Curr Cardiol Rep (2013) 15:380
DOI 10.1007/s11886-013-0380-4

Cardiorenal Syndrome: Pathophysiology and Treatment

Dmitry Shchekochikhin · Robert W. Schrier · JoAnn Lindenfeld

Published online: 23 May 2013

Abstract CRS is a common problem in patients with advanced heart failure. Arterial underfilling with consequent neurohormonal activation, systemic and intrarenal vasoconstriction, and salt and water retention cause the main clinical features of CRS which include a progressive decline in renal function, worsening renal function during treatment of heart failure (HF) decompensation and resistance to loop diuretics. Impaired renal function in HF patients often reflects more advanced stages of cardiac failure, and thus is associated with a worse prognosis. However, a transient fall in glomerular filtration rate may be a result of successful treatment of congestion, and thereby might not be associated with decreased survival in HF patients. This review covers basic pathophysiological mechanisms underlying the CRS and current trends in practical approaches to treat these patients.

Keywords Cardiorenal syndrome · CRS · Arterial underfilling · Ultrafiltration · Heart failure · Worsening renal function

Introduction

In 2004 a working group was appointed by the National Heart, Lung, and Blood Institute to "evaluate the current state of knowledge regarding interactions between the cardiovascular system and the kidney, to identify critical gaps in our knowledge, understanding, and application of research tools, and to develop specific recommendations for NHLBI in cardio-renal interactions related to HF and other cardiovascular diseases" [1]. This group attributed cardiorenal dysregulation in HF (HF) to interactions between the kidney and circulatory systems that result in increased circulating volume and exacerbate the course of HF [1]. The group defined CRS (CRS) as the extreme form of cardiorenal dysfunction in which therapy to relieve the congestive symptoms of HF is limited by a decline in renal function manifested as a reduction in glomerular filtration rate (GFR). Worsening renal function (WRF) during HF management and the development of resistance to loop diuretics were included in the clinical features of CRS [2]. Although substantial attention has been focused on CRS in the setting of acutely decompensated HF (ADHF), a widely accepted definition of CRS had not been developed [3–6]. CRS has been defined as a complex pathophysiological disorder of the heart and kidneys, in which acute or chronic dysfunction of one organ may induce acute or chronic dysfunction in the other. According to chronicity and the primary organ affected, CRS was classified into 5 types [7].

- Type 1 (acute) — Acute HF results in acute kidney injury (AKI), previously called acute renal failure.
- Type 2 — Chronic cardiac dysfunction (e.g., chronic HF) causes progressive chronic kidney disease (CKD), previously called chronic renal failure.
- Type 3 — Abrupt and primary worsening of kidney function due, for example, to renal ischemia or glomerulonephritis causes acute cardiac dysfunction, which may be manifested by HF.
- Type 4 – Primary CKD contributes to cardiac dysfunction, which may be manifested by coronary disease, HF, or arrhythmias.
- Type 5 (secondary) - Acute or chronic systemic disorders (e.g., sepsis or diabetes mellitus) that cause both cardiac and renal dysfunction.

This article is part of the Topical Collection on *Congestive Heart Failure*

D. Shchekochikhin (✉)
Department of Preventive and Emergency Cardiology, I.M.Setchenov's First Moscow State Medical University, 119992, 6 (1), Bolshaya Pirogovskaya str., Moscow, Russia
e-mail: agishm@list.ru

R. W. Schrier
University of Colorado Denver, 12700 East 19th Ave C281, Aurora, CO 80045, USA
e-mail: robert.schrier@ucdenver.edu

J. Lindenfeld
University of Colorado Denver, 1635 Aurora Ct F745, Room 7083, Aurora, CO 80045, USA
e-mail: Joann.Lindenfeld@ucdenver.edu

Thus, Types 1 and 2 could be designated as CRS since cardiac dysfunction is the initiating event. In contrast, Types 3 and 4 could be designated as renocardiac syndrome since renal dysfunction is the initiating event. Lastly, in some circumstances, mainly Type 5, involve both cardiac and kidney dysfunction may be initiating events. Moreover, in Types 1 and 2, the terms AKI and CKD respectively could be misinterpreted, since the majority of the effects on the kidney may be functional and thus reversible. In this review we will focus on CRS during ADHF, i.e., Type 1.

Pathophysiology of CRS

In normal conditions, cross-talk between the heart and kidneys occurs through atrial-renal reflexes [8], which maintain total body volume in normal range. For example, an increase in atrial pressure suppresses release of arginine vasopressin (AVP) through the Henry-Gauer Reflex and also suppresses renal sympathetic tone [9]. The increase in filling pressures also results in the release of natriuretic peptides (ANP and BNP) [10]. The result of these atrial-renal reflexes is to increase renal sodium and water excretion. However, in the setting of HF these normal responses are attenuated by activation of neurohumoral systems caused by arterial underfilling [11]. Underfilling of the arterial circulation occurs because of a decrease in cardiac output in low-output HF and arterial vasodilatation in high-output HF. In both types of HF the inhibitory effect of the arterial stretch baroreceptors on the neurohumoral systems are decreased, leading to systemic and intrarenal vasoconstriction, as well as enhanced renal water and sodium reabsorption [12] (Fig. 1). The main mediators of these events are the renin-angiotensin-aldosterone system, catecholamines and AVP.

