Cardiorenal Syndrome: A Call to Action for a Pressing Medical Issue

Thomas Lewis used the term "cardiorenal" in his lecture titled "Paroxysmal Dyspnoea in Cardiorenal Patients" in which he discussed his clinical observations on patients with dyspnea related to advanced heart and kidney disease (referred to as cardiac and uremic asthma in the lecture).[1] However, researchers in the 19th and early 20th century had already noted the interactions between the heart and the kidney and performed eloquent experiments highlighting the impact of venous congestion on kidney function.[2-4] Seminal work by Schrier and his colleagues promoted interest in the possibilities that cardiac dysfunction could "drive" progression of kidney disease and vice versa. Importantly, cardiorenal syndrome (CRS) was not simply a matter of salt and water imbalance.[5-7]

The term CRS has now been in use over the last decade because of its description as a distinct entity by Ronco and colleagues. As described by Ronco, Bellasi, and Di Lullo in this issue, 5 subtypes of the syndrome have been described, based on acuity and primary organ involvement.[8-11] Over the last 2 decades, there have been emerging new data on CRS.

Communication between the heart and kidneys occurs through a variety of pathways. These include perfusion pressure, filling pressure, vascular bed resistance, and neurohormonal activity. As outlined by Palazzuoli and Ruocco in this issue, some of the key mediators include the sympathetic nervous system, the renin-angiotensin-aldosterone system, and natriuretic peptides. These cell signals have receptors in the heart, the kidneys, and the vasculature that affect volume status, vascular tone, and cardiac inotropy and output. A change in the performance of one of these organs elicits a cascade of mediators that affects the other.[12]

Worsening renal function (WRF), with varying definitions has been used to describe the renal dysfunction in patients with acute heart failure (AHF); however, WRF is not benign. Uduman describes the epidemiology of CRS in this issue and highlight several studies demonstrating that WRF is associated with increased mortality in both inpatients and outpatients with larger increases in serum creatinine (SCr) predicting worse outcomes.[13] Varying definitions of WRF make comparisons of these studies challenging.[14] Recent observations show that WRF was only associated with poor outcomes if the clinical status of a patient simultaneously deteriorated. In other words, if the status improved or remained equal and SCr increased, pseudo-WRF had occurred. Pseudo-WRF does not necessarily translate to a poor prognosis.[13]

One of the most common clinical scenarios occurs in a patient with AHF and preserved renal filtration who is treated with intravenous loop diuretics after hospital admission. There is an initial diuresis of several liters of urine. However, owing to inadequate plasma refill from the extravascular space, renal perfusion is decreased. Because there is high renal venous pressure, renal filtration begins to drop. In addition, a variety of factors including angiotensin II appear to trigger mesangial cell contraction within the glomerulus. Contractile elements within these structural cells may take entire nephrons "offline" for days before they relax again and allow the nephron to resume filtration. Thus, understanding the determinants of renal-forward perfusion, venous congestion, initial response to diuresis, plasma refill, and mesangial cell contraction appear to be critical research vistas in CRS type 1 (CRS-1) or WRF, in which there is no evidence of tubular injury.[15-19]

CRS-1 or WRF has different clinical implications if prior CKD exists. Duration of WRF is an important aspect which is not well addressed in current definitions, given the concept of pseudo-WRF, which suggests successful decongestion with mildly delayed plasma refill but not sustained mesangial cell contraction. Clearly, as echoed in the article by Palazzuoli and Ruocco, there is a need for a unifying definition for WRF, which would reflect transient renal dysfunction, its prognostic significance, and guide prevention and management strategies.

Diuretics have been the first-line therapy for achieving decongestion in patients with CRS. There is no unifying definition of diuretic resistance and the start of WRF. Testani and colleagues have described a simple method to predict diuretic responsiveness, which should be further validated.[20] Along this line, Novak and Chitturi highlight the potential causes for diuretic resistance in this issue. Having more effective diuresis without aggravating azotemia is a laudable goal, and more research is needed on innovative diuretic approaches.

Biomarkers are key contributors to risk stratification, diagnosis, prognosis, disease monitoring, titration of therapy, and identification of therapeutic targets in cardiovascular disease.[21] Wettersten, Maisel, and Cruz stress that clinical markers of kidney dysfunction must provide more actionable information than currently available hospital laboratory assays, than currently available in community practice. Marker-based information must add substantially to that already known from serial measurements of SCr, blood urea nitrogen, and cystatin C. Similar to cardiac troponin or B-type natriuretic peptide, acute kidney injury or WRF biomarkers must be actionable in the context of evidence-based care—particularly to guide diuretic therapy.[21]

The advent of simplified, portable, and user-friendly devices dedicated to ultrafiltration (UF) therapy for patients with CRS-1 renewed the interest in this therapeutic

