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Review

Management of the Cardiorenal Syndrome in Decompensated Heart Failure

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Key Words
Cardiorenal syndrome · Congestion · Diuretics · Heart failure · Sodium · Ultrafiltration

Abstract
Background: The management of the cardiorenal syndrome (CRS) in decompensated heart failure (HF) is challenging, with high-quality evidence lacking. ***Summary:*** The pathophysiology of CRS in decompensated HF is complex, with glomerular filtration rate (GFR) and urine output representing different aspects of kidney function. GFR depends on structural factors (number of functional nephrons and integrity of the glomerular membrane) versus hemodynamic alterations (volume status, renal perfusion, arterial blood pressure, central venous pressure or intra-abdominal pressure) and neurohumoral activation. In contrast, urine output and volume homeostasis are mainly a function of the renal tubules. Treatment of CRS in decompensated HF patients should be individualized based on the underlying pathophysiological processes. ***Key Messages:*** Congestion, defined as elevated cardiac filling pressures, is not a surrogate for volume overload. Transient decreases in GFR might be accepted during decongestion, but hypotension must be avoided. Paracentesis and compression therapy are essential to remove fluid overload from third spaces. Increasing the effective circulatory volume improves renal function when cardiac output is depressed. As mechanical support is invasive and inotropes are related to increased mortality, afterload reduction through vasodilator therapy remains the preferred strategy in patients who are normo- or hypertensive. Specific therapies to augment renal perfusion (rolofylline, dopamine or nesiritide) have rendered disappointing results, but recently, serelaxin has been shown to improve renal function, even with a trend towards reduced all-cause mortality in selected patients. Diuretic resistance is associated with worse outcomes, independent of the underlying GFR. Combinational diuretic therapy, with ultrafiltration as a bail-out strategy, is indicated in case of diuretic resistance.

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Introduction

Ever since, according to the theory of the Darwinian evolution, species left the sea in the Devonian period about 400 million years ago, selection pressure has pushed terrestrial organisms towards salt- and water-preserving strategies. Therefore, it should not be surprising that precisely these strongly evolved mechanisms – when becoming maladaptive – have progressed to central elements in the pathophysiology of heart failure (HF). Indeed, signs and symptoms of congestion are the major drivers of frequent readmissions in HF [1, 2]. Obviously, the kidneys are pivotal organs in this respect, as they are responsible for sodium and water excretion. Importantly, it has been demonstrated that the renal capacity to elicit natriuresis is already diminished early on in HF, even before symptoms emerge [3, 4]. Later in the disease process, when patients present with decompensated HF, biomarkers of kidney dysfunction are among the strongest predictors of all-cause mortality [5]. Finally, end-stage HF is frequently complicated by the situation, whereby treatment to relieve congestive symptoms is limited by a further decline in renal function, i.e. by the cardiorenal syndrome (CRS). This review focuses upon the optimal management of such patients, who are often hard to treat. Available evidence from randomized clinical trials is summarized and discussed. Yet, as many aspects remain insufficiently elucidated, a pathophysiology-based approach is proposed most of the time.

CRS – What Is in a Name

Acknowledging the strong intertwining of heart and kidney function, Ronco et al. [6] have proposed a classification for CRS based on the organ affected by the primary insult and the subsequent time frame of development. According to this taxonomy, acute kidney injury (AKI) in the context of decompensated HF or its treatment is termed CRS type 1, and the present review focuses exclusively on this specific context (table 1). From the nephrologist's perspective, AKI is usually defined by the RIFLE criteria (Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Renal Disease) [7]. Importantly, the RIFLE criteria incorporate both changes in serum creatinine [or estimated glomerular filtration rate (GFR)] and urine output. While these two factors are, to a certain level, interrelated, the latter may better reflect

