Renal Dysfunction in Heart Failure

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KEYWORDS

• Chronic kidney disease • Heart failure • Worsening renal function
• Cardiorenal syndrome

KEY POINTS

- Both chronic kidney disease and worsening renal function are associated with worse outcomes, but our understanding of the complex bidirectional interactions between the heart and kidney remains poor.
- When addressing these interactions, one must consider the impact of intrinsic renal disease resulting from medical comorbidities on outcomes of patients with heart failure.
- Worsening renal function in heart failure is the result of a complex, multifactorial process that includes: RAAS and SNS activation, hemodynamic aberrations, pharmacological interventions, and inflammation/cytokine activation..
- The development of novel renal biomarkers will enable earlier detection of WRF and someday allow for the administration of reno-protective strategies.

INTRODUCTION

Renal dysfunction is common in patients with heart failure (HF), with a prevalence ranging from 20% to 57% in patients with chronic, stable HF[1–9] and 30% to 67% in large registries of patients admitted with acutely decompensated HF (ADHF).[10–12] In addition, worsening renal function (WRF) occurs in 18% to 40% of patients during hospitalization for ADHF,[13–19] an important subset of patients with generally guarded prognosis. The interplay between the heart and the kidney in patients with HF is a complex relationship, and a complete understanding of the bidirectional interactions between these 2 organs remains elusive. While attempts have been made to better define and categorize these interactions, to date these definitions lack clinical utility. In its simplest form, the so-called cardiorenal syndrome (CRS) has been described as a complex disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may result in acute or

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chronic dysfunction in the other.[20] The syndrome has been further broken down into 1 of 5 categories, based on the acute or chronic nature of the disease course and whether or not the primary precipitant of dysfunction is the heart, the kidney, or a third independent process affecting both the heart and kidneys (**Table 1**).[20]

Yet such categorization does little to shed light on the underlying pathophysiology of the CRS as it pertains to the patient with HF. In truth, many factors must be considered in the development of a comprehensive construct of renal dysfunction in HF. One must first consider the importance of intrinsic renal disease and the adverse effects of common medical comorbidities on kidney function in HF patients. Diabetes mellitus, hypertension, and renovascular disease are common in the HF population, and can lead to significant intrinsic, chronic kidney disease (CKD). Next, it is important to recognize the significance of WRF in HF and the many factors that can predispose to it, including: (1) the deleterious acute and chronic effects of activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), (2) the direct effects of hemodynamic aberrations, (3) the effects of pharmacologic interventions (eg, diuretics, angiotensin-converting enzyme [ACE] inhibitors), and (4) the role of inflammation and cytokine activation. All of these factors likely play critical roles to varying degrees in the individual HF patient, perhaps accounting for the heterogeneous presentations of patients with WRF in HF. Although the pathophysiology may not be entirely clear, most HF patients with CKD or WRF have a worse prognosis than those without renal involvement.[9,13,16,21–27] In the near future, the development of novel biomarkers of renal dysfunction may enable earlier and more accurate detection of renal damage in HF, and pave the way for the administration of future renoprotective strategies.

Table 1
Cardiorenal syndrome (CRS) subtypes

Cardiorenal Subtype	Description	Examples/Etiology
CRS Type 1 (acute CRS)	Rapid worsening of cardiac function leading to acute kidney injury	Acute MI with cardiogenic shock, ADSHF, acute valvular insufficiency
CRS Type 2 (chronic CRS)	Chronic abnormalities in cardiac function leading to chronic kidney disease	Chronic inflammation, long-term RAAS and SNS activation, chronic hypoperfusion
CRS Type 3 (acute renocardiac syndrome)	Acute worsening of renal function leading to cardiac dysfunction (HF, arrhythmia, and so forth)	Uremia causing impaired contractility, hyperkalemia causing arrhythmias, volume overload causing pulmonary edema
CRS Type 4 (chronic renocardiac syndrome)	Chronic worsening of renal function leading to worsening cardiac function	CKD leading to LVH, coronary disease and calcification, diastolic dysfunction, and so forth
CRS Type 5	Acute or chronic systemic disease leading to both cardiac and renal dysfunction	Diabetes mellitus, amyloidosis, sepsis, vasculitis

Abbreviations: ADSHF, acute decompensated systolic heart failure; CKD, chronic kidney disease; HF, heart failure; LVH, left ventricular hypertrophy; MI, myocardial infarction; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

