Diuretic therapy in acute decompensated heart failure

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Episodes of congestion characterize the disease course of patients with heart failure, resulting in a high morbidity with the need for urgent hospitalization. The main treatment goal is to alleviate signs and symptoms of congestion to reach euvolemia. Loop diuretics remain the cornerstone in the treatment, however diuretic response is unpredictable and therapy should be individualized. The neurohormonal activation result in an increased sodium reabsorption along the whole nephron. Each segment provides a different target site to increase diuretic and natriuretic response. This manuscript provides further insight in the pathophysiology behind the cardiorenal interactions, which lead to the increased sodium avidity in heart failure. In addition, the different therapeutic options to enhance diuretic response in patients with acute heart failure is discussed, as well as the assessment of the diuretic response based on the urinary sodium concentration.

Keywords: heart failure, diuretics, loop diuretics, natriuresis, treatment

Introduction

The disease course of patients with heart failure (HF) is characterized by recurrent episodes of acute HF, which are clearly linked with an increased morbidity and mortality. Signs and symptoms of congestion are the main drivers prompting patients to seek urgent medical attention (1). This manuscript will be primarily focused on the treatment of patients with acute decompensated heart failure (ADHF) with volume overload, as only the minority acute patients have signs and symptoms of low cardiac output. Neurohumoral upregulation with its renal interactions leads to an increased sodium avidity in the kidneys. Therefore, as loop diuretics promote increased sodium excretion, they remain the cornerstone of the treatment for patients with ADHF to alleviate signs and symptoms of congestion (Class I recommendation) (1). However, diuretic resistance may occur in patients with more advanced HF, necessitating an intensification of their diuretic therapy in order to achieve adequate decongestion (2). This manuscript will discuss the neurohumoral impact and renal alterations in the setting of ADHF, along with various therapeutic options and monitoring tools.

Abbreviations:
ADHF: acute decompensated heart failure; ESC: European Society of Cardiology; FF: filtration fraction; GDMT: guideline-directed medical therapy; GFR: glomerular filtration rate; HF: heart failure; ID: iron deficiency; LoE: level of evidence; MRA: mineralocorticoid receptor antagonist; Na⁺/K⁺/2Cl⁻: sodium/potassium/2chloride pump; NCC: sodium-chloride cotransporter; RAAS: renin-angiotensin-aldosterone system; RBF: renal blood flow; SGLT2i: sodium-glucose cotransporter 2-inhibitors

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**Pathophysiology of congestion in heart failure**

Sodium is freely filtered across the glomerular membrane. In patients with normal kidney function, approximately 25.500 mmol of sodium reaches the tubules each day (sodium 142 mmol/L multiplied by a glomerular filtration rate [GFR] of 180 L/day). Consequently, the renal tubules reabsorb more than 99% of the filtered sodium and only a fraction is eventually excreted in the urine (3). Although minuscule, this fraction is heavily regulated by the kidneys to match dietary intake over time, thereby maintaining a neutral sodium balance (4). In patients with HF, hemodynamic alterations and neurohumoral upregulation result in an even more increased sodium avidity and consequently positive sodium and water balance (5).

In patient with HF, renal blood flow (RBF) can be diminished due to increased filling pressures, elevated abdominal pressure and decreased cardiac output. The body aims to maintain a stable GFR by adjusting the resistance of the afferent arterioles (called autoregulation). This is the result of both a direct myogenic response and indirect by the tubuloglomerular feedback. In the light of a decreased RBF, the filtration fraction (FF) is subsequently increased (6–8). The majority of the filtered sodium is reabsorbed in the proximal tubules (65%). This process is even more facilitated in patients with HF. The increased FF in HF raises peritubular capillary oncotic pressure, promoting sodium reabsorption (called glomerulotubular balance). In addition, the increased renal lymph flow in the setting of HF washes out interstitial proteins and reduces the colloid osmotic pressures in the renal interstitium even more. As a result, the amount of sodium reaching the distal tubules will be severely reduced in the setting of HF (3, 5, 9).

