Cardiorenal Syndrome Type 1: Renal Dysfunction in Acute Decompensated Heart Failure

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ABSTRACT

- **Objective:** To present a review of cardiorenal syndrome type 1 (CRS1).
- **Methods:** Review of the literature.
- **Results:** Acute kidney injury occurs in approximately one-third of patients with acute decompensated heart failure (ADHF) and the resultant condition was named CRS1. A growing body of literature shows CRS1 patients are at high risk for poor outcomes, and thus there is an urgent need to understand the pathophysiology and subsequently develop effective treatments. In this review we discuss prevalence, proposed pathophysiology including hemodynamic and nonhemodynamic factors, prognosticating variables, data for different treatment strategies, and ongoing clinical trials and highlight questions and problems physicians will face moving forward with this common and challenging condition.
- **Conclusion:** Further research is needed to understand the pathophysiology of this complex clinical entity and to develop effective treatments.

A cute decompensated heart failure (ADHF) is an epidemic facing physicians throughout the world. In the United States alone, ADHF accounts for over 1 million hospitalizations annually, with costs in 2012 reaching $30.7 billion [1]. Despite the advances in chronic heart failure management, ADHF continues to be associated with poor outcomes as exemplified by 30-day readmission rates of over 20% and in-hospital mortality rates of 5% to 6%, both of which have not significantly improved over the past 20 years [2,3]. One of the strongest predictors of adverse outcomes in ADHF is renal dysfunction. An analysis from the Acute Decompensated Heart Failure National Registry (ADHERE) revealed the combination of renal dysfunction (creatinine > 2.75 mg/dL and blood urea nitrogen (BUN) > 43 mg/dL) and hypotension (systolic blood pressure (SBP) < 115 mm Hg) upon admission was associated with an in-hospital mortality of > 20% [4]. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry documented a 16.3% in-hospital mortality when patients had a SBP < 100 mm Hg and creatinine > 2.0 mg/dL at admission [5].

The presence of acute kidney injury in the setting of ADHF is a very common occurrence and was termed cardiorenal syndrome type 1 (CRS1) [6]. The prevalence of CRS1 in single-centered studies ranged from 32% to 40% of all ADHF admissions [7,8]. If this estimate holds true throughout the United States, there would be 320,000 to 400,000 hospitalizations for CRS1 annually, highlighting the magnitude of this problem. Moreover, with the number of patients with heart failure expected to continue to rise, CRS1 will only become more prevalent in the future. In this review we discuss the prevalence, proposed pathophysiology including hemodynamic and nonhemodynamic factors, prognosticating variables, data for different treatment strategies, ongoing clinical trials, and highlight questions and problems physicians will face moving forward in this common and challenging condition.

Pathogenesis of CRS1

Hemodynamic Effects

The early hypothesis for renal dysfunction in ADHF centered on hemodynamics, as reduced cardiac output was believed to decrease renal perfusion. However, analysis of invasive hemodynamics from patients with ADHF suggested that central venous pressure (CVP) was actually a
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better predictor of the development of CRS1 than cardiac output. In a single-center study conducted at the Cleveland Clinic, hemodynamics from 145 patients with ADHF were evaluated and surprisingly baseline cardiac index was greater in the patients with CRS1 than patients without renal dysfunction (2.0 ± 0.8 L/min/m² vs 1.8 ± 0.4 L/min/m²; P = 0.008). However, baseline CVP was higher in the CRS1 group (18 ± 7 mm Hg vs 12 ± 6 mm Hg; P = 0.001), and there was a heightened risk of developing CRS1 as CVP increased. In fact, 75% of the patients with a CVP of > 24 mm Hg developed renal impairment [9]. In a retrospective study of the Evaluation Study of Congestive Heart Failure and Pulmonary Arterial Catheter Effectiveness (ESCAPE) trial, the only hemodynamic parameter that correlated with baseline creatinine was CVP. However, no invasive measures predicted worsening renal function during hospitalization [10]. Finally, an experiment that used isolated canine kidneys showed increased venous pressure acutely reduced urine production. Interestingly, this relationship was dependent on arterial pressure; as arterial flow decreased smaller increases in CVP were needed to reduce urine output [11]. Together, these data suggest increased CVP plays an important role in CRS1, but imply hemodynamics alone may not fully explain the pathophysiology of CRS1.