CHRONIC KIDNEY DISEASE IN HEART FAILURE

Definition

To fully understand the potential adverse effects of CKD in HF, one must first define CKD. According to the National Kidney Foundation (NKF) practice guidelines, glomerular filtration rate (GFR) is the best measure of renal function.[28] Of importance, the NKF practice guidelines do not recommend the use of serum creatinine (sCr) concentration as the sole measure of renal function,[28] as this value can be greatly affected by an individual's age, sex, race, muscle mass, and diet. Direct assessment of GFR requires measuring the renal clearance of a nontoxic exogenous marker such as inulin, which is freely filtered without any tubular secretion or reabsorption. Unfortunately, such a method is cumbersome and impractical for use in routine clinical practice. In lieu of directly measuring GFR, several formulas have been developed that reliably estimate GFR with relative accuracy. Of note, all of these formulas incorporate the sCr and some combination of age, sex, body size, and race, all factors that affect GFR to varying degrees. The formulas most frequently used in clinical practice include the Cockcroft-Gault (C-G),[29] Modification of Diet in Renal Disease (MDRD),[30] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[31] equations (**Table 2**). Based on the estimated GFR (eGFR), individual patients can be classified into 1 of 5 categories of CKD (**Table 3**).

It is important to understand potential pitfalls in the various formulas for GFR, especially as they pertain to the HF population. Although the equations for estimating GFR are all relatively similar, the MDRD may be more precise in patients with lower GFR,[32] whereas the C-G equation is more precise in those with milder forms of CKD.[29] Unfortunately, both the MDRD and C-G formulas may misclassify the degree of CKD in up to 30% of patients and may be off by as much as 13.5 mL/min and 15.1 mL/min in their GFR estimations, respectively.[32] Of importance, all of these formulas tend to overestimate GFR in the setting of severe renal disease.[33,34] Finally, the MDRD equation was derived from a relatively young population (mean age 50 $\pm$ 12 years) with established CKD and excluded older patients.[30] It therefore may be inaccurate in the HF population, which comprises mostly patients older than 65 years.[35,36]

Table 2
Clinically used formulas for estimating glomerular filtration rate (GFR)

	Equation/Formula
Cockcroft-Gault (mL/min)	Male: $[(140 - \text{age}) \times (\text{weight})]/72 \times \text{sCr}$ Female: GFR $\times$ 0.85 BSA corrected: $\text{GFR}_{cg} \times (1.73/\text{BSA})$ (= mL/min/1.73 m^2)
MDRD (mL/min/1.73 m^2)	Male: $170 \times (\text{sCr})^{-0.999} \times (\text{age})^{-0.176} \times (\text{sU})^{-0.170} \times (\text{sAlb})^{+0.318}$ Black male: MDRD $\times$ 1.180 Female: MDRD $\times$ 0.76 Black female: MDRD $\times$ 0.762 $\times$ 1.180
CKD-EPI (mL/min/1.73 m^2)	Male: $141 \times \text{minimum}(\text{sCr}/0.9, 1)^{-0.411} \times \text{max}(\text{sCr}/0.9, 1)^{-1.209} \times 0.993^{\text{Age}}$ Black male: CKD-EPI $\times$ 1.159 Female: $141 \times \text{minimum}(\text{sCr}/0.7, 1)^{-0.329} \times \text{max}(\text{sCr}/0.7, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ Black female: CKD-EPI (female) $\times$ 1.159

Abbreviations: BSA, body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Diseases; Alb, serum albumin; sCr, serum creatinine; sU, serum uric acid.

Table 3
Stages of chronic kidney disease (CKD)

CKD Stage	Description	GFR (mL/min/1.73 m^2)
Stage 1	Kidney damage with preserved GFR	≥90
Stage 2	Kidney damage with mildly decreased GFR	60–89
Stage 3	Moderately reduced GFR	30–59
Stage 4	Severely reduced GFR	15–29
Stage 5	Kidney failure/end-stage renal disease	<15 (or dialysis)

Epidemiology and Prognosis

Retrospective analysis of several clinical trials has shown that the prevalence of CKD ranges between 20% and 57% in chronic, stable HF populations.[3–9] Of importance, many of these analyses included only patients with at least moderate renal dysfunction, defined as an eGFR of less than 60 mL/min (CKD stage III). Therefore patients with milder forms of CKD may not have been included, and represent a large population at risk for worse outcomes. A meta-analysis of 16 studies and more than 80,000 patients revealed that approximately 51% of outpatients with HF have some degree of renal dysfunction (eGFR <90 mL/min, sCr >1.0 mg/dL).[25]

