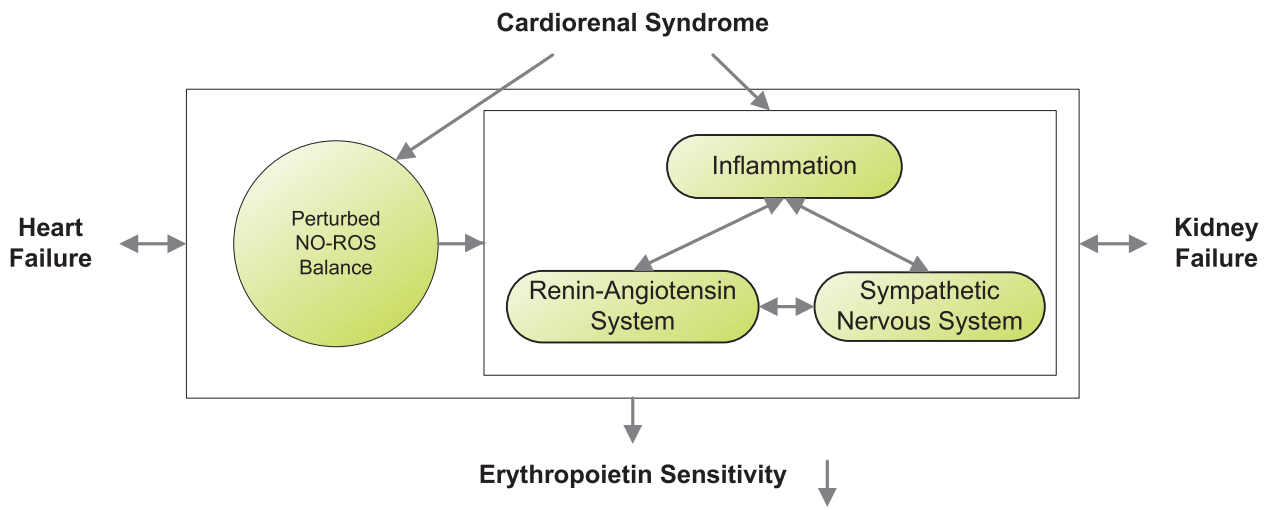

Figure 1. Cardiorenal connection and its effect on erythropoietin. Imbalance between nitric oxide and reactive oxygen species, by increased inflammation, increased activity of the rennin-angiotensin system, and increased activity of the sympathetic nervous system, causes cardiorenal syndrome. Together, these "cardiorenal connectors" decrease sensitivity to erythropoietin. NO-ROS indicates nitric oxide-reactive oxygen species.

Classification of Cardiorenal Syndrome Proposed By Ronco and Colleagues[16]*

Type	Name	Mechanism	Clinical Conditions	Markers	References
Type I	Acute cardiorenal syndrome	Abrupt worsening of kidney function leading to acute kidney injury	Acute cardiogenic shock and acutely decompensated congestive heart failure	ET-1, Troponin, CPK-MB	17
Type II	Chronic cardiorenal syndrome	Chronic abnormalities in kidney function causing progressive and potentially permanent kidney disease	Chronic congestive heart failure	ET-1, BNP	17, 18
Type III	Acute renocardiac syndrome	Abrupt worsening of kidney function causing acute cardiac disorder	Acute kidney ischemia and glomerulonephritis	TNF-α, IL-1, IL-6, IL-8	3, 19
Type IV	Chronic renocardiac syndrome	Chronic kidney disease contributing to decline in cardiac function	Chronic glomerular and Interstitial disease	PTH, CPP product, Cystatin C	16, 20, 21,22
Type V	Secondary cardiorenal syndrome	Systemic condition causing both cardiac and kidney dysfunction	Diabetes mellitus, Sepsis	…	…

