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The Effects of Heart Failure on Renal Function

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Summary

Heart-kidney interactions have been increasingly recognized by clinicians and researchers involved in the study and treatment of heart failure and kidney disease. A classification system has been developed to categorize the different manifestations of cardiac and renal dysfunction. Recent work has highlighted the significant negative prognostic effect of worsening renal function on outcomes for individuals with heart failure. The etiology of the concomitant cardiac and renal dysfunction remains unclear; however, increasing evidence supports alternatives to the established theory of underfilling, including effects of venous congestion and changes in intra-abdominal pressure. Conventional therapy focuses on blockade of the renin-angiotensin-aldosterone system with expanding use of direct renin and aldosterone antagonists. Novel therapeutic interventions using extracorporeal therapy and antagonists of the adenosine pathway show promise and require further investigation.

Keywords

Cardiorenal; decompensated heart failure; acute kidney injury; management; prognosis

Introduction

Increasingly, heart-kidney interactions are being recognized as fundamentally important in the prognosis of each organ individually as well as the prognosis of the overall patient. Recently, Ronco and colleagues have more explicitly outlined and classified the clinical cardiorenal syndrome with five distinct types (See table 1).[1] While each of the subtypes has different underlying etiologies, the definition of the syndrome and the classification highlights the important interactions between the two organ systems and how the function of each system, itself, is dependent on the other. Further, classification highlights the importance of focusing on both organ systems when establishing a therapeutic plan, i.e. one must treat both the underlying cardiac and renal dysfunction in order to improve the function of both organ systems.

As the cardiorenal syndrome (and its subtypes) has been defined, its incidence appears to be on the rise and the impact of organ dysfunction on long-term prognosis has been recognized.[2,3] Conventional understanding of the managing patients with dual organ dysfunction has

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focused on treating underlying risk factors for cardiac and renal dysfunction (hypertension, diabetes, atherosclerotic disease, etc.) for prevention of chronic organ dysfunction as well as the optimization of cardiac output in acute organ dysfunction. Increasingly the focus of optimal care has shifted toward volume management and preservation of euvolemia.[4] Accordingly, while treatment of chronic organ dysfunction has been well established with existing pharmacologic therapy—with focus on blockade of the renin-angiotensin-aldosterone-system (RAAS)—novel treatment strategies are being explored to identify the optimal use of vasodilators, non-RAAS neurohumoral therapy and extracorporeal therapy.

The purpose of this review is to highlight the epidemiology of concomitant cardiac and renal dysfunction and its prognostic significance for long term organ and patient survival. Additionally we will outline evolving theories of the etiology of worsening renal function in the setting of worsening cardiac function, identify conventional and innovative therapeutic strategies to treat the syndrome and to explore novel markers of renal dysfunction in the setting of worsening cardiac function.

Epidemiology and Prognosis

Chronic Heart Failure and Chronic Kidney Disease

The relationship of renal function with congestive heart failure (CHF), as highlighted by type I and type II cardiorenal syndromes (CRS), is present in both chronic heart failure syndromes as well as acute decompensated heart failure (ADHF). Increasing recognition of the syndrome has revealed a growing incidence of Type I and II as well as the prognostic importance of each, i.e. renal dysfunction in the setting of congestive heart failure portends an independently worse outcome compared to those with preserved renal function. While often the more clinically apparent scenario is worsening renal function in the setting of ADHF, long-term follow-up of patients with concomitant cardiac and renal dysfunction has highlighted its significance. Ahmad, et al, in an analysis of the SOLVD (Studies of Left Ventricular Dysfunction) study population demonstrated the impact of chronic kidney dysfunction on outcomes in heart failure. Approximately 6600 subjects were studied with an overall mortality of 23.5% over the course of the study period, 89% of which was determined to be related directly to cardiovascular disease. Estimated baseline glomerular filtration rate (eGFR) was a small, but statistically significant independent predictor of mortality. For each 10 ml/min lower an individual's baseline eGFR, there was a 1.064 increased risk of death (95% CI 1.033–1.096)).[5] In a more recent and in-depth analysis assessing the impact of stage of kidney disease and rate of progression, Khan et al confirmed the prognostic importance of renal dysfunction in patients with left ventricular systolic dysfunction. Once again, using the SOLVD study population, the investigators assessed the all-cause mortality of patients stratified by estimated baseline glomerular filtration rate (eGFR). There was no difference in mortality for those with eGFR greater than 90 ml/min or between 60–90 ml/min, however the risk of mortality increased significantly once baseline eGFR fell below 60 ml/min, with a hazard ratio (HR) of 1.32 for 30–59 ml/min and 2.54 15–29 ml/min ($p = 0.004$ and 0.0003, respectively). Rate of CKD progression was also an important predictor of overall mortality; in patients whose eGFR fell greater than 10 ml/min/year, mortality significantly increased: for the group falling 11–15 ml/min/year during the study period, the hazard ratio for mortality was 2.23 and for those > 15 ml/min/year, the hazard ratio for mortality was 5.63 ($p < 0.0001$ for both). Not only did the finding highlight the impact of baseline CKD and progression of renal dysfunction on mortality in patients with systolic dysfunction, but it also discovered that the phenomenon is not rare, as 17% of patients had a fall in eGFR by greater than 10 ml/min/year during the study period. Further the highest risk group for rapid progression were the individuals with an eGFR > 90 ml/min at baseline.[6] Thus, it appears that preserved renal function does not protect an individual with systolic dysfunction from developing worsening renal function and those that have renal dysfunction have a poorer prognosis than those with stable, preserved renal function. Similar

