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Review Article

Diuretic Resistance in Cardio-Nephrology: Role of Pharmacokinetics, Hypochloremia, and Kidney Remodeling

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Heart failure · Diuretic resistance · Fluid overload · Vaptans

Abstract
Background: Diuretic resistance is among the most challenging problems that the cardio-nephrologist must address in daily clinical practice, with a considerable burden on hospital admissions and health care costs. Indeed, loop diuretics are the first-line therapy to overcome fluid overload in heart failure patients. The pathophysiological mechanisms of fluid and sodium retention are complex and depend on several neuro-hormonal signals mainly acting on sodium reabsorption along the renal tubule. Consequently, doses and administration modalities of diuretics must be carefully tailored to patients in order to overcome under- or over-treatment. The frequent and tricky development of diuretic resistance depends in part on post-diuretic sodium retention, reduced tubular secretion of the drug, and reduced sodium/chloride sensing. Sodium and chloride depletions have been recently shown to be major factors mediating these processes. Aquaretics and high-saline infusions have been recently suggested in cases of hyponatremic conditions. This review discusses the limitations and strengths of these approaches. ***Summary:*** Long-term diuretic use may lead to diuretic resistance in cardio-renal syndromes. To overcome this complication intravenous administration of loop diuretics and a combination of different diuretic classes have been proposed. In the presence of hyponatremia, high-saline solutions in addition to loop diuretics might be beneficial, whereas aquaretics require caution to avoid overcorrection. ***Key Messages:*** Diuretic resistance is a central theme for cardio-renal syndromes. Hyponatremia and hypochloremia may be part of the mechanisms for diuretic resistance. Aquaretics and high-saline solutions have been proposed as possible new therapeutic solutions.

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Introduction

Heart failure (HF) is a worldwide highly prevalent and invalidating clinical condition with a considerable burden on hospital admissions and health care costs, especially in the elderly [1, 2]. Loop diuretics (LDs) are the core therapy to reduce congestion symptoms and hospitalizations, unfortunately without an impact on disease progression [3]. Furthermore, the efficacy of diuretics often decreases in the long term [4] (Fig. 1A). The underlying mechanisms are poorly understood and might involve enhanced sodium reuptake in the distal tubules [5] or altered chloride sensitivity [6, 7].

Several pharmacological strategies have been proposed to overcome diuretic resistance, including: (i) continuous diuretic infusions, (ii) hypertonic saline infusion, and (iii) association of diuretics acting on different parts of the nephron (sequential blockade). The latter is now available in the class of vasopressin receptor antagonists, acting on the last portion of the nephron.

This review aims to explore the new insights on mechanisms sustaining the resistance to diuretics in HF. Furthermore, it provides an updated reading of the available studies exploring the efficacy and safety of different optional therapeutic approaches to overcome resistance to diuretics in HF patients.

Pathophysiology of Fluid Overload in HF

The mechanism of progression of HF is unclear, and it possibly changes according to the initial myocardial injury, such as coronary ischemic damage, severe hypertension, valvulopathies, dilatative cardiomyopathy, or myocarditis, etc. [8–10]. The resulting reduction of the ejection fraction and diastolic compliance [9] lead to tissue and organ hypoperfusion. This, in turn, triggers a compensatory change of arteriolar resistance and renal water and salt reabsorption to preserve the effective plasmatic volume [11, 12]. Specifically, non-osmotic vasopressin release, renin-angiotensin-aldosterone system (RAAS) activity, and sympathetic tone are increased in HF patients [13]. Indeed, adrenergic β-receptors in the kidney appear to play a key role in the induction and maintenance of the renal compensatory responses [14]. Overall, the kidneys play a central role in HF-related congestion, as they are the major effectors of compensatory activities, and are mostly affected by organ hypoperfusion. Furthermore, they are the targets of diuretics, the first-line therapy in congestive HF patients [5]. However, long-term diuretic therapy, especially in cardio-renal patients, is often accompanied by a reduced pharmacological response and renal function deterioration.

Mechanisms of Diuretic Resistance

Approximately 25–30% of HF patients develop diuretic resistance, that is a clinical condition characterized by fluid retention despite the use of a high dose of oral LDs [4]. Although several definitions have been proposed in the literature, all agree that the reduced diuretic and natriuretic effect of LDs makes volume overload difficult to control.

