renal insufficiency is prevalent and clinically relevant in the setting of congestive heart failure. When admitted for acute decompensation, on average 1 out of 5 patients has a rise in serum creatinine, 1 out of 10 requires some form of dialysis, and 1 out of 20 requires long-term renal replacement therapies (1). These startling observations highlight the fact that adequate renal function plays a pivotal role in the clinical stability of heart failure. Hence, the term “cardio-renal syndrome” (CRS) has been coined to describe the extreme of cardio-renal dysregulation whereby therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function (the 2004 National Heart, Lung, and Blood Institute [NHLBI] Working Group definition). However, the Acute Quality Dialysis Initiative (AQDI) has expanded this concept to a conceptual CRS classification scheme, which broadens the definitions to include a wide range of concomitant dysfunction between the heart and the kidneys (2). Unfortunately, such contemporary nomenclature is largely descriptive, and the lack of pathophysiologic basis has limited its clinical applicability in triaging distinct therapeutic approaches to individual patients while ignoring many confounding factors. Indeed, when both heart and kidney impairment progresses, as indicated by rising natriuretic peptide levels and worsening glomerular filtration rate, the long-term outcomes are the poorest (3). Nevertheless, the prognostic value of natriuretic peptides remains robust even though the range of the absolute values are higher than those without renal insufficiency.

There is a natural tendency for clinicians, researchers, and investigators alike to gravitate on quantifying renal dysfunction with an easily available metric that is useful in outcomes research. Indeed, a concerted effort was made to examine the clinical relevance of changes in daily serum creatinine during heart failure hospitalization. A rise in serum creatinine ≥0.3 mg/dL was deemed to provide the optimal sensitivity (65 percent) and specificity (81 percent) in predicting in-hospital mortality (4)—a threshold that has been used (and perhaps misused in retrospect) over the past decade in a wide range of outcomes research studies. Such a creatinine rise in patients (often termed “worsening renal function” or WRF) has been associated with an increase in length of hospital stay by 2.5 days, a 67 percent increase in risk of death within 6 months after discharge, and a 33 percent increased risk for readmission (5). However, several new observations have recently emerged regarding the complexity of creatinine changes during decongestive therapy and what they may imply. Improvement in renal function following decongestive therapy may not always reflect better clinical status, as evident that those whose fall in serum creatinine requires progressive renal impairment prior to admission (6). At the other end of the spectrum, the ability to achieve sustained decongestion despite worsening renal function (as evident by evolving hemoconcentration) has been associated with paradoxically better outcomes (7). Interestingly, the main determinants of worsening renal function during decongestion appeared to be inadequate systemic perfusion pressure (i.e., drop in systemic blood pressure during treatment) as well as inadequate responses to decongestive therapy (i.e., drop in net urine output) rather than changes in central hemodynamics or acute tubular injury as determined by novel AKI biomarkers (8–10, Figure 1). These contemporary observations have thus revealed the increasingly clear picture that creatinine-based concepts of CRS may not account for concomitant large intravascular fluid shifts and the lack of true nephrotoxicity during aggressive decongestion—a concept that is still in evolution. Nevertheless, the good news is that not all rises in creatinine during decongestion for decompensated heart failure signal the grave consequence of AKI.

Perhaps the biggest challenge in contemporary approaches to CRS is the lack of effective “renal-sparing” or “renal-enhancing” therapies in the treatment of congestion for patients with heart failure. Much effort has been made over the past decade by investigators and industries alike. These included the clinical development of natriuretic peptide analogues, adenosine receptor antagonists, vasopressin receptor antagonists, and ultrafiltration—all have met with mixed results or off-target effects. Indeed, the treatment approach to acute decompensated heart failure has not changed over the past 5 decades, with the sole reliance on intravenous loop diuretics in various forms of dosing, route, and formulations, plus some adjunctive therapeutics. While future insightful mechanism biomarkers to guide therapeutic choices are still needed, they are more likely to be utilized to prevent rather than to react to AKI.

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References