An increase in renin secretion with secondary stimulation of angiotensin II (Ang II) is observed during early stages of HF [13]. Ang II has many effects, including increase in thirst, stimulation of the sympathetic nervous system [8, 14], and systemic and renal vasoconstriction [13, 14]. Moreover, Ang II stimulates the synthesis of aldosterone, the main salt-retaining hormone [15]. In normal settings aldosterone-induced sodium retention is temporary and does not cause edema because the increase in vascular volume enhances sodium delivery to distal renal tubules which overrides the sodium retaining effect of aldosterone within 3 days (aldosterone escape) [13, 14]. However, in patients with HF this "aldosterone escape" is prevented by diminished renal perfusion and impaired sodium delivery to the distal tubule. The sodium that reaches the distal tubules is reabsorbed, with resultant pulmonary congestion and edema [8, 13, 14]. Prolonged elevation in aldosterone also promotes fibrosis in the failing myocardium which exacerbates cardiac dysfunction which in turn exacerbates the CRS [15].

Intrarenal vasoconstriction and decreased sodium delivery to the distal tubules also attenuates the salt losing effects of natriuretic peptides [8, 16]. Another possible mechanism of impaired natriuretic peptides action is the downregulation of their receptors [14] (Fig. 2).

Although serum catecholamines are increased in patients with HF, a decrease in myocardial catecholamines has been observed [17]. The decrease in cardiac catecholamines is a result of maximal myocardial secretion with limited uptake. Thus the heart cannot respond to increased sympathetic stimulation. Sympathetic stimulation also results in several renal effects. Stimulation of alpha adrenergic receptors on the proximal tubule enhances sodium reabsorption, while beta-stimulation activates renin secretion in the juxtaglomerular apparatus [8]. Moreover, in HF patients postglomerular capillary pressure falls and oncotic pressure rises, further enhancing proximal tubular sodium reabsorption. Thus it is not surprising that elevated plasma norepinephrine levels correlate with poor prognosis in HF patients [16].

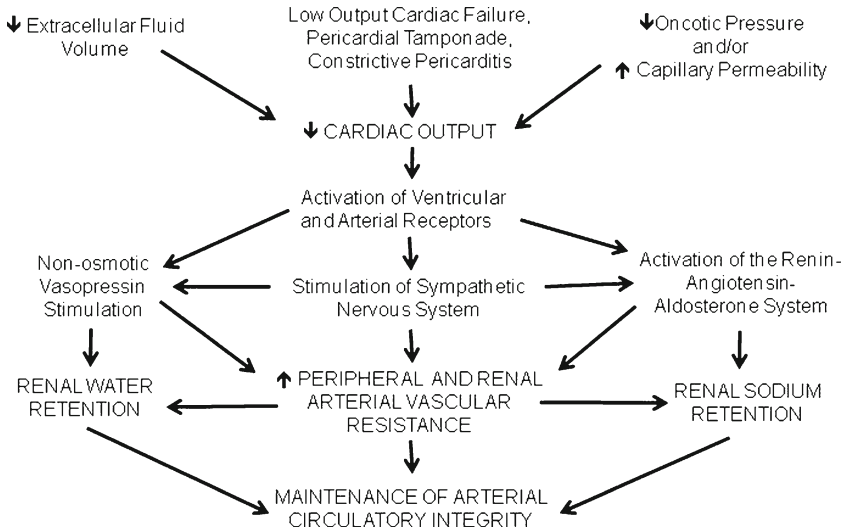

Fig. 1 Volume regulatory hypothesis. Sequence of events in which reduced cardiac output initiates renal sodium and water retention. (With permission from: Schrier RW. Body fluid volume regulation in health and disease: a unifying hypothesis. Ann Intern Med. 1990;113(2):155-9) [12]

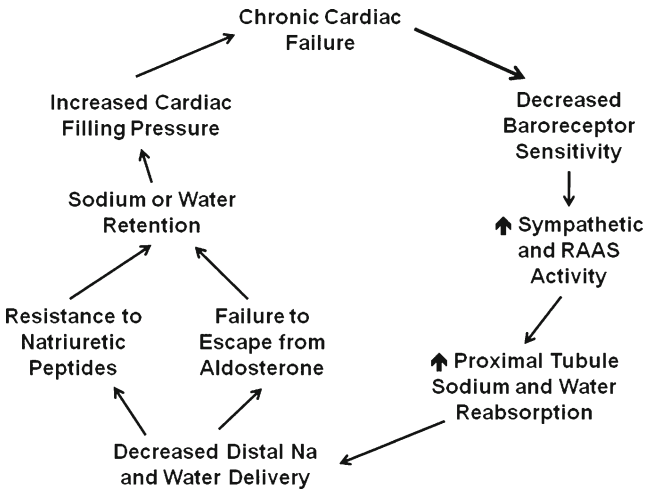

Fig. 2 Cardiorenal syndrome. Decreased baroreceptors sensitivity in patients with chronic heart failure can worsen cardiac function by increasing renin-angiotensin-aldosterone system (RAAS) and sympathetic activity, enhancing proximal fluid reabsorption, impairing aldosterone escape, and blunting the response to natriuretic peptides. Na, sodium. (With permission from: Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenic factor? J Am Coll Cardiol. 2006; 47:1-8) [8]

AVP, the antidiuretic hormone, is secreted from posterior pituitary gland in response to increased plasma osmolality and arterial underfilling. In HF there is nonosmotic release of AVP, despite normal or even decreased serum osmolality [18]. Activation of vasopressin V1 receptors results in an increase in systemic vascular resistance and whereas V2 receptor activation results in an increase in water reabsorption in the renal collecting ducts leading to hyponatremia. AVP also enhances the activity of urea transporters in collecting ducts, resulting in increased blood urea nitrogen [19].