Among the proposed mechanisms causing diuretic resistance, the activation of sodium retentive systems as a counter-regulatory response and the changes in LD pharmacokinetics in HF have received the most attention [15].

Sodium and water loss due to diuretics administration triggers RAAS activation [13], leading to an increased sodium absorption along the distal nephron [16]. Since the plasma concentration of the orally administered drug declines during the day, these compensatory mechanisms determine post-diuretic sodium retention that involves all tubular segments. Indeed, post-diuretic sodium retention is enhanced when the drug-free intervals are longer than four half-lives of the LD. Thus, neuro-hormonal systems as well as renal adaptations contribute to determining the post-diuretic resistance and rebound sodium retention, both

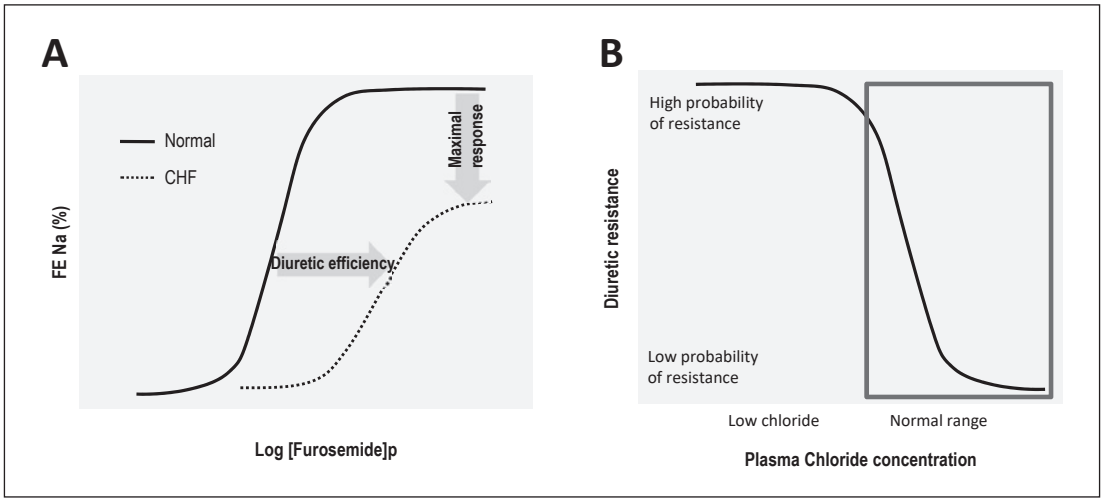

Fig. 1. A Changes of urinary sodium excretion fraction in response to furosemide administration. A shift of the dose-response curve is evident in CHF patients. **B** Relationship between serum chloride and the probability of developing diuretic resistance (redrawn from Hanberg et al. [22]).

leading to a reduced diuretics efficacy [16, 17]. Interestingly, functional and structural adaptive changes in the kidney occur, constituting the so-called braking phenomenon, consisting of the upregulation of proteins involved in renal sodium absorption [16]. The latter is the effect of the chronic adaptation to prolonged LD administration that implies a chronically increased urinary sodium burden to the distal nephron segments [17, 18]. After the first-dose administration of LDs, short-term tolerance occurs in response to volume depletion and is mediated by angiotensin II and the sympathetic nervous system through the increased expression and activity of sodium transporters, including the sodium-hydrogen exchanger NHE3 [19]. In experimental models of rats chronically treated with LDs, sodium transport along the nephron has been studied. The increased sodium delivery to the distal tubular segments due to furosemide-dependent inhibition of Na^+-K^+-$2Cl^-$ (NKCC2) in the thick ascending limb of the Henle loop stimulates the expression and activity of the thiazide-sensitive cotransporters (Na-chloride cotransporter; NCC) along the distal tubules. Moreover, an increase of Na^+-K^+ ATPase activity on the basolateral membrane has been demonstrated [5, 19]. Further studies have reported an upregulation of all α-, β-, and γ-subunits of the epithelial sodium channel (ENaC), along the collecting duct (CD) [20]. As a consequence, a tubular lumen widening and a size enlargement of epithelial cells has been observed [21]. Similarly, an experimental model of HF showed the upregulation of these sodium transporters [19], together with the overexpression of NKCC2 and NHE3. HF animals also exhibited an overexpression of the water channel aquaporins (AQPs) in the principal cells of CD, with a predominant localization onto the apical membrane [19].

