Changes in Renal Function in Congestive Heart Failure

Guido Boerrigter · Berthold Hocher · Harald Lapp

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Abstract Both cardiovascular and renal diseases are common and frequently coexist in the same patient. Indeed, renal dysfunction has been shown to be a more powerful independent predictor of poor outcomes in heart failure (HF) than left ventricular ejection fraction or functional class. Furthermore, acute kidney injury is a frequent therapeutic concern in heart failure. Consequently, there has been much interest in developing new renoprotective treatments and novel biomarkers to monitor renal function. Additionally, given the crucial cardiorenal interaction and interdependence, the concept of a cardiorenal syndrome with five different subtypes has been advanced to better categorize patients and facilitate research.

Keywords Cardiorenal syndrome · Heart failure · Chronic kidney disease · Acute kidney injury · Diuretics · Ultrafiltration · Creatinine · Cystatin C · Diuretic resistance · Glomerular filtration rate

Introduction

Both cardiovascular and renal diseases are increasing in prevalence, are major contributors to morbidity and mortality, and require large healthcare expenditures [1]. Given that both are often the result of general vascular disease, it is not surprising that they frequently coexist in the same patient. Indeed, in recent years, renal dysfunction and worsening renal function have been demonstrated to be important independent predictors of poorer outcomes in HF [2–5]. And because both the heart and kidneys have crucial functions in maintaining homeostasis, it is also no surprise that dysfunction of one organ could negatively affect function of the other, a condition that has been termed "cardiorenal syndrome" (CRS). Given the heterogeneity of cardiac and renal disease and their presentations, attempts have been made to categorize CRS into 5 types [6].

Here we will review (1) relevant pathophysiology of renal function and cardiorenal interaction, (2) conventional and emerging biomarkers for monitoring renal function, (3) classifications for chronic kidney disease (CKD), acute kidney injury (AKI), and CRS, (4) HF treatment strategies as they relate to renal function, and (5) novel therapeutic strategies.

Renal Physiology and Neurohumoral Relevance to Heart Failure

The basic functional unit of the kidney is the nephron (Fig. 1). Blood flows through the afferent arteriole into the capillaries of the glomerulus and exits via the efferent arteriole. Renal autoregulation by differential regulation of the vascular tone of the afferent and efferent arteriole can adjust the hydrostatic pressure in the glomerulus and maintain a relatively constant glomerular filtration rate (GFR). The filtrate flows through different segments of the tubule, which differ in their water permeability and their expression of transporters and channels, the activity of which are to some extent regulated by the autonomic nervous system and neurohormones. Along the nephron, molecules are reabsorbed or secreted, and water follows passively according to the water permeability of the segment. Importantly, the site of action of diuretics also differs along the tubule, and most diuretics have to be secreted by the tubular cells into the lumen to be active. At the juxtaglomerular apparatus, the
distal tubule comes in close contact with the afferent arteriole. Under physiological conditions, increased delivery of sodium to the distal tubule leads to an increase in afferent vascular tone, thus reducing hydrostatic pressure in the glomerulus and decreasing GFR.

Of note, loop diuretics both increase sodium delivery to the distal tubule and inhibit this feedback mechanism [7, 8]. If GFR decreases (e.g., due to systemic hypotension) then sodium delivery to the distal tubule decreases. This is sensed by the macula densa, with consequent release of renin and activation of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II can increase efferent vascular tone, thus increasing GFR. Furthermore, relative arterial underfilling with decreased activation of baroreceptors will increase sympathetic tone [9]. As a result, vasoconstriction and renal sodium and water reabsorption will be promoted, all in an effort to increase blood pressure. Arginine vasopressin (AVP) is released in response to an increase in plasma osmolality. By promoting the insertion of the aquaporin-2 water channel via the V2-receptor, AVP promotes free water reabsorption and thus reduces plasma osmolality. Furthermore, AVP via the V1a receptor can cause vasoconstriction. In HF, AVP may be released independently of plasma osmolality and contribute to hyponatremia and fluid retention.