studies with different patient cohorts have confirmed these results. Weiner, et al evaluated the associations between baseline and change in renal function and cardiovascular events over a three year period in a community-based population combining the Atherosclerosis Risk in Communities (ARIC) cohort and the Cardiovascular Health Study (CHS) cohort. In total, approximately 18,000 patients were studied and were stratified into 4 groups by baseline eGFR less than or greater than 60 ml/min that remained within that range for the study period or individuals that started with eGFR greater than 60 ml/min whose eGFR fell to less than 60 ml/min and the converse. 891 subjects had a stable eGFR < 60 ml/min, 278 subjects had an increase in their eGFR from < 60 ml/min to > 60 ml/min, 972 subjects had a fall in their eGFR from > 60 ml/min to < 60 ml/min and the remainder had a sustained eGFR >60 ml/min throughout the study period. The authors discovered that patients with the highest cardiovascular morbidity risk were the individuals with a sustained eGFR < 60 ml/min (HR=3.66, 95% confidence interval 3.12–4.30). Further, the authors discovered that either a fall in eGFR during the study period to below 60 ml/min *or* an initial eGFR below 60 ml/min and a subsequent increase above 60 ml/min during the study period carried an added risk (HR 2.48, 95% confidence interval 2.08–2.95 and HR 2.10 95% confidence interval 1.50–2.92)—suggesting the presence of abnormal renal function, even with some degree of variability where there is biochemical improvement is associated with increased cardiovascular morbidity.[7] The findings, however, did not differentiate between cardiovascular outcomes related to heart failure versus coronary artery disease or cerebrovascular disease. Nevertheless, the findings confirm the significant association of small decrements in renal function with cardiovascular morbidity even when renal function may transiently improve, and perhaps points to a flaw in the utility of eGFR as a surrogate for renal function.

The phenomenon does not appear to be limited to Western societies. In an analysis of the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD), investigators demonstrated similar long-term outcomes in Japanese patients with CKD hospitalized with heart failure. The JCARE-CARD followed a cohort of approximately 2000 patients after their hospitalization for a mean of 2.4 years and demonstrated that CKD (defined by eGFR <60 ml/min by MDRD equation) was prevalent among the study population (70.3%), and carries increased morbidity and mortality.[8] The composite endpoint (all-cause mortality and rehospitalization for heart failure) increased with the worsening renal function (HR 1.520 and 2.566 for eGFR 30–59 ml/min and < 30 ml/min, respectively as compared to eGFR > 60 ml/min, p values for both < 0.001). Of note, patients with renal dysfunction (eGFR < 60 ml/min) were also less likely to be prescribed ACE-Inhibitors, Angiotensin receptor blockers (ARB) and β-blockers upon hospital discharge than those with preserved renal function—but it deserves noting that less than 50% of patients in each group were prescribed any of the medications established to improve mortality in patients with heart failure.[8] Recent literature has confirmed the findings of earlier studies that the presence of renal dysfunction in the setting of heart failure is associated with adverse outcomes over extended, out-of-hospital follow-up. The recent findings have highlighted that smaller decrements in renal function, even transient, are similarly associated with poorer outcomes in patients with heart failure and this association transcends European and American populations.

Acute Decompensated Heart Failure and Worsening Renal Function—Previous studies have confirmed the impact of worsening renal function (WRF) or acute kidney injury in the setting of acute decompensated heart failure on length of hospitalization. In a study of approximately 300 European patients hospitalized with ADHF, approximately one third of the patients developed WRF (72 of 248 individuals included in analysis). The presence of WRF did not appear to have an impact on overall mortality, but extended hospital stay.[9] However, more recent literature has identified that the worsening renal function has broader impact than simply extending hospitalization. Rather, WRF, even if its presence is transient, independently predicts a poorer clinical outcome.

Metra and colleagues in a study of 318 consecutive patients admitted with ADHF demonstrated the impact of worsening renal function on mortality. 107 patients developed WRF: defined by increase in serum creatinine (SCr) by 0.3 mg/dl and increase of Scr by 25% or more from the admission serum creatinine). Importantly, the study's intention was to identify patients who developed worsening renal function through the course of standard heart failure therapy. The study population, thus, included patients hospitalized with acute heart failure syndromes, however excluded patients who "developed complications or underwent procedures which may cause a rise in S-Cr." Specifically, patients with a cardiac arrest, shock, cardiac surgery or underwent invasive procedures requiring intravenous contrast administration were excluded. After a mean follow-up period of approximately 480 days, patients who experienced WRF in the hospital had a significantly higher rate of the primary outcome—urgent hospitalization for heart failure or cardiovascular mortality with a hazard ratio 1.47 (95% confidence intervals 1.13–1.81p = 0.024).[10]

Logeart and colleagues discovered similar findings in a study of a similar patient population of 416 individuals hospitalized with acute heart failure. As in the study performed by Metra and colleagues described above, individuals with cardiogenic shock, in-hospital death, and severe low-output heart failure requiring ionotropes were excluded. Also, patients with advanced chronic kidney disease with a serum creatinine > 230 μmol/L (approximately 2.6 mg/dL) were excluded in attempt to include only patients where the WRF was directly related to ADHF. Despite the strict exclusion criteria, the investigators also discovered a high incidence of WRF, 152 out of 416 patients (36.3%), with WRF defined as an increase in SCr of 25 μmol/L (approximately 0.3 mg/dl). Despite a shorter follow-up period than the previous study described, the investigators also found WRF to be an independent risk factor for their primary outcome—rehospitalization for ADHF or all-cause mortality with a hazard ratio of 1.48 (95% confidence interval 1.20–2.82, p= 0.01). [11] Importantly, the study included patients whose renal function improved during the course of their hospitalization as those with WRF. Thus, the authors concluded that despite improvement, the mere presence of worsening renal function in the setting of ADHF portends a poor prognosis.

