# The relevance of congestion in the cardio-renal syndrome

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**Worsening renal function (WRF) during the treatment of acute decompensated heart failure (ADHF) occurs in up to a third of patients and is associated with worse survival. Venous congestion is increasingly being recognized as a key player associated with WRF in ADHF. Understanding the hemodynamic effects of venous congestion and the interplay between venous congestion and other pathophysiological factors such as raised abdominal pressure, endothelial cell activation, anemia/ iron deficiency, sympathetic overactivity, and stimulation of the renin–angiotensin–aldosterone system will help in devising effective management strategies. Early recognition of venous congestion through novel techniques such as bioimpedance measurements and remote monitoring of volume status combined with customized diuretic regimens may prevent venous congestion and perhaps avoid significant WRF.**

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Acutely worsening renal function (WRF) in the setting of acute decompensated heart failure (ADHF), known as Type 1 cardiorenal syndrome, affects 25–45% of hospitalized patients.[1] Apart from increasing the complexity of managing such patients, WRF accompanying ADHF is now recognized as an independent predictor of mortality.[2,3] A retrospective analysis of the ADHERE database suggests that serum creatinine $>2.75$ mg/dl is a significant risk factor for mortality in patients with ADHF.[4] Although systemic underfilling leading to neurohumoral activation is likely a key event in heart failure (HF), WRF in ADHF is not always from hypoperfusion of the kidneys, but is now increasingly recognized to be associated with venous congestion.[5,6] A better understanding of the relationship between renal injury and venous congestion in ADHF will enable physicians to focus on the appropriate treatment strategy. Further, long-standing HF may be associated with significant renal fibrosis and consequent irreversibility despite hemodynamic improvement. Thus, preventing venous congestion and consequently acute episodes of WRF becomes an important long-term goal.[7] This review will focus on the role of venous congestion in WRF and examine the optimal management strategies in the treatment of these patients.

## THE LINK BETWEEN VENOUS CONGESTION AND RENAL DYSFUNCTION

The pathophysiology of renal injury in ADHF is complex (Figure 1). Ljungman *et al.*[8] showed that renal blood flow is preserved until cardiac index falls below 1.5 l/min/m$^2$. In many patients, it is venous congestion rather than arterial underfilling that is associated with decreased renal blood flow and WRF. In the following sections, we will examine the pathophysiological links between venous congestion and WRF.

### Hemodynamic effects and abdominal compartment syndrome

Renal perfusion pressure not only depends on arterial pressure but is also determined by the trans-renal perfusion pressure, which is equal to mean arterial pressure minus central venous pressure. As early as in 1861, Ludwig[9] found

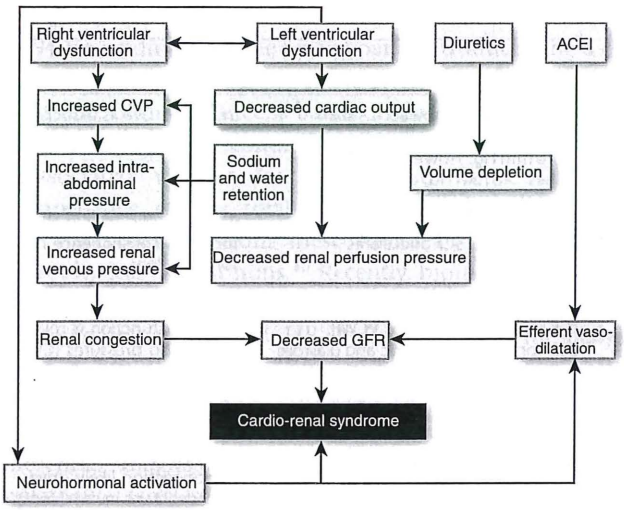


**Figure 1 | Cardiorenal interactions in the pathophysiology of cardiorenal syndrome.** ACEI, angiotensin-converting enzyme inhibitor; CVP, central venous pressure; GFR, glomerular filtration rate.

that if the renal vein pressure is raised beyond 10 mm Hg, it retards urinary flow. He attributed this to mechanical obstruction of the uriniferous tubules from compression by the surrounding venules. Winton[10] in 1931 showed that increased venous pressure was sufficient to produce a reduction of urine flow equal in amount to that produced by a decrease in arterial pressure on excised canine kidneys.