Renal venous congestion can decrease renal perfusion pressure and increase renal interstitial pressure, both of which decrease glomerular filtration [10]. Some studies have shown that central venous pressure is a better predictor of low GFR than cardiac output or systemic arterial pressure [11, 12]. Furthermore, abdominal congestion has been associated with cardiorenal syndrome [13]. Of note, venous congestion is also associated with increased atrial stretch, which, in addition to cardiac stress, is an important stimulus for the release of the pleiotropic cardiac natriuretic peptides ANP and BNP, which promote vasodilation and renal sodium excretion [14].

**Assessing and Monitoring Renal Function**

A biomarker should ideally have the following features: (a) provide objectivity in the evaluation and diagnosis of patients, especially those in whom signs and symptoms are not very sensitive or specific, (2) help with correct triage by assessment of prognosis and risk stratification, (3) help to guide objectively therapy or management, (4) enable an optimum screening process, and (5) guide the delivery of cost-effective medical care. In addition, the test should have high sensitivity, specificity, reproducibility, and accuracy; it should have a low coefficient of variation; it should be easy to perform and analyse; it should be applicable across sexes, ethnicity, and age spectra; and it should make physiological sense [15].

Besides urine flow, the most important renal functional parameter is GFR. The gold standard for measuring GFR is determining the clearance of a compound, such as inulin, that is freely filtered and neither secreted nor reabsorbed by the kidney. However, clearance methods are expensive and cumbersome. The creatinine clearance can be calculated from serum creatinine and the urine volume and creatinine concentration in a 24-h urine collection; however, these are time-consuming and are prone to collection error. Therefore, equations that estimate GFR based on serum creatinine (or cystatin C) and anthropometric variables have been developed and continue to be refined for specific patient populations. It was recently reported that the CKD-EPI equation was more accurate and provided a better risk assessment in patients with HF and reduced ejection fraction than the Modification of Diet in
Renal Disease (MDRD) equation that was often used previously [16–18]. Of note, these equations should only be used in patients with stable serum creatinine. Creatinine is not only filtered but is also secreted by the kidney, and its production is dependent on muscle mass. Due to the kidney’s capacity to compensate, an increase in serum creatinine will usually occur only after the loss of about 50 % of the nephrons. Given the shortcomings of creatinine, alternative markers are being evaluated. Cystatin C has emerged as a good albeit imperfect alternative to creatinine [19–21]. It is produced at relatively constant levels by all nucleated cells, and is filtered and completely reabsorbed and then metabolized by the kidney. Consequently, cystatin C levels rise with CKD.

When interpreting a biomarker such as creatinine, it is important to know what constitutes a significant change as compared to noise; i.e., random variation due to the limited test accuracy and consequential physiological variation. In healthy young men, repeated creatinine measurements over 48 hours showed a median intraindividual coefficient of variation of 4.2 % [20]. In a general population sample with low prevalence of CKD (few people with serum creatinine >1.5 mg/dL), the within-person coefficient of variation of two blood samples collected approximately 18 days apart was 7.6 % (eGFR CKD-EPI: 6.6 %) [21]. It would be interesting to know the variability in stable patients with HF and CKD. Presumably, the variability would be larger due to factors such as a decreased ability for compensation, secondary to a reduced number of nephrons with reduced renal functional reserve and the impact of drugs such as diuretics and inhibitors of the angiotensin-converting enzyme (ACE) [22].