In patients with advanced HF, arterial underfilling is more pronounced resulting in even greater activation of neurohormonal systems. This intense neurohumoral activation leads to volume retention, hyponatremia, and azotemia. Systemic and intrarenal vasoconstriction and increased proximal sodium and water reabsorption increase susceptibility of HF patients to secondary insults, such as nephrotoxic agents (e.g., contrast media), sepsis and hemodynamic alterations, including hypotension and increased renal venous pressure.

Increased Venous Pressure as a Cause of Diminished Renal Function

In 1861 Ludwig observed in an experimental model that a decrease in urine output as soon as central venous pressure (CVP) increased above 10 mmHg [20]. In 1931 Winton also showed the influence of elevated renal venous pressure on isolated kidneys from dogs [21]. A rise in CVP with transmission to the renal venous system increases renal afterload and intrarenal pressure. The increase in intrarenal pressure decreased renal perfusion and intratubular flow resulting in a fall in GFR and an increase in sodium and water reabsorption.

Volume overload therefore is a hallmark of ADHF. In a prospective cohort study from Cleveland Clinic, increased CVP and failure to decrease this elevated CVP with treatment were the most important hemodynamic factors causing WRF [22]. Retrospective analysis of 2557 HF patients who underwent cardiac catheterization revealed CVP as the most important predictor of WRF and mortality [23]. Moreover, increased intraabdominal pressure secondary to ascites and visceral edema has been shown to correlate with WRF in HF patients, and lowering intraabdominal pressure resulted in increased GFR [24]. This fall in GFR is related to increase in inferior vena caval and thus renal venous pressure secondary to the elevated intraabdominal pressure [25]. Thus, the influence of increased venous pressure on WRF makes decongestion a cornerstone of AHDF treatment in patients with CRS.

Epidemiology of Decreased Baseline Renal Function

Renal dysfunction is a prevalent comorbidity in HF, both in stable outpatients and in hospitalized decompensated patients. As many as 40 % of the patients with coronary artery disease and stable HF have been shown to have decreased GFR (<60 ml/min/1.73 m2) [26]. ADHF represents a phase of HF with dynamic changes in hemodynamics, neurohumoral activation and medication use, that could influence renal function.

Baseline renal function during a HF admission has been associated with prognosis in several studies. The Acute Decompensated HF National Registry (ADHERE) comprising 118,465 ADHF patients revealed that moderate (GFR 30-59 ml/min/1.73 m2) and severe renal dysfunction (GFR 15-29 ml/min/1.73 m2) and kidney failure (GFR < 15 ml/min/1.73 m2) occurs in 43.5 %, 13.1 % and 7.0 % of Acute HF patients respectively. In-hospital mortality increased from 1.9 % for patients with normal renal function to 7.6 % for patients with severe dysfunction [27]. Multivariate analysis showed that although GFR was an independent predictor of mortality, blood urea nitrogen (BUN) was the best predictor [27]. As renal function declines in ADHF, diuretic doses and use of vasoactive drugs and inotropic agents increase while ACE use decreases. The importance of BUN in this patient population has been evaluated in several studies. Data from the Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor (PRECEDENT) trial included

541 patients with systolic HF. BUN was found to be the only significant mortality predictor during 1-year follow-up. The BUN/creatinine ratio showed similar prognostic significance [28]. Post-hoc analysis of the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonists in Chronic HF (ACTIV in CHF) trial showed an increase in 60-day mortality and rate of death/rehospitalizations among the patients in the highest quartile of baseline BUN. After adjustment for covariates, BUN remained of prognostic significance; however GFR and serum creatinine did not [29].

Decreased renal function at the time of an admission for ADHF was associated with a negative prognostic impact during long-term follow up. The Worcester HF Study (WHFS) included 4350 ADHF patients followed for a total of 50 years follow-up and found that late mortality from increased from 39 to 51 % as renal dysfunction progressed from mild to severe [30]. A recent prospective study of 355 ADHF patients with 6.5 years follow-up demonstrated that the worsening discharge serum creatinine predicted a higher long-term mortality. Increasing tertiles of discharge GFR were independent predictors of better long-term survival. Multivariate analysis revealed BUN as the only significant predictor of long-term prognosis. BUN was more discriminative that GFR in predicting long-term survival [31].

Thus, baseline renal dysfunction in ADHF patients appears to be associated with increased mortality and rehospitalization, independent of etiology and systolic function [32•]. BUN is suggested to be a better prognostic factor than serum creatinine or GFR. This may be because AVP increases urea, but not creatinine, reabsorption [19].

Epidemiology of Worsening Renal Function

Worsening renal function in the setting of ADHF is a complex phenomenon. In a retrospective analysis of 1002 ADHF patients an increase in serum creatinine was observed in 70 % of the patients, including 20 % with an increase of 0.5 mg/dl or more. WRF was generally observed within the first 3 days of hospitalization, and was associated with increased in-hospital mortality and prolonged length of stay even with an increase as small as 0.1 mg/dl in serum creatinine. However, the best specificity and sensitivity for WRF has been shown to be an increase of 0.3 mg/dl or more in serum creatinine [33].

Analysis of the Milrinone for Exacerbations of Chronic HF (OPTIME-CHF) trial demonstrated a decrease in GFR and an increase in BUN from admission to discharge in most patients receiving milrinone. An increase in BUN of 10 mg/dl or more during hospitalization was associated with a worse 60-day survival [34].