While HF pathophysiology may contribute to the development of CKD, concomitant comorbidities also play an important role. For example, data from the Framingham Heart Study show that nearly 60% of patients with newly diagnosed HF had preexisting hypertension (HTN), and 25% were being treated for diabetes mellitus at the time of diagnosis, both important risk factors for CKD.[37] In addition, the median age at time of HF diagnosis was 78 years. It is known that GFR decreases by as much as 0.75 mL/min annually after the age of 30 years,[38,39] and this decline may accelerate in the elderly.[40] Finally, the presence of atheromatous renovascular disease (ARD) is increasingly recognized as a cause of renal dysfunction,[41] and ARD is reported to account for 15% of end-stage renal disease (ESRD) in the elderly.[42,43] One analysis found that 30% of HF patients have some degree of ARD when assessed by angiography.[44] ARD is therefore likely an important, often overlooked, source of renal dysfunction in HF.

Whatever the cause of CKD in HF, its presence is associated with a worse prognosis and poor outcomes. A retrospective cohort study of more than 600 recently discharged HF patients revealed that the presence of CKD (sCr >1.5 mg/dL in men, >1.4 mg/dL in women) was associated with a 43% increase in the relative risk of death.[26] Similarly, a large meta-analysis showed that any degree of renal dysfunction (eGFR <90 mL/min) was associated with a 48% increase in the relative risk of death[25]; those with moderate to severe renal dysfunction had an 81% increased risk. Many other studies have shown similarly poor survival in HF patients with CKD[4,9,27] as well as higher rates of readmission for HF.[45–49]

WORSENING RENAL FUNCTION IN HEART FAILURE

Definition, Epidemiology, and Prognosis

WRF in HF is common in patients with ADHF and complicates 18% to 40% of admissions.[13–19] Despite the association between WRF and worse clinical outcomes, a standard definition has not been adopted. The most commonly used definition in most studies is an increase in the sCr of greater than 0.3 mg/dL,[11,13,14,50,51] but others use a value of greater than 0.5 mg/dL,[15,21] greater than 0.2 mg/dL,[19] or a decrease in eGFR by 25%.[16] Regardless of the definition, development of WRF during hospitalization for ADHF is associated with poor outcomes in most, but not all studies. Several

studies have shown that WRF is associated with an increased risk of in-hospital mortality and prolonged length of stay.[11,14,15,21,52] Krumholz and colleagues[17] found that an increase in sCr by greater than 0.3 mg/dL resulted in an increase in length of stay by 2.3 days, an increase in the cost by $1758, and an increase in in-hospital mortality odds by 2.72 times. Other studies have also shown that even minimal changes in renal function (increased sCr >0.1 mg/dL) are associated with worse outcomes,[15,25] although greater degrees of WRF result in higher rates of death.[19] WRF is also associated with postdischarge mortality, including reductions in 60-day[16] and 1-year survival.[18] However, Nohria and colleagues[50] did not find a correlation between WRF and outcomes in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial. Instead, they found that admission and discharge renal dysfunction better predicted mortality and rehospitalization.

Many investigators have attempted to identify risk factors for the development of WRF in HF. Several risk factors have been identified to date, including the presence of baseline renal dysfunction (admission sCr),[13,14,17,21,53] diabetes mellitus,[14,21,53] hypertension,[14,17,53] pulmonary edema,[13,17] low serum sodium,[21] male gender,[17] diastolic dysfunction by echocardiography,[21] and the presence of atrial fibrillation.[13] Although these factors may predispose patients to the development of WRF, they do little to shed light on the etiology of the disease process. In truth, the etiology of WRF is a complex, multifactorial process that is incompletely understood (**Fig. 1**).

Role of Neurohormonal Activation in Worsening Renal Function

The kidney plays a fundamental role in the adaptive responses in HF. As a response to renal underperfusion, the activation of the RAAS initially maintains circulating blood volume (by increasing sodium reabsorption) as well as GFR (through angiotensin II–mediated renal efferent arteriolar constriction).[54,55] However, prolonged RAAS activation leads to volume overload, congestion, worsening HF, cardiac fibrosis, and

