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Reno-Cardiac Syndrome (RCS): A Clinical Review

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Abstract: ***Chronic Kidney Disease (CKD) and end-stage renal disease (ESRD) are associated with significant heart structure and function changes such as increased left ventricular muscle mass, arrhythmias, and sudden death. This interplay of pathophysiological phenomena secondary to either acute or chronic kidney disease leading to Chronic heart dysfunction is known as Reno-Cardiac Syndrome (RCS). RCS is an intricate forum between the heart and the kidneys due to the culmination of many interfaces, which are hemodynamic crosstalk between the failed kidneys and the heart. Changed neuro-hormonal markers and inflammatory molecular signatures are characteristic of the syndrome clinical phenotypes. Understanding the pathophysiological phenomenon in play for RCS is vital to improve therapeutic strategies to combat the cardiac pathological changes in CKD and ESRD patients thereby reducing morbidity, mortality, and improving the outcome of CRS. In this clinical review, we will discuss the pathophysiology and new advancements in RCS management. Potential areas of new research projects will also be elucidated.***

Keywords: Cardiorenal syndrome, CRS, type II CRS, Type IV CRS, terlipressin, ACE inhibitors, ARBs, inflammatory response

1. Introduction

Renal and cardiac dysfunction can occur simultaneously or consecutively. Renal dysfunction increases toxins such as creatinine and urea, and leads to electrolyte abnormalities, especially potassium which can eventually lead to arrhythmias and sudden death. Furthermore, renal malfunction leads to sodium and fluid retention, which can precipitate heart failure. On the other hand, cardiac dysfunction reduces blood pressure (BP) and blood flow in the kidney, promoting renal dysfunction due to ischemia. Therefore, malfunction of either of the two organs leads to the malfunction of the other organ. This harmony between the heart and the kidneys was discovered in 2004 and was known collectively as Cardio-Renal Syndrome (CRS). CRS has been classified based on the primary affected organ into CRS and Reno-Cardiac syndrome (RCS) [1,2].

The precision and gross relationship between the kidneys and the heart were reported in 1836, in which researchers found structural heart abnormalities in the late stages of kidney diseases[3]. ESRD patients have a higher incidence of cardiovascular complications, increasing the mortality rate at least 20 times compared to the normal population[4].

Serum creatinine increase as low as 26.5 µmol/L increases the death rate due to the Cardio-Vascular System (CVS) complications in CKD and ESRD patients[5].It was thought that uncontrolled hypertension, phosphate retention, secondary hyperparathyroidism, silent myocardial ischemia, vascular calcification, inflammation, and oxidant injury are the most important underlying causes of CVS complications[6].

CRS has been divided into five types, of which types IV &V have been renamed as RCS. RCS has been classified into two types – acute RCS (type III CRS), and chronic RCS (type IV CRS). Type III CRS is a sudden worsening of renal function due to acute kidney ischemia or glomerulonephritis, leading to acute heart failure, arrhythmia, and ischemia. On the other hand, type IV RCS is a clinical condition which occurs in CKD patients, causing progressive reduction of heart function, ventricle muscle hypertrophy, and diastolic dysfunction[7].

Previously, CRS was defined as a condition that is characterized by the initiation and/or progression of renal insufficiency secondary to heart failure. The lack of strict definition and the complexity of the CRS attribute to the paucity of evidence to have a firm diagnosis and clear management plan for the CRS in mankind [8].Currently, there are new developments in pathophysiology and clinical evidence that improved the understanding of kidney-heart crosstalk and the introduction of therapy modalities, reducing both cardiac and renal damage[9]. The harmonic sympathy between the heart and the kidneys is due to a complex pooled neurohormonal feedback mechanisms.

1) Acute RCS (type III CRS)

Acute RCS is primarily due to a sudden deterioration in kidney function due to AKI of any cause like acute ischemia, glomerulonephritis etc. This eventually can lead to cardiac malfunction which can manifest as heart failure, arrhythmia, and ischemia. It was reported that acute RCS is not widely studied, making its prevalence inaccurate and appearing less than the other types of CRS especially type I CRS [10].