In a prospective study of 509 ADHF patients WRF, defined as an increase in serum creatinine of 0.5 mg/dl or more, was observed in 21 % of patients; 70 % of WRF occurred during the first 6 days of hospitalization and was associated with increased in-hospital mortality and increased length of stay. Risk factors for WRF in that study included diabetes mellitus, baseline renal function and diastolic ventricular dysfunction. ACE inhibitors and diuretics however were not associated with WRF [35].

WRF in the setting of ADHF has been associated with specific complications such as sustained hypotension [34] and the need for cardiopulmonary resuscitation and mechanical ventilation [27]. Moreover, patients with WRF were twice as likely to have myocardial infarction, cardiogenic shock, stroke, sepsis and atrial fibrillation [36].

WRF and Long-Term Prognosis

A retrospective study of 2465 ADHF patients with 2-years follow-up reported an increase in post-discharge deaths and re-hospitalizations in patients with WRF. The survival, however, was significantly decreased in patients who had not recovered renal function on discharge, i.e. renal dysfunction persisted [37]. Furthermore, Analysis of Vasodilatation in the Management of Acute Congestive HF (VMAC) study found an increase in 6-month mortality in patients with persistent renal dysfunction for one month after admission compared to patients with transient WRF. Moreover, in multivariable model transient WRF did not increase mortality significantly [38•].

In-hospital changes in renal function may be related to different mechanisms and clinical pathways, and they reflect different prognoses [32•]. In the majority of patients with ADHF, elevated central venous pressure may be the major contributor to WRF [22]. The importance of decreasing congestion to improve survival in these patients has been shown in several studies. Analysis of the Evaluation Study of Congestive HF and Pulmonary Artery Catheterization Effectiveness (ESCAPE) demonstrated the importance of decreasing congestion on prognosis, as reflected by hemoconcentration, even if WRF occurs. Moreover, the patients with WRF had a greater decrease in systolic blood pressure due to greater doses of vasodilators and had greater decrease in body weight. In such cases WRF was not associated with increased mortality; however it was associated with an increased rate of post-discharge cardiovascular events [39, 40].

The Determining Optimal Dose and Duration of Diuretic Treatment in People with Acute HF (DOSE-AHF) Trial demonstrated the same 60-day outcome in high-dose and low-dose diuretic groups, even though increased rates of

WRF occurred in the high-dose group [41••]. Thus, a decrease in GFR during decongestion treatment may not indicate a worse prognosis.

In a recently published post-hoc analysis of the Efficacy of Vasopressin Antagonism in HF Study with Tolvaptan (EVEREST) patients with persistent (up to 4 weeks) WRF in ADHF were analyzed [42]. The patients with persistent WRF had greater reduction in systolic blood pressure, body weight and brain natriuretic peptide levels. In spite of these improvements in markers of volume overload, the patients with persistent WRF had decreased survival and increased re-hospitalization rates [42]. One potential explanation for these findings is that patients with WRF have higher neurohormonal activation with more secondary vasoconstriction and volume retention [32•, 43]. While the therapeutic reduction in congestion in these patients resolves pulmonary symptoms, it may cause more hypoperfusion with more cardiac impairment resulting in a worse prognosis.

These data suggest that relationship between congestion, WRF and prognosis in ADHF is complex and requires further investigation [32•]. Transient WRF may reflect short-term alterations in fluid status, associated with successful treatment of congestion, and may not be associated with poor outcome. In contrast, persistent WRF may occur in patients with more severe HF, neurohumoral activation, and hemodynamic abnormalities, which are associated with a worse prognosis [32•].

Treatment

Treatment of patients with HF and decreased or decreasing renal function is a vexing clinical problem. To date there is no specific treatment of CRS in ADHF that unequivocally demonstrates benefit. We will discuss HF treatments in patients with CRS, including treating congestion with diuretics and ultrafiltration, and use of vasoactive medications.

Diuretics

Decreasing congestion is a cornerstone of ADHF treatment. Congestion not only causes HF symptoms but likely contributes to myocardial remodeling and progressions of HF [44, 45]. Diuretics therefore have become a first line treatment in ADHF patients with CRS. However, overdiuresis can further decrease renal function, activate neuroactive hormones, and thereby complicate further treatment. The rate of fluid removal by diuretics should not exceed the interstitial fluid mobilization rate. In patient with end-stage renal disease such fluid mobilization has been estimated to be 12-15 ml/min [46]. In patients with HF and arterial underfilling there is little information about the optimal rate of fluid mobilization.

The randomized double-blind controlled l trial Diuretic Optimization Strategies Evaluation (DOSE) demonstrated that there was no significant difference in global symptom relief or change in renal function at 72 hours between intermittent versus continuous infusion of furosemide or between low dose (as patient outpatient dose) versus high dose (x 2.5 times) furosemide [41••]. The high-dose strategy caused a mild renal dysfunction that was reversible at one week. At 60-day follow-up there were no differences in outcomes between strategies. However, the high-dose group experienced more benefit at 72 hours in secondary outcomes, such as dyspnea, weight-loss and cardiac biomarkers. The mode and doses of diuretics in patients with CRS, especially those who are unresponsive to initial doses, needs investigation. The HF Society of America guideline for AHDF recommends switching from bolus to continuous infusion of diuretics in patients who appear to be nonresponsive to diuretics [47]. However, this recommendation needs to be assessed in randomized studies. The DOSE suggested that continuous infusion was not better that bolus diuretics in all patients with ADHF but did not specifically study patients initially unresponsive to diuretics.