The recent literature highlights important updates in the association between WRF and ADHF. First, in concordance with literature in other clinical settings, small increases in serum creatinine (50% increase or absolute increase of 0.3mg/dl from baseline as in stage I AKI as defined by the Acute Kidney Injury Network), previously thought to be of questionable clinical importance, are independently associated with both short-term and long-term clinically important outcomes.[12,13,14,15]. Further, even when the small changes in serum creatinine are transient and renal function "improves," patient's clinical prognosis remains worse than those whose renal function remains intact throughout their hospital stay.

Etiology—The natural question resulting from this finding is what are the underlying clinical or patient characteristics that lead to WRF in the setting of ADHF? Given that even transient WRF in individuals hospitalized with ADHF have worse outcomes this suggests that the worse outcomes cannot be related only to presence of renal dysfunction, but suggests that the presence of heart failure or other aspects of the clinical milieu of patients developing WRF is different.

The studies outlined above give some insight into the differences in patient characteristics associated with WRF. Specifically, in the population studied by Metra and colleagues individuals with WRF were more likely to have pre-existing renal dysfunction (36% vs. 19%, p = 0.002), rales above the lung bases on auscultation (67% vs. 46%, p = 0.001), presence of increased jugular venous pressure (41% vs. 26%, p = 0.009) and, on echocardiography, lower mean ejection fraction (31.4% vs. 36.0%, p = 0.007), greater likelihood of left ventricular dilation (79% vs. 65%, p = 0.001), higher mean pulmonary artery pressure (47 mm Hg vs, 43 mm Hg, p = 0.004) and a greater likelihood of a having a restrictive pattern of filling (50% vs.

35%, p = 0.015). [10] In contrast, in the population studied by Logeart and colleagues left ventricular ejection fraction, the sole echocardiographic data reported, did not differ between those who did and did not develop WRF. Rather, individuals developing WRF were more likely to be older, have baseline renal dysfunction, a history diabetes mellitus, a history of hypertension, lower baseline hemoglobin (mean 12.1 g/dl versus 13.1 g/dl) and hypertensive crisis (systolic blood pressure ≥ 200 mm Hg) as a precipitating cause of heart failure decompensation.[11] Thus, while recognizing differences between the groups, the identified characteristics offer limited insight into etiology of WRF in ADHF outside of presence of baseline renal dysfunction. Further, while the concept of arterial underfilling is often used to explain WRF in the setting of ADHF, systolic and diastolic blood pressure, the presumed manifestation of hypoperfusion and arterial underfilling, did not differ between the groups in either study.[10,11] A study by Mullens and colleagues with invasive monitoring of 145 patients admitted with ADHF offered additional information about characteristics of patients developing WRF with a suggestion of a biological explanation as well. Consecutive patients admitted with ADHF underwent invasive monitoring with a pulmonary artery catheter. Similar to the previous studies outlined, WRF was defined as an increase in SCr by 0.3 mg/dl and was common (occurring in 40% of subjects). Once again renal dysfunction on admission was the only baseline difference between the two groups. Investigators assessed admission systolic blood pressure, cardiac index (CI), pulmonary capillary wedge pressure, pulmonary artery systolic pressure and central venous pressure (CVP). Only mean central venous pressure was predictive of WRF with a mean CVP 18 ± 7 mmHg in the group developing WRF vs. 12 ± 6 mmHg, p<0.001 in the group without WRF. Further, cardiac output, which is often considered to be the focus of optimized ADHF therapy, was actually *higher* in the group developing WRF (mean CI 2.0 vs. 1.8, p = 0.008). The study authors concluded that, perhaps, rather than arterial underfilling as the central physiologic derangement leading to WRF in ADHF, venous congestion is the primary culprit--similar to the development of cardiac cirrhosis in patients with chronic heart failure.[16] Other investigators, in a re-analysis of data from the ESCAPE trial and an investigation by Damman et al have discovered similar findings.[17,18]

The effect of increased renal venous pressure to reduce renal blood flow, decrease single-nephron GFR and decrease urinary sodium excretion has been well recognized in previous animal studies. Specifically, Wathen and Selkurt outlined the relationship between increases in renal venous pressure, creatinine clearance, urine volume and urinary sodium excretion in the setting of saline loading. Once dogs were loaded with intravenous saline, renal venous pressure was increased by partial occlusion of the renal vein. Increased renal venous pressure was associated with decreased creatinine clearance, urine volume and urinary sodium excretion as compared to dogs where renal venous pressure was left unaffected. Importantly, this only occurred in the dogs that were salt-loaded and not those who were *truly* volume depleted via removal of access to food and water for 24 hours.[19] Burnett and Cox demonstrated similar findings in their experiments. Once again, they compared the effect of increasing renal venous pressure on urinary sodium excretion and glomerular filtration rate in dogs that were restricted from any food for 24 hours before the experiment. Urinary sodium excretion, renal blood flow and GFR were compared between the dogs prior to and after administration of 5% body weight of parenteral saline solution. As discovered in the study outlined above, the saline expanded and the “hydropenic” dogs behaved differently with increases in renal venous pressure. Increases in renal venous pressure decreased urinary sodium excretion, GFR and renal blood flow. Importantly, this study also included measures of renal interstitial pressure. Renal interstitial pressure increased to a much greater degree in the saline-expanded state for the same degree of increase in renal venous pressure than the “hydropenic” state.[20] Thus it appears that the effect of increased venous pressure on single-nephron GFR, urinary sodium excretion and renal blood flow vary depending on the organism’s state of sodium balance; with interstitial pressure mediating this effect. The above experiments, while carried out in dogs, give a putative mechanism for the clinical manifestations seen in ADHF and identified in the trials outlined

above. While not definitive proof, it provides direction for future investigation on the link between worsening renal function and decompensated heart failure.