*ET-1 indicates endothelin-1; CPK-MB, creatine phosphokinase-MB; BNP, B-type natriuretic peptide; TNF, tumor-necrosis factor; IL, interleukin; PTH, parathyroid hormone; and CPP, calcium-phosphate product. Ellipses indicate not applicable.

dysfunction is defined, in turn, as a glomerular filtration rate of less than 60 mL/min/m^2. Thus, worsening kidney function as determined by a decline in creatinine clearance in patients with decompensated heart failure is an identifier of this syndrome.[15] 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[16] 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). Emergeing 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.[16]" 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.[3,18,23,24] Further, it is at least as powerful adverse prognostic factor as most clinical variables, including ejection fraction.[25] 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 determent of survival.[26] 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.[27]

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.[28] Analyses of this database showed that the mean estimated GFR was 48.9 mL/min/m^2 for men and 35.0 mL/min/m^2 for women.[11] 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

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.[29,30] An epidemic of heart failure is also in progress, due to increasing age and better survival after myocardial infarction.[31] 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.[17]

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.[3,18,19] Similarly, changes in body weight and diuresis was not significantly related to the development of kidney dysfunction amongst hospitalized patients with heart failure.[22] 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[12] 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,[32]

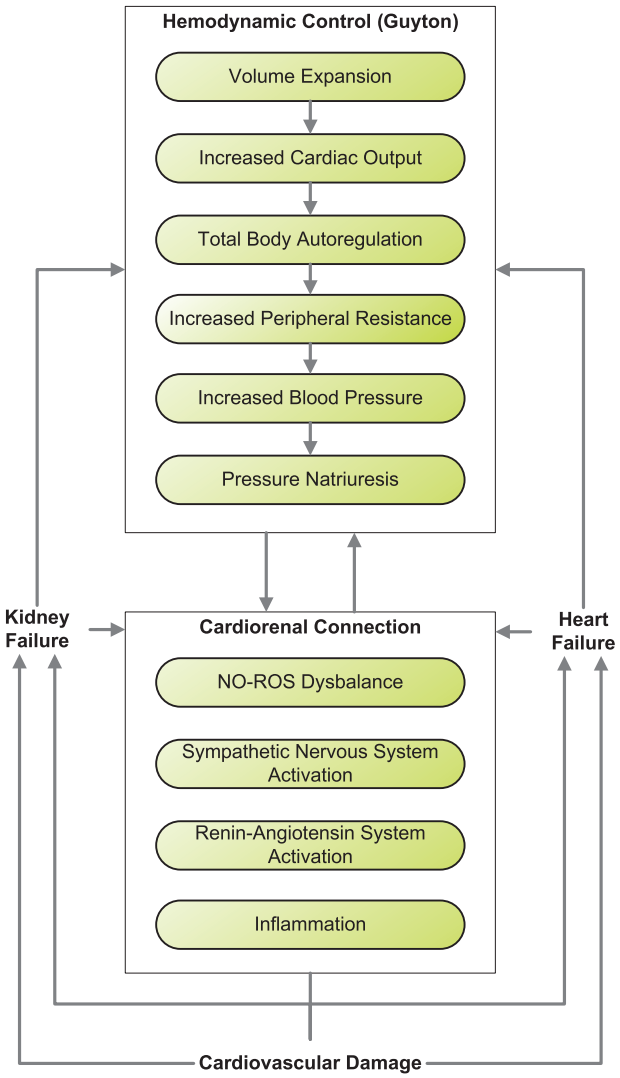

Figure 2. Pathophysiological basis of the severe cardiorenal syndrome. The model of Guyton explains heart-kidney interaction with respect to extracellular fluid volume, cardiac output, and mean arterial pressure. When one of these organs fails, a vicious circle develops in which the rennin-angiotensin system, the nitric oxide-reactive oxygen species (NO-ROS) balance, the sympathetic nervous system, and inflammation interact and synergize, here called the "cardiorenal connection." Adapted from an article by Bongartz and colleagues with permission of the publisher.[12]

results in formation of ROS via activation of nicotinamide adenine dinucleotide phosphate oxidase,[33,34] leads to vascular inflammation via the nuclear factor-kappa B pathway,[35,36] and increases sympathetic activity.[37] On the other hand, the imbalance between NO and ROS, by increased ROS production,[38] a low antioxidant status, and lower availability of NO may increase activity of preganglionic sympathetic neurons and stimulate