Clinically, Damman *et al*[11] and Drazner *et al*[12] have shown that increased central venous pressure and increased jugular venous pressure (JVP) on examination are associated with impaired renal function. In patients who had elective cardiac surgery, the preoperative presence of high central venous pressure was an independent predictor of acute kidney injury.[13–15] In the ESCAPE (Evaluation Study of Congestive heart failure and Pulmonary Artery Catheterization Effectiveness) trial, poor forward flow did not correlate with baseline creatinine—the only predictor was right atrial pressure.[16] The major studies linking venous congestion and renal dysfunction are summarized in Table 1.

The presence of venous congestion, visceral edema, ascites, and abdominal wall edema can lead to an increase in intra-abdominal pressure (IAP) in ADHF. In addition, gaseous distension of the bowel, urinary retention, and obesity and elevation of head end of the bed $>30°$ can also raise the IAP. The normal IAP is usually $<5$–7 mm Hg, and a constant elevation of IAP $>12$ mm Hg defines intra-abdominal hypertension.[17,18] Renal blood flow is determined by the abdominal perfusion pressure, which is directly related to mean arterial pressure and inversely related to IAP.[19] The formula for abdominal perfusion pressure is as follows:

Abdominal perfusion pressure = mean arterial pressure − IAP (normal = 60 mm Hg). The prevalence of raised IAP in patients with ADHF is as high as 60%.[20,21] In one study, the greater the IAP was lowered, the more renal function improved, independent of hemodynamic changes.[18]

### Neurohormonal effects

More recent neurophysiological studies indicate that increases in renal venous pressure and distension of intrarenal veins can stimulate mechanoreceptors and enhance local sympathetic renal nerve activity, resulting in intrarenal arterial vasoconstriction and a fall in glomerular filtration rate.[22–24] Conversely, increasing renal blood flow does not always translate into an increase in glomerular filtration rate.[25] These effects can be explained as being due to the neurohormonal regulation of the tone of the afferent and efferent arterioles. HF results in venous congestion and activation of the renin–angiotensin–aldosterone system (RAAS) and nonosmotic release of arginine–vasopressin and other neuroendocrine hormones, such as endothelin, which further promote congestion and renal function.[26]

Diuretic therapy in ADHF increases the delivery of sodium to the distal tubule stimulating adenosine secretion via tubuloglomerular feedback. Adenosine causes afferent arteriolar vasoconstriction, reducing renal blood flow. It also enhances sodium reabsorption in the proximal and distal tubules, with resultant venous congestion. Increased adenosine reduces glomerular filtration rate.[27] Although this pathway represents an appealing explanation, as it is susceptible to interruption with specific A1 adenosine receptor antagonists, a randomized trial comparing rolofylline, an adenosine receptor antagonist with placebo in patients hospitalized for acute HF, failed to prevent WRF.[28]

### Endothelial activation and proinflammatory cytokines

The vascular endothelium is the largest endocrine/paracrine organ of the body. Endothelial cells that sense biomechanical forces can switch their synthetic profile from a quiescent state toward an activated state, which is pro-oxidant, proinflammatory, and vasoconstricting.[29] Circumferential stretch of venous endothelial cells from venous congestion activates endothelial cells (Figure 2). Under these circumstances, in addition to neurohormonal activation as outlined above, an increase in inflammation also occurs.[30] Concentrations of proinflammatory cytokines, such as such as tumor necrosis factor and interleukin-6, are increased and are imputed to impair myocardial function and accelerate HF progression, in addition to its deleterious effects on the kidneys.[31] They also stimulate renin secretion as a component of the systemic stress response and tubulo-interstitial inflammation, which may have effects on adaptive responses of glomerular hemodynamics, leading to impaired renal function.[32]

### Iron deficiency

Activation of inflammatory cytokines is thought to be involved in the development of functional iron deficiency, because proinflammatory cytokines appear to be involved in the displacement of iron into cells of the reticuloendothelial system.[33,34] The acute-phase reactant hepcidin also has an important role in this regard.[35] Inflammatory cytokines and alterations in gut morphology[36] have a major role in the development of iron deficiency and anemia in HF.[37] The triad