AKI affects the heart in non-coherent, unclear mechanisms. There is evidence that uremia modulates cardiac muscle contractility by different depressant factors[11]. AKI induces metabolic acidosis, generating pulmonary vasoconstriction[12], causing myocardial strain and failure. Additionally, acidosis has a substantial negative inotropic effect on cardiac muscle [13]. Acidosis also increases potassium migration to the extracellular fluid, leading to hyperkalemia and risk of cardiac arrhythmias[14]. Furthermore, it was reported that renal ischemia releases substances that activate inflammatory reaction(s) and apoptosis of the heart muscle cells [15].

In RCS, there is Sympathetic Nervous System (SNS) over activation which causes reduction in myocardial β-adrenergic receptor density, insulin resistance, and dyslipidemia precipitating vasoconstriction, and leading to abnormal renal sodium handling[16].SNS over activation is also associated with Renin-Angiotensin-Aldosterone-System (RAAS) activation which causes sodium-eager state and adverse ventricular remodeling. Sodium and fluid retention due to RCS may also contribute to the SNS and RAAS activation, elevating the renal venous pressure, reducing glomerular filtration rate (GFR) and AKI in the animal model[17]. This evidence made the baseline for the complementary role of increased renal venous, central venous, and the role of intra-abdominal pressures in the pathophysiology of CRS[18].

There are systemic and specific markers which are released when the heart is damaged. These markers can be used to diagnose acute RCS and follow up the treatment[19]. Troponins are released due to myocardial injury [20], and they correlate well with the outcome of acute RCS[21]. B-type natriuretic peptide (BNP) is a peptide produced by the heart. BNP and N-terminal (NT)-prohormone BNP NT-proBNP are formed by the heart as a response to alteration in cardiac chamber pressure. Serum BNP and NT-proBNP serum concentration alter with the heart failure status [22].BNP level is an independent CVS event-predictor in CKD and AKI[23]. The physiological effects of BNP are diuresis via renal arterial vasodilatation, and in increasing sodium loss by nephron. In some cases, especially in AKI, these actions are reduced due to unclear mechanisms. Although, recently, it was claimed that it might be due to some resistance to the BNP action[24].

Pathophysiology of acute RCS (type III CRS)

By and large, there has been a misunderstanding that the nephron tubules can regenerate after damage in AKI patients because serum creatinine normalizes after recovery in some patients. This misconception has resulted in very limited number of studies to investigate the pathophysiological changes of kidney injury and its effect on the heart in humans [2,25]. The possible mechanisms of Type 3 CRS categorization are based on the hemodynamic or non-hemodynamic criteria[26] as explained below.

Hemodynamic factors

The hemodynamic factors for CRS interactions are generally explained on the basis of extracellular fluid volume homeostasis and blood pressure control criteria[27]. Consequences of heart failure including reduced cardiac output and blood pressure stimulate both the SNS and RAAS which result in volume expansion[28] to improve the renal blood flow. Data for kidney hemodynamics and nephron sodium handling are very scanty for patients with combined heart and renal failure. The bi-directional pairing between renal failure and cardiac malfunction increases sodium and water retention, increasing in the risks of heart failure and increased renal venous pressure. The effect of the hemodynamic factors can be appreciated in the RCS progression that occurs due to increased renal venous pressure which can eventually reduce the renal blood flow [17].