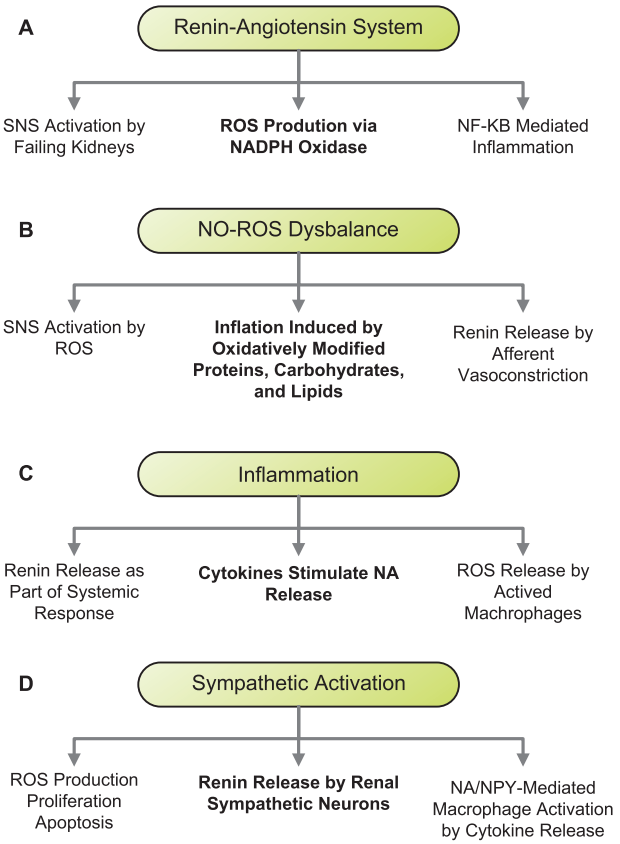

Figure 3. A, Angiotensin-II affects the other cardiorenal connectors: sympathetic nervous system (SNS) activation in kidney failure, generation of reactive oxygen species (ROS), and nuclear factor-kappa B (NF-KB)-mediated pro-inflammatory gene expression. B, Imbalance between nitic oxide (NO) and ROS is a central event in cardiovascular diseases. In the cardiorenal connection, this balance may influence SNS activity, release renin and angiotensin, and promote inflammation by oxidative modification of substances. C, Persistent inflammation has been found in both renal and heart failure. By altering ROS functioning, and promoting ROS and noradrenaline (NA) formation, inflammation contributes to the positive feedback loops in the cardiorenal connection. D, The SNS activity is increased in both renal and heart failure. By affecting the other cardiorenal connectors, it can play a significant role in severe cardiorenal syndrome. It stimulates renin release from the kidneys, generates ROS, and induces inflammation. NPY indicates neuropeptide Y and NADPH, nicotinamide adenine dinucleotide phosphate. Adapted from an article by Bongartz and colleagues with permission of the publisher.[12]

RAAS directly by damaging the renal tubular or interstitial cells or by afferent vasoconstriction with chronic inhibition of NO synthesis.[39] 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.[40] Finally, the increased sympathetic nervous system activity in both kidney and heart failure may induce inflammation by norepinephrine-mediated cytokine production,[41] 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.[42] 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.[43] 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.[37,44,45] In the presence of ACEI therapy, aggressive induction of diuresis can be associated with worsening kidney function.[19,46] 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.[47,48] 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 ototoxity) or thiazides to alleviate symptoms.[49]

Ionotropes

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.[50, 51] 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.[52] 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.[53]

