Pathophysiological Mechanisms in Cardiorenal Syndrome

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Cardiorenal syndrome represents the confluence of intricate hemodynamic, neurohormonal, and inflammatory pathways that initiate and propagate the maladaptive cross talk between the heart and kidneys. Several of these pathophysiological principles were described in older historical experiments. The last decade has witnessed major efforts in streamlining its definition, clinical phenotypes, and classification to improve diagnostic accuracy and deliver optimal goal-directed medical therapies. The ability to characterize the various facets of cardiorenal syndrome based on its pathophysiology is poised in an exciting vantage point, in the backdrop of several advanced diagnostic strategies, notably cardiorenal biomarkers that may help with accurate delineation of clinical phenotype, prognosis, and delivery of optimal medical therapies in future studies. This promises to help integrate precision medicine into the clinical diagnosis and treatment strategies for cardiorenal syndrome and, through a heightened understanding of its pathophysiology, to deliver appropriate therapies that will reduce its associated morbidity and mortality.

Key Words: Cardiorenal, Renin-angiotensin-aldosterone system, Central venous pressures, Intraabdominal pressure, Diuretic resistance

INTRODUCTION

The complex and multifaceted relationship between the heart and kidneys has been described as early as in the 19th century, with ever increasing knowledge of the bidirectional cross talk between the two organs.[1] Although cardiorenal cross talk manifests across several interfaces such as hypertension, atherosclerosis, and chronic kidney disease (CKD)-associated cardiomyopathy, the term "cardiorenal syndrome" (CRS) refers specifically to a spectrum of disorders involving both the heart and kidneys, wherein acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.[2,3] The last decade has seen major strides toward a more refined understanding of the pathophysiological mechanisms involved in CRS, with rigorous attempts to define, phenotype, and prognosticate CRS in clinically meaningful ways. This review summarizes key concepts involved in the pathophysiology of CRS, with emphasis on the cardiocentric phenotype of kidney dysfunction (type 1 and type 2 CRS), in the setting of acute and chronic heart failure (HF), respectively. It also outlines the pathophysiology of worsening kidney function in the setting of decongestive therapies in acute heart failure (AHF) and describes the physiology of diuretic resistance in CRS. Finally, it highlights the application of novel urinary biomarkers in delivering optimal decongestive therapies in CRS as well as extensions of these concepts toward future cardiorenal trial designs, toward delivering optimal goal-directed medical therapies in HF with concomitant kidney dysfunction.

NOMENCLATURE AND PHENOTYPES OF CARDIORENAL SYNDROME: A HISTORICAL PERSPECTIVE

As early as in 1913, Rowntree and colleagues elegantly demonstrated the effect of passive renal venous congestion on kidney function in dogs, whereby selective banding of unilateral renal veins resulted in a 20-40% reduction in phenolsulphonphthalein excretion and a diminished urine chloride concentration and chloride output.[4] Subsequently in 1937, Winton and colleagues confirmed these observations, and these findings were believed to result from partial obstruction to urinary flow in the tubules secondary to increased intrarenal pressure.[5] Several investigators in the mid-20th century including Warren and Stead,[6] Merrill,[7] and Mokotoff and colleagues[8] suggested that reduced natriuresis seen in AHF resulted from a primary reduction in glomerular filtration rate (GFR). In contrast to this, others suggested that impaired natriuresis in AHF was a result of increased tubular sodium reabsorption and less related to a primary decline in GFR. In a landmark series of experiments in 1949, Blake and colleagues extensively documented the effect of increasing values of renal venous pressures on renal hemodynamics and water and sodium excretion.[9] They observed that through a range of increasing values of renal venous pressures, hemodynamic parameters such as renal plasma flow, GFR, and filtration fraction were minimally influenced. In striking contrast, renal sodium and water excretion were significantly reduced even with modest elevations in renal venous pressures in proportion to the height of the renal venous pressure column, with demonstration of reversibility of impaired natriuresis/aquaresis with reduction in renal venous pressures. These sentinel observations form the basis for the hemodynamic pathophysiology of CRS as we understand it today and highlight the importance of venous congestion as a sine *quo non* for the development of CRS (Fig 1).