Inflammation

As information about how hemodynamics incompletely predict renal dysfunction in ADHF became available, alternative hypotheses were investigated to gain a deeper understanding of the pathophysiology underlying CRS1. A pathological role of inflammation in CRS1 has gained attention due to recent publications. First of all, serum levels of the pro-inflammatory cytokines TNF-α and IL-6 were elevated in patients with CRS1 when compared to health controls [12]. Interestingly, Virzi et al showed that the median value of IL-6 was 5 times higher in CRS1 patients when compared to ADHF patients without renal dysfunction [13]. The negative consequences of elevated serum cytokines were demonstrated when incubation of a human cell line of monocytes with serum from CRS1 patients induced apoptosis in 81% of cells compared to just 11% of cells with control serum [12]. It is possible that cytokine-induced apoptosis could occur in other cell types in different organs in patients with CRS1, which may contribute to both cardiac and renal dysfunction. Finally, analysis from a rat model of CRS1 revealed macrophage infiltration into the kidneys and increased numbers of activated monocytes in the peripheral blood. Interestingly, monocyte/macrophage depletion using liposome clodronate prevented chronic renal dysfunction in the rat model [14]. In summary, these data suggest inflammation contributes to CRS1 pathophysiology, but more experimental data is needed to determine if there is a causal relationship.

Oxidative Stress

Very recently, oxidative stress was proposed to play a role in CRS1. Virzi et al analyzed serum levels of markers of oxidative stress and compared ADHF patients without renal impairment to CRS1 patients. The markers of oxidative stress, which included myeloperoxidase, nitric oxide, copper/zinc superoxide dismutase, and endogenous peroxidase, were all significantly higher in CRS1 patients [13]. While provocative, the tissues responsible for the generation of these molecules and the subsequent effects have not yet been fully elucidated.

The proposed pathophysiology is seen in the Figure.

Prognostication

Severity of Acute Kidney Injury

Initial publications did not document a strong link between kidney injury and poor outcomes in ADHF. Firstly, Ather et al performed a single-centered study that investigated how change in renal function defined by change in creatinine, estimated GFR, and BUN affected outcomes one year post admission for ADHF. Kidney injury defined by a change in creatinine or in estimated GFR was not associated with increased risk of mortality, but a change in BUN was associated with increased mortality in a univariate analysis [15]. Testani et al retrospectively analyzed patients from the ESCAPE trial and found worsening renal function defined by a ≥ 20% reduction in estimated GFR was not significantly associated with 180-day mortality, but there was a trend towards higher mortality (hazard ration 1.4; P = 0.11) [16]. Importantly, neither of 2 these studies assessed how severity of AKI impacted outcomes, which may have contributed to the weak relationships observed.

However, when AKI severity in CRS1 was quantified, poor outcomes were more likely as AKI severity increased. Firstly, Roy et al determined how AKI impacted adverse events (mortality, rehospitalization, or need for dialysis) rates in 637 patients with ADHF. Severity of AKI was quantified using RIFLE, AKIN, and KDIGO guidelines.
(Table 1), and the authors found that as the severity of renal injury increased, the likelihood of an adverse event was higher. In fact, the most severe AKI grade using all 3 AKI grading systems resulted in an odds ratio ranging from 45.3 to 101.6 for an adverse event at 30 days when compared to no kidney injury [7]. Hata et al documented that AKI (defined using RIFLE criteria) in ADHF resulted in a longer ICU stay, total hospital length of stay, and higher in-hospital mortality rates, and patients with a failure-grade AKI had in-hospital mortality rate of 49.1% [17]. Finally, Li et al evaluated AKI in 1005 patients with ADHF and showed that AKI defined by RIFLE, AKIN, or KDIGO methods increased risk of in-hospital mortality, and that a KDIGO grade 3 AKI was associated with a 35.5% in-hospital mortality rate [8]. These data indicate CRS1 is associated with poor outcomes, and there is a heightened risk of adverse events as AKI severity increases.