**Table 1 | Studies linking venous congestion and WRF in patients with heart failure**

| Author, year (reference) | Key question assessed | Study type | Main findings | Conclusion |
|---|---|---|---|---|
| Damman *et al.*, 2009[11] | Is there a relationship between CVP, renal function, and mortality in patients with cardiovascular diseases? | Retrospective data review of 2557 patients with right heart catheterization. | Estimated GFR showed a small increase when CVP increased from 1to 6 mm Hg. However, in CVP, values >6 mm Hg, a steep decrease in eGFR, was observed. | Increased CVP is associated with impaired renal function. |
| Nohria *et al.*, 2008[16] | What hemodynamic measurements on pulmonary artery catheterization correlate with renal function? | Prospective randomized control study of 433 patients with HF treatment guided by pulmonary artery catheter versus clinical assessment alone. | Significant, correlation of RAP with baseline sCr and eGFR. | Renal insufficiency in HF is not merely a consequence of poor forward flow. |
| Guglin *et al.*, 2011[13] | Is venous congestion more strongly associated with renal dysfunction than with low cardiac output? | Retrospective data analysis of 178 patients who underwent right heart catheterization for HF evaluation. | sCr correlated with CVP, PCWP, pulmonary artery systolic and diastolic pressure, renal perfusion pressure, and velocity of tricuspid regurgitation, but not with CI and LVEF. | Renal dysfunction is related to high filling pressures (CVP and PCWP) and to lower renal perfusion pressure. |
| Testani *et al.*, 2010[14] | Does diuresis in patients with ADHF and RV dysfunction lead to a decrease in venous congestion and resultant improvement in RF? | Retrospective review of 141 patients with HF for echocardiographic evidence of RV function and venous congestion assessed by the lack of inspiratory inferior vena cava collapse. | Those with composite RV dysfunction had an increased incidence of venous congestion evidenced by the lack of inspiratory inferior vena cava collapse. Worsening RF with diuresis was significantly less common in those with RV dysfunction. | RV failure leads to venous congestion, and the relief of congestion likely drives improvement in renal function. |
| Mullens *et al.*, 2009[15] | Is venous congestion, rather than impairment of cardiac output, primarily associated with WRF in patients with ADHF? | Prospective observational study of 145 subjects, with mean LVEF 20±8%,with treatment guided by PAC. | There was an incremental risk in WRF, with increasing categories of baseline CVP, with 75% of subjects presenting with a baseline CVP >24 mm Hg developing WRF. | The strongest hemodynamic determinant for development of WRF is elevated CVP |

Abbreviations: ADHF, acute decompensated heart failure; CI, cardiac index; CVP, central venous pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RF, renal function; RV, right ventricle; sCr, serum creatinine; WRF, worsening renal function.

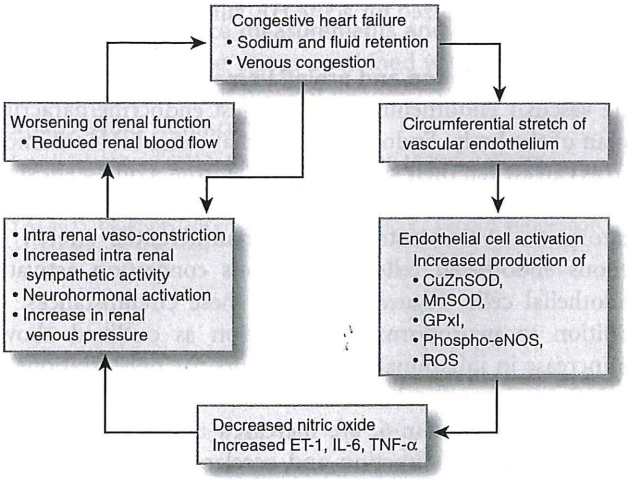


**Figure 2 | Venous congestion, endothelial activation, and renal dysfunction: the vicious cycle.** CuZnSOD, copper zinc superoxide dismutase; eNOS, endothelial nitric oxide synthase; ET, endothelin; GPx, glutathione peroxidase; IL, interleukin; MnSOD, maganese superoxide dismutase; ROS, reactive oxygen species; TNF, tumor necrosis factor.