A similar, yet distinct, potential mechanism for WRF in the setting of ADHF is mediated by the effect of decompensated heart failure on intrabdominal pressure. The importance of intrabdominal pressure on renal function in the critically ill (e.g. trauma, acute pancreatitis, decompensated liver disease) has been increasingly recognized. In a recent single-center study of critically ill patients, those with acute renal failure were twice as likely to have intrabdominal hypertension than those without.[21] Similarly, in a separate single-center study of critically ill patients with sepsis, increasing intrabdominal pressure correlated with higher peak serum creatinine, abdominal perfusion pressure was inversely correlated with peak serum creatinine and individuals with abdominal compartment syndrome (defined by intrabdominal pressure greater than 20 mm Hg and organ dysfunction) had a significantly higher serum creatinine.[22]

Congestive heart failure has also been recognized as a clinical scenario where the effect of intrabdominal pressure may be important. In a single-center study of 40 consecutive patients admitted to a heart failure unit with intrabdominal pressure monitoring. Patients with increased intrabdominal pressure ($\geq$ 8 mm Hg) had a higher baseline serum creatinine (on admission) than those with lower intrabdominal pressures. Further, changes in intrabdominal pressure were directly proportional to changes in renal function (as measured by creatinine clearance). [23] The data do not provide a causative relationship; nevertheless, the findings do suggest a relationship of ADHF, WRF and increased intrabdominal pressure. A potential causative link is suggested by a separate study conducted by the same investigators on the effect of fluid removal on increased intrabdominal pressure and renal function in the setting of ADHF. 9 patients with elevated intracardiac filling pressures, severe systolic dysfunction (LVEF < 30%) and with failure of response to medical therapy (as determined by attending cardiologist) were treated with fluid removal via paracentesis or continuous ultrafiltration. Mean intrabdominal pressure was elevated prior to fluid removal (13 mm Hg). After fluid removal, the mean intrabdominal pressure fell to 7 mm Hg. All patients had an increase in serum creatinine after admission to the heart failure unit prior to fluid removal and had a significant fall in serum creatinine after fluid removal (mean SCr 3.4 mg/dl prior to fluid removal and 2.4 mg/dl after fluid removal $p = 0.01$).[24] While there is not a definitive link between the mechanical removal of fluid and the change in serum creatinine, the findings do suggest that intrabdominal pressure is the determinant of changes in renal function in the patients with ADHF and increased intrabdominal pressure. The investigators theorize that the benefit observed in patients with mechanical fluid removal was mediated by amelioration of renal “tamponade” physiology. Prior to fluid removal, the kidney existed in a state bordering on ischemia resulting in worsening renal function. Fluid removal increased abdominal perfusion pressure, thus, improving renal perfusion pressure. The clear limitations of the theory are that they are founded on experience solely published from a single-center and single heart failure unit without confirmation in other institutions. Further, no other indices are reported as surrogates for renal blood flow or renal perfusion. Specifically, neither urinary sodium excretion nor urinary urea excretion is reported as possible confirmation of the effect of fluid removal to ameliorate a state of renal ischemia. Nevertheless, the findings offer additional insight and an alternative pathway on how decompensated heart failure leads to worsening renal function (WRF).

Highlighting the effects of venous congestion and increased intrabdominal pressure on renal function have offered novel perspectives on the phenomenon of WRF in ADHF. While the theories remain to be definitely proven, they have sound foundations in observed renal physiology and offer new targets for monitoring as well as therapeutic intervention. Most importantly, the theories offer alternatives to the conventional theories of “over-diuresis” and “inadequate cardiac output” that have led to misguided interventions including deleterious use

of volume expansion and vasoactive drugs when alternative strategies may have been more effective.

Importantly, the above mechanisms appear to contribute to worsening renal function in the setting of an *acute* worsening of heart failure. Worsening renal function in the setting of chronic heart failure syndromes is even less clear. WRF may be due to chronic hypoperfusion, venous congestion or intrabdominal hypertension or, simply, a concomitant manifestation of the underlying disease processes that have lead to the cardiac dysfunction are unclear.

Manifestations of worsening renal function

In the above studies evaluating patients with concomitant cardiac and renal dysfunction, serum creatinine and eGFR, calculated by the modified MDRD equation, are used to monitor renal function. However, serum creatinine has clear limitations. Given its dependent on muscle mass, serum creatinine-based estimations of renal function can underestimate or overestimate renal function at the extremes of age and body size. Further, the kidney's ability to hyperfilter in the setting of early renal injury can hide the evidence of true renal injury when tubular or glomerular damage has already begun. The finding that chronic heart failure patients have microalbuminuria in the setting of serum creatinine slightly above the normal range suggests that more renal damage is present than suggested by serum creatinine.[25]

