Epidemiology of Cardiorenal Syndrome

Junior Uduman

Cardiorenal syndrome is a spectrum of disorders that emphasizes the bidirectional nature of cardiac and kidney injury. Observational and retrospective studies have helped us to understand the prevalence and burden of each of the 5 types of cardiorenal syndromes. Cardiorenal syndrome type 1 is the most common. The nature of epidemiologic data limits clear delineation between cardiorenal syndrome types 2 and 4. Overall, the presence of cardiac or renal dysfunction strongly predicts a poor outcome of the contrary organ.

Key Words: Cardiorenal syndrome, Acute kidney injury, Congestive heart failure, Prevalence, Mortality

INTRODUCTION

The relationship between cardiac and renal dysfunction has been a well-recognized entity for well over a century. The Acute Dialysis Quality Initiative (ADQI) consensus group formalized a definition in 2010.[1,2] This classification system divides cardiorenal syndrome (CRS) into 5 types based on the primary organ dysfunction and chronicity. The 5th type is a subset of cardiac and renal impairments that occur because of systemic conditions. Pathophysiologically, cardiac contractile dysfunction and resultant volume overload is no longer the sine qua non of CRS as venous congestion and neurohormonal mechanisms are also thought to be at play.[3] As such, additional pathophysiological classification schemes have also been proposed to supplement the current definition.[4]

The individual prognosis and economic burdens of CKD or cardiac disease, particularly congestive heart failure (CHF), have been well recognized. For instance, the global prevalence of CKD in 2015 was estimated to be around 323 million by the Global Burden of Disease study.[5] In addition to CHF being associated with frequent hospitalization, cardiovascular disease (CVD) is also the number one cause of death in the CKD population.[6,7] This review of the prevalence, risk factors, and implications of each cardiorenal disorder aims to assist in contextualizing the close pathophysiological cardiorenal link and help shed insights into future directions.

General Risk Factors in Cardiorenal Disorders

CRS type 1 (CRS-1) and type 2 (CRS-2) encompass disorders where primary cardiac dysfunction leads to acute kidney injury (AKI) or CKD, respectively. Although precise delineation of risk factors for AKI or CKD in patients with primary heart failure is difficult because of the shared nature of comorbidities of both conditions and definitions of kidney injury vary in the CRS literature. Certain mutual risk factors play a role in worsening renal function (WRF), for instance, atherosclerotic risk factors are implicated in kidney disease in the setting of CRS (Table 1).[8]

The presence of baseline kidney dysfunction has been shown to predict kidney failure. In a prospective evaluation of 299 patients hospitalized with decompensated systolic heart failure, baseline serum creatinine (SCr) independently predicted WRF (odds ratio [OR], 3.02; 95% confidence interval [CI], 1.58-5.76).[9] Similarly, in a retrospective study of hospitalized heart failure patients, SCr at admission >1.5 mg/dL and history of prior CHF were predictors for WRF among heart failure patients. Butler and colleagues demonstrated the same associations in a nested case-control study.[10,11] These 2 studies also highlight the close association of history of heart failure and baseline kidney function as strong predictors of WRF. Traditional risk factors, such as diabetes mellitus (DM) and hypertension (HTN) that predict CKD progression have also shown close association with WRF.[11] A post hoc analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, a randomized multicenter study that evaluated the role of pulmonary artery catheters in the management of acute decompensated heart failure (ADHF), showed prior history of DM and HTN being associated with an increase in SCr of >0.3 mg/dL.[12] Patients who develop WRF in the setting of heart failure tend to be older and have atherosclerotic disease.[10,13]

Albuminuria has a graded association with AKI and correlates with future risk of developing heart failure in the general population.[14,15] Extremes of body weight, that is, obesity and cachexia are postulated to contribute to CRS in this population. In addition to hyperfiltration injury, cytokines of adipocyte origin have been implicated in kidney injury.[16] Cachexia can exert a similar inflammatory response in the setting of heart failure and facilitate kidney injury.[3] Although an association with weight and WRF in CRS has not been shown in epidemiologic studies, this seems to be a viable hypothesis given the strong association of these host factors with CKD and progression of heart disease.[17-19]

Finally, treatment-related factors are frequently feared clinically to be associated with WRF in CRS. The use of renin-angiotensin-aldosterone system inhibitors and diuretics is a cornerstone in the therapy of most cardiac and renal disorders. The Survival and Ventricular

From the Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI, and Division of Pulmonary and Critical Care Medicine, Henry Ford Hospital, Detroit, MI.