of anemia, renal failure, and HF multiplies the mortality rate.[38]

## CLINICAL MARKERS AND BIOMARKERS OF VENOUS CONGESTION

### The utility of clinical examination

Certain symptoms and signs in clinical exam can reliably predict the presence of venous congestion. A systematic review of 12 studies suggested that increased JVP was a 'very helpful' finding for detecting increased filling pressure.[39] In the ESCAPE trial, the comparison of estimated hemodynamics from history and physical examination with invasive measurements by a pulmonary artery catheter revealed the following: measured right atrial pressure was <8 mm Hg in 82% of patients, with right atrial pressure estimated from jugular veins as <8 mm Hg, and was >12 mm Hg in 70% of patients when estimated as >12 mm Hg. Elevated JVP of >12 mm Hg predicted pulmonary capillary wedge pressure of >22 mm Hg with a sensitivity of 65% and specificity of 64%. The presence of orthopnea (use of ⩾2 pillows) predicted pulmonary capillary wedge pressure to be >22 mm Hg, with a sensitivity and specificity of 86% and 25%, respectively. Hence, elevated JVP and the presence of orthopnea can identify patients with high filling pressures and venous congestion.

### B-type natriuretic peptide

A recently released consensus statement stated that patients admitted with acute breathlessness due to HF and an elevated natriuretic peptide level (generally 600 pg/ml for B-type natriuretic peptide (BNP) or 6000 pg/ml for *N*-terminal pro-BNP) have a high filling pressure secondary to volume overload, and a treatment-induced decrease in pulmonary capillary wedge pressure will commonly lead to a rapid drop in natriuretic peptide levels.[40] As BNP levels correlate with capillary wedge pressure, it can also serve as an indirect marker for WRF during the treatment of ADHF.[41]

### Bioimpedance

In 1940, a landmark article by Nyboer[42] introduced the use of the bioimpedance technique to study changes in the volume in a tissue. Bioimpedance is based on the principle that fluid (edema) is a good conductor of electrical current and is associated with a low impedance value. Decreased bioimpedance reflects total body water excess, with total body water derived from these values by making certain electrophysical assumptions.[43] Recently, bioimpedance vector analysis has been suggested as a tool to assist in volume status assessment in patients with HF. Bioimpedance vector analysis allows a rapid, accurate, and noninvasive determination of body hydration status, correlates with NYHA class, and seems to demonstrate high diagnostic accuracy for the differential diagnosis of HF-induced dyspnea.[44,45] Non-implantable wireless devices using bioimpedance, as used in the MUSIC (Multi-Sensor Monitoring in Congestive Heart Failure) study, are capable of continuously monitoring patient fluid status and help in detecting HF decompensation early with good sensitivity and specificity, allowing for timely intervention and avoiding complications such as WRF.[46]

## MANAGEMENT OF VENOUS CONGESTION IN CARDIO RENAL SYNDROME

The development of WRF in a patient with ADHF is a common but difficult clinical problem to manage. Hence, a multilevel, multidimensional systematic, and strategic approach with special attention to relieving venous congestion is required for the prevention and treatment of WRF in ADHF (Table 2). This section will focus on optimizing management strategies in dealing with this common problem based on the evidence available to date.

### Anticipation and prevention

Congestion should ideally be prevented, often initially through water and salt restriction. Any patient admitted for ADHF is at high risk for the development of WRF. A careful history and physical examination will identify a certain subset of patients at high risk for WRF. History of anorexia may point toward splanchnic congestion, and these patients may have renal congestion as well. Early satiety may indicate elevated abdominal pressure and ascites. Easy fatigability might identify patients with low cardiac output. History also should focus on use of nephrotoxic drugs (nonsteroidal anti-inflammatory drugs, antibiotics, high-dose diuretics, etc.).

Signs suggesting venous congestion, such as elevated JVP, tender hepatomegaly, ascites, and pedal edema, will help identify individuals who are at a high risk of developing renal injury due to renal congestion. Hypotension should be avoided and systolic blood pressure should be maintained at least $>80$ mm Hg, and a mean arterial blood pressure of $>60$ mm Hg.[47] Laboratory findings such as elevated blood urea nitrogen, elevated baseline creatinine, hyponatremia, and elevated right atrial pressure will also identify patients who are at a high risk for WRF during the treatment of ADHF. A variety of renal markers, such as cystatin C and neutrophil gelatinase-associated lipocalin, are emerging that may allow better discrimination of changes in renal function due to hemodynamic perturbations versus frank renal injury.[48,49] The use of drugs that perturb intrarenal hemodynamics, such as nonsteroidal anti-inflammatory drugs and contrast agents, must be avoided in HF patients with WRF.