Novel biomarkers of renal function, specifically serum cystatin C and serum and urine Neutrophil Gelatinase Associated Lipocalin (NGAL), have been studied in the evaluation of, both, acute and chronic changes in renal function.[26,27] Additionally these markers have been investigated in the setting of heart failure. Poniatowski and colleagues measured serum cystatin and serum and urine NGAL in 150 patients with known coronary artery disease and variable ejection fraction and New York Heart Association (NYHA) functional class without pre-existing kidney disease (denoted by elevated serum creatinine). Both serum NGAL and cystatin C increased as NYHA functional class worsened and ejection fraction decreased, with statistically significant mean value differences for NYHA class III versus class I (no class IV individuals were studied). Urinary NGAL also increased with worsening NYHA functional status class, differences were noted between class II and class I as well as class III and class I heart failure. Urine NGAL, serum creatinine and eGFR (MDRD) were statistically significantly higher in patients with NYHA class III versus class I heart failure.[28] The utility of urinary NGAL has been investigated in the setting of stable heart failure Ninety patients with known CHF were compared with 20 age and sex matched controls with regard to serum creatinine, eGFR and urinary NGAL. Urinary NGAL was significantly higher in the individuals with congestive heart failure and concentrations correlated with serum creatinine, eGFR and N-terminal brain natruiretic peptide (NT-BNP). These study findings confirm the ability of serum NGAL and cystatin C to correspond with renal function in patients with chronic congestive heart failure. Further, it appears the markers correspond better with functional status than creatinine alone. However, it does not appear that the serum markers are superior to MDRD-based eGFR equations. Urinary NGAL, however, does appear to have added sensitivity in detecting worsening functional class prior to significant changes in serum creatinine or eGFR. More importantly, the elevations in serum and urinary NGAL suggest that the changes in renal function manifested by changes in urinary sodium excretion, single-nephron GFR and creatinine clearance are not merely manifestations of purely reversible hemodynamic derangements. Given that NGAL has been demonstrated to serve as a marker of true tubular injury, its elevation in the urine suggest that renal tissue injury occurs and is ongoing in the setting of chronic heart failure. The conclusion suggests that all changes in renal function observed in patients with chronic heart failure, even in the absence of concomitant hypertensive and/or diabetic nephrosclerosis will not ameliorate simply with improvement in heart failure. Whether NGAL (or other markers of tubular injury) have value in longitudinal studies of

patients with chronic heart failure and reflect intermittent decompensations and improvements in functional status remains to be studied.

Serum NGAL appears to demonstrate a similar pattern in patients with acute heart failure as in chronic heart failure patients. In a nested analysis of patients enrolled in the Optimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), patients were randomized to received either captopril or losartan following a myocardial infarction that was complicated by heart failure.. In these 236 subjects serum NGAL levels were elevated initially and fell significantly after the initial hospitalization. Similar to the studies outlined above, serum NGAL corresponded to mean NYHA functional class over the follow-up period as well as the NYHA functional class determined at the end of the follow-up period (median 2.7 years).[29]

The limitation in measurement of serum NGAL alone is that NGAL is not kidney-specific. Therefore, while elevations in serum or urine NGAL suggest possible renal tubular injury, it may be, rather, an indicator of extra-renal tissue injury. The search for the perfect kidney injury biomarker continues both for states of congestive heart failure and non-cardiac causes of kidney injury. NGAL and cystatin C have demonstrated promise, but their full clinical utility remains to be determined.

Treatment

Treatment of chronic heart failure—While the treatment of chronic heart failure as a whole is beyond the scope of this review, the agents that are particularly applicable to renal function (and changes in renal function) are those that effect the renin-angiotensin-aldosterone axis. The positive effect of Angiotensin-converting enzyme (ACE)-inhibitors and Angiotensin II receptor blockers (ARB) on cardiac function and mortality in patients with heart failure has been well established. [30,31,32] Despite their known beneficial effects in patients with heart failure, ACE-inhibitors and ARBs remain under-prescribed.[33,34] Further, renal failure remains a common identified reason for not prescribing ACE-inhibitors or ARBs.[33,35] Therefore, the question arises, should ACE-inhibitors and ARBs be used in patients with heart failure and CKD? Further, what is the appropriate response if the serum creatinine increases with use of an ACE-inhibitor or ARB?

Both the CONSENSUS (a randomized controlled trial demonstrating the benefit of enalapril on symptoms and survival in NYHA class IV heart failure) and CHARM (a randomized controlled trial demonstrating the benefit of candesartan on survival in congestive heart failure) trials included individuals with renal dysfunction, however the effect of treatment on these groups was not addressed specifically. Limited data is available regarding the specific use of ARBs or ACE-inhibitors in patients with chronic kidney disease and heart failure. Using the database from the Digitalis Investigation Group, a randomized trial of digoxin for individuals with systolic heart failure, individuals with CKD, defined by serum creatinine greater than 1.3 mg/dl in women and 1.5 mg/dl in men a propensity-score based on the analysis of the effect of ACE-inhibitors on outcomes in heart failure in patients with CKD was created. Approximately 1700 individuals were identified and those taking ACE-inhibitors were matched by propensity score with those not taking ACE-inhibitors. Ultimately 208 individuals with CKD on ACE-inhibitors were studied. After adjusting for covariates and propensity score, individuals taking ACE-inhibitors had a lower risk of death at 2 years (HR 0.58, 95% CI 0.35–0.96), and were less likely to have hospitalizations for decompensated heart failure (HR 0.69, 95% CI 0.48–0.90).[36] While the propensity-score based analysis and matching attempts to control for the possible confounding, the study findings are limited by the non-experimental nature of the study.