Another approach to loop diuretic resistances is to add agents that act in the distal nephron, such as thiazides or metolazone. Alternatively, high, natriuretic doses of mineralocorticoid receptor antagonists (e.g., spironolactone 50-100 mg) can be added. This approach was shown to be safe in patients with advanced HF in a small, retrospective single-center study [48], but should be tested in a large scale randomized trial. With high dose mineralocorticoid receptor antagonists, care must be taken to avoid patients with severe renal dysfunction and to monitor potassium carefully. Ultrafiltration is another option.

Ultrafiltration

Ultrafiltration (UF) can theoretically avoid excess neurohormonal activation which occurs with loop diuretic blockade of macula densa transport [49]. As early as 1974 UF was used by Silverstein et al. to treat volume overload [50]. Since that time several small studies have demonstrated benefit of UF in HF patients. In 2007 the first large study on ultrafiltration in ADHF was published. The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated HF (UNLOAD) included 200 patients in 28 centers with ADHF and volume overload. Patients in UF arm had significantly greater weight loss at 48 hours and fewer requirements for vasoactive drugs. These patents demonstrated a trend to increase serum creatinine during first week of the treatment. However, treatment with

UF resulted in significantly fewer hospital readmissions during 90-day follow-up [51]. Another study, Effects of Ultrafiltration versus Diuretics on clinical, biohumoral and hemodynamic variables in patients with Decompensated HF (ULTRADISCO), showed greater clinical improvement and larger decreases in aldosterone and N-terminal pro-B type natriuretic peptide in the UF arm [52]. These studies predicted a specific benefit of UF treatment in ADHF patients with CRS. The recent study Ultrafiltration in Decompensated HF with CRS (CARRESS-HF) included 188 patients with acute decompensated HF, WRF, and persistent congestion, however, failed to demonstrate benefit of UF compared to stepwise pharmacological approach [53••]. Patients in both groups had the same weight loss, but patients in the UF group had a greater increase in serum creatinine and more adverse events. There were no differences in outcomes during 60-days follow-up. One potential explanation for these results is the heterogeneity of patients with ADHF and CRS. A small study analyzed the impact of UF on ADHF in three different subgroups of patients with 1) volume overload and urine output less then 1000 ml/24 h, 2) volume overload and urinary output more then 1000 ml/24 h and 3) euvolemic patients. UF treatment resulted in increased diuresis with a fall in serum neurohormone levels in the first group but increased neurohormone levels in the other two groups [54]. As noted earlier, a transient increase in serum creatinine in HF patients during treatment can represent short-term dehydration and be a hall-mark of successful treatment. UF may be indicated in some elderly populations with HF and preserved ejection fraction. These patients often have CKD and are admitted with severe volume overload. Due to hemodynamic instability in this setting vasodilators or inotropes are not well tolerated and diuretic resistance may be present. Thus, UF might be the only option for treating congestion. It is clear, however, that further studies are needed to test this hypothesis.

Vasodilators

The central focus in treatment of ADHF patients is to decrease congestion with the expectation that as intravascular volume falls, cardiac filling pressures will decline and symptoms will resolve. One approach is to decrease systemic vascular resistance, which would decrease mitral regurgitation, increase forward flow, and decrease filling pressures.

Sodium nitroprusside, nitroglycerine (higher doses for arterial vasodilatation) and nesiritide are the main vasodilators used in ADHF patients. These medications may be of value when there is a poor response to diuretics or the necessity to resolve symptoms rapidly. Afterload reduction by vasodilator agents can increase cardiac output reducing arterial underfilling and thus resulting in improved renal function in selected patients, such as those with dilated cardiomyopathy and substantial mitral regurgitation [55, 56]. However, vasodilators may also cause hypotension with resultant decreased renal perfusion pressure. Their influence on renal function, therefore, is unpredictable. Concerns about WRF during natriuretic peptide, nesiritide, treatment have been reported [57]. Nevertheless, vasodilators may be of value in highly selected patients with ADHF.

Inotropes

Inotropes may be indicated in hemodynamically unstable patients with low CO (e.g., cardiac index < 2.0 l/min/m2), and low systolic blood pressure (SBP), that restricts the use of other vasoactive agents. Patents with high cardiac pressures (e.g., PCWP > 18 mmHg and/or right atrial pressure > 10 mmHg) and worsening of clinical symptoms may benefit even though they are receiving optimal oral (ACE inhibitors, b-blockers, aldosterone antagonists) or intravenous (diuretics, vasodilators) therapy. Inotropes may also be of benefit in critically ill patients with hemodynamic impairment and significant exercise limitation, and fluid overload resistant to diuretics with renal and/or liver dysfunction [47, 58•].

In more severe HF renal dysfunction may be a marker of low CO. Thus, the need for inotrope use is crucial in order to preserve blood pressure and peripheral perfusion both improving central and renal hemodynamics. The need for inotropic therapy is associated with increased mortality; both because it is a marker of advanced HF and also possibly due to the agent's adverse events [58•, 59]. Nevertheless, these agents may be used as first line treatment in HF patients with hypotension (SBP < 100 mmHg) and peripheral hypoperfusion on a short-term basis and under close monitoring [58•, 60]. Inotropes may be used as a bridge to more definitive treatment (e.g., cardiac transplantation) or, most often, to facilitate a diuresis, decrease volume overload and mitral regurgitation, thereby improving renal perfusion and hemodynamics. The main inotropes in clinical practice are dobutamine and the phosphoesterase inhibitor milrinone. The calcium-channel sensitizer levosimendan is available in Europe but not in the United States. A cross-over study of dopamine and dobutamine in dilated cardiomyopathy revealed a sustained inotropic response at higher doses only to the latter [61] which is why dobutamine is preferred over dopamine as an inotrope. Several studies have assessed the renal protective effect of low-dose ("renal"-dose) dopamine. Meta-analysis in intensive care unit patients, however, revealed no benefit of low-dose dopamine for renal protection [62]. Meanwhile, the recent Dopamine in Acute Decompensated HF Study (DAD-HF) comparing high-dose furosemide infusion with low-dose furosemide plus low-dose dopamine demonstrated that both treatment