The loop of Henle plays a key role in the diluting and concentrating ability of the kidney. Overall, the loop of Henle reabsorbs more sodium than water, therefore the fluid reaching the distal tubules will be iso-osmotic and the final urine will be determined by the amount of water reabsorbed in the distal tubules. In HF, less tubular fluid will reach the loop of Henle as a result of the increased FF. Neurohumoral activation promotes even more sodium reabsorption in the ascending part of the loop of Henle. In addition, vasconstriction and consequently low flow in the vasa recta prevents wash out of the renal medulla, which impairs the capacity of the distal tubules to excrete free water and dilute urine (3, 4).

The macula densa is located at the end of the ascending part of the loop of Henle, in close communication with the afferent arteriole. After luminal transport by the Na⁺/K⁺/2Cl⁻ transporters, the intracellular chloride concentration triggers a hormonal response (called tubuloglomerular feedback). Due to an increased sodium reabsorption in the proximal tubule and loop of Henle, less chloride reaches the macula densa in patients with HF. This activates cyclo-oxygenase-2 and nitric oxide synthetase I, leading to secretion of prostaglandin E and nitric oxide. This induces a decrease in the afferent arteriolar resistance. In addition, the juxtaglomerular cells are stimulated to secrete renin with consequently activation of the renin-angiotensin-aldosterone system (RAAS), resulting in vasoconstriction of the efferent arterioles. Hence, intraglomerular hydrostatic pressure further increases, leading to an initially rise in GFR and FF. The increase in FF will again lead to an increased sodium reabsorption in the proximal tubule with a further reduction in chloride delivery to the macula densa, hence contributing to disease progression (4).

Only a minority (<10%) of the amount of sodium filtered is reabsorbed in the distal tubules. The distal tubules and collecting ducts are responsible for the fine-tuning of the urinary composition, for which they heavily depend on sodium delivery. In HF, tubular flow in the distal tubules is rather low due to the increased proximal reabsorption. In addition, high aldosterone levels due to the former mentioned RAAS activation results in increased sodium reabsorption. The high osmotic interstitial oncotic pressures as a result of the increased reabsorption in the loop of Henle, in combination with the low flow in the vasa recta promotes water retention in the distal tubules (3, 4).