Non-hemodynamic factors

The non-hemodynamic factors contributing to the development of acute RCS include activation of SNS, RAAS, and coagulation systems, as well as the inflammatory response, oxidative stress, and changes in the nitric oxide levels [29]. AKI generates abrupt and critical cardiac changes like left ventricle dilatation and reducing left ventricular relaxation time, leading to the reduction in the end-diastolic volume. These cardiac changes accompanying the AKI were thought due to cardiomyocyte apoptosis, mediated by inflammatory mediators, thereby inducing acute and chronic kidney disease in rodents. The inflammatory response is due to increased serum pro-inflammatory cytokines and inflammatory cell infiltration[30]. At early stage of AKI, SNS is activated to preserve the cardiac output, and at the same time activates cardiac muscle cell apoptosis[31], new intima formation, and immune system function alteration[30]. Besides the activation of SNS, the RAAS is also activated, augmenting the vaso active effects of SNS on the afferent renal arteries and cardiac contractility, producing further ischemia to the heart and the kidneys. The RAAS activation increases ADH and aldosterone hormone secretion which leads to sodium and water retention, further overloading the circulation and thereby minimizing adequate oxygen delivery to the heart and the kidneys. All these possible factors and mechanisms are potential causes for the pathogenesis of type 3 CRS. However, the exact mechanism(s) and the certainty of these pathophysiological changes are not well established in humans yet**.**

CKD progression to ESRD in non-diabetic patients is directly proportional to the serum BNP concentration[31]. Myeloperoxidase is a signal for neutrophils activation, myocyte metabolism changes, oxidative stress, and inflammation, especially in acute coronary syndrome[32]. Oxidative stress can lead to myocyte apoptosis and necrosis, and it is associated with arrhythmias and endothelial dysfunction which possibly have essential roles in the pathogenesis of RCS [33].Furthermore, tumor necrosis factor (TNF), interleukins (IL-1 and 6) besides their possible diagnostic role in CRS diagnosis, may induce myocardial cell necrosis, and apoptosisin AKI[7].

2) CRS type 4 (chronic RCS)

Type 4 CRS occurs in chronic kidney pathological conditions, leading to progressive cardiac dysfunction. It is well documented that CKD is associated with high CVS complications, starting at early stages of CKD[6],and become more prevalent in advanced CKD stages IV and V[34]. The

CVS complications increase the death rate by 17-20 folds of which 50% are due to cardiac events[35].The poor outcome of CVS complications in CKD patients is possibly multifactorial including less interventional diagnostic and therapeutic procedures performed in such patients and uncertainty in the indications and contraindications in using cardioprotective drugs such as ACE inhibitors and ARBs in Ischemic Heart Disease (IHD) which preserve the cardiac muscle function [36].It has been reported that the risk of myocardial ischemia and other CVS complications increases significantly with GFR reduction, increasing the mortality and morbidity rates [37].

Pathophysiology of chronic RCS (type 4 CRS)

In patients with kidney disease, the toxic effect of uremia, vascular disease, and endothelial dysfunction are all risk factors for the failure of multiple organs including the heart. Associated uremic toxins such as guanidine, phenols, parathyroid hormone, proinflammatory cytokines either alone in combination might produce metabolic and physiologic imbalances that affect RCS progression. Heart failure and kidney dysfunction reduce oxygenated blood delivery to the cardiac myocytes, affecting the vascular remodeling of the microvasculature which then leads to focal low perfusion and/or maldistribution of blood, promoting more cellular injury.

It has been reported that AKI induced by partial nephrectomy in animals leads to a major reduction of ventricle wall perfusion, and it was typically related to the degree of renal ischemia and the worsening of the serum creatinine[38].It has been reported that impairment of renal autoregulation leads to severe reduction in blood perfusion in the coronary vessels [39]. Vascular remodeling in the presence of uremic toxins increases oxidative stress, inflammation, and lipid metabolism, exacerbating endothelial dysfunction. Troponins, asymmetric dimethylarginine, plasminogen-activator inhibitor type 1, homocysteine, natriuretic peptides, C-reactive protein, serum amyloid A protein, low hemoglobin, and ischemia-modified albumin are all biomarker for the CVS complication in CKD patients[40], and their plasma levels are related directly to the CVS complications and outcome[41]. It was concluded that there is a strong relationship between chronic inflammatory response [42], subclinical infections[43], heart-kidney interactions, cardiovascular complications, and outcome in CKD-CRS patients. Thus, it seems that prevention of the early microvascular inflammation and dysfunction may be at the core of limiting the adverse effects of progressive kidney and heart dysfunction.