Table 1. CRS

Type	Definition
CRS type 1 (acute CRS)	Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or acute decompensated HF) leading to kidney injury
CRS type 2 (chronic CRS)	Chronic abnormalities in cardiac function (e.g. chronic HF) causing progressive chronic kidney disease
CRS type 3 (acute reno-cardiac syndrome)	Abrupt worsening of renal function (e.g. acute kidney failure or glomerulonephritis) causing acute cardiac disorder (e.g. HF, arrhythmia, pulmonary edema)
CRS type 4 (chronic reno-cardiac syndrome)	Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of cardiovascular events
CRS type 5 (secondary CRS)	Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

nephron function as a whole, also including tubular function [4]. In contrast, the cardiologic literature has tended to report on worsening renal function (WRF), defined as a 0.3 mg/dl rise in serum creatinine during treatment of decompensated HF. The reason for this is largely historical as this cutoff demonstrated optimal sensitivity and specificity to predict adverse clinical outcomes in an early study [8]. Although simplicity makes its use tempting, WRF has proven to be an unreliable prognostic marker, associated with worse, neutral or even better outcome depending on the clinical context [9–11]. In contrast, complete and effective decongestion in case of clear volume overload has been consistently associated with better outcomes in decompensated HF patients [10, 12, 13]. This further supports the use of more direct measurements of decongestion such as weight change, urine output and natriuresis in the evaluation of CRS [4, 14].

Pathophysiology of CRS in Decompensated HF

The kidneys basically perform 3 important functions, all of which might be disturbed in decompensated HF and warrant specific notion during treatment: (1) detoxification and excretion of hydrophilic waste products, which is primarily dependent on glomerular filtration, (2) volume homeostasis, which is essentially a function of the renal tubules, and (3) a neuroendocrine function.

Glomerular Filtration

Glomerular filtration is a key aspect in the detoxification function of the kidneys. The kidneys' unique ability to eliminate hydrophilic waste products is so important that GFR is often used synonymously for renal function. It has been well established, both in stable and in decompensated HF patients, that GFR is an important predictor of survival, even more so than measurements of intrinsic cardiac function such as ejection fraction [5, 15]. More specific, the accumulation of uremic toxins, especially protein-bound solutes with a clearance that is sensitive already to small changes in GFR, has been linked to both cardiac dysfunction and worse survival [16, 17]. However, whether transient changes in GFR during treatment of decompensated HF patients also provide prognostic information is less clear and probably depends more on the mechanism of GFR decrease. The total GFR is determined by the number of functional nephrons, the area and permeability characteristics of the glomerular filtration barrier, and the Starling forces in the glomerular capillaries and in Bowman's space (fig. 1) [18]. Those glomerular Starling forces vary substantially during the treatment of decompensated HF patients because of the changes in volume status, renal perfusion, blood pressure, central venous pressure, intra-abdominal pressure and neurohumoral activation (fig. 1) [19–22]. As all these causes are potentially reversible when managed appropriately, their impact on GFR – especially when short-lived – is probably less important. In contrast, structural damage to the kidneys resulting in a loss of glomeruli and/or dysfunctional filtration barrier gives rise to a more permanent decrease in GFR that is prognostically more relevant [23].

Tubular Function

Volume homeostasis is another important function of the kidneys and, in contrast to detoxification, depends more on an effective tubular function than GFR [4]. Indeed, even when GFR is severely impaired at 15 ml/min, 21.6 liters plasma is still filtrated each day. This is well above the average daily urine production and illustrates the pivotal contribution of tubular reabsorption to volume homeostasis. Similarly to GFR, tubular injury is associated with worse clinical outcome in both stable and decompensated HF patients [24, 25]. Nevertheless, tubular injury biomarkers generally show only moderate elevations in decompen-