Recent studies have also identified chloride, a major factor in renal salt sensing, as a key electrolyte in HF-related congestion (Fig. 1B) and possibly in the development of resistance to diuretics in this clinical setting [6]. Sodium/chloride sensing is a key physiological process to maintain fluid homeostasis and involves both the central nervous system and the kidneys. Within the kidney, a major advancement has been the recent identification of a family of chloride-sensitive kinases such as WNK1, which represent the molecular mechanism of chloride sensing [20]. Therefore, hypochloremia is both the cause and the consequence of the demodulated salt and water transport along the renal tubule in response to the different

pathologic mechanisms involved in volume expansion and salt tubular handling in HF. This might explain the link between hypochloremia and resistance to diuretics. Indeed, Hanberg et al. [22] tested this hypothesis in 2 HF patient cohorts on high LDs doses and reported a prevalence of hypochloremia that exceeded that of hyponatremia, especially in patients needing higher LDs doses. Surprisingly, in these patients, free water excretion was not modified, suggesting depletion and not dilution as the main mechanism sustaining diuresis reduction. In the intervention study, oral chloride lysine was administered to one cohort of patients, with a resulting improvement of the response to diuretics, and positive reflexes on several cardio-renal parameters. Indeed, additional basic science studies would be relevant for a better understanding of the underlying mechanisms of resistance to diuretics addressing novel therapeutic strategies based on hypochloremia correction. The epidemiological evidence of hypochloremia as a poor prognostic factor raises the question whether this is mediated by LD resistance or simply indicates the intensity of diuretic treatment. Although no data about the hard outcome (survival) with chloride supplementation are available, the correction of hyponatremia using vaptans (see below) did not show changes in mortality. Furthermore, we should consider that LD do not improve survival in HF, and therefore approaches to overcome LD resistance should have limited effects on survival. Therefore, it is unlikely that the correction of hyponatremia/hypochloremia may also improve survival. An additional support to this conclusion if that hypochloremia is also an independent mortality predictor in patients with pulmonary hypertension (PAH) [23]. Given the difference between PAH and HF, this observation also suggests that hypochloremia is mainly an indicator of the intensity of diuretic treatment and, indirectly, disease severity. It cannot be excluded that the high-dose diuretics are actually detrimental for survival through as yet unexplored mechanisms.

LDs have a sigmoid-shaped dose-response curve (Fig. 1A) with the greatest urinary sodium excretion effect between the minimal effective dose and the ceiling dose [5, 24]. Determining the renal threshold and maximally effective doses of LDs is a crucial step, as any further dosage increase above the maximum does not improve the diuretic effect. Several conditions related to HF may affect LDs pharmacokinetics and result in a shift of the dose-response curve rightward and downward [25]. Commonly, the chronic tissue hypoperfusion generated by HF results in a delayed and decreased gastric emptying and reduced intestinal motility [26]. Furthermore, the sympathetic hyperstimulation and concomitant morbidities (diabetes, atherosclerosis, etc.) may contribute to these alterations. Moreover, abdominal organ congestion in HF produces gastric and intestinal wall edema. All these alterations may reduce and delay drug absorption, with an unpredictable response to diuretic stimulation, particularly for compounds such as furosemide, which have a variable bioavailability (ranging from 10 to 100%) [27, 28].

The coexistence of chronic kidney disease (CKD) may enhance renal hypoperfusion [25, 29]. The glomerular filtration rate only accounts for a very limited part of tubular diuretic delivery, mostly because diuretics (LDs but also thiazides and carbonic anhydrase inhibitors) have a significant binding to albumin, and thus a limited amount is freely filtered. The active tubular secretion, principally at S2 and S3 tubular proximal segments, plays a major role in allowing diuretics to reach the luminal sites of action [30, 31] and is mediated by organic anion transporters (OATs) [32]. Therefore, a defective diuretic secretion in the luminal fluid could also account for diuretic resistance [33]. OAT proteins also mediate peritubular urate and weak anions uptake. Renal failure, as well as all conditions leading to chronic renal hypoperfusion, may result in the progressive accumulation of organic anions competing with diuretics for active secretion [31]. Moreover, in the presence of metabolic acidosis mediated by renal failure, the cellular membranes are depolarized, which might contribute to a reduced OATs activity [34, 35] (Fig. 2A, B).