**Diuretic therapy: mode of action**

**Loop diuretics**

Loop diuretics remain the backbone of the diuretic therapy in patients with ADHF (10). They are bound to plasma proteins (>90%) and are actively secreted in the proximal tubules by several organic anion transporters (11). Therefore, adequate dosing is of utmost importance as kidney dysfunction with renal hypoperfusion and hypoproteinemia are common in patients with HF. Their mode of action is at the luminal membrane of the ascending loop of Henle, where they block the Na⁺/K⁺/2Cl⁻ symporter, by which they have potent diuretic effects (Figure 1). It is important to recognize that they also block the Na⁺/K⁺/2Cl⁻ symporter at the macula densa by which they reduce the chloride load intracellular leading to the release of renin. In addition, chronic use of loop diuretics may induce distal tubular hypertrophy with an accompanied increased sodium reabsorption, resulting in diuretic resistance (10). In patients with ADHF, it is advised to administer loop diuretics intravenously instead of orally as bowel edema and malabsorption might reduce its bioavailability (Class I, LoE B) (1). A minimal drug dose is necessary as loop diuretics have a threshold concentration, after which they induce natriuresis. After this threshold, log-linear increases in dose result in reaching maximal natriuretic response. Further increases in dose, will not result in a higher peak natriuretic effect, however it will enhance overall.
natriuresis as there is a longer period above the natriuretic threshold (10). The European Society of Cardiology (ESC) guidelines advise a starting dose of at least 20-40 mg of furosemide intravenously in diuretic naive patients with a higher dose reserved for the patients with chronic kidney disease (1). If patients are already treated with a home maintenance loop diuretic, they advise to give at least the preexisting oral dose intravenously. The Diuretic Optimization Strategies Evaluation (DOSE-AHF) study compared low-dose with high-dose and bolus with intravenous administration of loop diuretic therapy. The high-dose was associated with greater increase in diuresis, weight change and dyspnea relieve. However, there was no significant difference with regard to symptom relieve between bolus or continuous infusion (12). Intravenous loop diuretic should be given as soon as possible (minimizing door-to-diuretic time) as early administration is associated with better natriuresis, diuresis and lower in-hospital mortality. In general, loop diuretics have a half-live of maximal 6 hours, therefore they should be given multiple times a day (2-3 times) with at least a 6-hour time interval to maximize time above the threshold and to avoid rebound sodium retention in between gifts. Torsemide has a longer half-life than bumetanide and furosemide (13). The Torsemide Comparison with Furosemide for Management of Heart Failure (TRANSFORM-HF) study evaluated torsemide with furosemide in patients discharged after an ADHF event, however it was not able to demonstrate a significant difference in all-cause mortality over 12 months between both agents (14). Importantly, diuretic and natriuretic response varies intra- and interindividual. Therefore, it is crucial to monitor the effectiveness of the initiated treatment (15). The urinary sodium concentration has been postulated as a novel interesting marker for the effect of diuretic therapy as this is a direct reflection of their mode of action (see ‘Diuretic response evaluation’) (5). Bolus administration of loop diuretics are generally preferred over continuous infusion because urinary sodium concentration becomes uninterpretable after continuous infusion. However, if continuous infusion is chosen, this should be preceded by a bolus infusion in order to reach the threshold.

**Acetazolamide**
Acetazolamide is a carbonic anhydrase inhibitor, which blocks sodium bicarbonate reabsorption in the proximal tubules (Figure 1) (10, 16, 17). Blocking proximal sodium reabsorption has various additional benefits in patients with HF: 1) the increased FF results in an even higher amount of sodium reabsorption in the proximal sodium reabsorption, 2) blocking proximal sodium reabsorption enhances the amount of sodium and chloride delivered to the macula densa, resulting in less renin release, 3) endogenous natriuretic peptides acting in the distal tubules might regain their natriuretic properties as more sodium is delivered distally. Therefore, acetazolamide

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**Figure 1. Target site and mode of action of different diuretic agents along the nephron**

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might have a role in preventing loop diuretic resistance. The Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) trial demonstrated that the upfront use of acetazolamide in addition to treatment with intravenous loop diuretics in patients with ADHF resulted in a greater incidence of successful decongestion within 3 days. This was also reflected by a higher cumulative urine output and natriuresis without an increased incidence in adverse events (18).

**SGLT2i**

Sodium-Glucose Cotransporter 2-inhibitors (SGLT2i) also act in the proximal tubule at which it blocks the sodium and glucose reabsorption (Figure 1). It induces an increased glucosuria, associated with an increased osmotic diuresis and small subsequently transient increase in natriuresis (19). The RECEDE-CHF trial demonstrated that the association of an SGLT2i to loop diuretic therapy led to a significant increase 24-hour diuresis, without an increase in urinary sodium excretion at both 3 days and 6 weeks treatment (20). Therefore, SGLT2 inhibitors probably have little role in achieving a net negative sodium balance and reaching euvolemia but do have important disease modifying, pleiotropic effects. They have demonstrated to be renoprotective, to reduce cardiovascular morbidity and mortality and have now an indication in all patients with HF (irrespective of ejection fraction). Therefore, a HF hospitalization should be addressed as an opportunity to improve guideline-directed medical therapy in order to improve long-term outcome and quality of life. SGLT2i have been proven to be safe when combined with conventional diuretic therapy in patients with HF and congestion. In addition, they remain effective in the reduction of cardiovascular morbidity and mortality and should therefore be introduced (early) whenever possible (21–25).