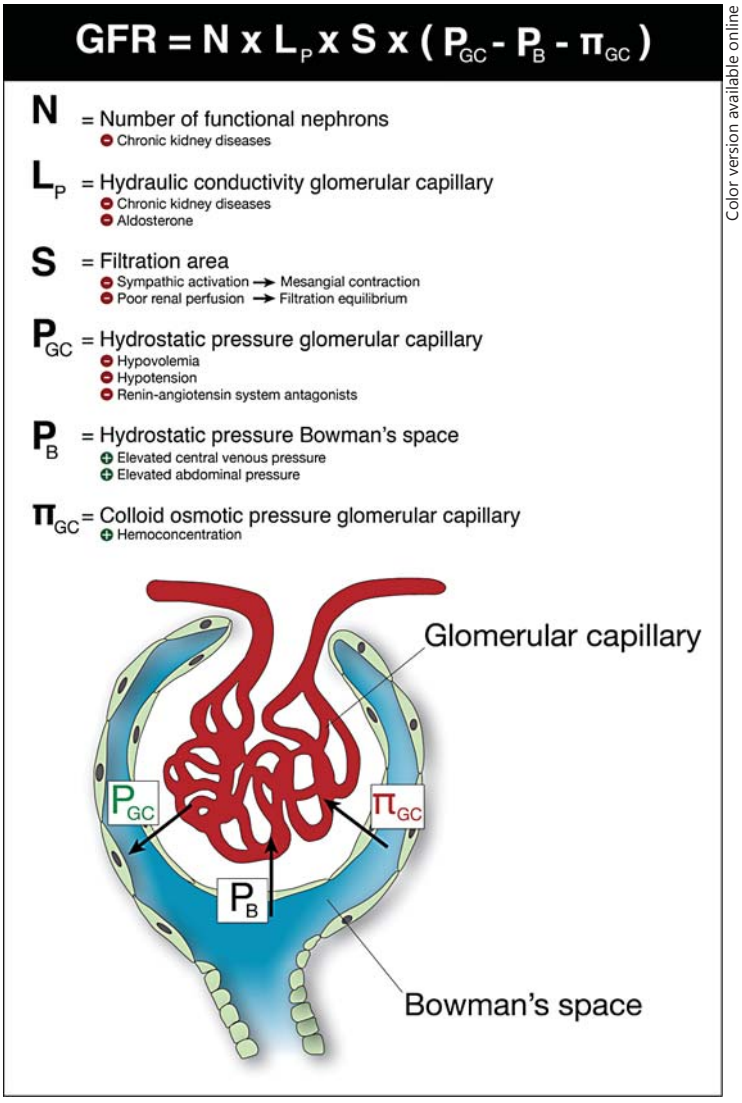

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Fig. 1. Determinants of the glomerular filtration rate (GFR).

sated HF, at much lower levels when compared to AKI caused by direct tubular insults such as contrast nephropathy [26, 27]. One plausible interpretation might be that structural tubular damage is rather uncommon in decompensated HF – although it is an ominous sign –, with impaired volume homeostasis being more likely due to functional alterations such as altered hemodynamics, poor renal perfusion, increased proximal sodium reabsorption, unrestrained neurohumoral stimulation and aldosterone breakthrough [4, 27, 28].

Renal Neuroendocrine Function

Finally, the kidneys are crucially involved in many neuroendocrine pathways. Most relevant to HF, renin is released by the afferent arteriole, stimulated by low tubular chloride delivery to macula densa cells at the end of Henle's loop [29]. The inhibition of the renin-angiotensin system is a cornerstone in the treatment of HF patients with reduced ejection fraction, as both angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers significantly reduce mortality as well as morbidity [30, 31]. Diuretics, on the other side, have been demonstrated to promote neurohumoral activation, presumably by inducing

Table 2. Randomized clinical trials in patients with CRS

Study	First author [Ref.]	Patients, n	Intervention	Outcome
PROTECT	Massie [56]	2,033	Placebo versus rolofylline 30 mg	More seizures with rolofylline
CARRESS-HF	Bart [67]	188	Stepped pharmacological therapy (combinational diuretic therapy) versus ultrafiltration	Neutral effect on weight loss, better improvement in GFR with diuretics
ROSE AHF	Chen [57]	360	Placebo versus dopamine (2 μg/kg/min) Placebo versus nesiritide (0.005 μg/kg/min)	Neutral effects on decongestion and GFR

intravascular volume depletion [32]. In addition, loop diuretics also directly cause renin release by their chloride-depleting effect on macula densa cells [4]. Whilst, by no means, this should stimulate clinicians to withhold appropriate therapy in HF patients with clear signs of volume overload, it calls into question the frequent use, especially at high doses, of loop diuretics as maintenance therapy to achieve persistent decongestion [33].

Management of CRS in Decompensated HF

Few randomized clinical trials have actually focused on patients with CRS type 1 (table 2). Therefore, the challenging management of this condition remains largely empirical, deduced from general evidence on the treatment of HF, chronic and acute kidney disease. Our practical approach, which is mostly based on the aforementioned physiologic reasoning and is therefore intended to be more a helpful tool for the practicing clinician than an exhaustive guideline, is delineated as flowchart in figure 2.