Diuretic Responsiveness

Using change in serum creatinine as a marker of renal impairment may not be the best choice for predicting outcomes in CRS1 because the lab values are not a real-time measure of kidney function and serum creatinine can be affected by both body mass and pharmaceutical agents. Therefore, the prognosticating ability of urine production relative to diuretic dose as a surrogate measure of renal function in ADHF was investigated by several groups (Table 2). Testani et al examined urine output per 40 mg of furosemide and tracked outcomes in 2 cohorts: patients admitted with ADHF at the University of Pennsylvania (657 patients) and patients from the ESCAPE trial (390 patients). Patients were split into high responders or low responders based on the median value. In both of the patient cohorts, low diuretic efficiency was associated with increased mortality using a multivariate model (hazard ratio of 1.36 in the Penn patients and 2.86 in the ESCAPE patients). The combination of low diuretic efficiency and high diuretic dose (> 280 mg in the Penn cohort and > 240 mg in the ESCAPE cohort) resulted in the worst prognosis, with mortality rates of approximately 70% at 6 years in the Penn cohort and approximately 35% at 180 days in the ESCAPE cohort [18]. Voors et al performed a retrospective analysis of diuretic responsiveness in 1161 patients from the Relaxin in Acute Heart Failure (RELAX-AHF) trial. Diuretic responsiveness was defined as weight change (kg) per diuretic dose (IV furosemide and PO furosemide) over 5 days and then patients were separated into tertiles. The lowest tertile group had an approximate 20% incidence of 60-day combined end-point of death, heart failure or renal failure readmission compared to less than 10% incidence in the middle and upper tertiles. Interestingly, when the effects of worsening renal function (WRF), defined as creatinine change of $\geq 0.3$ mg/dL, were examined in patients stratified by diuretic response, WRF did not offer additional prognostic information [19].

Finally, Valente et al analyzed diuretic response in 1745 patients from the PROTECT trial (Placebo-Controlled Randomized Study of the Selective A1-Adenosine

\[ \text{Figure. Proposed pathophysiology of CRS1. A combination of reduced cardiac output, increased central venous pressure, systemic inflammation, and oxidative stress result in renal dysfunction in acute decompensated heart failure.} \]
Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function. Diuretic response was calculated using the weight change per 40 mg of furosemide, and as diuretic response declined there was increasing risk of 60-day rehospitalization and 180-day mortality rates. In fact, the lowest quintile responders had a 25% mortality rate at 180 days [20].

**Emerging Biomarkers**

**Urine Neutrophil Gelatinase-Associated Lipocalin**

Because previous studies showed urinary levels of NGAL was an earlier and more reliable marker of renal dysfunction than creatinine in AKI [21], it was studied as a possible biomarker for the development of CRS1 in ADHF. A single-centered study quantified levels of urine NGAL in 100 patients admitted with heart failure and then tracked the rates of acute kidney injury. Urine NGAL was elevated in patients that developed AKI and a cut-off value 12 ng/mL had a sensitivity of 79% and specificity of 67% for predicting CRS1 [22]. While promising, further studies are needed to better define the role of NGAL in CRS1.