Importantly, after an AKI affecting GFR, it takes some time for creatinine to rise appreciably. Furthermore, creatinine may be too insensitive a marker to clearly indicate AKI, especially if compensatory mechanisms of the kidney are activated. Therefore, it would be desirable to have a biomarker that would quickly indicate that kidney injury had occurred so that appropriate steps could be initiated as early as possible. Indeed, there is currently a good deal of research dedicated to finding new markers of early AKI [23]. As an example, neutrophil gelatinase-associated lipocalin (NGAL) is a 21 kD-protein released during cellular stress to act, among other things, to bind free iron and thus reduce oxidative stress. Its plasma and urine concentrations increase shortly after AKI [24]. Haase et al. dichotomized 1,296 patients based on their level of serum creatinine and NGAL [25]. Patients in whom both markers were increased had the highest rate of adverse outcomes in terms of need for renal replacement therapy, mortality, ICU, and hospital length-of-stay, whereas patients in whom neither marker increased had the lowest incidence. Patients with only NGAL or only creatinine increased had intermediate rates, suggesting that there is a subset of patients with tubular injury that goes undetected when only creatinine is considered. Kashani et al. reported the discovery and validation of two biomarkers of AKI that predicted subsequent AKI within 12 hours after sample collection, specifically urine concentrations of the two cell-cycle inhibitors insulin-like growth factor-binding protein-7 (IGFBP7) and tissue inhibitors of metalloproteinase-2 (TIMP-2) [26]. Taken together, the discovery of novel markers that indicate AKI earlier than conventional markers seems to be just around the corner, and it may turn out that a multimarker approach is the best. With these new tools, novel and earlier interventions can be tested and will hopefully lead to better renoprotection.

Classification of Renal Disease

Given the heterogeneity and wide spectrum of cardiac and renal disease, management and treatment of the disease may need to be tailored. Over the years, several classifications and definitions have been proposed and refined to categorize patients with renal disease.

Chronic Kidney Disease (CKD)

The CKD classification by Kidney Disease Outcomes Quality Initiative (KDOQI, Table 1) categorizes patients according to the presence of kidney damage (i.e., albuminuria or proteinuria) and

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>Description; findings need to be present for ≥3 months</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or relatively high GFR (Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies)</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild reduction in GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate reduction in GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe reduction in GFR. Preparation for renal replacement therapy</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Established kidney failure, which includes end-stage renal disease (defined as a need for renal replacement therapy, i.e., dialysis or kidney transplantation)</td>
<td>&lt;15</td>
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</table>

CKD chronic kidney disease, GFR glomerular filtration rate
the level of GFR, and the findings must be present for at least 3 months [27]. The CKD classification by Kidney Disease: Improving Global Outcomes (KDIGO) categorizes patients according to GFR (G1: ≥ 90; G2: 60–89; G3a: 45–59; G3b: 30–44; G4: 15–29; G5 <15 mL/min/1.73 m²) and persistent albuminuria (A1: <30; A2: 30–300; A3: >300 mg/g creatinine) [19••].

Acute Kidney Injury (AKI)

With regard to acute renal injury, many definitions and terms (e.g., “worsening renal function”) have been proposed and used in the past. The Risk, Injury, Failure, Loss, End-stage Kidney Disease (RIFLE) and Acute Kidney Injury Network (AKIN) criteria were proposed in 2004 and 2007, respectively [28, 29]. The most recent suggestion for a classification (Table 2) was made by KDIGO [30••]. A critique from a U.S. perspective was published by the KDOQI [31••]. One criticism was the inclusion of urine output, a decrease in which would be considered an appropriate response in the setting of prerenal failure.