Management Challenges and prevention of RCS

Medications used in progressed stages of CKD such as phosphate binders, partially activated vitamin D, iron, folic acid, erythropoietin, and cardiac medications which are safe in CKD and AKI can be continued in some patients of CRS [44]. New treatments such as endothelin system antagonists, adenosine and vasopressin receptor antagonists, and inflammation suppressors have promising roles [45].Immunosuppressive drugs and immune-modulating agents have been tried, but there are some controversies regarding using them to prevent or treat the CVS complications[46], hence larger studies are needed to assess their efficacy to be used in the management of CRS.

ACE inhibitors and ARBs administration with aldosterone antagonists increases the risk of sudden cardiac events especially arrhythmias due to their hyperkalemic side effects. It has been reported that either ACE inhibitors or ARBs or combined ACE inhibitors and ARB increases the rate of severe hyperkalemia in patients on maintenance hemodialysis, although anuric patients who are receiving renin-angiotensin blockade need careful serum potassium monitoring to avoid hyperkalemia[46]. This effect led to evidence-based advice that ACE inhibitors and ARBs can be used in CKD cautiously. Although ARBs, ACE, and spironolactone increase serum potassium, some physicians have used them cautiously either separately or as a combination in ESRD on HD to minimize the left ventricular hypertrophy and failure [47]. The appearance of hyperkalemia has made physicians avoid using ACE inhibitors or ARBs in most ESRD patients with left ventricle dysfunction [48], increasing the poor outcomes. KO et al reported that ACE inhibitors, ARBs, and aldosterone antagonists can be used in some patients who had diminished LV ejection fraction, but the serum creatinine and serum potassium concentration must be<2.5 mg/dl and < 5 mmol/l respectively in CKD patients [49]. Uremic patients are liable for bleeding due to thrombocyte malfunction, making the usage of aminosalicylic acid less suitable [50], although it may improve CVS outcomes in some CKD-ESRD patients, despite the risk of bleeding [51]. Clopidogrel has not showed any significant effect on protection and the reduced outcomes of CVS complications [52]. These controversies in using antiplatelets in CVS complications for prevention and treatment in CKD and ESRD patients need more clarification with further clinical trials.

Hypertension control is essential to prevent further damage of both the heart and the kidneys in CKD and ESRD patients [53]. Using ACE inhibitors and ARBs, as mentioned above, must be assessed, and further larger multicentric studies are needed to investigate these drugs' benefits and hazards before they are widely applied. Careful monitoring of blood pressure is essential through ambulatory BP monitoring to prevent the long-term effects of hypertension on the heart and the kidneys. Cardiac and renal function assessment is needed to ensure adequate clinical response and to avoid these side effects of these drugs.

High serum cholesterol level is common in CKD, but its reduction by statins potentiates the transformation of growth factor-β which mediates renal tissue fibrosis, however, this effect of statins has not yet been proven in clinical trials [54]. It has been reported that statins might have renoprotective effects which is manifested by the reduction of urinary loss of protein in CKD patients [55]. Pravastatin reduced the death rate due to acute myocardial infarction in acute mild renal impairment [56].A study reported that reduction of serum LDL cholesterol by simvastatin with ezetimibe reduced the atherosclerosis events [57]. On the other hand, reducing serum cholesterol in HD-ESRD patients increased the death rate [58].Low serum LDL-cholesterol is a marker for inflammation and malnourishment, associating with reduced

survival rate in dialyzed patients[59], although another study has not shown a significant change in CVS events following serum LDL-cholesterol reduction in diabetic hemodialyzed patients [60]. A post hoc analysis study reported a reasonable decrease in cardiac events and mortality following atorvastatin administration in CKD patients who had high serum LDL cholesterol [61].

Diabetes mellitus (MD) affects the kidney which manifests early by micro-albuminuria. The severity of albuminuria is an independent marker for CVS morbidity and mortality in diabetic and non-diabetic patients[62]. A report cited that microalbuminuria lower than the conventional definition related to cardiovascular events, and therapy to decrease this lower value of albuminuria diminishes the CVS events and retarded the annual decline in GFR[62].Macro and microvascular complications were reduced after rigorous glycemic control (HbA1c ≤7 %)[63], however, tight glycemic control did not alter the CVS events[64].