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More recent attempts at defining CRS came from the Working Group of the National Heart, Lung and Blood Institute in 2004, wherein CRS was defined as the result of interactions between the kidneys and other circulatory compartments that increase circulating volume, which exacerbated symptoms of HF and disease.[10] This definition also observed that therapies to relieve congestive symptoms of HF are limited by further decline in renal function in patients with CRS. Recognizing that the heart-kidney interface in CRS extended beyond this cardiocentric approach, the Acute Dialysis Quality Initiative outlined a consensus approach in 2008 which phenotyped CRS into two major groups, namely, cardiorenal and renocardiac syndromes, based on the *primum movens* of the disease.[3] This was further grouped into five subtypes based on disease acuity and sequential organ involvement, which are outlined in Table 1.[2,3,11] The following sections describe in detail the hemodynamic, neurohormonal, and inflammatory pathways involved in the pathogenesis of CRS with emphasis on specific clinical phenotypes in the appropriate contexts.

Hemodynamic Perturbations in Cardiorenal Syndrome

Elevated Central Venous Pressures. Although the conventional explanation for the development of CRS in the setting of a cardiocentric "*primum movens*" (type 1 and type 2 CRS) focuses on the inability of the failing heart to generate "forward" flow with resultant prerenal hypoperfusion, emphasis on renal venous congestion as a determinant of reduced GFR has been placed in the recent literature, reappraising this aspect of CRS hemodynamics from older observations.[5] The ADHERE registry (Acute Decompensated Heart Failure National Registry) noted that the incidence of rising serum creatinine (SCr) was similar among patients with (ADHF) and reduced vs preserved systolic function, suggesting that a low flow state *per se* was not the only determinant of CRS.[12] This observation has been replicated in patients hospitalized with evidence of acute CRS who have preserved or even elevated blood pressure and normal left ventricular ejection fraction[13] (Fig 2). Using invasive hemodynamic monitoring, Mullens and colleagues demonstrated that central venous congestion was the most important determinant of worsening renal function (WRF) in a cohort of 145 patients admitted with AHF.[14] On similar lines, renal blood flow was shown to be the primary determinant of GFR as measured with I-125 iothalamate clearance in a cohort of patients with AHF, wherein venous congestion was the most important determinant of kidney function in patients with lower ranges of renal blood flow.[15] A *post hoc* analysis of the ESCAPE trial (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) confirmed that right atrial pressure was the only hemodynamic parameter associated with baseline renal dysfunction.[16] Several hypotheses have been postulated to explain the effect of venous congestion on kidney function in CRS. These include distension of the renal venules obliterating distal tubular luminae,[5] increased renal interstitial pressure due to back pressure to the renal veins transmitted from elevated central venous pressures,[17] and renal venous hypertension further triggering increased angiotensin II concentrations and a parallel increase in sympathetic nervous system activity.[18]

CLINICAL SUMMARY

- Cardiorenal syndrome represents the interplay of several patho-physiological pathways in its pathogenesis.
- Notable pathways involved in the genesis of cardiorenal syndrome include elevated central and renal venous pressures, arterial underfilling, elevated intra-abdominal pressures, neuro-hormonal perturbations, and oxidative stress.
- Biomarkers of cardiac and kidney injury have the potential to provide important clinical information in the diagnosis and management of cardiorenal syndrome in the future.

Arterial Filling and Reduced Renal Perfusion in Cardiorenal Syndrome

In the general setting of AHF, different hemodynamic profiles have been proposed based on the clinical phenotypes of patients as determined by adequacy of perfusion (decreased cardiac output [CO] and decreased effective circulation fluid volume [ECFV] and extent of [pulmonary] congestion [increase in CVP or wedge pressure]). As such, these can be combined into four distinct profiles deemed "wet or dry" and "warm or cold".[19] Given the differences in patient characteristics and cardiorenal hemodynamics between these profiles, it is plausible that the cause of kidney injury in the setting of type 1 CRS may be determined by the combination of forward filling and venous congestion by these hemodynamic models and may shift from one profile to another during the course and treatment of AHF[20] (Fig 3). This clinical approach, in addition to its simplicity in defining hemodynamic profiles in subjects with HF, also offers predictive value in determining those in urgent need for transplantation or at risk for death.[21]

In hemodynamic profiles with the "cold" phenotype, the predominant alteration in systemic hemodynamics is a reduction in CO and ECFV, and this may be accompanied by marked increase in CVP in the wet profile. However, there are scarce data on the relative contributions of reduced CO and central venous pressures toward determining intrarenal blood flow distribution in AHF. With a strong decrease in ECFV as is to be expected in AHF, neurohormonal activation including renin-angiotensin system and systemic nervous system activation result in afferent (relatively lower efferent) vasoconstriction, leading to a decrease in RBF and renal perfusion pressure.[2,19,22] In these 'cold' profiles, low CO and ECFV may also be associated with low systemic blood pressure. The low resistance nature of the renal vasculature and parenchyma and very low oxygen tension in the outer medulla are partial explanations for the unique sensitivity of the kidneys for hypotension-induced injury.