Cardiorenal Syndrome Types 1–5

Recognition of the interdependency of the heart and kidneys has helped to advance the concept of cardiorenal syndrome, in which dysfunction of one of the organs impacts the function of the other. Ronco et al. have proposed the classification of 5 types of CRS, the pathophysiology and gaps of knowledge of which have recently been reviewed [29, 32••, 33–37]:

<table>
<thead>
<tr>
<th>CRS type</th>
<th>Description</th>
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<tbody>
<tr>
<td>CRS type 1:</td>
<td>Rapid worsening of cardiac function leads to AKI</td>
</tr>
<tr>
<td>CRS type 2:</td>
<td>Chronic abnormalities in cardiac function cause progressive CKD</td>
</tr>
<tr>
<td>CRS type 3:</td>
<td>Abrupt and primary worsening of kidney function leads to acute cardiac dysfunction</td>
</tr>
<tr>
<td>CRS type 4:</td>
<td>Primary CKD contributes to decreased cardiac function</td>
</tr>
<tr>
<td>CRS type 5:</td>
<td>An acute or chronic systemic disorder promotes combined cardiac and renal dysfunction</td>
</tr>
</tbody>
</table>

Change in Renal Function in Congestive Heart Failure

Improving Renal Function

If renal dysfunction is due, at least in part, to heart failure, then improving cardiac function would be expected to improve renal function. This can be seen in cases of successful treatment of acute decompensated HF. There is also evidence of improved renal function with heart transplantation, ventricular assist device implantation, and cardiac resynchronization therapy [38, 39].

Prevention of Worsening Renal Function

In patients with CKD, the prevention of additional kidney injury is critical. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) should be discouraged in CKD, as they interfere with the synthesis of prostaglandins important for renal function in CKD and HF [40]. Drug doses may need to be adjusted for the degree of CKD. With regard to intravenous contrast media, there is the concern of contrast-induced AKI (CI-AKI, also referred to as contrast-induced nephropathy (CIN)). Alternative imaging techniques should be considered. If contrast needs to be given, the amount should be as low as reasonably possible. Many interventions have been tested for the prevention of CI-AKI. However, only hydration has definitively been shown to be beneficial [30••]. An innovative approach in reducing renal exposure to contrast media during coronary angiography and intervention is the use of a coronary sinus catheter that removes the contrast from the circulation [41, 42].

### Table 2

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine</th>
<th>Urine output</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1.5–1.9 times baseline</td>
<td>&lt;0.5 ml/kg/h for 6–12 hours</td>
</tr>
<tr>
<td></td>
<td>OR ≥0.3 mg/dl (≥26.5 μmol/l) increase</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.0–2.9 times baseline</td>
<td>&lt;0.5 ml/kg/h for ≥12 hours</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline</td>
<td>&lt;0.3 ml/kg/h for ≥24 hours OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 μmol/l) OR Initiation of renal replacement therapy OR Anuria for ≥12 hours</td>
</tr>
<tr>
<td></td>
<td>In patients &lt;18 years, decrease in eGFR to &lt;35 ml/min per 1.73 m²</td>
<td></td>
</tr>
</tbody>
</table>
Of note, serum creatinine can change in hospitalized patients even in the absence of contrast administration. It is useful to know this background variation before attributing any change in serum creatinine to prior contrast administration. Newhouse et al. reported that significant increases in serum creatinine, both in absolute and relative terms, are frequently seen in hospitalized patients not receiving contrast; if they had received contrast, the increase would likely have been attributed to the contrast [43]. Bruce et al. reported similar changes in serum creatinine in patients undergoing imaging studies both with and without contrast administration [44].

Worsening Renal Function

In general, a change in renal function can be due to trivial random variation as well as prerenal, intrarenal, and postrenal causes. Furthermore, the change can be rapidly reversible and thus ultimately inconsequential or irreversible, contributing to further decline in renal function. If relevant worsening of renal function is detected, it is important to identify and, if possible, treat the causes, prevent further aggravation by discontinuing or reducing potentially nephrotoxic medications, and use intravenous iodinated contrast media judiciously.