Anemia is common between CKD and ESRD patients. Anemia increases the workload on the heart, causing high cardiac output failure. A part of the other causes of left ventricle hypertrophy in CKD and ESRD, anemia produces left ventricular muscle mass increase and arterial modeling, decreasing the cardiac muscle perfusion and oxygen delivery [65]. Reports reveal that correction of anemia improves heart failure and cardiac output[62,66]. Low hemoglobin induces CVS complications, and conversely, high hematocrit and hemoglobin increase stroke risk, hypertension, and hemodialysis (HD) vascular access thrombosis[67]. Normal hemoglobin in CKD and ESRD patients improves the life quality but may adversely affect the outcome in some patients. Therefore, it is almost agreed that a hemoglobin value of 12 g/100ml is recognized as suitable to reduce anemia-associated CVS complications.

Calcium and phosphorous equilibrium is normally controlled via interaction between parathyroid hormone, vitamin Dactivation by the kidneys, bone, and intestine. The deficiency of active vitamin D decreases serum calcium that stimulates the release of parathyroid hormone, increasing bone resorption and phosphate retention. Raised phosphate-calcium product increases coronary vessel calcification and stiffness, reducing subendocardial blood perfusion[68]. Therefore, therapies that reduce phosphate and regular parathyroid hormone secretion may reduce the risk of CVS complications. Further new studies are urged to investigate this issue.

It was reported that elevated homocysteine is an independent predictor of IHD risk in healthy subjects. Serum homocysteine is usually high in CKD in proportion to the decline in GFR [69]. Homocysteine interacts with vitamin D and affects serum phosphate-calcium-parathyroid hormone balance, and it acts as a mediator for atherothrombosis via endothelial injury and oxidative stress[70].The metabolic pathways involving homocysteine are not clear. Other studies are needed to establish the effect of homocysteine in CVS complications in RCS especially the type 3 CRS.

Patients who do not tolerate ACE inhibitors were grouped as high mortality rate CRS patients. Testani et al reported that serum creatinine increased initially after starting enalapril then stabilized[71], mainly due to the first doses hypotension side effect and the concomitant use of diuretics, but other studies showed the continuation of enalapril improved survival[72]. In chronic RCS, benazepril reduced mortality significantly, but it did not significantly affect the abnormalities of myocardial structure and function[72]. ESRD patients who had left ventricular ejection fraction (LVEF) <40 % and NYHA class II or III symptoms showed better improvement in survival and cardiovascular morbidity and mortality with the addition of telmisartan to standard therapy with ACE-inhibitor[73]. Losartan reduced left ventricle hypertrophy compared to enalapril in HD patients in addition to controlling hypertension [74]. Left ventricle muscle mass and arterial stiffness reduced with the addition of aldosterone in early CKD stages, and markers of regional systolic and diastolic function also improved [75]. The renoprotective effect of RAAS-inhibitors is marked by the improvement of microalbuminuria, and cessation of overt nephropathy progression and their antihypertensive effects [76].

The serum concentrations of Aldosterone hormone are positively correlated to the severity of proteinuria, and it is an important marker for deterioration of kidney disease. There is evidence that spironolactone has additive action when combined with ACE inhibitors and/or ARBs, improving the severity of proteinuria[77]. Despite the risk of hyperkalemia with spironolactone, its use increased recently in the early stages of CKD patients[78]. The combined use of ACE-inhibitors and/or ARBs plus spironolactone can be done cautiously, but serum potassium must be assessed constantly. There is promising evidence of novel potassium binder (RLY5016) in heart failure patients, providing hope for its use in CKD and ESRD patients, and possibly in RCS[79].