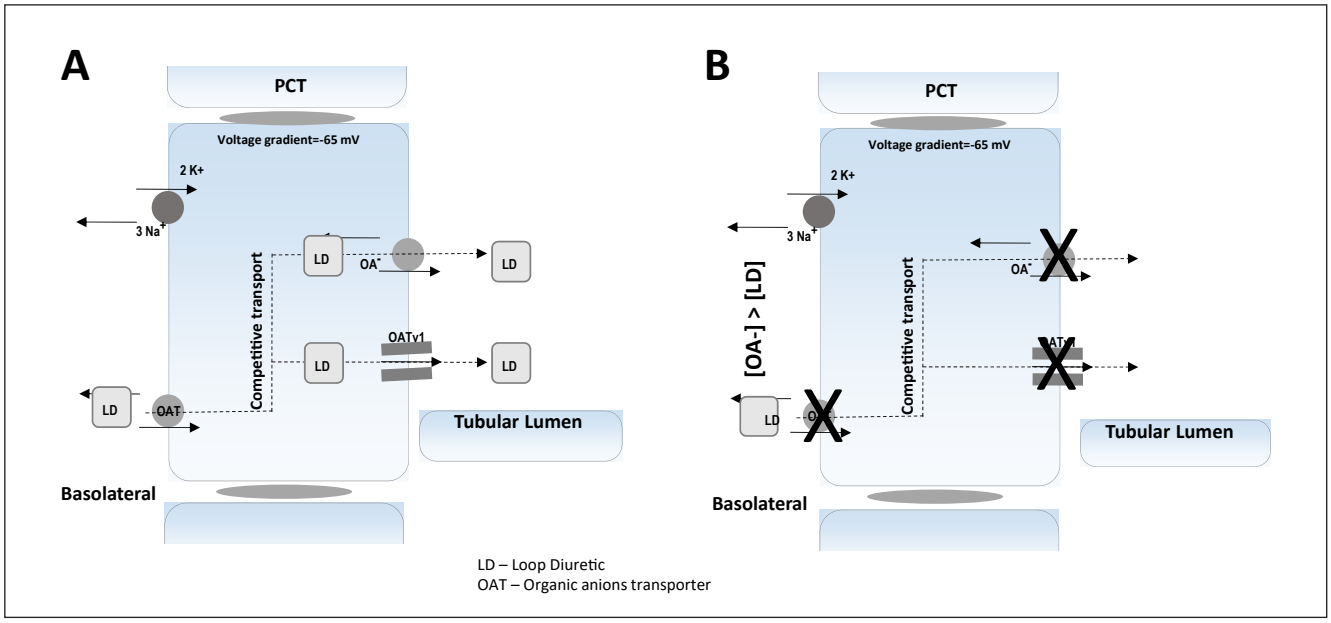

Fig. 2. A LD secretion by proximal tubular cells is mediated by a competitive transport on OATs. **B** In CKD, the accumulation of organic anions in the blood overcomes LD transport ability by epithelial proximal tubular cells.

Strategies to Overcome Diuretic Resistance

Dietary Sodium Intake and Compliance to Therapy

It is commonly accepted that the first step to counteracting diuretics resistance is to ensure patient compliance with an appropriate dietary sodium restriction. This is mainly based on the theoretical assumption that dietary salt restriction helps control fluid overload. However, this assumption has been recently questioned. Indeed, a very low sodium diet is actually associated with worse outcomes, and may lead to hyponatremia and hypochloremia, which may themselves be responsible for the diuretic resistance [7]. Furthermore, a chronic low sodium diet may lead to a sodium repletion within the extracellular matrix and the bones, with resulting osteoporosis.

Therefore, according to the cardiac disease severity (NYHA class), LD dose adjustments should be tailored to the patient [35]. Moreover, in order to maintain the diuretic plasmatic concentration at the steady state, it would be necessary to reduce drug-free intervals by increasing the daily administration frequency [36].

When excessive fluid retention persists, despite dietary and drug adjustments, the clinician faces a few options: (a) to switch to a combined oral diuretic therapy or to the intravenous drug administration; (b) in the case of hyponatremia, to start an infusion of high saline, combined with LDs; (c) in the case of hyponatremia, to use vaptans, and finally (d) to start ultrafiltration when the medical therapy fails to obtain a clinical improvement. The latter is associated with quality of life worsening and elevated mortality [37] (see also Fig. 3, 4).