strategies had similar effects on urinary output, dyspnea score and outcomes; however, the dopamine group had a lower occurrence of WRF [63]. The inotrope, levosimendan, showed an improvement in renal function in a small randomized study [64]; however, the main effect of any inotropic agent in ADHF is to improve cardiac function and consequently renal function. There is no general consensus about timing for starting inotropes. In a recent trial fluid overloaded ADHF patients with WRF a stepwise approach included inotropic treatment on day 3 in a case of poor response to diuretics, low blood pressure and/or right-ventricular failure. This approach was as effective as UF [53••].

ACE and ARB

The role of neurohumoral inhibitors in patients with advanced HF with CRS is not well defined in the literature. ACE inhibitors or ARBs are often withheld or their doses decreased when there is WRF. Short-term WRF during initiation of ACEI/ARB however does not necessarily lead to long-term renal dysfunction [65•]. In chronic HF patients with WRF treated with ACE inhibitors, serum creatinine was stable over a 6-month period [66]. However, there are no data on patients with advanced HF and CRS where extreme activation of neurohumoral axis occurs. Neurohormonal activation results in vasoconstriction of afferent and efferent renal arterioles potentially exacerbating renal dysfunction. This scenario may be worsened in cases of diuretic-induced arteriolar hypovolemia and hypotension [65•]. WRF reflects maximal pre- and post-glomerular vasoconstriction and blocking angiotensin II may decrease GFR. The initial decrease in GFR represents impaired renal perfusion, but not intrinsic renal damage. In spite of WRF these HF patients may benefit from ACE/ inhibitors or angiotensin receptor blockers (ARB) stabilizing both cardiac and renal function [65•]. Studies reveal that patients with baseline renal dysfunction were less likely to receive ACE/ARB, and the prescription rate of these medications has been shown to be inversely related to the renal function in HF patients [42]. Nevertheless, the clinical decision to withhold ACE/ARB in cases of WRF may not be necessary, and any evaluation of short-term risk versus long-term benefits needs to be addressed in future studies [65•].

Risk factors for WRF with initiation of ACE/ARB are hypotension (mean BP <60 mmHg), lower left ventricular filling pressures (<15 mmHg), higher doses of loop diuretics and hyponatremia (serum sodium <137 mEq/L) [66, 67]. These risk factors reflect severe HF with extreme neurohormonal activation.

Timing of initiation ACE/ARB in ADHF has not been studied. As a general rule, neurohumoral inhibitors should be initiated after treatment of severe congestion. Recommendations are to decrease the doses of diuretics when initiating ACE/ARB in patients with baseline decreased renal function or WRF and use lower doses of medications [68]. Close monitoring of renal function and avoiding falls in blood pressure are important.

Conclusions

CRS, including progressive decline in renal function, WRF during cardiac decompensation, and diuretic resistance, is frequently present in HF patients, especially with advanced HF. The main symptom in this setting is congestion due to salt and water retention. Thus, treating congestion is a cornerstone of the treatment. However, this therapy should not cause further perturbation of hemodynamic and neurohormonal systems. An increase in serum creatinine during treatment of congestion does not necessarily require termination of medication. In some cases it reflects treatment success and unmasks severe HF. While clinical judgment is pivotal in treating patients with CRS, there is a need for better evidence-based medicine.

Acknowledgments Dr. D. Shchekochikhin's cardiorenal fellowship was sponsored by the Russian President's Scholarship for Studying Abroad and Gambro UF Solutions, Inc.

Compliance with Ethics Guidelines

Conflict of Interest Dmitry Shchekochikhin declares that he has no conflict of interest.

Robert Schrier has been a consultant for Otsuka Pharmaceutical, Janssen Pharmaceutical.

JoAnn Lindenfeld has been a consultant for St. Jude, Medtronic, Boston Scientific. She has received grant support from Zensun and Medtronic. She has received travel/accommodations expenses covered or reimbursed from FDA, NIH, AHA, ACC, HFSA, and University of Colorado.

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.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. National Heart Lung Blood Institute: NHLBI Working Group. – cardiorenal connections in HF and cardiovascular disease – august

