Working Toward an Improved Understanding of Chronic Cardiorenal Syndrome Type 4

Daniel Edmonston, Jessica D. Morris, and John P. Middleton

Chronic diseases of the heart and of the kidneys commonly coexist in individuals. Certainly combined and persistent heart and kidney failure can arise from a common pathologic insult, for example, as a consequence of poorly controlled hypertension or of severe diffuse arterial disease. However, strong evidence is emerging to suggest that cross talk exists between the heart and the kidney. Independent processes are set in motion when kidney function is chronically diminished, and these processes can have distinct adverse effects on the heart. The complex chronic heart condition that results from chronic kidney disease (CKD) has been termed cardiorenal syndrome type 4. This review will include an updated description of the cardiac morphology in patients who have CKD, an overview of the most likely CKD-sourced culprits for these cardiac changes, and the potential therapeutic strategies to limit cardiac complications in patients who have CKD.

Key Words: Chronic kidney disease, Heart failure, Cardiorenal syndrome

INTRODUCTION

In 2004, an analysis of more than a million individuals enrolled in a Kaiser health program in the United States described an alarming relationship. Even after adjusting for comorbid illnesses and traditional cardiac risk factors, there is a prominent, graded relationship among the prevalence of cardiovascular events and glomerular filtration rate (GFR).[1] In this analysis, compared to those with GFR $\geq$ 60 mL/min, individuals with GFR in the 30-44 mL/min range had a 2-fold greater risk, those with GFR in the range of 15-29 mL/min had a 2.8-fold greater risk, and those with GFR $<$ 15 mL/min had a 3.4-fold greater risk of suffering from a cardiovascular event. These observations, along with similar studies over the past decade, cemented the concept that persistently reduced GFR is a potent independent risk factor for the development of cardiovascular disease. The chronic cardiac condition that results from chronic kidney disease (CKD), including abnormal heart morphology and function, is termed type 4 cardiorenal syndrome (CRS).[2] Our full understanding of the interplay of CKD and heart disease remains elusive. As we gain knowledge about the pathogenesis of type 4 CRS, we will be able to develop more effective management strategies.

CKD affects 30 million people in the United States, or approximately 15% of adults,[3] and a diagnosis of some form of congestive heart failure (CHF) affects 5.7 million people.[4] It is not clear, however, how many cases of CHF can be traced to having an origin in renal failure. Mavrakanas and colleagues performed a retrospective study to address this question.[5] The authors described 2512 patients who were documented to have combined heart and kidney failure. Using sequential laboratory and echocardiogram data, the authors observed that 26.2% of these patients had CRS type 4. Compared with the acute forms of CRS (types 1 and 3) and CRS type 2 (chronic CHF resulting in CKD), the patients with CRS type 4 were older, had lower estimated glomerular filtration rates (eGFRs), and were more likely to have preserved ejection fraction. Some of the patients who had baseline CRS type 4 also presented during the study period with an overlay of an acute cardiac decompensation. However, compared with the acute forms of CRS, the patients with CRS type 4 exhibited better overall survival (Fig 1). The goal of the present review is to summarize what is known about the presentation, pathogenesis, and treatment of this common form of CRS.

CARDIAC MORPHOLOGY AND FUNCTION IN CKD: NEW EVIDENCE FOR "UREMIC CARDIOMYOPATHY"

The existence of a "uremic cardiomyopathy" has been recognized for centuries, but new evaluations are enhancing our understanding of this condition. The cardiac substrate that results from longstanding CKD is unique with prominent features including dramatic left ventricular hypertrophy (LVH), inflammation, and diffuse myocardial fibrosis. One of the most striking changes of the heart in patients who have CKD is distortion of the configuration of the left ventricle. In the late 1990s, echocardiography studies demonstrated that LVH was present in more than 80% of patients who were starting dialysis for end-stage renal disease (ESRD), and this group included a substantial proportion of young patients who did not have other comorbidities.[6] The accuracy of echocardiography can be limited, however, based on volume status of the patient and interoperator variability. Many investigators rely on cardiac magnetic resonance imaging (CMRI) to better assess cardiac morphology, particularly in CKD.[7] But even with CMRI, 72% of patients with ESRD have evidence for LVH, and only 11% have LV dilatation and 8% have LV systolic dysfunction.[8] It also seems likely that the prevalence of LVH increases in a stepwise manner as GFR worsens in progressive CKD. An echocardiographic study of 3487 patients reported prevalence rates of LVH of 32%, 48%, 57%, and 75% in groups of patients with estimated GFRs of $\geq$60, 45-59, 30-44, and $<$30 mL/min/

From the Division of Nephrology, Department of Medicine, Duke University, Durham, NC 27705.

Address correspondence to John P. Middleton, MD, Duke Nephrology, 2424 Erwin Road, Suite 605, Durham NC 27705. E-mail: j.p.middleton@duke.edu

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1.73 m^2, respectively.[9] Thus, remodeling of the left ventricle occurs early in the course of CKD progression.