Combined Diuretic Therapy

Combined diuretic therapy (CDT) consists of a sequential blockade of the sodium absorption along the nephron, in order to escape rebound sodium retention [18]. Most recent

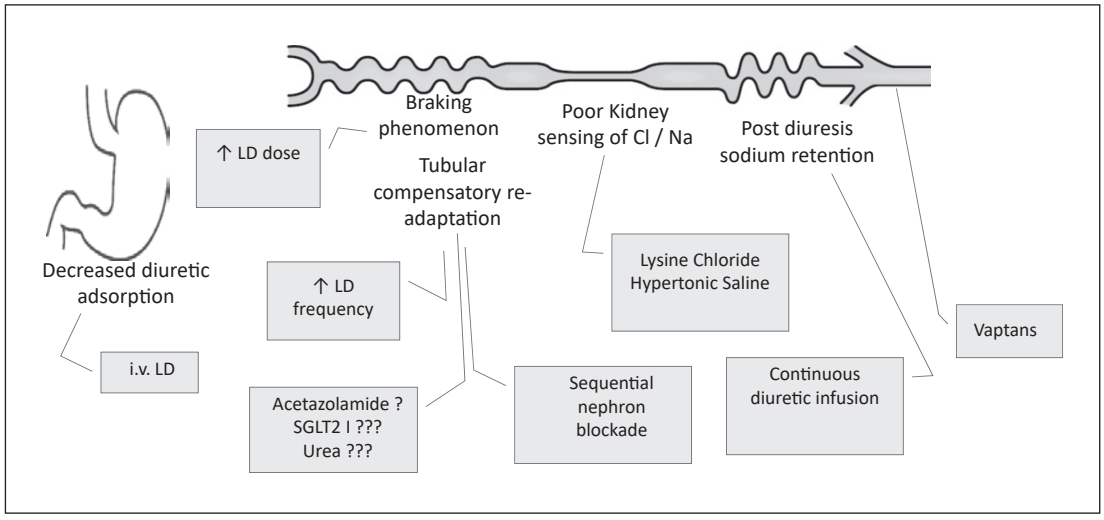

Fig. 3. Pathways involved in diuretic resistance and the therapeutic options (gray boxes) aimed at overcoming these mechanisms. LD, loop diuretics.