20, 2004. Available at http://www.Nhlbi.Nih.Gov/meeting/workshops/cardiorenalhf-hd.Htm.
2. Liang KV, Williams AW, Greene EL, Redfield MM. Acute decompensated HF and the CRS. Crit Care Med. 2008;36:S75–88.
3. Bongartz LG, Cramer MJ, Doevedans PA, Joles JA, Braam B. The severe CRS: 'Guyton revisited'. Eur Heart J. 2005;26:11–7.
4. Heywood JT. The CRS: lessons from the adhere database and treatment options. Heart Fail Rev. 2004;9:195–201.
5. Boerrigter G, Burnett Jr JC. CRS in decompensated HF: prognostic and therapeutic implications. Curr Heart Fail Rep. 2004;1:113–20.
6. Bock JS, Gottlieb SS. CRS: new perspectives. Circulation. 2010;121:2592.
7. Ronco C, Haapio M, House AA, et al. CRS. J Am Coll Cardiol. 2008;52:1527.
8. Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenic factor? J Am Coll Cardiol. 2006;47:1–8.
9. Linden RJ, Kappagoda CT. Atrial receptors and renal blood flow. In: Linden RJ, Kappagoda CT, editors. Atrial Receptors. Cambridge: University Press; 1982. p. 235–9.
10. Packer M. Neurohormone interaction and adaptations in congestive HF. Circulation. 1988;77:721–30.
11. Sarraf M, Masoumi A, Schrier RW. CRS in Acute Decompensated HF. Clin J Am Soc Nephrol. 2009;4:2013–26.
12. Schrier RW. Body fluid volume regulation in health and disease: a unifying hypothesis. Ann Intern Med. 1990;113(2):155–9.
13. Blankstein R, Bakris GL. Renal hemodynamic changes in HF. Heart Fail Clin. 2008;4:411–23.
14. Schrier RW, Abraham WT. Hormones and hemodynamics in HF. N Engl J Med. 1999;341:577–8.
15. Weber K. Mechanisms of disease: aldosterone in chronic HF. N Engl J Med. 2001;345:1689–97.
16. Cohn JN, Levine TV, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive HF. N Engl J Med. 1984;311:819–23.
17. Kramer RS, Mason DT, Braunwald E. Augmented sympathetic neurotransmitter activity in the peripheral vascular bed of patients with congestive HF and cardiac norepinephrine depletion. Circulation. 1966;33:629–34.
18. Schrier RW, Berl T, Anderson RJ. Osmotic and nonosmotic control of vasopressin release. Am J Physiol. 1979;236:F321–32.
19. Schrier RW. Blood urea nitrogen and serum creatinine: not married in HF. Circ Heart Fail. 2008;1(1):2–5.
20. Ludwig C. Lehrbuch d. Physiol, 2nd edition, 1861.
21. Winton FR. The influence of venous pressure on the isolated mammalian kidney. J Physiol. 1931;72(1):49–61.
22. Mullens W, Abrahams GS, Francis GS, et al. Importance of venous congestion for worsening renal function in advanced decompensated HF. J Am Coll Card. 2009;53(7):589–96.
23. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol. 2009;53(7):582–8.
24. Mullens W, Abrahams Z, Skouri HN, et al. Elevated intraabdominal pressure in acute decompensated HF. A potential contributor to worsening renal function? J Am Coll Cardiol. 2008;51(3):300–6.
25. Kirsch AJ, Kayton M, Hensle TW, et al. Renal effects of CO2 insufflation: oliguria and acute renal dysfunction in a rat pneumoperitoneum model. Urology. 1994;43:453–9.
26. Ezekowitz J, McAlisher FA, Humphries KH, et al. The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with HF and coronary artery disease. J Am Coll Cardiol. 2004;44(8):1587–92.
27. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated HF: a report from the ADHERE database. J Card Fail. 2007;13(6):422–30.
28. Aronson D, Mittlemann MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated HF. Am J Med. 2004;116(7):466–73.
29. Filippatos G, Rossi J, Lloyd-Jones DM, et al. Prognostic value of blood urea nitrogen in patients hospitalized with worsening HF: insights from the Acute and chronic therapeutic impact of a vasopressin antagonists in chronic HF (ACTIV in CHF) study. J Card Fail. 2007;13(5):360–4.
30. Ismailov RM, Goldberg RJ, Lessard D, Spencer FA. Decompensated HF in the setting of kidney dysfunction: a community-wide perspective. Nephron Clin Pract. 2007;107(4):c147–55.
31. Gotsman I, Zwas D, Planer D, Admon D, Lotan C, Keren A. The significance of serum urea and renal function in patients with HF. Medicine (Baltimore). 2010;89(4):197–203.
32.• Brandimarte F, Vaduganathan M, Mureddu GF, et al. Prognostic implications of renal dysfunction in patients hospitalized with HF: data from the last decade of clinical investigations. Heart Fail Rev. 2012. doi:10.1007/s10741-012-9317-z. *Excellent review on epidemiology and prognosis in CRS.*
33. Gottlieb SS, Abraham W, Butler J, et al. The prognostic importance of different definitions of worsening renal function in congestive HF. J Card Fail. 2002;8(3):136–41.
34. Klein L, Massie BM, Leimberger JD, et al. Admission or changes in renal function during hospitalization for worsening HF predict postdischarge survival: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic HF (OPTIME-CHF). Circ Heart Fail. 2008;1(1):25–33.
35. Cowie MR, Komaja M, Murray-Thomas T, Underwood J, Tiko B. Prevalence and impact of worsening renal function in patients hospitalized with decompensated HF: results of the prospective outcomes study in HF (POSH). Eur Heart J. 2006; 27(10):1216–22.
36. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with HF. J Am Coll Cardiol. 2004;43:61–7.
37. Lanfear DE, Peterson EL, Campbell J, et al. Relation of worsening renal function during hospitalization for HF to long-term outcomes and rehospitalization. Am J Cardiol. 2011;107(1):74–8.
38. • Aronson D, Burger AJ. The relationship between transient and persistent worsening renal function and mortality in patients with acute decompensated HF. J Card Fail. 2010;16(7):541–7. *The difference between transient and persistent WRF for prognosis.*
39. Nohria A, Hasselblad V, Stebbins A, et al. Cardiorenal interactions: insight from the ESCAPE trial. J Am Coll Cardiol. 2008;51(13):1268–74.
40. Testani JM, Coca SG, McCauley BD, Shannon RP, Kimmel SE. Impact of changes in blood pressure during the treatment of acute decompensated HF on renal and clinical outcomes. Eur J Heart Fail. 2011;13(8):877–84.
41. •• Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated HF. N Engl J Med. 2011;364(9):797–805. *First randomized study on diuretics in ADHF.*
42. Blair JE, Pang PS, Schrier RW, et al. Changes in renal function during hospitalization and soon after discharge in patients admitted for worsening HF in the placebo group of the EVEREST trial. Eur Heart J. 2011;32(20):2563–72.
43. Ruggenenti P, Remuzzi G. Worsening kidney function in decompensated HF: treat the heart, don't mind the kidney. Eur Heart J. 2011;32(20):2476–8.
44. Zile MR, Bennett TD, St John Sutton M, et al. Transition from chronic compensated to acute decompensated HF:pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation. 2008;118:1433–41.