Progression of Chronic Kidney Disease

Usually, renal function starts to decline in the fourth decade of life at a rate of about 8 mL/min/1.73 m² per decade. As muscle mass, and thus creatinine production, decreases, serum creatinine remains relatively unchanged. In patients with CKD, the remaining nephrons must compensate for the loss of other nephrons. This is associated with hyperfiltration and intraglomerular hypertension, both of which promote further nephron loss. Important factors that promote progression of CKD are hypertension, hyperglycemia, and hyperlipidemia. ACE inhibition or antagonism of the angiotensin II type 1 receptor, which reduce hyperfiltration and intraglomerular hypertension by dilating the efferent arteriole, can reduce long-term renal decline [45, 46].

Identify Causes of Renal Function Decline

The major workup in a HF patient with deterioration of renal function should consider the major prerenal, intrarenal, and postrenal causes of renal function decline such as low cardiac output and systemic hypotension, hypovolemia, venous congestion, renal ischemia, renal toxins, obstructive nephropathy, systemic infection, or inflammatory diseases. The workup usually includes history, physical examination (signs of congestion or dehydration), vital signs (hypotension, heart rate), blood sample (electrolytes, creatinine or cystatin C, blood urea nitrogen, B-type natriuretic peptide or aminoterminal B-type natriuretic peptide, troponin, complete blood count, inflammatory markers such as C-reactive protein), urine sample (infection, sodium, protein, leukocytes, erythrocytes, cell casts), monitoring of urine output, abdominal ultrasound for obstructive nephropathy, and electrocardiogram (ischemia, arrhythmia, electrolyte disturbance).

Patients with obstructive uropathy should be seen by a urologist; patients with suspected intrinsic renal disease, by a nephrologist. In patients in whom hypovolemia is suspected as the cause for the renal deterioration (e.g., due to overdiuresis, lack of intake, blood loss), fluid resuscitation should be attempted. The following discussion will focus on changes in renal function due to heart failure.

Change in Renal Function due to Therapy

Heart failure and its treatment can contribute to deterioration of renal function in a variety of ways. In stable heart failure, ACE inhibitors can be expected to raise serum creatinine given that they act to decrease efferent vascular tone and thus reduce glomerular filtration pressure. A serum creatinine increase of about 30% (depending on the baseline value) can usually be tolerated. However, ACE inhibitors should be carefully titrated, and in the setting of an acute renal function decline, the ACE inhibitor is frequently reduced or paused. Overdiuresis can lead to volume depletion with subsequent increase in creatinine due to hypotension. If hypotension appears to contribute to renal dysfunction, hypotensive drugs may need to be paused.

Change in Renal Function due to Acute Decompensated Heart Failure

In acute decompensated HF (ADHF), renal function can be impacted by multiple factors, including low cardiac output, systemic hypotension, renal venous congestion, and neurohormonal activation. If a precipitating cause for worsening cardiac function can be identified, such as hypertension, ischemia, arrhythmias, or anemia, it should be treated appropriately. If there is hypotension without fluid overload, fluid resuscitation should be attempted. If this does not improve blood pressure and cardiac output, vasopressors or inotropes, or both, may be required.

Often, volume overload is a problem, which increases cardiac preload and afterload, promoting further deterioration of cardiac function. Worsening cardiac function and venous congestion will cause the kidney to further retain sodium and fluid, thus aggravating congestion and cardiac overload. Treating volume overload can improve both cardiac and renal function by reducing cardiac preload and afterload, potentially reducing valvular regurgitation and decreasing venous congestion. Hence, diuretic therapy can improve renal function.

Diuretic Therapy

Conventional diuretics such as loop diuretics continue to be the mainstay of therapy. In recent years, there was a discussion
as to whether diuretic use contributed to worse outcomes or whether the use of diuretics, including their dose, was simply a marker of more severe disease [47, 48]. The use of diuretics can lead to excessive volume loss, disturbances of electrolyte and acid base homeostasis, and neurohumoral activation. Many diuretics have been around for decades and therefore have not been tested in the now-standard randomized controlled trials. However, the frequently dramatic improvements with the use of diuretics suggest that a comparison with placebo would be unethical.