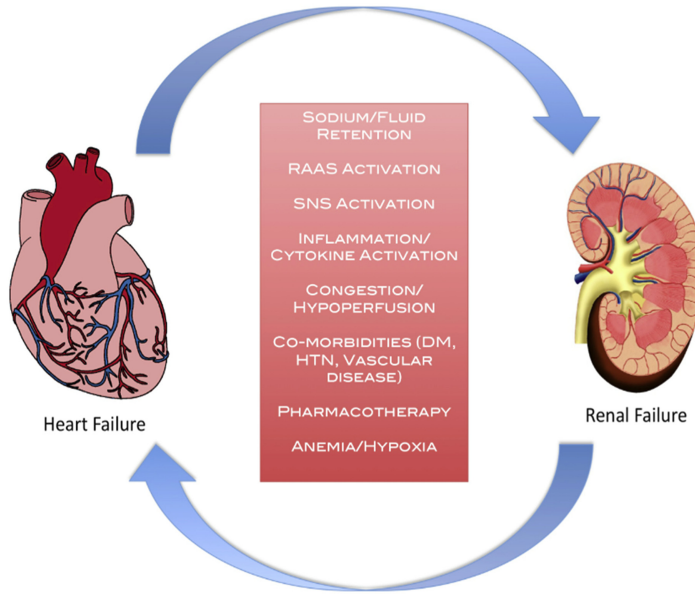

Fig. 1. The complex bidirectional relationship between heart failure and renal disease.

adverse myocardial remodeling.[56–60] RAAS inhibition is therefore the cornerstone of long-term HF therapy. In addition to the harmful effects of RAAS activation on the heart, there is significant evidence that angiotensin II leads to progressive fibrosis of the kidney by activating fibroblasts and increasing extracellular matrix deposition, and through its effects as a proinflammatory cytokine (**Fig. 2**).[61] The use of agents that antagonize RAAS activation can prevent fibrosis and inflammatory cell infiltration[62–64] and prevent WRF.

The SNS is closely linked to RAAS activation in the kidneys and plays a significant role in renal physiology. Renal dysfunction, like HF, is associated with sympathetic overactivity, and the level of activity is an independent predictor of death in patients with CKD.[65,66] The renal sympathetic nerves modulate many functions of the kidney through their innervation of the tubules, the afferent and efferent vessels, and the juxtaglomerular granular cells.[67] Sympathetic overactivity as found in HF and CKD ultimately leads to WRF through multiple mechanisms. The stimulation of α1-adrenergic receptors in vascular smooth muscle results in increased renal vascular resistance[68] and preferential efferent arteriolar constriction, thus serving to increase the filtration fraction at the expense of renal blood flow.[69] Stimulation of β1-adrenergic receptors of the juxtaglomerular cells results in the release of renin[70] and therefore

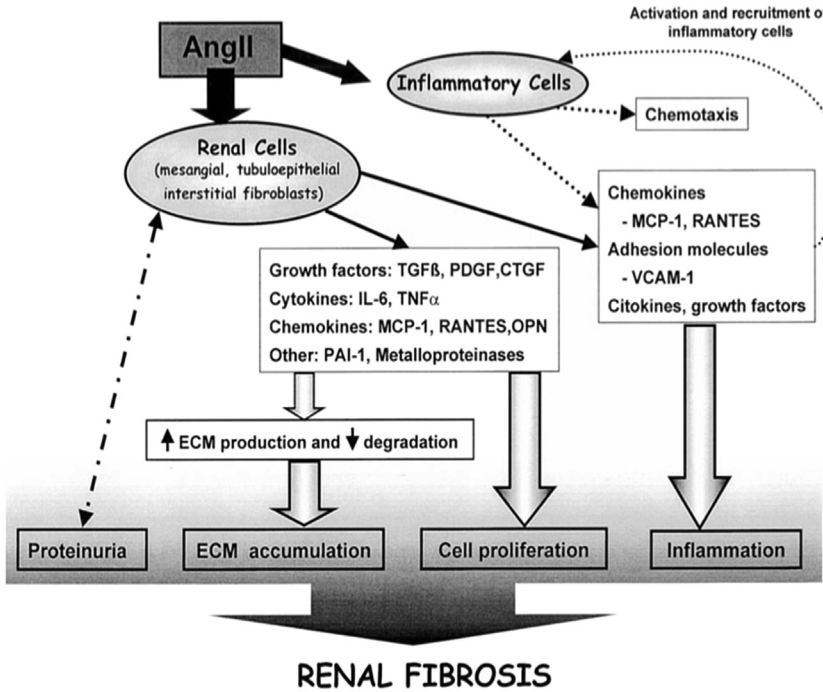

Fig. 2. The pathophysiology of angiotensin II and renal fibrosis. Angiotensin II leads to renal fibrosis through direct effects on renal cells and through activation of inflammation. CTGF, connective tissue growth factor; ECM, extracellular matrix; IL, interleukin; MCP, monocyte chemotactic protein; OPN, osteopontin; PAI, plasminogen activator inhibitor; PDGF, platelet-derived growth factor; RANTES, regulated upon activation, normal T-cell expressed, and secreted; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule. (*Reprinted from* Mezzano SA, Ruiz-Ortega M, Egido J. Angiotensin II and renal fibrosis. Hypertension 2001;38:635–8.)

downstream RAAS activation, further worsening both HF and WRF. Of importance, the use of carvedilol ($\alpha 1/\beta 1$-receptor blocker) has been shown to reduce renal vascular resistance, increase renal blood flow, and decrease tubular atrophy and interstitial fibrosis.[71] Considering these data, it is clear that the fundamental pathophysiology leading to progressive HF, RAAS and SNS activation, is also a cause of WRF, and highlights the importance of the bidirectional relationship of these 2 organs.