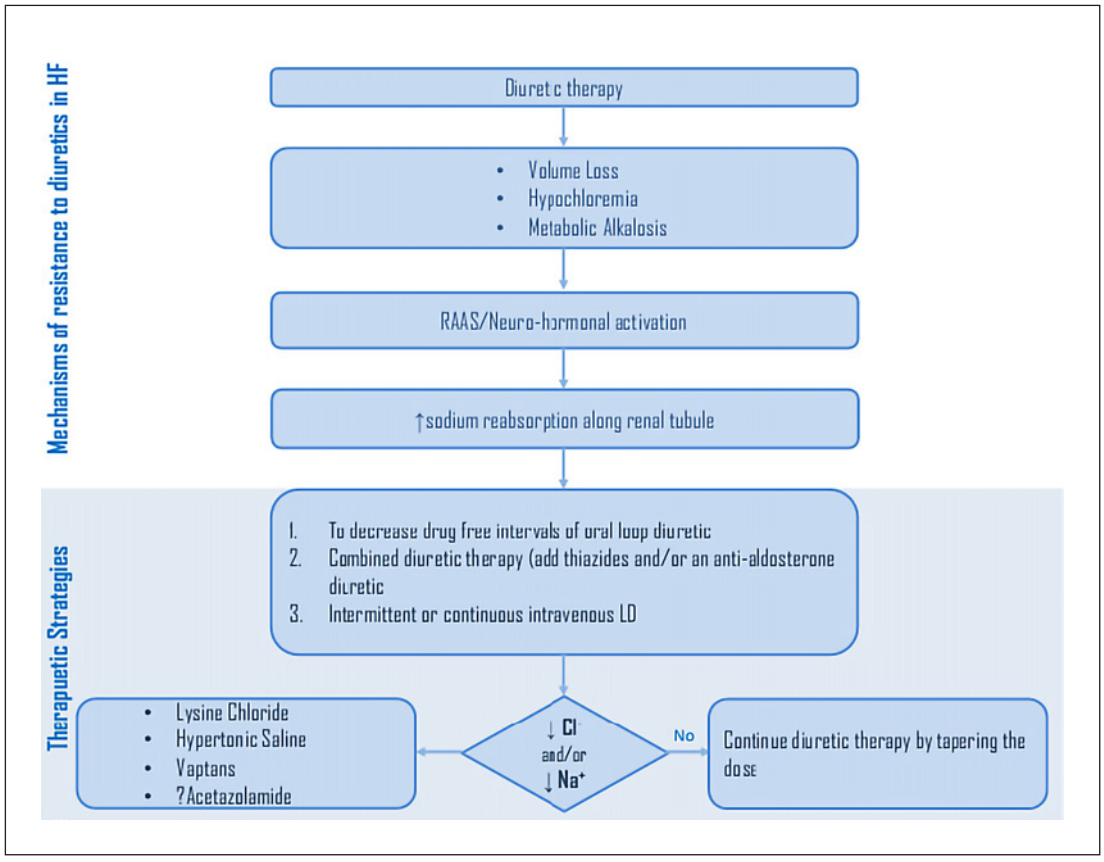

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Fig. 4. Therapeutic algorithm to treat diuretic resistance.

evidence on diuretic therapy in patients with HF and acute decompensated HF is based on expert opinion and population studies, while randomized controlled trials are scanty.

A landmark study in 1994 [38] evaluated the effectiveness of the combination of a thiazide (bendrofluazide or metolazone) with furosemide in HF patients with symptomatic fluid congestion compared to LD monotherapy. The results showed considerable weight loss in patients treated with CDT as compared to those taking the LD alone. Similar results were also reported in a recent observational study [39] in which HF patients refractory to LDs experienced improvements in blood pressure and weight loss, despite a tendency to electrolyte homeostasis disturbances, when metolazone was added to furosemide.

In another study testing the CDT in HF-CKD patients, valid diuresis and natriuresis were achieved with congestion symptoms relief, ejection fraction improvement, ameliorated self-assessed quality of life, earlier hospital discharge, and less hospital readmission. Unfortunately, CDT does not ensure an improvement in mortality [40]. The American Heart Association recommends the use of CDT in HF patients with considerable fluid overload refractory to optimized doses of LDs in monotherapy (at least 160–320 mg/day of intravenous furosemide in bolus or as a continuous infusion) with level C evidence (experts opinion only) [41].

The overactivation of the RAAS axis provides the rationale for also using anti-aldosterone agents in HF patients [42]. Aldosterone is known to enhance renal sodium absorption by regulating the abundance and the apical membrane localization of ENaC along the distal nephron [43]. Moreover, aldosterone contributes to myocardial sclerosis and arterial wall fibrosis [44]. Accordingly, several studies have demonstrated that high aldosterone plasma levels are associated with higher mortality in HF patients [45]. All these considerations support the potential benefit of aldosterone antagonists (either a cellular receptor antagonist such as canrenone, or a sodium channel blocker such as amiloride) together with other diuretics.

However, the use of these diuretics in CKD patients should be carefully evaluated because of their higher risk of developing electrolyte disturbances (hyperkalemia, hyponatremia, hypochloremia). In general, close monitoring of kidney function is mandatory in concomitance of diuretics administration in HF patients with CKD [46].

Intermittent versus Continuous Intravenous Administration of Bolus Loop Diuretics Administration

It is generally accepted that LDs should be administered intravenously in cases of poor oral bioavailability of LD or when rapid reversal of fluid overload is required. Although the intravenous LD bolus may allow faster positive effects on the congestive symptoms [24, 47], the continuous infusion is supposed to be more efficient by ensuring a constant plasma drug level [48, 49]. Furthermore, intermittent high LD doses are associated with severe kidney hypoperfusion due to an imbalanced vascular refilling [50], especially in patients with impaired cardiac function. Finally, the oscillating plasma drug concentration after intermittent intravenous therapy is associated with a rapid fluctuating in the natriuresis and post-diuretic congestion rebound.

At variance, a randomized double-blind trial comparing continuous versus intermittent intravenous infusion of furosemide in acutely decompensated HF patients did not support the superiority of continuous versus intermittent LDs infusion. As the primary endpoint, the trial considered congestion symptoms relief and preserving renal function. Moreover, a not significant trend towards congestion symptoms and transient worsening of renal function were apparent with higher doses of LDs. No differences between the groups were found in hospital readmissions and mortality [18].

A recent meta-analysis comparing continuous versus intermittent infusion of LDs included 669 acute decompensated HF patients in eight clinical trials. No differences were

found in terms of hospitalizations and mortality between continuous and intermittent LD regimens. Conversely, a significant improvement of clinical status (weight loss, urine output, congestion symptoms) was evidenced by the continuous infusion of furosemide [51].