Diuretic approaches can differ with respect to doses employed, route of administration, duration of therapy, and combination with other diuretics. Postdiuretic sodium retention occurs when, after diuretic administration, the diuretic levels fall below efficacious levels. This can be remedied by more frequent or continuous administration. Loop diuretics will increase sodium delivery to the distal nephron, where sodium can be reabsorbed as this segment is not responsive to the loop diuretic effect. However, addition of a thiazide or thiazide-like diuretic, which acts in the distal nephron, can significantly increase sodium excretion in combination with loop diuretics ("sequential nephron blockade" or combination diuretic therapy) [49–51]. In addition, a mineralocorticoid receptor antagonist such as spironolactone or eplerenone can promote sodium excretion, especially in states in which aldosterone metabolism in the liver is impaired [49, 52].

With regard to the use of loop diuretics, the Determining Optimal Dose and Duration of Diuretic Treatment in People With Acute Heart Failure (DOSE-AHF) trial addressed two important questions: the dose to be used and the mode of administration – specifically, bolus administration vs. continuous administration [53•]. Patients with acutely decompensated chronic HF were randomized in a 2x2 factorial design to either low-dose or high-dose furosemide and either bolus or continuous intravenous administration. Low-dose was considered the usual oral loop diuretic dose given IV, whereas high-dose was defined as 2.5 times the usual oral loop diuretic dose (accounting for potency and bioavailability, the oral torsemide dose was converted into the equivalent oral furosemide dose by multiplying by 2; the bumetanide dose was converted into the furosemide dose by multiplying by 40). Bolus administration was as efficacious as continuous administration, and high-dose loop diuretic resulted in better decongestion. Interestingly, the high-dose regimen also resulted in a significant increase in serum creatinine, which, however, was not associated with worse outcomes during the follow-up of 60 days. While it is doubtful that the follow-up was sufficient and the study adequately powered to demonstrate a difference, it would be important to know whether treatment was actually associated with relevant AKI with long-term consequences for renal function, or whether the increase in serum creatinine reflected only brief phases of hypovolemia during aggressive diuresis, with no negative impact on renal function. Novel markers of renal function and longer-term follow-up may be helpful in further elucidating these issues. It may also be worthwhile to test whether a more renal-protective diuresis can be achieved, for example, by monitoring hematocrit or hemoglobin [54–56]. Too rapid an increase in hematocrit could indicate that volume loss via diuresis exceeds the plasma refill rate, leading to intravascular hypovolemia. Furthermore, blood urea nitrogen is an important predictor of poor outcomes in HF, perhaps due to the fact that AVP, which is activated in more severe HF, promotes urea reabsorption [57–60]. It should be noted that the patients enrolled in the DOSE-AHF trial were not required to show diuretic resistance or worsening renal function. A trial enrolling only such patients may show different results regarding continuous infusion.

Ultrafiltration
In the setting of renal dysfunction, if medical therapy is unable to control fluid status adequately, hyperkalemia, or acid base status, or if patients become uremic, then, in consultation with nephrology, some form of renal replacement therapy (RRT) needs to be commenced. Theoretically, it may even be beneficial to use RRT to remove sodium and fluid at an earlier stage in HF patients with fluid overload. In the Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial, early ultrafiltration was compared to conventional loop diuretic in patients with ADHF and hypervolemia [61]. Of note, patients did not need to demonstrate diuretic resistance. Ultrafiltration resulted in greater fluid and weight loss at 48 h, with no increase in serum creatinine and no difference in dyspnea or hospital length of stay. Interestingly, rehospitalization rate during 90-day follow-up was lower in the ultrafiltration group, which was a secondary efficacy endpoint. In the more recent Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRRESS-HF), ultrafiltration was compared to a specified diuretic step-up approach in HF patients with hypervolemia and worsened renal function, which was defined as an increase in serum creatinine of at least 0.3 mg/dL (26.5 μmol/L) within 12 weeks before or 10 days after the index admission for HF [62••]. The bivariate primary endpoint was change in body weight and change in serum creatinine. Ultrafiltration resulted in the same amount of weight loss as the pharmacological approach, but was associated with significantly increased serum creatinine. Furthermore, ultrafiltration was associated with a higher rate of adverse events in the 60-day follow-up, specifically higher incidences of renal failure, bleeding complications, and intravenous catheter-related complications.