Accurate Assessment of Volume Status

Both arteriolar underfilling and systemic venous congestion are important factors that may contribute to an impaired GFR in decompensated HF patients [20, 34, 35]. The former results in a drop of the glomerular filtration pressure, while the latter causes an increased pressure in Bowman's capsula and the tubular system, opposing filtration (fig. 1). Consequently, it is of pivotal importance to accurately assess volume status in patients with CRS. Most patients who are admitted with decompensated HF present with signs and symptoms of congestion, especially elevated cardiac filling pressures [1]. Yet, nearly half of them gain less than 1 kg of weight during the week before hospitalization, arguing against volume overload as the sole mechanism of elevated cardiac filling pressures [36]. Moreover, it is remarkable that only 2.5% of variability in central venous pressure is actually determined by blood volume per se [37]. This obvious disconnect between cardiac filling pressures and circulatory volume is likely explained by the role of venous capacitance vessels, most notably in the abdomen [28]. Normally, these splanchnic veins dynamically pool and release blood in response to a changing volume status, aiming to maintain an optimal preload and cardiac output [38]. In HF, unrestrained sympathetic activation with concomitant vasoconstriction may result in impaired capacitance function and volume shifts from the splanchnic towards the systemic circulation, possibly leading to or exacerbating decompensation [39]. Such

patients may be particularly prone to intravascular underfilling when treated with powerful loop diuretics that are the mainstay therapy in decompensated HF, as a volume shift rather than overload is causing congestion [28, 33]. Relying on unambiguous signs of volume overload such as edema and weight increase might help to differentiate between both conditions.

Aggressive Treatment of Volume Overload

As residual congestion after treatment of decompensated HF patients is a major predictor of adverse outcomes, it is recommended to try and achieve strict normovolemia, not tolerating any volume overload, even if a decrease in GFR is observed [10, 13]. However, it often remains challenging in clinical practice to appreciate subtle signs of volume overload. Clinical signs, although invaluable in case of marked volume overload, lack sensitivity in such incidents, while biomarkers like the natriuretic peptides relate better to cardiac filling pressures than volume status per se [40, 41]. Consequently, there is an urgent need for easy tools to better assess volume status at the bedside. Routine evaluation of invasive hemodynamics has not been recommended in decompensated HF, since the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) did not show a reduction in either mortality or rehospitalizations with such strategy [42]. Nevertheless, pulmonary artery catheterization proved to be a safe procedure and might still be warranted in CRS patients who are difficult to treat, aiming to identify and treat subclinical congestion while at the same time avoiding intravascular underfilling.

Avoidance of Arterial Hypotension and Intravascular Underfilling

Autoregulatory mechanisms maintain glomerular perfusion pressure relatively constant in the face of a dynamic arterial blood pressure [18]. Yet, a frequent use of powerful diuretics, vasodilators and/or ultrafiltration during decongestive treatment may temporarily overwhelm their capacity and induce a state of intravascular underfilling with arterial hypotension. It has been clearly demonstrated that such hypotensive episodes are correlated with incident WRF in decompensated HF patients [21, 22]. This should not be surprising as the glomerular capillary pressure is a direct determinant of GFR (fig. 1). Albeit in a totally different context, the Assessment of Two Levels of Arterial Pressure on Survival in Patients With Septic Shock (SEPSISPAM) trial provided further arguments to carefully monitor arterial blood pressure and avoid hypotensive episodes also in decompensated HF. This multicenter open-labeled trial randomized 776 patients with septic shock to a conventional (65–70 mm Hg) versus a high (80–85 mm Hg) mean arterial pressure target. In patients with a history of arterial hypertension, the need for renal replacement therapy was significantly lower in the higher blood pressure group [43]. As it is well known that patients with chronic arterial hypertension experience a shift in their autoregulation range – requiring a higher blood pressure to maintain glomerular filtration – this argues for a critical blood pressure needed to maintain GFR [44]. Currently, no prospective randomized studies have determined optimal blood pressure targets in decompensated HF or CRS patients. However, it is prudent to avoid a mean arterial blood pressure <65 mm Hg – especially for prolonged episodes – because this is the critical level below which normal renal autoregulation starts to fail and renal perfusion drops [18, 22].