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modality. Costanzo and Kazory provide a concise overview of the key clinical findings of the most recent landmark trials assessing UF therapies in CRS. They discuss the shortcomings of these studies and provide appropriate context to which the results should be interpreted, while highlighting existing knowledge gaps that can be addressed in future studies. UF is a promising modality in the management of CRS-1. However, specific questions remain regarding the exact role of UF therapies in the management of CRS-1: timing (to be used as first-line therapy for severe CRS-1 or only in the setting of diuretic resistance); implications of changes in SCr noted in clinical trials of UF, ie, WRF or "pseudo-WRF" and its long-term implications; cost; and long-term outcomes. During UF, estimates of plasma refill become critical and are quantifiable in real time. Nonetheless, there is significant patient-to-patient variability, and varying clinical circumstances can impact the plasma refill rate beyond that predicated upon traditional hydrostatic and oncotic pressures models of normal physiology. Such factors include arterial perfusion and regional shunting, venous congestion, venous capacitance, serum albumin, anemia, serum and tissue sodium content, and inflammation. Many of these factors conspire to impair plasma refill. The complexity of this process renders it difficult to clinically identify those patients who will develop worsening azotemia and/or hypotension on UF. Thus, there is an urgent need to at least attempt to measure plasma refill rate in real-time UF/dialysis management.[22-26]

Maintenance of effective circulating volume depends on the ability of fluid from the interstitial space to refill the vascular space; this refill varies from patient to patient. In the outpatient hemodialysis unit, the UF rate is determined by the predialysis weight and the desired postdialysis weight as a function of the total fluid removed and time devoted to removing that fluid, adjusted for patient weight. This aspect is important to keep in mind when employing UF therapies. Use of continuous online blood volume monitors or other emerging newer technologies (bioimpedance) can facilitate the evaluation of plasma volume changes during UF in CRS-1 and decisions regarding optimal rates of UF during AHF management[27]. The clinical examination of the patient in this setting is insufficient. Therefore, it is time to meaningfully employ technology to aid disease management.

Cowger and Radjef provide a comprehensive review of therapeutic options with advanced HF. Shared decision-making is critical, with palliative treatment options as the most appropriate choice in some instances. Improvements in coordinated HF medical management by internists, cardiologists, and nephrologists will likely lead to reduced hospitalizations and cardiovascular death for AHF, particularly HF with reduced ejection fraction. This means consistent use of evidence-based therapies at maximally efficacious doses. Timely referral of patients with stage D class 4 HF to centers providing advanced HF therapies to patients for whom pump failure is imminent, including ventricular assist devices, total artificial heart, and transplant, is the best way of utilizing these precious resources without burdening HF centers with common issues such as routine medical management. It is estimated that if each board-certified HF specialist consulted on as many as 10,000 patients per year, the "HF physician community" would touch less than 1% of the prevalence pool of HF patients. Thus HF, alongside diabetes and hypertension, is a core internal medicine problem. Its management resides with clinical cardiologists and nephrologists for the vast majority of patients.[28]

Cardiomyopathy ("uremic cardiomyopathy") has been described in patients with kidney disease since the mid-twentieth century.[29,30] Edmonston, Morris, and Middleton provide a comprehensive review of CRS type 4 (CRS-4), addressing the extent of the condition. They include traditional and nontraditional risk factors for atherosclerosis, myocardial disease, and vascular calcification in patients with CKD. Chronic kidney disease affects 30 million people in the US, or approximately 15% of adults, and a diagnosis of some form of congestive heart failure affects 5.7 million people.

The enhanced risk of cardiac arrest in patients who have CKD 3-5 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. A collaborative approach between nephrologists and cardiologists, among others, can help mitigate this risk.

Evidence-based advances in the management of CRS have been relatively limited in the past 100 years, in part because of exclusion of patients with significant renal dysfunction from clinical trials and high level of morbidity and mortality, particularly in patients with CRS-1. In Lewis' time, the patient with acute decompensated or advanced chronic congestive HF was offered bed rest, dietary restriction, diuretics, digitalis, supplemental oxygen, and, of course, morphine.[31] As Rangaswami and Matthew point out, the ability to characterize the various facets of CRS based on its pathophysiology is poised at an exciting vantage point, in the backdrop of several advanced diagnostic strategies, notably cardiorenal biomarkers and physiologic measures that may assist the accurate delineation of clinical phenotypes. Only with phenotypic characterization can we make progress in the delivery of optimal clinical strategies including drugs, procedures, and devices.

Clearly, now we must stand on the "shoulders of giants"[32,33] who have paved the path forward, collaborate, and rapidly develop evidence-based strategies for screening and detection, prevention, and management of CRS with the goals of improving survival, reducing hospitalizations, and avoiding the use of renal and cardiac replacement therapies the vast majority of patients who can be managed without them.[20] For those with a near-complete organ failure, our extracorporeal renal strategies, hemodynamic support devices, and heart transplantation will play a critical role as they continue to be improved and refined.

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