45. Jain P, Massie BM, Gattis WA, Klein L, Gheorghiade M. Current medical treatment for the exacerbation of chronic HF resulting in hospitalization. Am Heart J. 2003;145(2 Suppl):S3–S17.
46. Fauchauld P. Effects of ultrafiltration of body fluid and transcapillary colloid osmotic gradient in hemodialysis patients, improvements in dialysis therapy. Contrib Nephrol. 1989;74:170–5.
47. Lindenfeld J, Albert NM, Boehmer JP, et al. Executive summary: HFSA 2010 comprehensive HF practice guidelines. J Card Fail. 2010;16(6):475–539.
48. Shchekochikhin D, Lindenfeld J, Schrier RW. Increased Spironolactone in Advanced HF: Effect of Doses Greater Than 25 mg/day on Plasma Potassium Concentration. Cardiorenal Med. 2013;3:1–6.
49. Francis GS, Siegel RM, Goldsmith SR. Acute vasoconstrictior response to intravenous furosemide in patients with chronic congestive HF. Activation of the nuerohumoral axis. Ann Intern Med. 1985;103(1):1–6.
50. Silverstein ME, Ford CA, Lysaght MJ, Henderson LW. Treatment of severe fluid overload by ultrafiltration. N Engl J Med. 1974;291(15):747–51.
51. Constanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated HF. J Am Coll Cardiol. 2007;49(6):675–83.
52. Giglioi C, Landi D, Cecchi E, et al. Effect of ultrafiltration vs diuretics on clinical, biohumoral and haemodynamic variables in patients with decompensated HF : the ULTRADISCO study. Eur J Heart Fail. 2011;13(3):337–46.
53. •• Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated HF with CRS. N Engl J Med. 2012;367(24):2296–304. *Randomized study on UF versus pharmacological approach in CRS.*
54. Marenzi G, Grazi S, Giraldi F, et al. Interrelation of humoral factors, hemodynamics, and fluid and salt metabolism in congestive HF: effects of extracorporeal ultrafiltration. Am J Med. 1993;94(1):49–56.
55. Rosario LB, Stevenson LW, Solomon SD, et al. The mechanism of decrease in dynamic mitral regurgitation during HF treatment: importance of reduction in the regurgitant orifice size. J Am Coll Cardiol. 1998;32:1819–24.
56. Stevenson LW, Brunken RC, Belil D, et al. Afterload reduction with vasodilators and diuretics decreases mitral regurgitation during upright exercise in advanced HF. J Am Coll Cardiol. 1990;15(1):174–80.
57. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive HF: a randomized control trial. J Am Coll Cardiol. 2002;288(5):577–2002.
58. • Parissis JT, Rafouli-Stergiou P, Stasinos V, et al. Inotropes in cardiac patients: update 2011. Curr Opin Crit Care. 2010;16:432–41. *Good review on inotropes in ADHF and CRS.*
59. Follath F, Yilmaz MB, Delgado JF, et al. Clinical presentation, management and outcomes in the Acute HF Global Survey of Standard Treatment (ALARM-HF). Intensive Care Med. 2011;37:619–26.
60. Elkayam U, Tasissa G, Binanay C, et al. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe HF. Am Heart J. 2007;153:98–104.
61. Leier CV, Heban PT, Huss P, Bush CA, Lewis RP. Comparative Systemic and Regional Hemodynamic Effects of D opamine and Dobutamine in Patients with Cardiomyopathic HF. Circulation. 1978;58:466–75.
62. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Ann Intern Med. 2005;142(7):510–24.
63. Giamouzis G, Butler J, Starling RC, et al. Impact of dopamine infusion on renal function in hospitalized HF patients: results of the Dopamine in Acute Decompensated HF (DAD-HF) Trial. J Card Fail. 2010;16:922–30.
64. Zemljic G, Bunc M, Yazdanbakhsh AP, Vrtovec B. Levosimendan improves renal function in patients with advanced chronic HF awaiting cardiac transplantation. J Card Fail. 2007;13(6):417–21.
65. • Valika AA, Gheorghiade M. Ace inhibitor therapy for HF in patients with impaired renal function: a review of the literature. Heart Fail Rev. 2012. doi:10.1007/s10741-011-9295-6. *Review on ACE inhibitors treatment in patients with CRS.*
66. Ljungman S, Kjekshus J, Swedberg K. Renal function in severe congestive HF during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] Trial). Am J Cardiol. 1992;70(4):479–87.
67. Oster JR, Meterson BJ. Renal and electrolyte complications of congestive HF and effects of therapy with angiotensin-converting enzyme inhibitors. Arch Intern Med. 1992;152(4):704–10.
68. Packer M. Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic HF. Ann Intern Med. 1987;106(3):346–54.