Removal of Fluid Accumulation in Third Spaces

Accumulation of fluid in third spaces, most notably the abdominal compartment, is not unusual in decompensated HF. It has been demonstrated that this might be accompanied by intra-abdominal pressure elevations, in which case GFR is also impaired [19, 28]. Alleviation of ascites through paracentesis in decompensated HF is therefore associated with a decrease

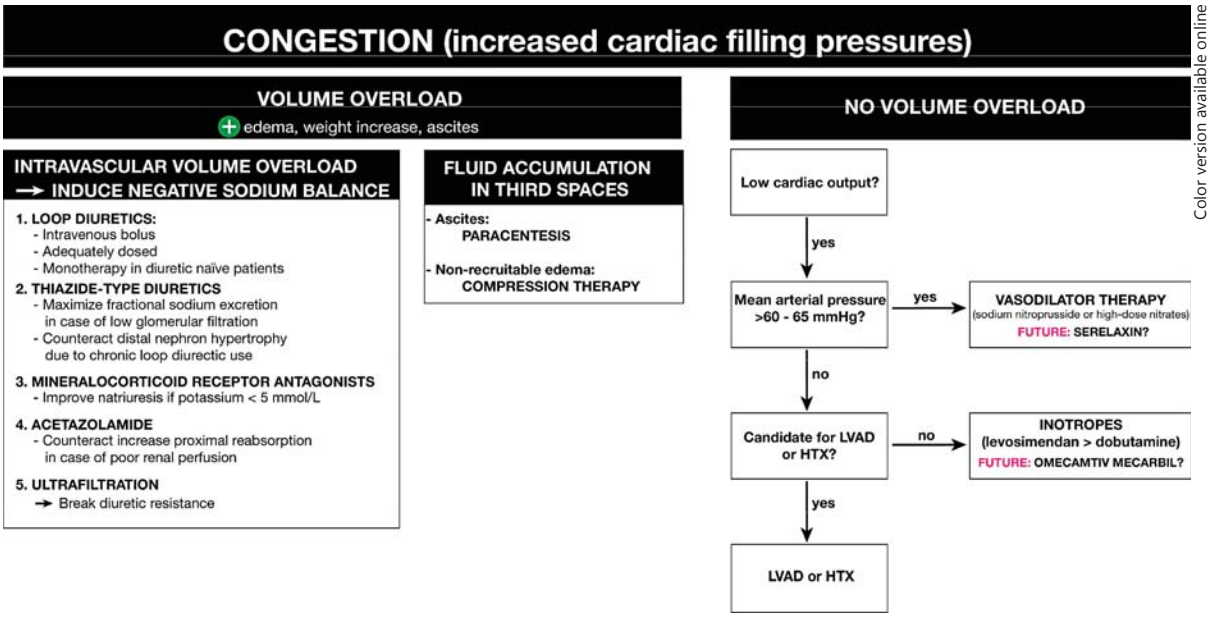

Fig. 2. Flowchart of the treatment of patients with CRS. HTX = Heart transplantation; LVAD = left ventricular assist device.

in intra-abdominal pressure and improvement in GFR [45]. Most likely, intra-abdominal hypertension contributes to extrinsic compression of the kidneys, resulting in increased interstitial pressure in Bowman's capsula, directly opposing the filtration forces (fig. 2). Alternatively, fluid accumulation may develop as lower extremity edema that is not recruitable to the systemic circulation and therefore cannot be alleviated through diuretic therapy. Due to alterations in the microcirculation and emerging protein-rich edema, this might facilitate further leakage out of the vascular system, especially when plasma protein levels are low [28]. Compression therapy might be helpful in such cases to promote lymphatic drainage and return interstitial fluid to the systemic circulation.

Increasing the Effective Circulatory Volume

From a pathophysiological perspective, increasing the cardiac output to restore organ perfusion is sensible in decompensated HF. Since the cardiac output in decompensated HF is rather insensitive to changes in cardiac preload as the Frank-Starling mechanism is depleted, an improvement can usually only be obtained through direct stimulation of contractility with inotropes, reducing afterload with vasodilators or mechanical support through a left ventricular assist device (LVAD). Indeed, in most patients with advanced low-output HF and CRS, renal dysfunction is reversible after LVAD implantation, indicating that impaired renal perfusion is the underlying problem [46, 47]. However, as LVAD therapy remains to be associated with long-term complications such as driveline infection, bleeding and thrombosis, it still cannot be considered a treatment solely for CRS. Furthermore, because long-term administration of inotropes is associated with worse survival in HF patients, afterload reduction probably remains the best option to increase the effective circulatory volume, yet its use is limited by a low arterial blood pressure [48, 49]. Observational data have demonstrated that titrated nitroprusside with conversion to combinational treatment with oral hydralazine and nitrates is feasible and potentially associated with better outcomes in advanced decompen-