Treatment with Beta-blockers significantly reduces mortality and hospital stay in heart failure patients with CKD who had (estimated) eGFR of<45 mL/min[80]. It was reported that carvedilol had a positive effect on cardiac geometry, function, and symptoms of heart failure in ESRD patients [81]. The reno-protective effect was reported for β-blockers, although it was not as effective as the ACE-inhibitors[82]. β-blockers improved the survival rate in HD-patients [83]. Despite the beneficial effect of β-blockers in heart failure, they are not commonly used in CKD. This may be due to the fact that these medications can precipitate metabolic disturbances, deterioration in renal function, and hemodynamic abnormalities such as hypotension. However, the efficacy and safety profile of β-blockers including metoprolol, atenolol, and carvedilol have been well documented in CKD[84].

Excess fluid removal is important in the treatment and prevention of RCS. Diuretics reduce volume overload and relieve symptoms of heart failure, and they may disable the cascade between the heart and the kidneys. Diuretics decrease preload by decreasing the venous return to the heart, improving the ventricular filling and contractility which consequently improves the stroke volume due to ventricular interdependence. This is known as the reverse Bernheim phenomenon. These cardiac changes lead to a

reduction in intra-abdominal pressure and central venous pressure in CRS [85] thereby improving renal perfusion. Although diuretics improve symptoms and outcomes of RCS, their overuse can deteriorate renal dysfunction. Therefore, careful assessment and close follow-up is needed with diuretic use. Furthermore, frequent diuretic dose assessment is required to prevent hemoconcentration [86]. Slow fluid removal by long HD sessions such as nocturnal HD improves left ventricle hypertrophy [87]. Peritoneal dialysis may cause body fluid expansion, leading to hypertension, and worsens the left ventricle hypertrophy [88]. Fluid expansion may occur in peritoneal dialyzed patients due to either improper dialysis prescription or poor permeability of the peritoneal membrane to fluid and electrolytes. Currently, high osmotic dialysis fluids such as icodextrin seem more effective in fluid removal and may improve the left ventricle function, hypertrophy, and CRS outcome than the lower osmolarity peritoneal dialysis fluids [89].

Residual renal function is essential in CRS prevention. ACE inhibitors, ARBs, and β-blockers help to preserve the residual kidney function. Usage of these agents in ESRD with heart failure despite their cardiac and renal beneficial effects, may promote intradialytic or post-dialytic hypotension due to their inhibitory effects on SNS and RAAS activation. Excessive fluid reduction with dialysis and/or diuretic plus ACE inhibitor and/or ARBs plus β-blockers may have adverse effects in RCS patients. Despite all these efforts, differentiation between the underlying cause of overload in CRS is difficult, choosing between these modalities of fluid removal is difficult and controversial. Further studies are needed to clarify these uncertain areas of controversies.

2. Conclusions and Perspectives

There are strong relationships and interactions between the kidney and the heart. Acute and chronic kidney diseases, either directly or indirectly, have a negative effect on the heart function, causing RCS. GFR value is a marker for kidney function, and it is inversely related to the CVS complications and the outcome of RCS. Despite the advancements in understanding the pathophysiology of the RCS, the endpoint treatment for the RCS is still unclear and the outcome is difficult to predict and estimate. The available human clinical studies to date lack in precisely quantifying the cardiac changes in renal failure patients. Therefore, large multicenter human studies with severe kidney and heart involvement are needed to find the crosstalk and the exact harmony between the kidney and heart to elucidate the mechanism(s) underlying the development of CRS.

Further thorough studies are need to ascertain the role of fluid overload management by using β-blockers, ACE inhibitors, ARBs, diuretics, and hemofiltration to assess if such measures do actually prevent cardiac and renal damage by decreasing the SNS and RAAS activation. More multidisciplinary and collaborative effort is needed from physiologists, pathologists, pharmacologists, physicians, and nephrologists to explore the underlying pathophysiology, disease markers, early detection of clinical features to assess the available management modalities, and to find and investigate new options of prevention and therapy of RCS.

3. Conflict of Interest

The authors have declared no conflict of interest in the publication of this topic.

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Nil

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