**Thiazides**

Thiazides work more distally and block the sodium-chloride cotransporter (NCC) in the early part of the distal convoluted tubule (Figure 1). In addition to their natriuretic properties, they have a kaliuretic effect with the excretion of 2 to 3 ions of potassium per lost sodium ion (26, 27). Like loop diuretics, thiazides are protein-bound and require active secretion in the tubules. Therefore, dosing should be adequate in patients with renal impairment and hypoproteinaemia (10, 27). In contrast to other diuretics, they have a slow gastro-intestinal absorption and longer half-life. Therefore, when a thiazide-like diuretic (hydrochlorothiazide or metolazone) is added to loop diuretic therapy, it should ideally be given hours prior to the intravenous loop diuretic administration in order to work synergistically. Chlorothiazide has a shorter half-life and requires therefore a shorter time-interval. The Safety and Efficacy of Combination of Loop with Thiazide-type Diuretics in patients with Decompensated Heart Failure (CLOROTIC) trial evaluated whether the addition of hydrochlorothiazide to intravenous furosemide was safe and effective in patients with ADHF. They demonstrated that the addition of hydrochlorothiazide to loop diuretics improved diuresis and weight loss. The effects were more pronounced in patients treated with chronic loop diuretic use (28). This as expected as chronic loop diuretic use may result in distal tubular hypertrophy, leading to loop diuretic resistance (10). As demonstrated by the CLOROTIC trial, these patients may especially benefit from the addition of a thiazide to overcome the increased distal sodium avidity. This has been confirmed by the Diuresis Efficacy in Ambulatory Congestive Heart Failure Patients (DEA-HF) trial, which demonstrated that patients with long-term high-dose loop diuretic therapy might benefit from the addition of thiazides in order to overcome the distal tubular hypertrophy (29).

**Mineralocorticoid receptors antagonists**

In addition to their direct neurohumoral inhibition, mineralocorticoid receptor antagonists (MRA) also induce natriuresis by modulating the activity and expression of the sodium and potassium channels in the late part of the distal nephron (Figure 1). MRA take part in the quadruple guideline-directed medical therapy for patients with HF with reduced and mildly reduced ejection fraction (10). Therefore, like SGLT2i, every encounter with HF patients should be used to optimize therapy. However, the Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial demonstrated that high dose (100 mg) spironolactone was not superior to low dose (25 mg) with regard to NT-proBNP reduction and 96-h diuresis in patients with ADHF (30). The result might be the consequence of the slow onset of spironolactone as a prodrug, which takes 48-72 hours to work after oral intake (10). So, although limited diuretic effects, the initiation of the high dose MRA during an ADHF episode was safe and did not result in a higher incidence of renal impairment. Therefore, the introduction of MRA (regular dose) should not be postponed, irrespective of the diuretic effect. On top, early introduction of MRA during an ADHF event might be helpful in reducing the incidence of hypokalaemia due to potassium-wasting loop diuretics and thiazides (28, 31). Of course, treatment should always be individualized with temporary cessation in case of hyperkalaemia.

**Ultrafiltration**

In contrary to classic hemodialysis, ultrafiltration removes water, sodium and non-protein bound small and medium sizes molecules. Evidence supporting the use of ultrafiltration is limited (10). The UltrafiltrationN versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial demonstrated that ultrafiltration can safely remove wa-
The ongoing DECONGEST (NCT05411991) also evaluates the applicability of the protocol till decongestion is achieved. On top, it evaluates whether a more aggressive protocol with upfront combinational therapy and early initiation of the so-called full nephron blockade is superior to usual care. Despite the clear evidence supporting a natriuresis-guided diuretic protocol, implementation is still cumbersome in current daily practice, as this strategy is quite intense with the requirement of frequent timely collections of urine samples, synchronized with diuretic prescriptions by the cardiologist, and laboratory assessments. The REadily available UrinAry Sodium analYsis in Patients with Acute Decompensate Heart Failure (EASY-HF) study tested a nurse-led natriuresis-guided protocol with urinary sodium concentration measurements via a point-of-care bedside sensor and compared this with the standard of care. The study demonstrated that a nurse-led protocol is feasible and safe. In addition, it led to a higher natriuresis and diuresis and both the protocol and the sensor were considered to be easy usable and applicable in daily practice by the cardiac nursing team (38).