**Cystatin C**

Cystatin C is a ubiquitously expressed cysteine protease that has a constant production rate and is freely filtered by the glomerulus without being secreted into the tubules, and has effectively prognosticated outcomes in ADHF [23]. Lassus et al showed an adjusted hazard ratio of 3.2 (2.0–5.3) for 12-month mortality when cystatin C levels were elevated. Moreover, patients with the highest tertile of NT-proBNP and cystatin C had a 48.7% 1-year mortality. Interestingly, patients with an elevated cystatin C but normal creatinine had a 40.6% 1-year mortality compared to 12.6% for those with normal cystatin C and creatinine [24]. Furthermore, Arimoto et al showed elevated cystatin C predicted death or rehospitalization in a small cohort of ADHF patients in Japan [25]. Also, Naruse et al showed cystatin C was a better predictor of cardiac death than estimated GFR by the Modification of Diet in Renal Disease Study (MDRD) equation [26]. Finally, Manzano-Fernandez et al showed the highest tertile of cystatin C was a significant independent risk factor for 2-year death or rehospitalization while creatinine and MDRD estimates of GFR were not [27]. In agreement with Lassus et al, elevations in either 2 or 3 of cystatin C, troponin, and NT-proBNP predicted death or rehospitalization when compared to those with normal levels of these 3 markers [27]. In conclusion, cystatin C either alone or in combination with other biomarkers identifies high-risk patients.

**Kidney Injury Molecule 1**

Kidney injury molecule 1 (KIM-1) is a type-1 cell membrane glycoprotein expressed in regenerating proximal tubular cells but not under normal conditions [28]. Although associated with increased risk of hospitalization and mortality in chronic heart failure [29,30], elevated levels of urinary KIM-1 did not predict mortality in...
ADHF [31]. Further studies are needed to elucidate the utility of KIM-1 in CRS1.

Treatment Approaches

Diuretics

Loop diuretics are the main treatment for decongestion of patients with CRS1. To date, no clinical trial has compared the different loop diuretics (furosemide, bumetanide, torsemide, or ethacrynic acid) to each other, so there is no clear choice of which loop diuretic is the best. However, dosing scheme was investigated in the Dose Optimization Strategies Evaluation (DOSE) trial. In this trial, 308 patients were randomized in a 1:1:1:1 design in which patients were placed in groups with low-dose (equivalent to oral dose) or high-dose (2.5 times oral dose) intermittent parental therapy or alternatively low-dose or high-dose continuous drip therapy. There were no differences in dyspnea, fluid changes, change in creatinine, hospital length stay, or rehospitalization and death rates when the intermittent and drip approaches were compared. However, the high-dose arm had decreased dyspnea, increased volume removal, but there were more occurrences of AKIs when compared to the low-dose arm [32].

In clinical practice, if loop diuretic treatment does not result in the desired urine output, a second-site diuretic may be added to potentiate diuresis. Unfortunately, there is little data on this common clinical practice and thus the optimal choice of second site agent (chlorthiazide or metolazone) is unknown. Frequently, the deciding factor is based upon cost or concern that oral absorption of metolazone will be ineffective. However, Moranville et al recently performed a retrospective assessment comparing chlorthiazide (22 patients) to metolazone (33 patients) in ADHF patients with renal dysfunction defined by a creatinine clearance of 15–50 mL/min. There was a non-significant trend towards increased urine output in the metolazone group, no differences in the rates of adverse events, and the chlorthiazide group actually had a longer hospital stay [33]. While potentially promising results, the retrospective nature of the study made it difficult to determine if the differences were due to treatment approach or dissimilarities of patient illness. Nonetheless, physicians must remain vigilant when implementing the second-site diuretic approach because it can lead to marked diuretic response leading to metabolic derangements including hypokalemia, hyponatremia, hypomagnesemia, and metabolic alkalosis.

Inotropes

The use of inotropic agents such as dobutamine or milrinone can be used to augment cardiac function when there is a known low-output state for better renal perfusion in CRS1. Unfortunately, there is little objective data available about the utility of this widely implemented approach. The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of a Chronic Heart Failure (OPTIME-HF) trial did not show improved renal function with milrinone treatment [34]. The use of levosimendan, a cardiac calcium sensitizer that increases contractility not currently approved in the United States, was compared to dobutamine in the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial, and there were no differences in rates of renal failure when the 2 groups were compared [35]. Nonetheless, if cardiac output is severely compromised, inotropes can be used for CRS1 treatment, but they should be used cautiously due the increased risks of lethal arrhythmias.