Consequently, intermittent LD administration appears non-inferior to continuous LD infusion, and the clinical decision on which regimen to adopt rests on personal experience or the consideration of which intervention is more practical.

Hypertonic Saline Infusion in Addition to High-Dose LDs

Resistance to diuretics is mostly demonstrated to be linked to an upregulation of sodium reabsorption in distal tubules. Chloride seems to play a major role in renal salt sensing mechanisms triggering neuro-hormonal sodium recovery. As a consequence, the possible negative consequences of salt restriction has been recently revised [12, 52]. Conversely, possible beneficial effects of the intravenous administration of hypertonic (1.4%) saline solution (HSS) in concomitance with LDs in HF patients have been reported. In fact, an increasing number of studies have recently described an enhanced pharmacological efficacy of furosemide when administered with HSS in HF [53]. Specifically, in 2015 Paterna et al. [54] reported the dose-response curve following the intravenous administration of high doses of furosemide diluted in HSS. They observed a significant improvement of both urinary output and sodium excretion rate, corresponding to a shift in the dose-response curve to the left.

More recently, in 2017, Lafrenière et al. [55] tested the association of HSS and furosemide in acute decompensated HF patients and found positive results in this critical clinical setting. In fact, they observed a relevant weight loss depending on a significant urinary output increase, without any notable impact on kidney function.

However, the combination of HSS with furosemide has also been recently tested in acute HF patients with severe renal impairment in a randomized, double-blind trial, with conflicting results. Diuresis was not significantly improved, while BUN increased in the HSS + furosemide group compared to the intravenous furosemide group [56].

Therefore, the efficacy of chloride supplementation or, similarly, hypertonic saline to overcome diuretic resistance supports the role of hypochloremia/hyponatremia in the development of resistance. However, the molecular mechanism remains purely speculative. On one side, the stimulation of the chloride-sensing WNK1 protein by chloride supplementation may activate, in turn, the sodium-potassium-2-chloride cotransporter, thereby increasing sodium fractional excretion. In other terms, in the distal convoluted tubule (DCT) low intracellular chloride leads to WNK1 phosphorylation and hence to NCC activation. Although no clear evidence of low intracellular chloride has been reported in the case of HF, it is plausible that hypochloremia is also mirrored by a low intracellular chloride, which would increase NCC activity and Na reabsorption. More explicitly, low extracellular chloride per se may activate NCC (sodium reabsorption in the DCT in response to low intracellular chloride), thereby contributing to "diuretic resistance"; thus normalizing/raising extracellular chloride, and thus intracellular chloride, would inhibit NCC and restore sodium excretion. On the other hand, it is possible that the kinetics of the sodium/chloride tubular transporters are less efficient in the presence of a low concentration of salts; speculatively, these transporters might even work in a reverse way if the blood concentration of sodium/chloride is lower in the tubules than in the plasma.

Role of Vasopressin Secretion in Chronic HF

Arginine-vasopressin (AVP) production by hypothalamic neurosecretory cells plays a principal role in regulating renal water handling and blood volume [57–60]. Both osmotic and not osmotic stimuli regulate AVP secretion. The non-osmotic AVP stimulation in HF leads to renal water retention with two main consequences: (a) the increase in cardiac preload and

(b) hypo-osmolality with dilutional hyponatremia [61]. However, these changes predispose to severe arrhythmias and acute heart decompensation [62].

Vasopressin Antagonism in HF

Due to the role of AVP in mediating fluid overload, vasopressin antagonism was initially thought to represent a therapeutic target in HF [63]. Therefore, several antidiuretic hormone (ADH) receptor antagonists, globally known as "vaptans," have been developed. Tolvaptan is an oral competitive V2 receptor (V2R) antagonist approved by the US Food and Drug Administration to correct euvolemic and hypervolemic hyponatremia in patients with HF, cirrhosis, and syndrome of inappropriate ADH (SIADH) [64, 65]. Tolvaptan interferes with the AVP-V2R binding and prevents AQP2 recruitment to the apical membrane along the CD, leading to free-water excretion [66].