sated HF patients with low cardiac output who are normo- or hypertensive [50, 51]. Afterload reduction in decompensated HF is further supported by a retrospective analysis of 4,953 patients, which used propensity-matching to demonstrate improved survival with vasodilator therapy versus increased mortality with inotrope therapy [52]. However, it is worth mentioning that the notion of increased mortality with inotropes mainly comes from data with β-agonists (i.e., dopamine and dobutamine) and phosphodiesterase-3 inhibitors (i.e., milrinone), with a potentially better safety profile of the calcium-sensitizer levosimendan, making the latter the preferred inotrope to use in decompensated HF patients with low cardiac output and arterial hypotension [48, 49, 53]. Nevertheless, the randomized double-blind Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study (n = 1,327) found no survival benefit of levosimendan over dobutamine, although plasma natriuretic peptide levels decreased significantly more with levosimendan [54]. Finally, the results of a phase II trial with the cardiac myosin activator omecamtiv mecarbil have been published only recently, showing improved systolic function and remodeling with this first-in-class agent [55]. While it is far too early to get the jury out on this agent, it might be a promising future therapeutic option to ameliorate cardiac output in patients with CRS.

Optimization of Renal Perfusion

As restoring cardiac output and organ perfusion in decompensated HF seems to be associated with improvements in GFR, strategies aiming to improve renal perfusion have been tested specifically in patients with CRS. Although results in general have been disappointing, it often remains unclear whether these treatments effectively succeeded to improve renal blood flow, because such evaluation is not readily available at the bedside. In the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT), which included 2,033 patients with decompensated HF and an estimated GFR between 20 and 80 ml/min/1.73 m^2, administration of the adenosine receptor antagonist rolofylline – with the aim of obtaining vasodilation of the afferent arteriole – failed to improve either clinical outcome or serum creatinine levels [56]. Furthermore, the Renal Optimization Strategies Evaluation (ROSE) study, including 360 patients with decompensated HF and an estimated GFR between 15 and 60 ml/min/1.73 m^2, did not show any benefit with low-dose dopamine (2 μg/kg/min) or nesiritide (0.005 μg/kg/min) [57]. As more patients experienced tachycardia and hypotension with dopamine and nesiritide, their use cannot be recommended in patients with CRS based on current evidence. Although not specifically a study that targeted patients with CRS, the Relaxin in Acute Heart Failure (RELAX-AHF) trial with serelaxin (recombinant human relaxin-2) deserves some attention. Relaxin-2, a naturally occurring peptide that regulates maternal adaptions during pregnancy, is a potent renal vasodilator [58]. In the RELAX-AHF trial, administration of serelaxin to patients presenting with decompensated HF unexpectedly lowered all-cause mortality after 180 days, a prespecified secondary end point [59]. While this finding warrants further investigation in an adequately powered randomized clinical trial, serelaxin interestingly improved congestion and lowered the need for intravenous loop diuretics. Moreover, the investigators found a highly significant improvement in GFR with serelaxin compared to placebo, which most likely contributed to the overall clinical outcome [60]. This finding makes serelaxin a promising agent for the future treatment of patients with CRS, yet more evidence is needed before any firm recommendations can be made.

Table 3. Non-loop diuretic agents

Agent	Mechanism and site of action	Mechanism to improve diuretic efficiency
Acetazolamide	Carbonic anhydrase inhibitor Proximal tubules	Targets increased proximal sodium reabsorption More sodium offered to Henle's loop
Thiazide-type diuretics	Sodium/chloride cotransporter Distal tubules	Targets distal nephron hypertrophy associated with chronic use of loop diuretics Increases fractional sodium excretion
MRA	Competitive aldosterone antagonist Distal tubules and collecting duct	Targets distal nephron hypertrophy associated with chronic use of loop diuretics Counteracts aldosterone breakthrough Increases fractional sodium excretion
Amiloride/ triamterene	ENaC blocker Distal tubules and collecting duct	Targets distal nephron hypertrophy associated with chronic use of loop diuretics Increases fractional sodium excretion

ENaC = Epithelial sodium channel; MRA = mineralocorticoid receptor antagonist.