Hemodynamics and Worsening Renal Function

The historical concept that WRF in ADHF is a direct result of reduced cardiac output and "underperfusion" is an oversimplification. Several reports have failed to show a correlation between lower ejection fraction (EF) and WRF.[10,72–74] While reduction in cardiac output may play a role in WRF, especially at extremes,[75] the pathophysiology is more complex. The maintenance of an adequate renal perfusion pressure (RPP) is certainly affected by alterations in forward flow, but recent data suggest that alterations in congestive forces (central venous pressure, intra-abdominal pressure, and therefore elevated renal vein pressure) may play a more critical hemodynamic role in WRF.[76–79] Mullens and colleagues[78] reported that the 2 strongest predictors of WRF were a higher CVP on admission (18 ± 7 mm Hg vs 12 ± 6 mm Hg, $P < .001$) and a higher CVP after therapy (11 ± 8 mm Hg vs 8 ± 5 mm Hg, $P < .04$). Of note, there was no difference in cardiac index (CI) in patients with or without WRF, suggesting that lower CI did not play a role in WRF in this population. In a report of less-sick HF patients, Guglin and colleagues[79] showed that elevated CVP is associated with higher sCr and lower GFR, whereas there was no association between CI and renal function. In a heterogeneous population of patients undergoing right heart catheterization, higher CVP was associated with WRF as well as mortality.[77] Of interest, the relationship between CVP and estimated GFR was most pronounced in those patients with normal CI, again suggesting that congestive forces play a more critical role in the development of WRF.

Elevation in intra-abdominal pressure (IAP), as may be seen in a variety of surgical emergencies and the abdominal compartment syndrome, has been linked to WRF.[51,52] Considering that many patients with ADHF have significant visceral edema and ascites, it is feasible to hypothesize that they may have significant elevations in IAP and therefore impaired renal function. Mullens and colleagues[76] measured IAP in a cohort of patients with ADHF requiring right heart catheterization and tailored therapy, and showed a high prevalence of elevated IAP (>8 mm Hg) that was associated with worse renal function (**Fig. 3**). In addition, reductions in IAP with therapy were associated with improvements in renal function. There was no correlation with improvement in renal function and other hemodynamic variables.

Not all studies support the role of hemodynamic alterations as a cause of WRF in ADHF. Data from the ESCAPE trial showed no correlation between baseline hemodynamics or changes in hemodynamics during hospitalization and WRF.[50] Similarly, Testani and colleagues[80] found no difference in baseline, final, or change in hemodynamics when comparing patients with WRF during hospitalization and those with improved renal function (IRF) during hospitalization. Of note, both sets of patients (WRF and IRF) had worse outcomes than those with stable renal function.

Role of Pharmacotherapy in Worsening Renal Function

Diuretic therapy

Congestion is the hallmark of HF[81] and diuretics remain the mainstay of therapy. Despite their role, diuretics have not been proved to improve outcomes in randomized controlled trials. In fact, some data suggest that use of loop diuretics is associated with

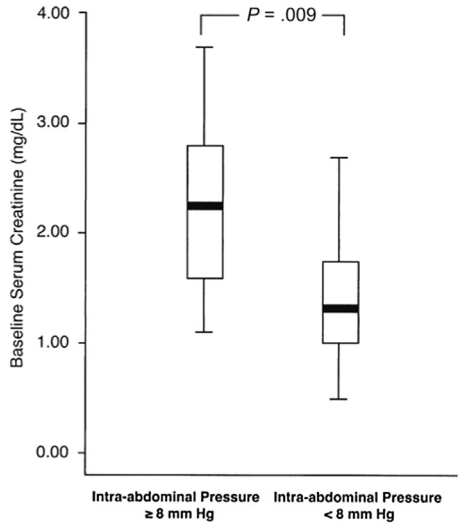

Fig. 3. Serum creatinine and intra-abdominal pressure. Patients admitted with intra-abdominal pressure greater than 8 mm Hg had higher creatinine levels on admission for acutely decompensated heart failure. (*Reprinted from* Mullens W, Abrahams Z, Skouri HN, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol 2008;51:300–6.)