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.[42] Proteinuria is a widely accepted surrogate marker for renoprotection.[54,55] In patients with advanced renal insufficiency, ACEI therapy is associated with significant long-term benefits.[56] 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.[42] 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 Natiuretic 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.[57] Renal insufficiency is not a contraindication to the use of vasodilators.[42] 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.[58,59] 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.[59,60] However creatinine clearance did not show any improvement in those patients who showed natriuresis and diuresis.[61]

In the context of cardiorenal dysfunction, renal effects of nestritide was first addressed by Wang and colleagues.[62] They found that nestritide 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.[63] 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 end point 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.[63]

Ultrafiltration

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.[49,64]

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.[65] Tezosentan, an endothelin receptor blocker, has recently emerged as a promising therapeutic agent.[66] Tolvaptan, a V2 receptor antagonist, has been shown in preliminary studies to increase urine output in patients with heart failure.[67] Early studies have indicated that adenosine A1 receptor antagonists show promising diuretic properties in patients with acute decompensated heart failure.[68] Finally, it appears that regular use of erythropoietin in anemic patients with diminished kidney function improves cardiac performance and delays progression of kidney disease.[69,70] It is not yet clear whether erythropoietin modulates inflammation, NO-ROS balance, sympathetic nervous system, or RAAS in a greater or lesser degree.[71]

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.

REFERENCES

1. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. USRDS 1997 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney diseases; 1997 [cited 2003 Nov 9]. Available from: http://www.usrds.org/adr_1997.htm/.
2. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular

disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108:2154-69.

3. Gottlieb SS, Abraham W, Butler J, et al. The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail. 2002;8:136-41.
4. Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol. 2003;41:1797-804.
5. Best PJ, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol. 2002;39:1113-9.
6. Rao V, Weisel RD, Buth KJ, et al. Coronary artery bypass grafting in patients with non-dialysis-dependent renal insufficiency. Circulation. 1997;96:II-38-43; discussion II-4-5.
7. Gibson CM, Pinto DS, Murphy SA, et al. Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality. J Am Coll Cardiol. 2003;42:1535-43.
8. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol. 2006;47:76-84.
9. Stevenson LW, Nohria A, Mielniczuk L. Torrent or torment from the tubules? Challenge of the cardiorenal connections. J Am Coll Cardiol. 2005;45:2004-7.
10. van Kimmenade RR, Januzzi JL, Jr., Baggish AL, et al. Amino-terminal pro-brain natriuretic Peptide, renal function, and outcomes in acute heart failure: redefining the cardiorenal interaction? J Am Coll Cardiol. 2006;48:1621-7.
11. Heywood JT. The cardiorenal syndrome: lessons from the ADHERE database and treatment options. Heart Fail Rev. 2004;9:195-201.
12. Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B. The severe cardiorenal syndrome: 'Guyton revisited'. Eur Heart J. 2005;26:11-7.
13. Putten KV, Braam B, Jie KE, Gaillard CAJM. Mechanisms of disease: erythropoietin resistance in patients with both heart and kidney failure. Nat Clin Pract Nephrol. 2008;4:47-57.
14. National Heart, Lung, and Blood Institute Working Group. Cardiorenal connections in heart and cardiovascular disease. National Heart, Lung, and Blood Institute; 2007 [cited 2007 Oct 31]. Available from: http://www.nhlbi.nih.gov/meetings/workshops/cardiorenal-hf-hd.htm/.
15. Francis G. Acute decompensated heart failure: the cardiorenal syndrome. Cleve Clin J Med. 2006;73 Suppl 2:S8-13; discussion S30-3.
16. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52:1527-39.
17. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation. 2004;109:1004-9.
18. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol. 2004;43:61-7.
19. Knight EL, Glynn RJ, McIntyre KM, Mogun H, Avorn J. Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy: results from the studies of left ventricular dysfunction (SOLVD). Am Heart J. 1999;138:849-55.
20. Neuhofer W, Pittrow D. Role of endothelin and endothelin receptor antagonists in renal disease. Eur J Clin Invest. 2006;36 Suppl 3:78-88.
21. Spanaus KS, Kronenberg F, Ritz E, et al. B-type natriuretic peptide concentrations predict the progression of nondiabetic chronic kidney disease: the Mild-to-Moderate Kidney Disease Study. Clin Chem. 2007;53:1264-72.
22. Butler J, Forman DE, Abraham WT, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J. 2004;147:331-8.
23. Krumholz HM, Chen YT, Vaccarino V, et al. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. Am J Cardiol. 2000;85:1110-3.
24. Smith GL, Vaccarino V, Kosiborod M, et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? J Card Fail. 2003;9:13-25.
25. Shlipak MG, Massie BM. The clinical challenge of cardiorenal syndrome. Circulation. 2004;110:1514-7.
26. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2000;35:681-9.
27. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000;102:203-10.
28. Adams KF Jr, Fonarow GC, Emerman CL, et al; ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149:209-16.
29. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1-266.
30. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. USRDS 1998 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney diseases; 1998 [cited 2004 Jan 20]. Available from: http://www.usrds.org/adr_1998.htm/.
31. McCullough PA, Philbin EF, Spertus JA, Kaatz S,