Dopamine

Use of low-dose dopamine to stimulate D1 and D2 receptors as a way to increase renal blood flow and promote increased glomerular filtration and urine production was extensively studied in ADHF. A small trial showed use of low dose dopamine had renal protective effects in a total of 20 patients [36]. However, when larger trials were conducted, such beneficial results were not consistently

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observed. The Dopamine in Acute Decompensated Heart Failure (DAD-HF I) trial compared low-dose furosemide plus low-dose dopamine (5 µg/kg/min) to high-dose furosemide alone in 60 patients. There were no differences in total diuresis, hospital stay, and 60-day mortality or rehospitalization rates, but there was a reduction in the renal dysfunction at the 24-hour time point in the dopamine-treated arm (6.7% versus 30%) [37]. The Dopamine in Acute Decompensated Heart Failure II trial randomized 161 ADHF patients to high-dose furosemide, low-dose furosemide and low-dose dopamine (5 µg/kg/min), or low-dose furosemide and assessed dyspnea, worsening renal function, length of stay, 60-day and one-year all-cause mortality and hospitalization for heart failure. Dopamine treatment did not improve any of the outcomes measured [38]. Finally, the most recent trial to examine the effects of dopamine was the Renal Optimization Strategies Evaluation (ROSE) trial. In this trial, there were 360 patients with ADHF randomized to nesiritide or dopamine versus placebo in a 2:1 design. When comparing dopamine (111 patients) treatment to placebo (115 patients), there were no differences in urine output, renal function as determined by cystatin C levels, or symptomatic improvements. However, there was more tachycardia in the dopamine group [39]. Currently, there is not strong evidence supporting routine use of dopamine in CRF.

Nesiritide

Use of nesiritide, recombinant brain natriuretic peptide, was also investigated as a way to enhance urine production through the natriuretic effects of the peptide. The first attempt to explore this hypothesis was the B-Type Natriuretic Peptide in Cardiorenal Decompensation Syndrome (BNP-CARDS) trial. BNP-CARDS showed a 48-hour infusion of nesiritide (39 patients) or placebo (36 patients) in patients with ADHF and renal dysfunction (estimated GFR between 15–60 mL/min) did not reduce the incidence of worsening renal function as defined by a rise in serum creatinine by 20% [40]. A similar approach was implemented in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial which examined over 7000 patients with ADHF. 3496 patients were treated with nesiritide and 3511 patients were treated with placebo for 24 hours and up to 7 days. Nesiritide treatment did not alter dyspnea at 6 and 24 hours, improve renal function as determined by creatinine change, or alter the combined end-point of rehospitalization or death 30 at days [41]. The ROSE trial examined the effects of nesiritide (117 patients) versus placebo (115 patients) for urine production, change in renal function as defined by change in cystatin C, and decongestion (urinary sodium excretion, weight change, and change in NT-proBNP) at 72 hours. Nesiritide did not alter any of the outcomes investigated [39]. Finally, a single-centered study conducted at the Mayo Clinic examined the effects of nesiritide (37 patients) or placebo (35 patients) with ADHF and pre-existing renal dysfunction (estimated GFR between 20 and 60 mL/min). These investigators found nesiritide treatment resulted in less renal dysfunction as measured by creatinine and BUN, but no changes in diuretic responsiveness, duration of hospitalization, or rehospitalization rates. Nesiritide did reduce serum endothelin levels, but had no effect on ANP, NT-pro BNP, renin, angiotensin II, or aldosterone [42]. In summary, nesiritide does not appear to have significant renal protective effects in ADHF.