Overall, a natriuresis-guided protocol (either nurse-led or physician-guided) allows individualized diuretic titration with early evaluation of the treatment. This should be key in all patients being treated with ADHF as it should be our primary goal during hospitalization to relieve patients of their signs and symptoms of congestion as this was the reason for their hospitalization.

**Diuretic response evaluation**

In patients with ADHF, diuretic therapy should be targeted to reach euvoema and relieve patients from signs and symptoms of congestion as this is associated with lower in-hospital mortality and associated with a lower risk for all-cause mortality and HF rehospitalization. However, there is no ‘one-size fits all’ model and optimization of diuretic therapy requires an individualized approach (5). Historically, diuretic titration was based on clinical, hemodynamic, biochemical and echocardiographic parameters. However, most of these parameters are rather inaccurate in evaluating adequate decongestion and do not allow an early adaptation of diuretic therapy as these metrics require some time to change after loop diuretic administration (34). The current ESC heart failure guidelines advise the timely assessment of the diuretic response in patients with ADHF by measuring the urinary sodium concentration 2 hours after diuretic administration or the urinary volume 6 hours after diuretic administration. In case that this is below 50-70 mmol/L or below 100-150 ml/u, diuretic response is inadequate and diuretic therapy should be escalated, by dose intensification or combination therapy (1). The efficacy of this protocol has been tested prospectively. The Pragmatic Urinary Sodium-based algorithm in Acute Heart Failure (PUSH-AHF) study was a single-centre, prospective, open-label randomized trial, which demonstrated that a natriuresis-guided protocol results in a higher 24-h natriuresis compared to conventional diuretic titration, however without an impact on long-term outcomes (35). These results have been confirmed by the Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF) study, a multicentre, open-label, two-phase study, in which a natriuresis-guided protocol improved natriuresis, diuresis and length-of-stay (36). Both studies only tested the protocol during the initial decongestion phase. Whether the protocol is extendable to the achievement of decongestion is evaluated by the ongoing ESCALATE trial (NCT04481919) (37). The ongoing DECONGEST (NCT05411991) also evaluates the applicability of the protocol till decongestion is achieved. On top, it evaluates whether a more aggressive protocol with upfront combinational therapy and early initiation of the so-called full nephron blockade is superior to usual care. Despite the clear evidence supporting a natriuresis-guided diuretic protocol, implementation is still cumbersome in current daily practice, as this strategy is quite intense with the requirement of frequent timely collections of urine samples, synchronized with diuretic prescriptions by the cardiologist, and laboratory assessments. The REadily available UrinAry Sodium analYsis in Patients with Acute Decompensate Heart Failure (EASY-HF) study tested a nurse-led natriuresis-guided protocol with urinary sodium concentration measurements via a point-of-care bedside sensor and compared this with the standard of care. The study demonstrated that a nurse-led protocol is feasible and safe. In addition, it led to a higher natriuresis and diuresis and both the protocol and the sensor were considered to be easy usable and applicable in daily practice by the cardiac nursing team (38).