Two large multicenter randomized double-blind placebo-controlled trials have tested tolvaptan efficacy and safety in hyponatremic diseases. SALT-1 and SALT-2 (Study of Ascending Levels of Tolvaptan in Hyponatremia) have addressed the effect of tolvaptan versus placebo in patients with euvolemic or hypervolemic hyponatremia associated with HF, cirrhosis, and/or SIADH. Both studies were focused on the following primary endpoints: (a) the exaltation of serum sodium concentration at day 4 versus baseline, and (b) the exaltation of serum sodium concentration at day 30 versus baseline. The use of tolvaptan was associated with a persistent and statistically significant improvement in serum sodium levels [67]. To increase clinical experience with tolvaptan and to better understand its strengths and weaknesses in combined optimized therapy, another wide clinical project has been conducted – the EVEREST study (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) [68]. This prospective multicenter randomized double-blind placebo-controlled trial evaluated the short- and long-term safety and efficacy of tolvaptan added on standard therapy in patients hospitalized for worsening HF. It included an inpatient period, and primary endpoints were the changes in body weight and in self-assessed global clinical condition. Data analysis showed that body weight loss was more consistent among patients receiving tolvaptan with the maximal effect on the first treatment day. Moreover, a greater number of patients in the tolvaptan group reported an improvement of dyspnea on day 1. These results went in parallel with a positive effect on serum sodium concentration in patients showing hyponatremia at baseline. However, the global clinical status was not improved by the use of tolvaptan compared to placebo on day 7. Similarly, long-term observation, with a mean of 9.9 months of follow-up, did not show any significant benefit of tolvaptan in all-cause mortality or cardiovascular death or hospitalizations [69]. The TACTICS-HF (Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure) study reached similar conclusions [70].

Therefore, at present tolvaptan does not represent a therapeutic option for HF, except in cases of hyponatremia. However, even in this condition, the clinician should take great precautions, because the correction of hyponatremia might be very rapid with tolvaptan, with the resulting risk for osmotic demyelination. In future studies it would be of great interest to verify chloride levels in HF patients using vaptans, as this information may help in answering the question of chloride per se serving as a direct or indirect mortality risk factor in HF.

Other Approaches

An additional intervention that has been suggested to correct hyponatremia is the oral administration of urea [71]. Urea has been used and recorded by some in the treatment of hyponatremia, usually euvolemic (e.g., SIADH), rather than the hypervolemic form seen in severe HF. Theoretically, it might be used as an osmotic diuretic, since it may be less likely to cause acute intravascular volume overload (and pulmonary edema), which is the risk with i.v. mannitol. However, urea is not very palatable when given by mouth and its role in HF is

unclear. Initial attempts in 1925 reported an increase in urine output after urea treatment in HF [72]. Subsequent single case reports also support this view [73]. However, liver toxicity and problems with patient management make this therapeutic option unfeasible in advanced HF [74]. No information is available regarding the effect of urea on diuretic resistance. A new therapeutic option to diuretic resistance are the selective blockers of the renal sodium-glucose transporter (SGLT2), which induce osmotic diuresis and exert protective effects on the cardiovascular system. The selective SGT2 inhibitors inhibit glucose transport in the proximal tubule, thus inducing glycosuria, blood pressure lowering, natriuresis, and osmotic diuresis [75]. SGLT2 inhibitors have been suggested and tested in hyponatremia, but not yet as an active treatment in HF, although, of course, diabetic patients are more likely to develop HF, especially if they have CKD, which is why the HF benefit of SGLT2 inhibition has been a consistent finding in the various clinical trials to date. However, their diuretic effect is transient, limited to the initial treatment phase, without intrarenal RAAS activation [76]. No data are available concerning their effect in the case of diuretic resistance.

Conclusion

In HF the compensatory activation of neurohormonal systems to maintain circulatory homeostasis leads to fluid overload with increased comorbidity and mortality. To date, diuretic therapy is still the cornerstone for preventing and treating congestion; however, long-term treatment may lead to diuretic resistance. Several strategies have been studied to prevent and overcome this complication, including diuretic dose adjustments and combinations of different diuretic classes. When acute decompensation occurs, intravenous administration of LDs should be adopted with no clear evidence to prefer an intermittent rather than continuous infusive strategy. Even the use of HSS in addition to furosemide is still controversial, but promising at least in normally functioning patients.

The vaptans, ADH-V2R antagonists, are able to improve fluid overload and reverse hyponatremia in HF patients, as is widely reported in large trials. However, they did not show any significant impact on long-term morbidity and mortality.

Disclosure Statement

The authors have no conflicts of interest to declare.

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