Adenosine A1 Receptor Antagonists

The use of adenosine receptor antagonists to prevent adenosine-mediated vasoconstriction of renal vasculature in ADHF has also been examined. The first study conducted was a small double-blind randomized-controlled trial that investigated the effects of rololofylline, an adenosine A-1 antagonist, in patients with ADHF and an estimated creatinine clearance of 20-80 mL/min. The study had 27 patients in the placebo arm, 29 patients that received 2.5 mg of rololofylline, 31 patients received 15 mg of rololofylline, 30 patients received 30 mg of rololofylline, and 29 patients received 60 mg of rololofylline, all of which was daily for up to 3 days. Rololofylline treatment increased urine output on day 1 and improved renal function on day 2 [43]. These positive results led to the Placebo-Controlled Randomized Study of Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) Trial. PROTECT assessed the effects of rololofylline (1356) or placebo (677) in patients with ADHF and an estimated creatinine clearance between 20 and 80 mL/min. There were no significant differences in renal function out to 14 days, but rololofylline led to more weight loss than placebo [44,45]. In a subgroup analysis of patients with severe baseline renal dysfunction (creatinine clearance of less than 30 mL/min), rololofylline reduced the combined 60-day end-point of
hospitalization due to cardiovascular or renal cause and death [45]. Finally, the Effects of KW-3902 Injectable Emulsion on Heart Failure Signs and Symptoms, Diuresis, Renal Function, and Clinical Outcomes in Subjects Hospitalized with Worsening Renal Function and Heart Failure Requiring Intravenous Therapy (REACH-UP) trial probed the effects of rolofylline (36 patients) or placebo (40 patients) in patients with ADHF and renal impairment (creatinine clearance of 20-60 mL/min). Rolofylline treatment did not alter renal function, but there was a nonsignificant trend towards reduction in 60-day combined end-point of hospitalization due to renal or cardiovascular causes or death [46]. In summary, the use of rolofylline has not been conclusively associated with improved outcomes in CRS1.

**Vasopressin Antagonists**

The use of vasopressin antagonists to induce aquaphoresis and combat hyponatremia was studied in ADHF. Vasopressin antagonists were first investigated in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist (ACTIV) trial. ACTIV involved 3 doses of tolvaptan (78 patients received 30 mg, 84 patients received 60 mg, and 77 patients received 90 mg) versus placebo (80 patients), and tolvaptan increased urine production and decreased body weight compared to placebo without compromising renal function. A post-hoc analysis of patients with renal dysfunction (BUN > 29 mg/dL) and severe volume overload revealed a survival benefit at 60 days [47]. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVERST) trial compared placebo (2061 patients) versus 30 mg/day of tolvaptan (2072 patients) within 48 hours after admission in an identical 2-trial design. Tolvaptan increased weight loss and reduced dyspnea acutely but did not alter all-cause mortality or cardiovascular or heart failure hospitalization rates out to 24 months post index hospitalization [48,49]. These data suggest vasopressin antagonists may potentiate diuresis acutely but likely do not improve long-term outcomes.

**Corticosteroids**

The use of corticosteroids in ADHF has been controversial as there were initial concerns that corticosteroids would increase fluid retention. However, corticosteroids augmented diuretic response and improved renal function in 13 ADHF patients who had inadequate response to sequential nephron blockage [50]. Furthermore, Zhang et al showed that prednisone treatment in 35 patients admitted with ADHF increased urinary volume, reduced dyspnea, reduced uric acid, and improved renal function [51]. These promising results led to the Cardiac Outcome Prevention Effectiveness of Glucocorticoids in Acute Decompensated Heart Failure (COPE-ADHF) trial. In this single-centered study, 102 patients with ADHF were randomized to either placebo [51] or corticosteroids [51] and the outcomes recorded included urinary volume, change in creatinine, and cardiovascular death at 30 days. Use of corticosteroids improved renal function, increased urine output, and reduced mortality (3/51 in corticosteroid group versus 10/51 in the placebo group) [52]. The mechanisms underlying the improvements with corticosteroids were not determined, but were hypothesized to be facilitation of natriuretic peptides or dilation of renal vasculature through activation of nitric oxide pathway or dopaminergic system.