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Address correspondence to Junior Uduman, MD, Division of Nephrology, Henry Ford Hospital, 2799 West Grand Boulevard, CFP-510, Detroit, MI 48202. E-mail: juduman1@hfhs.org

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Enlargement trial involved 2231 patients who had left ventricular dysfunction and acute myocardial infarction. Subjects were randomly assigned between 3 and 16 days (average 11 days) after acute myocardial infarction to receive captopril or placebo; those with an SCr >2.5 mg/dL were excluded from the Survival and Ventricular Enlargement trial. Use of captopril was not associated with WRF (5.7% vs 6.4%, $P = .38$).[20] Similarly, in a nested case-control study on 382 subjects who were hospitalized with heart failure, use of angiotensin-converting enzyme inhibitors was not associated with WRF.[11] Incidentally, patients in this trial who developed WRF were on higher doses of diuretics, a finding replicated by Cowie and colleagues.[9,21] On the contrary, an increase in SCr with use of the renin-angiotensin-aldosterone system inhibitors in chronic heart failure may be associated with favorable outcomes. Analysis of the ESCAPE trial, use of loop diuretics or total dose did not seem to impact renal outcomes, irrespective of baseline kidney function, but WRF was seen more with the use of thiazide diuretics when the estimated glomerular filtration rate (eGFR) was <60 mL/min (48% vs 29%; $P = .04$).[12] This finding may relate to the severity of heart or kidney failure, as thiazide is generally used when diuretic effects of loop diuretics are insufficient. In a post hoc analysis of a randomized, open label study designed to assess efficacy of continuous with intermittent infusion of furosemide in in-patients with ADHF, high dose diuretics (>125 mg/d) was associated with higher rate of in-hospital WRF (65% vs 29%; $P = .001$).[22] Collectively, these data do suggest an association of escalating dose of diuretics with CRS, causation is not definitive as numerous mechanisms that induce diuretic resistance with advanced heart failure can simply signify severity of underlying cardiac status.[23]

CLINICAL SUMMARY

- There is an increased risk of kidney failure in the setting of acute and chronic cardiac diseases.
- Prevalence of cardiorenal syndrome type 1 is as high as 50%, and even small increases in creatinine can be associated with worse outcomes.
- Chronic heart disease and chronic kidney disease frequently coexist, and the presence of one accelerates the decline in function of the other.
- The heterogenic nature of acute kidney injury in cardiorenal syndrome types 3 and 5 renders identification of true prevalence difficult.

Cardiorenal Syndrome Type 1

AKI in the setting of an acute cardiac event is a simplistic definition of CRS-1. The ADQI consensus definition clarifies that acute cardiac events precipitating AKI can be seen in a number of settings, namely, ADHF, acute coronary syndrome (ACS), cardiogenic shock, and cardiac surgery.[1] Transient acute and chronic valvular heart disease could be grouped in this category. Although the definition of cardiac dysfunction has been standardized, the definition of AKI has evolved with our knowledge of AKI.[24] WRF is the more commonly used term for kidney injury in AKI, although it is inadvertently used interchangeably with CRS-1. Although WRF was frequently defined as a SCr increase of >0.3 mg/dL, a wide range of parameters have been used in studies that examined outcomes in the setting of CRS (Table 2). This has been concisely summarized by Bagshaw and colleagues[41] for the ADQI consensus group. At least 6 different operational definitions of WRF have been used that ranged from change in SCr of 0.1 to 0.5 mg/dL, and even a 50% increase in SCr.[42-44] Due to the observational nature of most studies, determination of kidney injury is based on a few abstract SCr values that need to be interpreted in the appropriate clinical context. The timeline for assessing kidney injury has also varied considerably among studies.[41] It is plausible that an increase in SCr on day 1 of admission has different implications than that of an increase in SCr on day 5 of admission after aggressive diuresis.[45] In addition, several studies reported eGFR but application of estimation equations for kidney function is not validated in this setting.[46] Urine output, a determinant of AKI staging per Kidney Disease: Improving Global Outcomes (KDIGO), which can also predict mortality, is seldom reported in the CRS literature.[47] Interpretations of these epidemiologic data based on SCr can be imprecise. As our understanding of the pathophysiology improves, refining the definitions with more precise tools like biomarkers can add more accuracy and alter the paradigm of CRS. In a recently published study, urine tubular injury biomarkers from 283 patients enrolled in the Renal Optimization Strategies Evaluation-Acute Heart Failure trial were assessed for correlation with WRF. *N*-acetyl-β-glucosaminidase, kidney injury molecule 1, and neutrophil gelatinase–associated lipocalin (NGAL) were measured on admission and at 72-hours, whereas WRF was defined as a decrease in eGFR >20%. In this study, WRF with diuresis was not associated with changes in these tubular biomarkers.[48] Similarly, in a prospective study of 927 patients admitted with ADHF, plasma NGAL was not superior to creatinine in predicting WRF defined as rise in SCr >0.5 mg/dL or >50%.[49] That said, previous studies of these biomarkers have variably been associated with WRF and mortality.[50-52] The role of renal biomarkers in diagnosis and prognosis of CRS is evolving and needs further validation; until then, SCr-based definitions remains a strong tool in studying CRS.

Prevalence of CRS-1 varies among studies, a summary of studies that reported on prevalence and outcomes of CRS-1 is presented in Table 2. AKI in the setting of ADHF has been implicated in increased length of stay, hospital readmission, and mortality. The overall prevalence of CRS-1 by 3 of the most common etiologies is shown in Figure 1. In the largest retrospective study that evaluated Medicare claims data of 20,000 patients from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, 17.8% had WRF and 65% had 1-year survival after