As was alluded to in correspondence subsequent to the article, with ultrafiltration, creatinine is removed at the concentration it is found in the plasma. In CARRRESS-HF, the fluid-removal rate was 200 mL/h, which corresponds to a creatinine clearance of 3.3 mL/min. This highlights the fact that
ultrafiltration removes salt and fluid but does not replace some other important kidney functions – specifically, the concentration of certain metabolic waste products in the urine. Indeed, the ultrafiltration group also had significantly higher BUN levels. Further, by design, a large amount of fluid is removed by ultrafiltration, then less will be filtered and excreted by the kidney. Serum creatinine, therefore, appears to be a suboptimal outcome parameter for studies with ultrafiltration. Indeed, cystatin C levels were not different between groups. Nevertheless, outcomes generally favored the pharmacologic treatment arm.

As usual, the results of this trial apply mainly to the patient population enrolled and the specific treatment strategies used (e.g., diuretic regimen, ultrafiltration dose, and duration). It should be noted that outcomes with either treatment were generally poor, with many people not achieving proper decongestion and with high hospital readmission rates. The ongoing Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure (AVOID-HF) trial compares ultrafiltration with a diuretic strategy in patients as the initial treatment; i.e., not patients selected for already demonstrating worsening renal function.

Novel Therapeutic Strategies

Challenges regarding the development of new drugs for cardiorenal disease include not only choosing the best dose and duration of administration, but also the appropriate patient selection (e.g., blood pressure level and degree of renal dysfunction). In this section, we will discuss a few evolving therapeutic strategies.

Antagonists of AVP

Tolvaptan, a V2-antagonist, acts as a powerful aquaretic by antagonizing AVP-induced insertion of the aquaporin-2 water channel in the collecting duct. In the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST), a fixed dose of 30 mg of tolvaptan increased serum sodium and reduced body weight without affecting short-term or long-term outcomes [63, 64]. Given that 30 mg of tolvaptan showed quite a variable effect in a study by Udelson et al., there is the possibility that some patients had significant hypovolemia which may have led to neurohumoral activation and adverse outcome, potentially offsetting the benefit of better decongestion that other patients experienced [65, 66]. It may be useful to test tolvaptan with more individualized dose titration. Furthermore, given that tolvaptan does not block the V1A receptor with its vasoconstricting actions, the development of a V1a/V2-receptor antagonist for chronic therapy may be useful (the V1a/V2 receptor antagonist conivaptan is only approved for intravenous administration due to liver toxicity).

Adenosine Antagonists

Adenosine via the adenosine A1 receptor plays an important role in renal regulation by promoting vasoconstriction and sodium reabsorption [67, 68]. It is also a mediator of tubuloglomerular feedback. Several studies have reported renal-enhancing properties of a variety of adenosine A1 antagonists in clinical development [69–71]. However, in the largest study yet, the pivotal Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT), rolofylline did not meet the study’s endpoints [72]. While rolofylline use was associated with more patients fulfilling the trial’s “improved” definition, this was offset in the overall results by more patients with rolofylline fulfilling the “worsened” criteria (defined as a persistent serum creatinine increase, which was defined as an increase of 0.3 mg/dL or more on both day 7 and day 14, or initiation of hemofiltration or dialysis or death through day 7). The latter was primarily driven by a higher number of patients with persistent serum creatinine increase. More frequent adverse events with rolofylline were seizures and a trend for increased number of strokes [73].