**Serelaxin**

Serelaxin is a recombinantly expressed human relaxin-2, a peptide hormone present during pregnancy which facilitates physiological cardiovascular and renal adaptations [53–55], which showed potential benefits in CRS1. Analysis of the RELAX-AHF trial revealed serelaxin reduced incidence of worsening renal function at day 2 of treatment as defined by changes in serum creatinine, cystatin C, and BUN. Importantly, worsening renal function defined by cystatin C changes was associated with increased 180-day mortality in this analysis [56]. The mechanisms by which serelaxin prevented renal dysfunction are currently unknown as serelaxin treatment did not improve diuretic efficiency [19].

**Ultrafiltration**

Another treatment choice in CRS1 is mechanical removal of salt and water via ultrafiltration. Ultrafiltration showed early promise in Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure trial (UNLOAD) trial. In this study, 200 patients with ADHF were randomized to either ultrafiltration or medical management with loop diuretics. Use of ultrafiltration increased volume removal without any differences in renal function and reduced rehospitalization rates at 90 days [57]. However, when ultrafiltration was employed specifically in CRS1 patients in the Cardiorenal Rescue Study
in Acute Decompensated Heart Failure trial (CARESS-HF), UF was not superior to medical treatment. There were 188 patients studied in CARESS-HF, and in the ultrafiltration arm there was increased risk of renal dysfunction, no differences in volume removal, and no change in rehospitalization rates at 90 days [58]. When trying to reconcile UNLOAD and CARESS-HF, the medical treatment arm in CARESS-HF was much more standardized and aggressive and UNLOAD was earlier implementation of ultrafiltration, which may have explained the differences. Interestingly, ultrafiltration was hypothesized to be advantageous over diuretic therapy through reduced activation of the renin-angiotensin-aldosterone system, but analysis of the patients from CARESS-HF showed higher levels of plasma renin activity and no difference in aldosterone levels in ultrafiltration patients [59].

Two meta-analyses have examined the use of ultrafiltration versus medical management in ADHF and both showed ultrafiltration was more effective in volume removal than medical therapy but did not improve rehospitalization or mortality rates [60,61]. This fact combined with the risks of vascular access placement and bleeding from anticoagulation limits to routine use of ultrafiltration in CRS1.

Continuous Renal Replacement Therapy

Once renal function deteriorates to the point that renal replacement therapy is needed for both volume removal and solute clearance in CRS1, continuous renal replacement therapy (CRRT) may be implemented. Unfortunately, there are few available data for this group of advanced CRS1 patients to guide physicians. There was a single-centered study conducted in Egypt that randomized 40 ADHF patients to either IV furosemide or CRRT. The patients treated with CRRT had greater weight loss and decreased length of stay in the ICU, but there were no differences in dialysis dependence rates or 30-day mortality [62]. Two single-centered studies reported outcomes associated with advanced CRS1 requiring CRRT. In a study conducted at the Cleveland Clinic, 63 patients with CRS1 were treated with ultrafiltration, of which 37 were converted to CRRT due to worsening renal function. Of the 37 patients treated with CRRT, 16 died in the hospital and 4 were discharged with hospice care [63]. In another retrospective study performed at the University of Alabama-Birmingham, use of rescue CRRT in advanced CRS1 was examined in 37 patients. 23 patients died during hospitalization and 2 were discharged to hospice care [64]. Combination of the Cleveland Clinic and University of Alabama-Birmingham studies revealed patients requiring CRRT in the setting of advanced CRS1 had an in-hospital mortality or palliative discharge rate of 60.8% (45/74). Clearly, this population needs further investigation to prevent such poor outcomes.

A summary of treatment approaches for CRS1 is presented in Table 3.