Sandberg KR, Weaver WD. Confirmation of a heart failure epidemic: findings from the Resource Utilization Among Congestive Heart Failure (REACH) study. J Am Coll Cardiol. 2002;39:60-9.

32. Warren DJ, Ferris TF. Renin secretion in renal hypertension. Lancet. 1970;1:159-62.
33. Chabrashvili T, Kitiyakara C, Blau J, et al. Effects of ANG II type 1 and 2 receptors on oxidative stress, renal NADPH oxidase, and SOD expression. Am J Physiol Regul Integr Comp Physiol. 2003;285:R117-24.
34. Gorio A, Gokmen N, Erbayraktar S, et al. Recombinant human erythropoietin counteracts secondary injury and markedly enhances neurological recovery from experimental spinal cord trauma. Proc Natl Acad Sci U S A. 2002;99:9450-5.
35. Pueyo ME, Gonzalez W, Nicoletti A, Savoie F, Arnal JF, Michel JB. Angiotensin II stimulates endothelial vascular cell adhesion molecule-1 via nuclear factor-kappaB activation induced by intracellular oxidative stress. Arterioscler Thromb Vasc Biol. 2000;20:645-51.
36. Ruiz-Ortega M, Lorenzo O, Egido J. Angiotensin III increases MCP-1 and activates NF-kappaB and AP-1 in cultured mesangial and mononuclear cells. Kidney Int. 2000;57:2285-98.
37. Converse RL, Jr., Jacobsen TN, Toto RD, et al. Sympathetic overactivity in patients with chronic renal failure. N Engl J Med. 1992;327:1912-8.
38. Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatory cytokines on hypoxia-induced erythropoietin production. Blood. 1992;79:1987-94.
39. Katoh M, Egashira K, Usui M, et al. Cardiac angiotensin II receptors are upregulated by long-term inhibition of nitric oxide synthesis in rats. Circ Res. 1998;83:743-51.
40. Felker GM, Adams KF, Jr., Gattis WA, O'Connor CM. Anemia as a risk factor and therapeutic target in heart failure. J Am Coll Cardiol. 2004;44:959-66.
41. Liao J, Keiser JA, Scales WE, Kunkel SL, Kluger MJ. Role of epinephrine in TNF and IL-6 production from isolated perfused rat liver. Am J Physiol Regul Integr Comp Physiol. 1995;268:R896-901.
42. Shlipak MG. Pharmacotherapy for heart failure in patients with renal insufficiency. Ann Intern Med. 2003;138:917-24.
43. Leier CV. Renal roadblock in managing low output heart failure. Crit Care Med. 2004;32:1228-9.
44. Neuberg GW, Miller AB, O'Connor CM, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J. 2002;144:31-8.
45. Philbin EF, Cotto M, Rocco TA, Jr., Jenkins PL. Association between diuretic use, clinical response, and death in acute heart failure. Am J Cardiol. 1997;80:519-22.
46. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. Am Heart J. 1999;138:285-90.
47. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J. 1987;57:17-22.
48. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Ann Intern Med. 1985;103:1-6.
49. Geisberg C, Butler J. Addressing the challenges of cardiorenal syndrome. Cleve Clin J Med. 2006;73:485-91.
50. Felker GM, O'Connor CM. Inotropic therapy for heart failure: an evidence-based approach. Am Heart J. 2001;142:393-401.
51. Elkayam U, Tasissa G, Binanay C, et al. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. Am Heart J. 2007;153:98-104.
52. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329:1456-62.
53. Kittleson M, Hurwitz S, Shah MR, et al. Development of circulatory-renal limitations to angiotensin-converting enzyme inhibitors identifies patients with severe heart failure and early mortality. J Am Coll Cardiol. 2003;41:2029-35.
54. Remuzzi G, Bertani T. Is glomerulosclerosis a consequence of altered glomerular permeability to macromolecules? Kidney Int. 1990;38:384-94.
55. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. N Engl J Med. 1998;339:1448-56.
56. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med. 2006;354:131-40.
57. Chatterjee K, Parmley WW, Cohn JN, et al. A cooperative multicenter study of captopril in congestive heart failure: hemodynamic effects and long-term response. Am Heart J. 1985;110:439-47.
58. [No authors listed]. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA. 2002;287:1531-40.
59. Mehta R, Feldman D. Acute decompensated heart failure: best evidence and current practice. Minerva Cardioangiol. 2005;53:537-47.
60. Witteles RM, Kao D, Christopherson D, et al. Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction a randomized, double-blind, placebo-controlled clinical trial. J Am Coll Cardiol. 2007;50:1835-40.
61. Marcus LS, Hart D, Packer M, et al. Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure. A double-blind, placebo-controlled, randomized crossover trial. Circulation. 1996;94:3184-9.
62. Wang DJ, Dowling TC, Meadows D, et al. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. Circulation. 2004;110:1620-5.
63. Yancy CW, Krum H, Massie BM, et al. Safety and efficacy of out patient nesiritide in patients with advanced heart failure. Results of the serial infusion of nesiritide (FUSION-II) trial. Circ Heart Fail. 2008;1:9-16.

64. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2007;49:675-83.

65. Lehtonen L. Levosimendan: a calcium-sensitizing agent for the treatment of patients with decompensated heart failure. Curr Heart Fail Rep. 2004;1:136-44.

66. Torre-Amione G, Young JB, Colucci WS, et al. Hemodynamic and clinical effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2003;42:140-7.

67. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. Jama. 2004;291:1963-71.

68. Gottlieb SS, Brater DC, Thomas I, et al. BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. Circulation. 2002;105:1348-53.

69. Collins AJ. Anaemia management prior to dialysis: cardiovascular and cost-benefit observations. Nephrol Dial Transplant. 2003;2:ii2-6.

70. Kuriyama S, Tomonari H, Yoshida H, Hashimoto T, Kawaguchi Y, Sakai O. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. Nephron. 1997;77:176-85.

71. Jie KE, Verhaar MC, Cramer MJ, et al. Erythropoietin and the cardiorenal syndrome: cellular mechanisms on the cardiorenal connectors. Am J Physiol Renal Physiol. 2006;291:F932-44.

Correspondence to:
Himansu Sekhar Mahapatra, MD
Department of Nephrology, Postgraduate Institute of Medical Education & Research, Dr RML Hospital, New Delhi, India
Tel: +91 99 6847 4805
Fax: +91 11 2507 4100, ext 2457
E-mail: drhimanshu_cmo@yahoo.co.in

Received August 2008
Revised November 2008
Accepted January 2009