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**Long-term evaluation**

Although the relieve of congestion should be the primary goal, no prospective diuretic trials have demonstrated that they directly improve long-term outcome (18, 28, 35, 36). Achieving decongestion is associated with a reduction in all-cause mortality and HF hospitalization, however no causative relation has been proven. Therefore, every hospitalization should also be targeted as a possibility to optimize HF care, with education, improvement of guideline-directed medical therapy (GDMT), treatment of iron deficiency and evaluation for the implementation/optimization of cardiac resynchronization therapy (1). Quadruple HF therapy, which reduces neurohumoral activation and sodium avidity, has proven to improve survival and need for HF hospitalization. Therefore, once patients are hemodynamically stable, GDMT should be initiated and optimized during hospital stay (39, 40). The Safety, Tolerability and Efficacy of Up-titration of Guideline-Directed Medical Therapies for Acute Heart Failure (STRONG-HF) trial demonstrated that a rapid uptitration of GDMT with close follow-up after an ADHF admission is associated with an improvement in quality of life, lower symptom burden and reduction in all-cause mortality and HF rehospitalizations (41). The need for chronic loop diuretic
maintenance therapy should be evaluated continuously as this is associated with a poor long-term outcome. Iron deficiency is common in patients with chronic HF (up to 50%), and even more prevalent in patients with ADHF (up to 80%) (42). Iron deficiency (ID) is defined by the current ESC guidelines as a serum ferritin level <100 μg/L (absolute ID) or a serum ferritin level 100–300 μg/L in combination with a transferrin saturation <20% (functional ID) (1). Ferritin is an acute phase protein, which might even result in an underestimation of the prevalence in patients with ADHF (43). Intravenous iron substitution has been associated with an improvement in quality of life, symptom reduction and reduction in the need for hospitalization (44). A greater treatment benefit is observed in patients with lower transferrin saturation values (45).

Declarations of interest
The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

References

<table>
<thead>
<tr>
<th>Loop diuretics</th>
<th>SGLT2i</th>
<th>Acetazolamide</th>
<th>Thiazide</th>
<th>MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site of action</strong></td>
<td>Ascending part of loop of Henle</td>
<td>Proximal tubule</td>
<td>Proximal tubule</td>
<td>Early part of distal tubule</td>
</tr>
<tr>
<td><strong>Mode of action</strong></td>
<td>Blocking Na/K/2Cl symporter</td>
<td>Blocking sodium/glucose cotransporter</td>
<td>Inhibition of carbondic anhydrase</td>
<td>Blocking sodium-chloride cotransporter</td>
</tr>
<tr>
<td><strong>Starting dose</strong></td>
<td>At least equal home dose IV or double in case of CKD. In case of diuretic naïve: starting dose 20–40 mg of furosemide IV.*</td>
<td>Orally: empagliflozin 10 mg or dapagliflozin 10 mg</td>
<td>IV: 500 mg</td>
<td>HCTZ: 25–100 mg Metolazone: 2.5–10 mg Chlorothalidone: 25–200 mg Chlorthalidone: 500–1000 mg (IV formulation available)</td>
</tr>
<tr>
<td><strong>Maximum total daily dose</strong></td>
<td>Furosemide: 400–600 mg IV</td>
<td>Maximum dose of 25 mg</td>
<td>IV: 500 mg 3×/day</td>
<td>HCTZ: 200 mg Metolazone: 20 mg Chlorothalidone: 100 mg Chlorthalidone: 1000 mg</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>Furosemide: 1.5–3.0 h Bumetanide: 1–1.5 h Torsemide: 3–6 h</td>
<td>Empagliflozin: 12.4 h Dapagliflozin: 12.9 h</td>
<td>2.4–5.4 h</td>
<td>HCTZ: 6–15 h Metolazone: 6–20 h Chlorothalidone: 45–60 h Chlorthalidone: 45–120 min</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>IV: 5–10 min 1.5–2 h</td>
<td>IV: 15–60 min</td>
<td>PO: 1–2.5 h IV: 30 min</td>
<td>PO: 48–72 h IV: 2.5 h</td>
</tr>
</tbody>
</table>

Abbreviations: CKD: chronic kidney disease; HCTZ: hydrochlorothiazide; IV: intravenously
*Conversion factor: 40 mg furosemide = 1 mg bumetanide = 20 mg torsemide
#Canrenone is the active metabolite of spironolactone and its intravenous formulation potassium canrenoate.


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