Toward Precision Medicine in the Cardiorenal Syndrome

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Although the field of oncology has made significant steps toward individualized precision medicine, cardiology and nephrology still often use a "one size fits all" approach. This applies to the intersection of the heart-kidney interaction and the cardiorenal syndrome as well. Recent studies have shown that the prognostic implications of worsening renal function (WRF) in acute heart failure are variable; thus, there is a need to differentiate the implications of WRF to better guide precise care. This may best be performed with biomarkers that can give the clinician a real-time evaluation of the physiologic state at the time of developing WRF. This review will summarize current cardiac and renal biomarkers and their status in the evaluation of cardiorenal syndrome. Although we have made progress in our understanding of this syndrome, further investigation is needed to bring precision medicine into routine clinical practice for the care of patients with cardiorenal syndrome.

Key words: Acute kidney injury, Cardiorenal syndrome, Precision medicine

INTRODUCTION

Modern medicine has taught us that the "one size fits all" strategy is suboptimal. Therefore, there is a move to transition toward more personalized precision medicine. According to the Precision Medicine Initiative, precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." This approach will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people.[1] Nowhere is this more evident than in the field of oncology, where selection of therapy is based on the genetic profile of a patient's specific tumor.

The fields of cardiology and nephrology are behind in this respect. Although steps have been made toward precision therapy, such as the use of mexiletine for long QT syndrome type 3[2] and enzyme replacement therapy in Fabry's disease, these conditions are a small portion of cardiovascular and renal disease. Similar steps are lacking in the much larger areas of heart failure (HF) or diabetic kidney disease. This is an important gap which needs to be filled not only within their respective fields but also in their intersection of the cardiorenal syndrome (CRS). Biomarkers, with their ability to give a glimpse of current physiology, may serve as the best guide to deliver precision medicine. This review will discuss two common clinical scenarios in CRS and the current use and future needs of biomarkers to deliver precision medicine.

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HEART FAILURE AND THE CARDIORENAL SYNDROME

HF and its associated complications are emerging as the epidemic of the 21st century, especially in developed countries, in which the prevalence of HF is approximately 1-2% of the adult population. It is associated with high mortality, morbidity, and health-care costs. Kidney dysfunction in HF has received significant attention over the years because of its complex pathophysiology that is not fully understood, falling under the umbrella of heart-kidney crosstalk, termed the CRS.[3] CRS has been divided into five subtypes to recognize the significant interaction that occurs between the two organs (Fig 1). The pathophysiology of CRS is complex and believed to involve the interplay of hemodynamic mechanisms, neurohormonal activation, inflammation, oxidative stress, hypothalamus-pituitary stress, anemia, and iatrogenic causes.[3-5] The hemodynamic factors thought to be involved are impaired intrarenal hemodynamics, decreased cardiac output, and venous congestion, all contributing to reduced renal blood flow.[3] Though not fully understood, the state of HF itself leads to impairment in renal autoregulation out of proportion to the severity of cardiac impairment.[6] This may result from concurrent pathophysiologic process such as neurohormonal activation, inflammation, oxidative stress, and endothelial dysfunction.

Of the 5 subtypes, CRS types 1 and 2 are the most relevant to HF, given that the primary driver in these two situations is cardiac dysfunction.[3] Type 1 CRS refers to acute HF (AHF) leading to acute kidney injury (AKI) or acute or chronic kidney disease. Type 2 CRS denotes chronic HF leading to chronic kidney disease usually with a reduced GFR. CRS type 1, often referred to as worsening renal function (WRF), is one of the most common types of acute kidney "injuries" encountered in hospitalized patients, with a reported incidence ranging from 20 to 40%.[7,8] It is often defined as a creatinine rise of >0.3 to 0.5 mg/dL in the setting of AHF. Older cardiology literature used the cutoff of 0.5 mg/dL, whereas the 0.3-mg/dL cutoff has also been used more recently to align with current consensus AKI definitions.[7,8] In this article, we will use the terms CRS type 1 and WRF interchangeably. CRS

type 1 is believed to be associated with worse patient outcomes, such as longer hospital stay, higher readmission rates, and mortality. Such thinking has been challenged more recently; in some cases, WRF may be considered benign or is even associated with improved outcomes.[9,10] Although this remains controversial, there is little argument that the development of CRS type 1 complicates the management AHF and leads to prolonged hospital stay.