Similarly, while, not a study directly designed to study the use of ARBs in the setting of CKD and CHF, a secondary analysis of the Valsartan in Heart Failure Trial (Val-HeFT) database offers some additional insight on potential benefits of RAAS blockade. The study enrolled approximately 5100 individuals with stable, symptomatic heart failure with and ejection fraction less than 40%. The individuals were then classified according to the presence of CKD (eGFR < 60 ml/min) and/or proteinuria (1+ dipstick or more). All individuals were randomized to treatment with Valsartan or placebo. Importantly, individuals with baseline serum creatinine greater than 2.5 mg/dl were excluded. Valsartan had no effect on mortality (versus placebo) in individuals with or without CKD, however, in individuals with CKD, valsartan extended the time to first morbid event (death, sudden death with resuscitation, hospitalization for heart failure, use of vasodilators and/or ionotropes for at least 4 hours without hospitalization). [37] The limited studies suggest that the benefits of ACE-inhibitors and ARBs in heart failure carry over to patients with CKD. Nevertheless, individuals with more advanced renal dysfunction were excluded from the re-analyzed studies. Until further data is available, the use of ACE-inhibitors or ARBs for the indication of chronic heart failure must be individualized.

The hemodynamic effects of ACE-inhibitors and ARB on the intraglomerular circulation are well described and remain a primary reason for their use in patients with chronic kidney disease. However, a common association is seen between initiation of ACE-inhibitors and rise in serum creatinine or fall in eGFR. An increase in serum creatinine up to 30% is often seen after initiation and is associated with long-term stability of renal function.[38] Thus, an increase in serum creatinine of 30% or less is not associated with long-term renal damage and warrants continued use of the drug in the absence of other adverse effects. A greater than 30% increase is not as reassuring and suggestive of a state of angiotensin dependent glomerular perfusion such as volume depletion or severe renal atherosclerotic disease and warrants discontinuation of the drug.

Direct renin-inhibitors—The well established benefit of ACE-Inhibitors and Angiotensin receptor blockers have led physicians to seek additional benefit in the therapy of heart failure with other means of RAAS blockade. Direct renin-inhibitors (DRI) offer an alternative as well as a complementary therapy for complete RAAS blockade. Theoretically, the use of ACE-I or ARB upregulate renin activity to the degree where increased renin activity can overcome the effect of ACE-I or ARBs and lead to continued RAAS activity. The clinical effect of DRI on patients with heart failure, however, is not well known. McMurray, et al studied the effect of DRI on clinical and biological parameters (including plasma BNP (Brain natruiretic peptide) and NT-BNP (N-terminal Brain natruiretic peptide) in patients with NYHA Class II–IV heart failure, history of hypertension and stable use of β-Blockers and ACE-inhibitor (or ARB). 296 individuals were randomized to 150 mg of Aliskirein or placebo. At baseline patients were well matched according to demographic, clinical and biological parameters. After twelve weeks of follow-up, individuals receiving Aliskiren had a mean fall in NT-BNP 244± 2025 pg/ml versus a mean increase in NT-BNP of 762 ± 6123 pg/ml in the individuals receiving placebo (p= 0.0106). BNP fell in both groups, although more in the Aliskiren group (61 ± 257 pg/ml vs 12.2 ± 243 pg/ml). No statistically significant differences were seen in any clinical or echocardiographic parameters or adverse events between the groups.[39] The results of the study suggest that the use of DRI in addition to existing, standard of care therapy for heart failure is well tolerated. While there are appear to be neurohumoral benefits, whether this translates to short or long-term clinical benefit requires further investigation.

Aldosterone antagonists—Despite the use of ACE-inhibitors or ARBs, aldosterone levels remain elevated in patients with chronic heart failure, leading physicians to explore and discover the benefits of aldosterone antagonists. The Randomized Aldactone Evaluation Study (RALES) randomized 1663 patients with severe congestive heat failure (ejection fraction < 35% and NYHA class III or IV to an aldosterone antagonist, aldactone, versus placebo. The

patients receiving aldactone had a significantly lower risk of death than the placebo group (relative risk 0.70, 95% CI 0.60–0.82).[40] The Eplerenone Post-Acute Myocardial Infarction Heart Failure efficacy and survival Study (EPHESUS) investigated the effect of an alternate aldosterone antagonist, eplereneone, on patients with left ventricular dysfunction (ejection fraction < 40%) after an acute myocardial infarction with clinical signs of heart failure. Approximately 6600 individuals were randomized to eplerenone versus placebo. Similar to the RALES study, the individuals receiving the aldosterone antagonist had a lower risk of death (relative risk 0.85, $p = 0.008$).[41] The two landmark trials described above expanded the use of aldosterone antagonists to patients with advanced heart failure. The question remains, is their use safe and effective in patients with renal dysfunction? Importantly, in both studies, individuals with baseline serum creatinine greater than 2.5 mg/dl were excluded. Further, the hyperkalemic effect of aldosterone antagonists was increasingly recognized after the results of RALES study. Both the RALES and EPHESUS study excluded patients with baseline serum potassium greater than 5.0 mmol/L and individuals were closely monitored for hyperkalemia. In the RALES study, the risk of hyperkalemia was minimal (less than 2%) with no difference between the treatment and placebo groups. However, the widespread use of aldosterone antagonists led to much more significant hyperkalemia. After the publication of the RALES study, the rates of hyperkalemia requiring hospitalization increased from 2.4/1000 to 11/1000 in a population-based analysis of patients with a history of heart failure treated with ACE-inhibitors from the province of Ontario, Canada.[42] It is unclear the effect renal dysfunction had on the increased incidence of hyperkalemia. Nevertheless the findings question the safety and indication for aldosterone antagonists in heart failure, especially those with CKD or borderline potassium levels.