Often, the presence of LVH in CKD is associated with systolic or diastolic dysfunction, but is LVH also associated with a poor clinical outcome? One observational study of hemodialysis (HD) patients determined that LVH was the most potent predictor of sudden cardiac death.[10] Other investigators also observed an increased mortality risk in patients with ESRD who exhibit LVH, especially at the start of a dialysis regimen.[11] Furthermore, progression of LVH is probably also predictive of a poor clinical outcome. A study of 161 patients with ESRD who were treated with HD demonstrated that the rate of increase of left ventricle mass was substantially higher in patients who suffered a new cardiovascular event than that in those patients who did not have a cardiovascular complication.[12] Moreover, the risk of LVH may not be simple or straightforward but rather may serve as part of a "one-two punch." A cross-sectional study of nearly 300 patients with advanced CKD described a link between LVH and the prolongation of QT interval, suggesting that LVH might create underlying conduction disturbances that heighten the risk of cardiac arrest with exposure to extremes in serum electrolytes.[13]

The enhanced risk of cardiac arrest on patients who have CKD implies additional disturbances in cardiac morphology. Approximately 40% of patients who have ESRD and are treated with dialysis die as a direct result of cardiac arrhythmias or sudden cardiac arrest.[14] If one assumes that deaths attributed to hyperkalemia or to myocardial infarction are also due to arrhythmias, more than half of deaths in ESRD result from cardiac arrest.[14] But, even less severe reductions in GFR are associated with an increased risk of sudden cardiac death compared to the general population. Patients with known coronary artery disease (CAD) and CKD stages 3-4 are 3-4 times more likely to die from cardiac arrest than the general population, and patients with CKD stage 5 (but not on dialysis) are 4- to 5-fold more likely to die from cardiac arrest.[15] The risk increases to 7- to 8-fold higher than that for the general population for CKD 5 patients who are treated with dialysis. On one hand, patients with CKD are at risk to experience dramatic swings in serum electrolyte concentrations, and certainly, evidence supports the risks of extreme serum electrolytes in patients with CKD (discussed elsewhere in the article). However, the extraordinarily high rate of sudden death is incompletely explained by shifts of extracellular electrolytes, and this observation raises the question of other disturbances in cardiac structure.

Cardiac conduction can be disordered by the presence of myocardial fibrosis in patients who have CKD. The extent of heart fibrosis is reported to be more marked in patients with ESRD than in the non-ESRD diabetic and hypertensive cohorts with similar LV mass.[16] In a study of endomyocardial biopsies, samples were obtained from 40 patients with ESRD on dialysis who had dilated cardiomyopathy, and histologic results were compared with 50 nondialysis controls.[17] The biopsies of patients with ESRD showed hypertrophic and bizarre myocytes as compared with those of the control patients without ESRD, and a substantial fraction of dialysis patients had more than 30% of the myocardial volume occupied by fibrotic tissue. Studies with CMRI support this observation. In a study of patients with ESRD referred for transplant evaluation, 28% of patients demonstrated late gadolinium enhancement, which is indicative of myocardial fibrosis.[8] Although some of the gadolinium enhancement was located in the subendocardial space, consistent with prior myocardial infarction, the enhancement pattern in some patients was diffuse throughout the myocardium. These studies suggest that advanced CKD, or dialysis therapies for ESRD, promotes diffuse cardiac fibrosis. Similar observations were reported in a smaller series of patients with ESRD.[18] Albeit at a lower prevalence rate, diffuse myocardial scarring is reported in patients with less severe CKD. Edwards and colleagues described diffuse gadolinium enhancement in 6% of patients with CKD stages 2-3.[19] Data from biomarkers are emerging to further support the notion that CKD promotes myocardial fibrosis. Galectin-3 (Gal-3) is a ubiquitous protein that can serve as a biomarker of myocardial remodeling, fibrosis, and inflammation.[20,21] In an observational cohort study of 883 subjects, most of them who had CKD stage 3 and elevated baseline serum values of Gal-3 were significantly associated with mortality.[22] Elevated levels of Gal-3 in the study participants were not associated with CHF events however. This study does not establish causality, but in total, these observations document that patients with CKD are burdened with myocardial fibrosis and by diminished survival likelihood.

CLINICAL SUMMARY

- CRS type 4 is characterized by chronic cardiac dysfunction in the setting of CKD.
- Sequelae of CKD including anemia, dyslipidemia, oxidative stress, disordered mineral metabolism, and RAAS activation each contribute to abnormal cardiac function.
- Treatments for CRS4 include optimizing renal replacement therapy, RAAS inhibition, addressing derangements in mineral metabolism, and reversal of anemia and iron deficiency.

THE "HOSTILE MILIEU" OF CKD: FACTORS THAT ARE COMMON FOR CRS TYPE 4 AND OTHER FORMS OF CRS

Volume Overload

Some risk exposures to the heart in patients with CKD are shared by other forms of CRS. For example, volume expansion and the accumulation of excess body fluid occur in acute and chronic forms of CRS, not exclusively in patients who have CRS type 4. Certainly in the population with ESRD, volume overload is prevalent. A retrospective assessment of a large database of HD patients determined that 86% of patients gained >1.5 kg between 2 HD