***Diuretic strategies.*** Intravenous loop diuretics represent the first-line treatment for decompensated HF, reducing fluid overload and relieving symptoms. There is no clear-cut dosing guidelines for diuretics in ADHF, and often dosing regimens are based on physician's experience rather than scientific evidence. In the DOSE-AHF (Determining Optimal Dose and Duration of Diuretic Treatment in People with Acute HF) study, which compared patients who received high doses of furosemide (2.5 times their oral dose) with patients who received lower doses (equal to oral dose), there were no significant differences between the two groups in serum creatinine levels, but the prognosis was similar. There was also no benefit of continuous infusion over bolus dosing.[50]

In patients with ADHF, we recommend an initial intravenous dose of a loop diuretic twice that of the home oral dose and reassessment in 1–2 h for response. If there is no response to the initial dose, the loop diuretic should be increased until adequate diuresis occurs or the maximum recommended dose is reached. Single daily dosing of loop diuretics, such as furosemide, should be avoided to prevent rebound increase in sodium absorption. Intravenous rather than oral loop diuretics should be used in patients with ADHF to overcome decreased absorption due to splanchnic congestion. Long-acting loop diuretics, such as torsemide, can be considered to prevent neurohormonal activation from rebound increase in sodium absorption.[51] In patients who fail to respond to large doses of loop diuretics, the addition of a non-loop diuretic (i.e., thiazide or potassium-sparing diuretic) may be effective by decreasing the enhanced sodium absorption in the distal tubule above.[52]

***Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.*** The excessive use of diuretics and sympathetic overactivity in ADHF promotes the activity of the RAAS. Activation of the RAAS leads to excessive salt and water retention and vasoconstriction of the venous beds, altering cardiac preload and afterload, which further worsens renal function. Salt and water retention further increases venous congestion and worsening of symptoms in ADHF. This results in escalation of diuretic dose, further activating the RAAS. Ultimately, renal injury occurs either because of hypoperfusion from overdiuresis or from venous congestion, or from both. Breaking this vicious cycle by RAAS blockade with angiotensin-converting enzyme inhibitor (ACE-I) and/or angiotensin receptor blocker could prevent renal injury. However, in an acute setting in which aggressive diuresis is needed, these drugs may also cause WRF. The balance is tight

**Table 2 | Practical approach to the management of type 1 cardiorenal syndrome**

**1. Anticipation and prevention**

- On admission, assess for the presence of early satiety, anorexia, use of NSAIDs, elevated baseline creatinine, history of orthopnea, and elevated JVP.
- Bioimpedence monitoring if available.[46]
- Restrict sodium (and water if hyponatremic).
- Avoid hypotension (MAP <60 mm Hg), contrast agents, and NSAIDs.[47]
- Avoid urinary retention, constipation, and elevation of head end of the bed >30, which can all raise the intra-abdominal pressure.

**2. Diuretic strategies**

- Use intravenous route for diuretics.
- Continuous infusion has no benefit over bolus dosing.[50]
- Start the initial dose at 2–2.5 times the home oral dose.[50]
- Escalate the dose until adequate symptom relief is achieved and/or evidence of renal hypoperfusion is present.
- Avoid single daily dosing.[51]

**3. Judicious use of ACE-I and ARB**

- Consider holding ACE-I or ARB temporarily during aggressive diuresis in high-risk patients.[53]
- Addition of beta-blockers could be reno-protective when ACE-I is used.[53]

**4. Overcoming diuretic resistance**

- Consider adding thiazides/thiazide-like diuretics or potassium-sparing diuretics.[52]
- Add mineralocorticoid antagonists such as spironolactone or eplerenone in patients with ejection fraction <35%.[55]

**5. Diuretic refractory CHF**

- Peritoneal dialysis.[67,68]
- Peripheral veno-venous ultrafiltration.[64,65]