In a subsequent analysis focusing on renal function, it was reported that while loop diuretic dose was similar between placebo and rolofylline groups, the rolofylline group lost significantly more weight [74]. This may have contributed to the higher rate of persistent serum creatinine increase. Interestingly, when the treatment effect was analyzed according to baseline creatinine clearance, patients with lower creatinine clearance tended to do better with rolofylline. This was also true for the combined morbidity and mortality endpoint (hazard ratio 0.64, confidence interval 0.43, 0.95). While this may be a chance finding, there could be some benefit in adenosine A1 receptor antagonism in patients with more severely impaired renal function. It would also be important to test whether adenosine A1 receptor antagonists other than rolofylline would have fewer adverse effects on the central nervous system.

Relaxin

Relaxin is a hormone with vasodilating and antifibrotic properties. A recent trial with a 48-h infusion of a recombinant relaxin, serelaxin, showed some promising effects in HF patients, including improved creatinine and cystatin C [75, 76]. Unlike some recent vasodilator trials with nesiritide, patients enrolled in this study were required to have a baseline blood pressure of more than 125 mmHg, thus reducing the risk of hypotension and its adverse effects on renal function. While serelaxin reduced dyspnea during the hospital stay, the most interesting finding was improved survival in the serelaxin
group at 180 days. A drug given for only a few days that could affect long-term outcomes would be quite impressive.

Natriuretic Peptides

The cardiac natriuretic peptides ANP and BNP are secreted in response to cardiac stress, and have pleiotropic actions such as vasodilation, natriuresis, antifibrosis, and aldosterone suppression. Carperitide (recombinant ANP) was approved for the treatment of HF in Japan in 1995. Nesiritide (recombinant BNP) was approved for the treatment of ADHF in the USA in 2001 [77]. However, after initial enthusiasm for BNP, its use steeply declined after studies suggested increased renal dysfunction, mortality, and lack of efficacy. A subsequent definitive trial showed a non-significant trend for a small improvement in dyspnea, with no indication that nesiritide worsened renal function or improved outcomes [78]. The minimum systolic blood pressure at enrollment was 100 mmHg. Hypotension occurred more often with nesiritide than with placebo (26.6 vs 15.3 %), which may have offset potential beneficial effects of nesiritide. Urodilatin is a renal splice variant of ANP with four additional N-terminal amino acids [79, 80]. Ularitide (recombinant urodilatin) is currently being investigated in patients with ADHF; one inclusion criterion is systolic blood pressure ≥110 mmHg. While the role of natriuretic peptides in ADHF treatment remains unclear, they have shown some benefit in renal protection during cardiac surgery [81–84].

LCZ626

Due to their peptide nature, the long-term administration of natriuretic peptides, while not impossible, is a somewhat unattractive option. Therefore, strategies have been developed to augment the natriuretic peptide system by other means, such as inhibitors of neprilysin [14]. This enzyme, also known as neutral endopeptidase 24.11, is involved in the degradation of several hormones, including the natriuretic peptides. LCZ626 is a single molecule that, after ingestion, is cleaved into its two components: valsartan and the neprilysin inhibitor prodrug AHU377. In patients with hypertension, LCZ626 reduced blood pressure more than the corresponding dose of valsartan [85]. It is currently being investigated for the treatment of HF with reduced and preserved ejection fraction [86].

Conclusion

In summary, the concept of renal dysfunction as an important independent prognostic factor and disease modifier in HF has generated much research interest in the last few years. Novel markers of AKI are in development and will hopefully help us to distinguish between inconsequential and significant changes in renal function and to refine our therapeutic strategies to be more renal-protective.

Compliance with Ethics Guidelines

Conflict of Interest Guido Boerrigter declares that he has no conflict of interest.

Berthold Hocher declares that he has no conflict of interest.

Harald Lapp has received payment for lectures, including service on speakers bureaus, for scientific talks in the field of heart failure treatment.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- Of importance
- Of major importance


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