increased risk of arrhythmic death,[82] hospitalization,[83] and long-term mortality.[83–85] These adverse effects are thought to result from secondary neurohormonal activation[86] and diuretic-induced electrolyte depletion.[82] In addition, escalating doses of loop diuretics in patients with ADHF has been linked to WRF. In a nested case-control study of 382 ADHF patients, Butler and colleagues[53] showed that higher doses of loop diuretics were associated with an increased risk of WRF independent of the amount of fluid loss. Similarly, in another study of 318 patients with ADHF, daily furosemide dose was a predictor of WRF and subsequent poor prognosis.[87] Hasselblad and colleagues[88] reviewed data from the ESCAPE trial and also found that higher diuretic dose (especially >300 mg/d) was an independent risk factor for mortality after adjusting for several variables. Of note, however, they did not find a significant correlation between change in sCr and maximal diuretic dose. The mechanisms whereby diuretics precipitate WRF are likely more complex than simple depletion of circulating volume. By increasing the sodium load to the distal tubule, diuretics may precipitate increases in the release of adenosine from the juxtaglomerular cells. Elevations in intrarenal adenosine in turn may lead to increased sodium reabsorption in the proximal tubule and constriction of the renal afferent arteriole, which reduces GFR.[89]

While it is clear that many patients requiring higher doses of diuretics during hospitalization for ADHF have an increased risk of WRF and therefore a worse prognosis, it is not clear if higher doses or WRF are a cause of worse outcomes. These patients may simply represent a subset of more advanced disease. To further complicate the picture, there are data to suggest that aggressive diuresis that results in WRF is associated with improved survival.[90] A retrospective analysis of the ESCAPE trial showed that aggressive diuresis resulting in hemoconcentration was associated with WRF; however, these patients had lower mortality at 180 days (**Fig. 4**).[90] Also, in the recent DOSE (Diuretic Optimization Strategies Evaluation) trial assessing optimal loop diuretic dosing strategies, higher bolus doses of diuretics were associated with

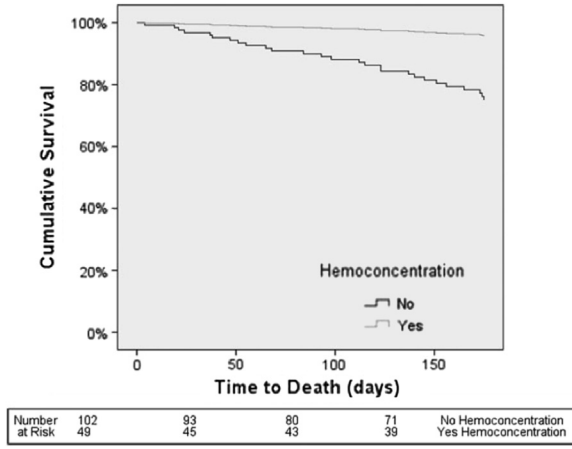

Fig. 4. Hemoconcentration and outcomes in heart failure. Patients who experienced hemoconcentration after dieresis had better long-term survival after discharge. (*Reprinted from* Testani JM, Chen J, McCauley BD, et al. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation 2010;122:265–2.)

greater diuresis, greater weight loss, improvement in dyspnea, and fewer serious adverse events compared with lower bolus doses, despite higher rates of transient WRF.[91] This transient WRF resolved by discharge and there was no difference in renal function at 60 days. Thus, in these 2 studies aggressive diuresis resulting in transient WRF was associated with improved outcomes.

ACE inhibition

ACE inhibition is a key component of HF therapy. The use of these agents results in reduced mortality, improved symptoms, and reduction in HF hospitalizations.[1,2,92] Use of ACE inhibitors is associated with an expected increase in sCr of up to 30%, especially in patients with a baseline sCr greater than 1.4 mg/dL.[93] This increase is the physiologic result of renal efferent arteriole dilation and subsequent decrease in GFR, and the value usually stabilizes within the first 2 months of treatment.[93] The continuation of ACE inhibition in these patients leads to long-term preservation of renal function, likely a result of inhibiting the proinflammatory and profibrotic effects of angiotensin II on the kidney.[62–64,94] Unfortunately, many patients are taken off this essential therapy in response to increases in sCr, despite their well-documented long-term benefits. Not all patients started on ACE inhibitors experience an increase in sCr, and an improvement in sCr in 24% of patients with ACE-inhibitor therapy has been reported.[95] There is clearly a subset of patients with HF who have difficulty tolerating ACE inhibition, including those with low blood pressure, higher doses of diuretics, volume contraction, and hyponatremia.[95,96] These patients may be more dependent on neurohormonal activation to maintain renal perfusion, and the inhibition of angiotensin II may result in marked WRF and hypotension.[97] Strategies to combat this issue include reduction in diuretic dose, reduction in ACE-inhibitor dose, or discontinuation of ACE inhibitors altogether in a few cases.[97]