Minimal data is available to guide clinicians on the use of aldosterone antagonists in CKD to improve cardiovascular outcomes. While not studied in patients with overt heart failure, British investigators evaluated the effect of spironolactone on left ventricular mass and aortic stiffness in patients with stage II and stage III CKD. Importantly, the inclusion criteria were individuals already being treated with ACE-inhibitors, making the population as close to a “real-world” sample as possible. Left ventricular (LV) mass was determined by magnetic resonance imaging. Aortic pulse wave velocity (APWV) was measured by sequential carotid and femoral artery waveforms. A total 112 patients were studied and followed for a total of 40 weeks including a 4-week open-label run-in period. Compared to placebo, individuals treated with spironolactone had a significant decrease in mean LV mass as well as a decrease in prevalence of LVH (-14 ± 13 g vs. 3 ± 11 g, $p < 0.01$ for spironolactone versus placebo). Aortic pulse wave velocity decreased and aortic distensibility increased as well in the spironolactone group. After randomization, only two patients in the spironolactone group had hyperkalemia (serum potassium 5.5 – 5.9 mmol/L) requiring modification to alternate day therapy. Serum potassium in the spironolactone group at the end of the study was slightly higher than the placebo group (4.6 ± 0.6 mmol/L vs. 4.4 ± 0.4 mmol/l ($p < 0.05$).[43] The results of the study suggest that, in a carefully selected and monitored population, aldosterone antagonists are safe and can be effective in improving some early anatomic and physiologic parameters of cardiovascular function. Importantly, the physiology of patients with CKD without systolic dysfunction may be very different than the population studied. In individuals with symptomatic heart failure much more reliant on single-nephron GFR for renal function, the hyperkalemia resulting from administration of aldosterone antagonists may be much more marked. Further, patients with diabetes, who often have coexisting renal and cardiovascular disease, were excluded from the study population. If individuals with diabetes have coexistent hypo-renin hypo-aldosteronism and type IV renal tubular acidosis physiology, the administration of aldosterone antagonists may have much more deleterious consequences, specifically increasing the rates of hyperkalemia. Nevertheless, the study provides promise that the early anatomic and physiologic changes in seen in CKD that often lead to overt heart failure may be intervened upon with the use of aldosterone antagonists.

Treatment of Acute Heart Failure—As outlined above, worsening renal function in the setting of acute heart failure syndromes not only is common, but also has significant effects on short and long-term prognosis. The optimal treatment of ADHF involves addressing two goals—restoration of euvolemia and preservation of end-organ (including renal) function. While the full-scope of the treatment of acute heart failure is beyond the scope of this review, two treatment options will be reviewed as they have specific pertinence to the prevention of WRF in the setting of ADHF: ultrafiltration and the use of novel vasodilators.

The use of ultrafiltration has become increasingly popular in the treatment of ADHF primarily due to diuretic resistance as well as the increasing recognition of venous congestion as an important determinant of worsening renal function. Despite its increasing use, minimal data exists to determine the exact short-term and long-term effects of ultrafiltration on renal function in ADHF. The available data on ultrafiltration has demonstrated its effectiveness as a tool for volume removal, however the effects of renal function remain unclear. The Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial randomized 40 individuals admitted with ADHF to ultrafiltration as initial therapy for 8 hours with progression to usual care versus usual care alone. The ultrafiltration group had more fluid removal after 24 and 48 hours than the usual care group (4650 ml vs. 2838 ml, p =.001 at 24 hours, 8415 vs 5375 ml, p = 0.012 at 48 hours). Both groups experienced similar rises in serum creatinine at the end of the 48 hour study period (+ 0.1 mg/dl).[44] The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized with Acute Decompensated Congestive Heart Failure (UNLOAD) trial found similar results. In the UNLOAD study, 200 individuals were randomized to ultrafiltration alone versus intravenous diuretics for 48 hours after enrollment (after 48 hours, the duration of ultrafiltration was determined by the treating physicians). Weight loss in the ultrafiltration group was greater at 48 hours 5.0 ± 3.1 kg versus 3.1 ± 3.5 kg, p = 0.001. Both groups once again had similar increases in serum creatinine, with the proportion of individuals with an increase of at least 0.3 mg/dl similar in both groups (14.4% vs. 7.7%, p = 0.528 at 24 hours, 26.5% vs. 20.3%, p = 0.430 at 48 hours, 22.6% vs. 19.8%, p = 0.709 at discharge). Further, there was no correlation between net fluid removal and changes in serum creatinine.[45] While these studies suggest the increased benefit of additional fluid removal with ultrafiltration as compared to diuretics with no additional renal adverse effects, other studies have yet to confirm this benefit or demonstrate improvement in renal function with the use of ultrafiltration. A retrospective analysis of patients treated with ultrafiltration versus individuals treated with usual care alone or usual care with nesiritide found that those treated with ultrafiltration had higher rates of worsening renal function (serum creatinine increase of at greater than 0.5 mg/dl). Although patients treated with ultrafiltration were matched by age, renal function, ejection fraction and etiology of heart failure with those receiving alternative regimens, the retrospective nature of the study makes it difficult to make definitive conclusions.[46] Thus, the role of ultrafiltration to prevent WRF in the setting of ADHF appears promising, but remains unclear.