**6. Emerging treatment options**

- Alternatively spliced BNPs (ASBNP and ASBNP.1).[61]
- Hypertonic saline with furosemide.[69]
- Vasopressin receptor antagonists.[73]
- Relaxin.[71]
- Catheter-based renal sympathetic denervation.[75]

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BNP, B-type natriuretic peptide; CHF, congestive heart failure; JVP, jugular venous pressure; MAP, mean arterial pressure; NSAIDs, nonsteroidal anti-inflammatory drugs.

and careful attention to renal parameters should be given in such patients, with adjustment of doses of both drugs.[53] Sometimes, it is prudent to withhold ACE-I and angiotensin receptor blocker particularly in patients at high risk of developing WRF, such as patients with advanced age and aggressive diuresis. Beta-blocker may be reno-protective in the setting of treatment with ACE-I.[53]

***Mineralocorticoid receptor antagonists.*** Aldosterone levels are inappropriately elevated in ADHF.[54] Aldosterone reduces natriuresis by enhancing sodium reabsorption in the distal tubules and collecting ducts. It also stimulates the neurohumoral compensatory mechanisms, including activation of the sympathetic nervous system and RAAS. These compensatory mechanisms lead to increased venous congestion and further deterioration in renal function. Mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, may attenuate the neurohumoral surge and prevent WRF. The recent introduction of highly specific and potent nonsteroidal mineralocorticoid receptor anatogonists also hold promise for overcoming diuretic resistance in these high-risk patients with reduced side effects as compared with conventional mineralocorticoid antagonists.[55] Previous small, nonrandomized, open-label trials have shown that these drugs at high doses overcome diuretic resistance in ADHF without a significant effect on serum creatinine.[56,57] However, large-scale, randomized trials are needed before these drugs could be recommended for preventing WRF in ADHF.

***Natiuretic peptides.*** Nesiritide, a recombinant form of endogenous human BNP has been shown to rapidly reduce cardiac filling pressure, increase cardiac output, promote diuresis and suppress RAAS and release of norepinephrine.[58] In a trial,[59] which involved 7007 patients with acute HF, the proportion of patients reporting improved dyspnea at 6

($P=0.03$) and 24 h ($P=0.007$) was higher with nesiritide than with placebo, but did not meet the prespecified level of statistical significance ($P\leqslant0.005$ for both or $P\leqslant0.0025$ for either) for dyspnea improvement. There was no increase in mortality or renal dysfunction with nesiritide, both of which had been raised as safety concerns in the previous studies.[60] Recently developed alternatively spliced BNPs (ASBNP and ASBNP.1) lacked the hypotensive side effects of nesiritide but increased the glomerular filtration rate, suppressed plasma renin and angiotensin, while inducing natriuresis and diuresis.[61]

*'Renal dose' dopamine.* Dopamine at a dose of 2–5 μg/kg/min stimulates dopaminergic receptors and increases renal blood flow. In addition, it also promotes sodium excretion and diuresis by inhibiting aldosterone.[62] Larger, randomized prospective studies have shown no convincing evidence of a beneficial effect of low-dose dopamine beyond the potential diuresis. Low-dose dopamine is not currently approved for the treatment of HF. The ongoing ROSE trial will assess the safety and efficacy of adjuvant low-dose dopamine versus low-dose nesiritide versus optimal diuretic therapy in patients with ADHF and chronic kidney disease.[63]

*Ultrafiltration and peritoneal dialysis.* Ultrafiltration removes isotonic sodium and water, reducing fluid overload and improving hemodynamics in patients with congestive HF. Compared with loop diuretics, peripheral veno-venous ultrafiltration removes more amount of sodium.[64] The UNLOAD (Ultrafiltration Versus Intravenous Diuretics For Patients Hospitalized For Acute Decompensated Heart Failure) trial by Costanzo *et al.*[65] compared 100 patients treated with peripheral ultrafiltration and 100 patients treated with intravenous diuretics during an episode of ADHF. This trial showed a significantly greater fluid and weight loss with ultrafiltration and fewer HF rehospitalizations; however, it lacked hard clinical end points and long-term outcomes past 90 days. The CARESS-HF trial is an ongoing prospective multicenter study that is assessing the efficacy of ultrafiltration compared with pharmacological therapy in patients hospitalized with ADHF and who have cardiorenal syndrome (defined as an increased in serum creatinine of $>0.3$ mg/dl from baseline).[66] Peritoneal dialysis with 1–4 exchanges daily also improved congestive symptoms, decreased the numbers and durations of hospitalizations, and enhanced the quality of life.[67] Once-daily exchanges with icodextrin can sustain peritoneal ultrafiltration for up to 12 h and has been shown to improve symptoms in ADHF.[68] Extracorporeal ultrafiltration and peritoneal dialysis may be considered in diuretic refractory congestive HF.