In patients with end-stage HF who are candidates for heart transplant, the presence of concomitant advanced chronic kidney disease (CKD) often poses a clinical dilemma. Studies have shown that the preoperative renal dysfunction is associated with higher mortality after heart transplant, and loss of renal function after transplant is also common.[11-13] At the same time, CRS type 2 is, by definition, theoretically at least partially reversible with correction of the underlying cardiac pathology.[3,5,14] Distinguishing patients who will have a lack of renal recovery or have progressive renal deterioration after a heart transplant vs renal recovery impacts greatly on organ allocation. In actual clinical practice, it is often difficult to distinguish between reversible and irreversible renal dysfunctions in such patients at this time. We will limit our discussion in this article to CRS in the context of HF and present two cases in which the approach could be personalized using biomarkers and pharmacogenomics.

CLINICAL SUMMARY

- Cardiorenal syndrome (CRS) types 1 and 2 are the most common forms of CRS.
- The biomarker combination assay of urinary tissue inhibitor of metalloproteinase 2 and insulin-like growth factor–binding protein 7 is currently approved by the Federal Drug Administration for diagnosis of acute kidney injury, but it has not been validated for use in acute kidney injury from CRS.
- Other biomarkers in blood and urine may facilitate diagnosis and management of CRS in the near future.

CASE 1

A 54-year-old woman with a history of HF with reduced ejection fraction secondary to a nonischemic cardiomyopathy presents with five days of increasing worsening dyspnea on exertion, weight gain, and edema. Her past medical history is notable for type 2 diabetes mellitus, hypertension, and hyperlipidemia. Her examination is notable for an elevated jugular venous pressure and peripheral edema. She is admitted to the hospital for AHF and started on intravenous furosemide. On hospital day five, her creatinine has risen to 1.4 mg/dL from 1.0 mg/dL at baseline. Is this patient experiencing renal injury and how should this rise in creatinine be managed?

Dilemmas in Type 1 CRS

Multiple studies have shown associations between WRF/CRS type 1 and worse clinical outcomes.[6-8] Although the pathophysiology of CRS is complex, a potentially modifiable mechanism is the therapy prescribed to the patient.[6] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers alter renal hemodynamics by decreasing vasoconstriction of the efferent arteriole (and the afferent arteriole to a lesser extent) in the glomerulus leading to a reduction in GFR. Loop diuretics are the main treatment for congestion and volume overload in AHF but also increase neurohormonal activation. High diuretic doses are often associated with WRF. When WRF develops, holding or de-escalating these medications is often considered. However, recent data have not shown adverse effects among patients developing hemoconcentration secondary to more aggressive diuretic dosing, despite an increase in creatinine. Indeed, WRF, when accompanied by hemoconcentration, has even been paradoxically associated with significantly lower long-term mortality.[9,10] Similarly, studies show that renin-angiotensin-aldosterone system (RAAS) inhibitors reduce all-cause mortality in patients both with and without WRF.[15-17] Furthermore, it has been shown that the reduction of mortality associated with the use of RAAS inhibitors was actually greater in the presence of WRF.[17] Although these epidemiologic studies address the AHF community at large, they are not specific to the AHF patient one is faced with that day in the hospital. Any clinician who has taken care of AHF patients has encountered at least 1 WRF patient with an adverse outcome attributable to the renal dysfunction. Precisely defining which patients need to have RAAS inhibitors held or diuretics stopped could potentially avert renal harm.

This suggests that WRF is heterogeneous in nature and that the mechanism underlying the WRF is key in determining its prognostic significance. In some cases, the rise in creatinine is clinically benign, whereas in others, this is associated with further clinical deterioration or lack of clinical improvement.[18-20] Therefore, the ability to distinguish between benign or "pseudo WRF" and clinically significant or "true WRF" would be very helpful in the management of such patients.

A number of novel renal AKI biomarkers have been investigated in the setting of AHF,[21,22] and among these, neutrophil gelatinase-associated lipocalin (NGAL) has been most extensively studied.[18,21,23] NGAL is a member of the lipocalin family, and its expression in the distal tubule is upregulated during kidney injury. It can be measured in the blood and urine with standardized commercially available assays and has been found to be prognostic for adverse outcomes in AKI. The earlier studies on NGAL in AHF were initially encouraging, with a strong relationship between high NGAL levels and increased risk for WRF and adverse outcomes.[23] However, a large prospective multicenter study failed to confirm these results for plasma NGAL.[24] It has been hypothesized that these disappointing results may in part be related to having an inappropriate definition of the desired outcome, which was entirely creatinine-based.[25] In other studies that qualify a creatinine-based WRF