Rather than the focusing on the role of extracorporeal therapy and volume removal as a primary goal, other, recent investigations have explored the role of adenosine in the setting of ADHF and its treatment. Tubuloglomerular feedback provides a mechanism to link distal sodium (and chloride) delivery to glomerular hemodynamics. Increased chloride delivery to the macula densa is sensed by the sodium-potassium-2-chloride co-transporter (NKCC2) and leads to the renal response of afferent arteriolar, vasoconstriction, leading to decrease in single-nephron GFR. Knowing that adenosine, a mediator of the vasoconstriction reaction, acts via direct stimulation of adenosine receptor 1 (AR1) on the afferent arteriole has led to the investigation of AR1 receptor blockers on renal function in ADHF.[47]. Givertz et al studied the effect of a novel A1 receptor antagonist, KW-3902, on diuresis and renal function in two groups individuals: patients admitted with decompensated heart failure and renal dysfunction (estimated creatinine clearance between 20 ml/min and 80 ml/min) and patients admitted and

currently treated for decompensated heart failure with treating physician-determined diuretic resistance. Individuals were randomized to 10 mg, 30 mg or 60 mg of the study drug versus placebo in conjunction with intravenous furosemide. In the group of individuals with ADHF, 146 individuals received the study drug with a greater urine output in the first 6 hours, lower serum creatinine at all dosages except the highest dose. Further the treatment groups all had higher rates of premature treatment discontinuation due to goal diuresis achieved. While at day 4, all the treatment groups had lower rates of worsening renal function (defined by increase in serum creatinine > 0.3 mg/dl) than the placebo group; but the difference did not achieve statistical significance. In the diuretic-resistant protocol 23 patients were treated with the A1 receptor antagonist and 12 individuals received placebo. At 6 and 24 hours, diuresis and natruiresis (increased urine output and urinary sodium excretion) were increased in the treatment group as compared to placebo. At 24 hours, the lowest and intermediate dose treatment arms were both associated with increased creatinine clearance as compared to the placebo and the highest dose group where creatinine clearance decreased. In both groups, rates of serious adverse events did not differ from placebo.[48] An alternative A1 receptor antagonist, SLV 320, has also been studied with regard to its effects on both cardiac and renal function in the setting of congestive heart failure. 111 individuals with NYHA Class II or III CHF, systolic dysfunction (EF < 35%) and persistent edema were randomized to placebo, furosemide 40 mg or escalating doses of SLV 320 (5 mg IV, 10 mg IV, or 15 mg IV). Individuals underwent pulmonary artery catheterization and had hemodynamic parameters followed throughout the study. After study drug infusion, urine volume, urinary sodium chloride and potassium excretion as well as hemodynamic variables were compared between the five groups. Similar to the study of KW-3902, urine sodium and chloride excretion were greatest in the groups receiving the infusion of KW-3902 (at any dose) or furosemide. Urine volume was greater than placebo in the group of individuals receiving the 10 mg or 15 mg dose of KW-3902 as well as the group receiving furosemide. Importantly, the group of individuals receiving furosemide had a corresponding increase in serum cystatin-C, suggesting a fall in GFR. The groups of individuals receiving any dose of KW-3902 did not have a significant change in serum cystatin-C as compared to placebo, suggesting that the effect of increase sodium and water excretion occurred in the A1 receptor antagonist group without compromising renal function. However, the use of furosemide did have the effect of decreasing pulmonary capillary wedge pressure, while the use of the A1 receptor antagonist had no effect on PCWP.[49] It is unclear whether increasing the intensity of treatment with the A1 receptor antagonist to achieve a fall in PCWP, i.e. a true therapeutic response, would also lead to a rise in serum cystatin C or evidence of worsening renal function. Nevertheless, the study contributes to the increasing awareness of a potential novel and promising therapy of acute heart failure that preserves renal function. While more investigation is required to define the optimal use of A1 receptor antagonists, the agents have a physiologic basis with initial human clinical data to suggest their effectiveness.

Conclusion

Worsening renal function in the setting of congestive heart failure, both chronic and acute, is increasingly recognized as an independent predictor of poor prognosis. Further, it appears that small, even, transient rises in serum creatinine are clinically relevant. The introduction of urinary and serum biomarkers to identify kidney injury highlight the early stages where kidney injury occurs in the setting of heart failure, even before clinically apparent by increases in serum creatinine. Further, the finding that biomarkers associated with renal tubular injury, as opposed to decreased filtration, are elevated in the setting of chronic and acute decompensated heart failure suggests “true” renal injury with heart failure and, that, optimization of cardiac function may not always be enough to restore renal function back to normal or reverse the damage that has occurred. The pathophysiology of worsening renal function in the setting of acute and chronic heart failure remains unclear, but different perspectives, focusing on venous congestion and intrabdominal pressure, have offered alternative pathways to conventional

thinking and serve as the stimulus for novel therapeutic interventions. Pharmacologic therapy has had minimal success in the past at improving renal outcomes, however, the novel agents offer some future promise. Extracorporeal therapy, while increasingly used and thought of as a treatment option, appears effective at increasing volume removal, but its effect on renal function remain varied. Future investigation directed at identifying which patients most benefit from each of these treatment strategies, along with the continued use of conventional ionotropes and vasodilators, is required to advance the treatment of the cardiorenal syndrome.

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Table 1

Classification of Cardiorenal syndrome	Clinical manifestation
Type : acute cardiorenal syndrome,	Development of acute kidney injury (AKI) in the setting of sudden worsening cardiac function
Type II: chronic cardiorenal syndrome	Progressive renal dysfunction in the setting of chronic cardiac dysfunction
Type III: Acute renocardiac syndrome	AKI precipitating worsening cardiac function
Type IV: Chronic renocardiac syndrome	Chronic renal dysfunction leading to chronic cardiac dysfunction
Type V: Secondary cardiorenal syndrome	Worsening renal and cardiac function in the setting of underlying systemic illness