## EMERGING THERAPEUTIC OPTIONS

Combining hypertonic saline with furosemide was thought to prevent the rebound sodium reabsorption and promote effective diuresis. This hypothesis was tested by Paterna *et al.*[69] who demonstrated that a combination of high-dose furosemide with bolus hypertonic saline infusion in patients with NYHA class IV HF improved diuresis, shortened hospital stay, decreased BNP levels, and reduced readmissions compared with IV diuretic therapy alone. Another ongoing trial, RELAX-AHF (Efficacy and Safety of Relaxin for the Treatment of Acute HF) trial, will provide definitive information of the impact of relaxin on congestion, renal dysfunction, and outcomes in ADHF.[70] Relaxin acts via the nitric oxide pathways and endothelin B receptors to produce systemic and renal vasodilatation. In a preliminary phase II trial (pre RELAX), relaxin was associated with relief of dyspnea and a tendency to greater weight loss with smaller doses of diuretics and nitrates.[71]

In HF, vasopressin levels are markedly elevated and contribute to hyponatremia and congestion. Vasopressin causes vasoconstriction and water reabsorption through its action on V1a and V2 receptors, respectively.[72] Hence, vasopressin antogonists are tested in clinical trials for the treatment of ADHF. In the EVEREST trial, oral selective V2 receptor antagonist tolvaptan achieved short-term symptom benefit and weight reduction, without WRF, as compared with the standard HF regimen.[73] There was no effect on morbidity or mortality in the long term.

The FAIR-HF study[74] has recently shown that among 459 patients with stable chronic HF, those receiving intravenous ferric carboxymaltose were more likely to report an improvement in their quality of life after 24 weeks of follow-up than those receiving placebo. It is not known whether intravenous iron application may positively affect symptom burden in patients with iron deficiency presenting with renal failure and ADHF.

Recently, catheter-based renal sympathetic denervation has been described as a potential safe and effective treatment option for refractory hypertension.[75] As similar mechanisms are involved in the pathogenesis of cardiorenal syndrome, it is likely that renal sympathetic denervation may be a potential therapeutic option in the management of cardiorenal syndrome.

## CONCLUSION

The management of venous congestion in cardiac failure remains an important but unresolved clinical challenge, owing to the lack of consistent data from randomized studies in this field, rendering it difficult to outline concise evidence-based treatment guidelines. Its pathophysiology is still incompletely understood. Renal congestion and its role in WRF during the treatment of ADHF are underrecognized. There is no single effective approach to the management of cardiorenal syndrome. Physicians should individualize the management of ADHF on the basis of individual patient characteristics, with focus on preventing renal injury rather than following a specific protocol driven by diuretics. Clinical characteristics of HF patients such as age, low output versus high output HF, venous congestion, right atrial pressure, baseline renal function, and the level of diuretic resistance should all be considered while managing a patient with cardiorenal syndrome. When diuretic resistance is

encountered, dosing strategies with loop diuretics, as mentioned above, and the addition of thiazides or potassium-sparing diuretics should be utilized to enhance diuresis and relieve symptoms from congestion. Ultrafiltration and peritoneal dialysis may be considered in patients not responding to diuretic treatment. Diuretics are effective in rapid relief of congestion and improvement of the symptoms, but should not be considered as the only therapeutic modality in ADHF. It should be combined with strategies to reduce venous and renal congestion to minimize renal injury. Emerging treatments, BNP analogs, sympathetic denervation, and combination therapy with hypertonic saline with furosemide may show promise.

## DISCLOSURE

All the authors declared no competing interests.

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