Diuretics and Diuretic Resistance

Diuretics in general and loop diuretics in particular remain the most frequently applied therapies in patients with decompensated HF as they are pivotal to treat volume overload [61]. Nevertheless, the Diuretic Optimization Strategies Evaluation (DOSE) trial represents the only large-scaled randomized clinical trial that provides high-quality evidence regarding their use [62]. The DOSE trial, which included 308 patients with decompensated HF, demonstrated similar outcomes with intravenous loop diuretics administered as bolus versus continuous therapy [62]. Furthermore, high-dose (2.5 times maintenance dose) compared to low-dose (equal to maintenance dose) loop diuretics resulted in a somewhat faster relief of congestion at the cost of a decrease in GFR [62]. However, patients with CRS regularly present with so-called diuretic resistance and congestion signs refractory to adequately dosed intravenous loop diuretics. Interestingly, loop diuretic efficiency, defined as urine output per diuretic dose, has recently been identified as an important prognostic indicator in decompensated HF, independent of the underlying kidney function [63, 64]. The most obvious explanation for this finding is that characteristics of more advanced cardiac and renal disease are contributing to decreased diuretic efficiency. However, one might speculate that the loop diuretic efficiency can be modulated by different therapeutic interventions and wonder if such strategies would be associated with better outcomes. At least some observational data suggest that the diuretic resistance can frequently be overcome by a combinational treatment with synergistically working diuretic agents in addition to loop diuretics (table 3). Thiazide-type diuretics inhibit sodium reabsorption in the distal nephron and primarily benefit patients who have distal nephron hypertrophy and hyperfunction due to chronic treatment with loop diuretics [65]. In addition, they markedly increase the fractional sodium excretion, which is needed to achieve a neutral or negative sodium balance if GFR is depressed [66]. Another important cause of diuretic resistance in decompensated HF is poor renal perfusion with an increased filtration fraction and, due to glomerulotubular balance, increased proximal sodium reabsorption [4]. As the problem in this case is insufficient tubular flow through Henle's loop and the distal nephron, thiazide-type diuretics are of little value to increase diuresis. In

contrast, increasing the effective circulatory volume through arteriolar vasodilators or inotropes should be considered, while proximal sodium reabsorption might also be directly inhibited by acetazolamide [4, 33, 66]. Indeed, it has been reassuring that in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF), stepwise pharmacological care including thiazide-type diuretics, vasodilator therapy and inotropes was as effective as ultrafiltration in relieving congestion, although the study specifically included patients with CRS [67].

Ultrafiltration

As loop diuretic therapy results in the production of hypotonic urine, while ultrafiltration removes isotonic plasma and hence more sodium for the same amount of water, it has been hypothesized that the latter might be a superior decongestion strategy [68]. Indeed, in the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) study, which included 200 patients with decompensated HF and clear signs of volume overload, ultrafiltration outperformed loop diuretics, producing greater weight and fluid loss [12]. Moreover, the 90-day readmission rate was also significantly lower in the ultrafiltration compared to the loop diuretic group, presumably due to more effective decongestion [12]. These findings are somewhat contrary to the results of the much larger CARRESS-HF study (n = 2,033), which found no better decongestion – and hence no better clinical outcome – with ultrafiltration compared to pharmacological care with strong emphasis on combinational treatment [67]. Moreover, catheter-related adverse events and bleeding complications were more frequent in the ultrafiltration group [67]. In addition, GFR improved significantly more with pharmacological care after 60 days [67]. In the light of these results, we would recommend optimizing the pharmacological therapy first, with ultrafiltration reserved as a bail-out therapy in cases of refractory congestion. Nevertheless, it should be noted that such patients generally have a very poor prognosis [69]. One important point of critic to the CARRESS-HF study might be, however, that the pharmacological care arm allowed decongestive treatment to be titrated very carefully on an individual basis according to the net fluid balance, which is an excellent marker of decongestion. In contrast, the ultrafiltration rate was preset at a constant rate of 200 ml/h, which was only changed for technical reasons or clinical requirements as assessed by the treating physician. This potentially has put patients in the ultrafiltration arm at a greater risk for intravascular volume depletion and hypotensive episodes, which might have been associated with more harmful neurohumoral activation. Therefore, future studies on ultrafiltration in decompensated HF and CRS patients should carefully monitor arterial blood pressure and avoid hypotensive episodes. With such individually titrated ultrafiltration therapy, maybe there are still some benefits to be shown. However, more well-conducted studies are needed to answer this important question.

Conclusion

The treatment of CRS in the context of decompensated HF is often challenging, and high-quality evidence is lacking. Therefore, a targeted approach is warranted, focusing on the underlying pathophysiological processes of kidney dysfunction, which is likely to be different in individual patients. A multidisciplinary approach with strong collaborations between cardiologists and nephrologists is important to ensure optimal treatment and care for this population of patients.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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