Future Treatment Options

Ongoing and Unreported Clinical Trials

Unfortunately, none of the current treatments for CRS1 have definitive improvements in outcomes, but there are several ongoing clinical trials which will hopefully identify novel treatment strategies. First of all, the Acetazolamide and Spironolactone to Increase Natriuresis in Congestive Heart Failure (Diuresis-CHF) trial is being conducted in Belgium. This study will examine the effects of acetazolamide with low dose diuretic versus high dose diuretics in one arm and the effects of upfront spironolactone in another. The outcomes analyzed will include total natriuresis, potassium homeostasis, NT-proBNP changes, change in renal function, peak serum levels of renin and aldosterone, weight change, urine volume, and change in edema (NCT01973335). The Protocolized Diuretic Strategy in Cardiorenal Failure (ProDius) trial is being performed at the University of Pittsburgh, and will determine the effects of a protocolized diuretic approach to target 3-5 liters of urine production a day versus standard therapy and will track the change in body weight, length of hospitalization, rehospitalization rates, mortality rates, venous compliance of internal jugular vein, clinical decongestion, change in renal function, and urine output (NCT01921829). The Levosimendan versus Dobutamine for Renal Function in Heart Failure (ELDOR) study is ongoing in Sweden and will probe the acute effects of levosimendan and dobutamine on renal perfusion. The endpoints will include changes in renal blood flow, GFR, renal vascular resistance, central hemodynamics, renal oxygen extraction and consumptions, and filtration fraction (NCT02133105). Finally, the Safety and Efficacy of Low Dose Hypertonic Saline and High Dose Furosemide for Congestive Heart Failure (REaCH) trial probed the effects of combination of hypertonic saline and furosemide versus furosemide in patients with ADHF and renal impairment defined by a GFR<60 mL/min.
The outcomes were change in renal function, diuretic response, length of hospital stay, readmission rates, weight loss, BNP levels, and included a cost analysis. The study was completed but results are not currently available (NCT01028170)

**Should Inflammation Be Targeted in CRS1?**

Although proposed to play a role in the pathophysiology of CRS1, inflammation has not been explicitly targeted as a treatment for CRS1. One possible way to combat inflammation could be inhibition of the IL-6 pathway, which is support by preclinical work as previous studies showed IL-6 knockout mice were resistant to HgCl$_2$-induced renal injury and death [65] and IL-6 has negative inotropic effects in both isolated cardiomyocytes [66] and intact animals [67]. Thus, IL-6 antagonism may improve both cardiac and renal function, an ideal scenario for CRS1 patients. The availability of tocilizumab, an FDA-approved humanized antibody to the IL-6 receptor, may allow for investigation of this hypothesis in the future. Although not examined in the COPE-ADHF trial, an alternative explanation for the improvements associated with corticosteroids treatment were the anti-inflammatory effects. If this were true, corticosteroids would represent a relatively cheap treatment option for CRS1 patients, but more studies need to be conducted before this approach is widely implemented. Finally, use of cytokine profiling may be used to enrich a population of CRS1 patients that could be investigated in future clinical trials using anti-inflammatory medications.

**Unanswered Questions Moving Forward**

**Severity of AKI and Treatment Effects**

An important unknown that warrants further investigation is if the severity of AKI should dictate treatment choice in CRS1. As discussed above, increasing severity...
of AKI resulted in elevated risk of adverse events, but it remains unknown whether different treatments offer benefits for more or less severe renal impairment. Perhaps, future studies aimed at defining outcomes from different treatment strategies stratified by severity of renal dysfunction may reveal which patients benefit from the various treatment options for CRS1.

**How Do We Best Define Renal Dysfunction in CRS1?**

Currently, there is no accepted definition of renal dysfunction in CRS1. As discussed above, using the AKIN, KDIGO, or RIFLE scoring systems or diuretic responsiveness effectively differentiated outcomes in patients with CRS1. However, an agreed-upon definition would likely benefit the field going forward so this population could be systematically investigated in future studies.

**Conclusion**

In summary, CRS1 is a common clinical entity associated with poor patient outcomes. A complex pathophysiology marked by reduced cardiac output, increased central venous pressure, inflammation, and oxidative stress underlies the disease process. Unfortunately, no current treatment approach shows consistent improvements in outcomes, highlighting the urgent need for further research to reduce the burden that CRS1 imposes.

**References**

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