Role of Inflammation

HF is associated with the activation of systemic inflammation and the upregulation of several inflammatory cytokines.[98] Of importance, these biomarkers correlate with HF

severity and poor outcomes. For example, tumor necrosis factor α (TNF-α) and interleukin (IL)-6 levels are increased in HF, and are associated with increased mortality and worsening New York Heart Association class.[99–101] Elevated C-reactive protein (CRP) levels independently predict death[102,103] and readmission for worsening HF.[103] There are several theories as to why HF is associated with inflammation, including: (1) RAAS activation and direct angiotensin II–induced expression of TNF-α and IL-6[94,104,105]; (2) SNS activation leading to β-adrenergic–induced expression of inflammatory cytokines[106,107]; (3) venous congestion leading to endothelial activation and release of proinflammatory mediators[108,109]; and (4) venous congestion leading to translocation of intestinal gram-negative endotoxin (lipopolysaccharide) and resultant imflammation.[110–112] Circulating cytokines lead to the infiltration of inflammatory cells into the renal interstitium, resulting in tubular injury, fibrosis, and WRF.[98,113–115] Both TNF-α and IL-1 induce production of free radicals in the mesangial cells,[116] which can result in significant glomerular damage. In addition, both TNF-α and reactive oxygen species have been shown to inhibit renal sodium excretion and lead to worsening volume expansion,[117,118] which then causes further activation of SNS[67,119] and RAAS.[120,121]

MARKERS OF RENAL FUNCTION AND INJURY

As previously discussed, sCr levels are affected by muscle mass, which can be substantially reduced in the setting of cardiac cachexia. To combat this, many formulas (MDRD, C-G, CKD-EPI) have been developed to account for body size, age, and gender, among other variables. However, these formulas only estimate the ability of the kidney to filter the blood; they do not assess glomerular permeability, tubular function, or other actions of the kidney such as erythropoietin and production of vitamin D.[122] In addition, these measures are slow to detect kidney injury and may lag injury by several days, making them clinically less useful. Newer serum and urinary biomarkers may offer advantages over sCr and sCr-based formulas to detect WRF and renal injury in HF, and may provide this information in a timely manner (**Table 4**).

Blood Urea Nitrogen

Blood urea nitrogen (BUN) has long been measured clinically, but only recently has its correlation with HF prognosis been recognized. In the ADHERE registry, BUN was the best predictor of in-hospital mortality (BUN $\geq$43 mg/dL).[123] In another study, BUN remained the most sensitive predictor of 1-year mortality.[124] Finally, a retrospective study of the OPTIME-HF registry showed that changes in BUN during hospitalization are an independent predictor of 60-day mortality (BUN increase of 10 mg/dL over baseline).[16] While BUN levels are affected by changes in renal function, they are also influenced by dietary protein intake, catabolism, and tubular reabsorption. Therefore, despite its potential for use as a prognostic marker, BUN is an inaccurate marker of true renal function.

Cystatin C

Cystatin C is a low molecular weight protein produced by all nucleated cells.[125] It is freely filtered in the glomerulus, completely reabsorbed, and degraded in the tubules.[126] Cystatin C is unaffected by muscle mass or turnover, and therefore is an ideal measure of glomerular filtration.[126,127] It is a more reliable predictor of GFR than sCr,[128,129] although this has not been assessed in HF. In ADHF, cystatin C levels were an independent predictor of mortality, even in the presence of normal sCr.[130]

Table 4
Beyond serum creatinine and estimated GFR: biomarkers of renal dysfunction

Marker	Pros and Cons
BUN	PRO: Correlates well with prognosis, inexpensive, and easy to measure CON: Greatly affected by protein intake, catabolism, and tubular reabsorption → poor measure of true renal function
Cystatin C	PRO: excellent marker of GFR (better than sCr); not affected by intake, catabolism, and so forth; good marker of prognosis in CHF CON: more costly than sCr; clinicians unfamiliar with use and normals/abnormals
NGAL	PRO: excellent sensitivity and specificity to detect AKI; levels increase >24 h before sCr increases in response to injury CON: Plasma NGAL levels increase in settings of inflammation, making them less specific than urinary NGAL levels
KIM-1	PRO: Levels are elevated even with minimal GFR reductions; associated with death or HF hospitalization independent of GFR; increases 24 h before sCr in response to renal injury CON: Very few studies in HF at this time
NAG	PRO: Excellent predictor of AKI; levels are elevated even in the setting of minimally reduced GFR; associated with risk of death or HF hospitalization CON: Very few studies in HF at this time
FABP	PRO: Presence in the urine is sensitive and specific for AKI and predicts the need for renal replacement therapy and death CON: No data on ability to predict WRF in CHF
Albuminuria	PRO: Inexpensive, easy to measure; correlates with worse prognosis in HF CON: can be found in other disease states (DM, HTN), therefore low specificity

Abbreviations: AKI, acute kidney injury; BUN, blood urea nitrogen; DM, diabetes mellitus; FABP, fatty acid–binding protein; HTN, hypertension; KIM-1, kidney injury molecule 1; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin.

Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a low molecular weight protein found in neutrophils, and plays a role in iron transport and sequestration.[125] In normal patients it can be found at low levels in both serum and urine. Because it may be elevated in the setting of inflammation, plasma NGAL is less specific than urinary NGAL in the detection of acute kidney injury.[131] Because NGAL is freely filtered by the glomerulus and fully reabsorbed, its presence in the urine is a marker of injury to the tubule or interstitium, making it a potentially useful clinical marker of renal injury. Both plasma and urinary NGAL levels have been shown to have excellent sensitivity and specificity in identifying acute kidney injury,[132] and the increase in NGAL occurs more than 24 hours before the increase in sCr. Aghel and colleagues[133] have shown that an elevated serum NGAL levels at the time of admission for ADHF is a strong predictor of WRF.

Kidney Injury Molecule 1

Kidney injury molecule 1 (KIM-1) is a transmembrane glycoprotein that is not found in the urine normally.[122] However, with acute tubular necrosis, the proximal tubule epithelial cells increase expression of KIM-1, and KIM-1 in the urine is associated with a 12-fold increased risk of acute tubular necrosis.[134] Of importance, the increase

in KIM-1 levels occurs a full 24 hours before an increase in sCr.[135] There are minimal data on the use of KIM-1 in HF; however, Damman and colleagues[136] have shown that KIM-1 is elevated in stable HF patients with only mildly reduced GFR, suggesting ongoing tubular damage in these patients. These investigators also found that elevated levels were associated with an increased risk of death and hospitalization for HF, independent of GFR.[136]

N-Acetyl-β-D-Glucosaminidase

N-Acetyl-β-D-glucosaminidase (NAG) is a brush-border lysosomal enzyme that is shed from the proximal tubule cells in response to renal injury.[122,125] Its presence in the urine is an excellent predictor of acute kidney injury.[137–139] Similar to KIM-1, elevated NAG levels were found in HF patients with only mildly reduced GFR, and these elevations were associated with increased risk of death and hospitalization for HF, independent of GFR.[136]

Fatty Acid–Binding Protein

Fatty acid–binding proteins (FABPs) are proteins that bind selectively to free fatty acids and are expressed in a tissue-specific pattern.[122] FABP-1 and FABP-3 are found in the proximal and distal tubules, where they play a role in energy metabolism.[140] Their presence in urine is a sensitive and specific marker of acute kidney injury, and predicts the need for renal replacement therapy and death.[141] There are currently no data on the ability of FABP to predict WRF.

Albuminuria

Albumin is not filtered by the glomerulus under normal circumstances, and its presence in urine suggests a disruption of the basement membrane, which may be seen in a variety of diseases including diabetic and hypertensive kidney disease.[142,143] Albuminuria may be found in up to 32% of patients with HF,[144] and is thought to result from poor renal perfusion and increased congestion. Several studies have shown that the presence of albuminuria in HF is associated with increased mortality, even in the presence of normal GFR.[145,146]

SUMMARY

Renal dysfunction is a common, important comorbidity in patients with both chronic and acute HF. Both CKD and WRF are associated with worse outcomes, but our understanding of the complex bidirectional interactions between the heart and kidney remains poor. When addressing these interactions, one must consider the impact of intrinsic renal disease resulting from medical comorbidities on HF outcomes. In addition, WRF may result from any number of important processes, including RAAS and SNS activation, hemodynamics aberrations, pharmacotherapy, and inflammation. Understanding the role of each of these factors and their interplay is essential in fully understanding how to improve outcomes in patients with renal dysfunction and HF. It is hoped that the continued development of novel biomarkers of renal function will allow earlier diagnosis of WRF and ultimately allow earlier interventions that target renal protection.

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