Diuretics and Clinical Management of Congestion in Heart Failure: A Review

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Abstract

Heart failure is a syndrome with variable presentations; congestion is the most common form in acutely decompensated patients. In this scenario, the main drug to resolve congestion is a loop diuretic. However, a portion of the population has diuretic resistance. In this context, adjuvant diuretic therapies are needed to resolve congestion in patients with heart failure. The main strategies studied so far are thiazide diuretics, mineralocorticoid receptors antagonists, vasopressin antagonists, nesiritide, sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors, hypertonic saline, and fluid and salt restriction. The purpose of this article is to review pharmacological modalities for management of congestion, associated or not with diuretic resistance, their positive and negative points, and the current state of knowledge about each drug.

Introduction

Heart failure (HF) is a syndrome in which variable cardiovascular or systemic diseases with cardiovascular involvement converge to similar signs and symptoms. However, even within the same syndrome, patients may have different presentations. For example, symptoms may range from dyspnea during high-intensity sports in an elite athlete who suffered an infarction up to a cardiogenic shock in a post-infarction patient or in an 80-year-old patient with longstanding hypertension. Furthermore, the presentation of HF may be chronic, acute, or acutely decompensated. The treatment of chronic HF has undergone very significant advances, which has, in clinical practice, changed its natural history, especially from the 1980s onwards. Acutely decompensated HF (ADHF) is the central theme of the present article.

ADHF is the leading cause of hospitalizations in patients older than 65 years of age,¹ accounting for around 1 million hospitalizations in the United States per year, having an impact both on morbidity and mortality. It is estimated that one out of two patients are readmitted within 6 months, with an in-hospital mortality rate from 4 to 12%. Even after hospital discharge, it is estimated that 35% of patients with ADHF

evolve to death within 1 year.^{2,3} This is a serious situation both from the individual point of view, due to worsened quality of life and reduced survival, and in terms of public health, due to the high costs involved.

Similar to chronic presentations, ADHF is very heterogeneous, with regard to both patient care demand and disease clinical presentation.³ One of the most common of these is clinical congestion.⁴ In patients with presentations, decision-making is simple; however, many patients have subtle signs of congestion on physical examination, thus hampering accurate diagnosis. Moreover, the process of congested patient is dynamic, since variations in intracardiac pressures may change within a short time,⁵ depending on a cascade of events, such as ventricular and atrial end-diastolic pressure, pulmonary capillary wedge pressure, pulmonary arterial wedge pressure, right chamber pressures, hemodynamic variations depending on patient's ventilation mode, among other factors.^{6,7}

New tools have helped understand and improve the definition of congestion; some of them are well-established, others are still in the establishment stage. The use of natriuretic peptides,⁸ in addition to pulmonary echography⁹ and point-of-care echocardiography, has become increasingly common for a better analysis of patient's hemodynamic profile, with potential improvements in outcomes.^{10,11} Furthermore, "congested" patients often have poor distribution of intravascular volume with but do not necessarily have increased total volume, which may also impact their therapy.⁵

Several therapies have been implemented in congested patients. With regard to therapeutic advances in chronic HF over the last 30 years, the most used drugs still belong to one class: diuretics.

Use of diuretics in congested patients

"The clamour for diuretics dates back many centuries to the earliest association of dropsy with impairment of renal function, but until twenty years ago these drugs were chiefly remarkable for the mediocrity of their therapeutic achievements". This sentence, retrieved from an article published in *Lancet*¹² in the 1940s, shows how the advent of diuretics occurred over the last 100 years, although dropsy dated back before Christ.¹³

The first diuretics used in the treatment of HF, were based on mercurial diuretics, and its form of use with sustained efficacy was an incidental finding, as well as many great medical discoveries. The hypothesis of using mercury as a diuretic was grounded nearly 500 years ago, but, for 4 centuries, it had successively similar results, all of them

Keywords

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frustrating. However, in the transition from the 1910s to the 1920s, sustained diuretic properties were found in mercurial compounds originally developed to treat syphilis.¹² The great limitation for their use was mercurial toxicity, which led to the development of progressively less toxic forms tested in oral, intravenous, intramuscular, and rectal routes of administration, with acceptable diuretic responses, especial the intravenous route.¹² Its mechanism of action is possibly related to sodium excretion in proximal convoluted tubule.¹⁴

Later, other diuretics were developed, such as carbonic anhydrase inhibitors, in 1937; a sulfanilamide, in 1949;¹⁵ and thiazides. The clinical use of loop diuretics, especially furosemide and etacrynic acid,^{16–18} initiated in the early 1960s and is indicated today for the treatment of patients with HF.

Loop diuretics

Loop diuretics, represented by furosemide, bumetanide, and torsemide (Table 1) are undoubtedly the main tool for decongesting patients with ADHF, being used in more than 90% of patients hospitalized with HF.¹⁹ These diuretics act on the Na-K-2Cl pump of the thick segment of Henle's loop, promoting diuresis through sodium excretion. Loop diuretics are possibly the most study class within this context, although evidence in this field is still considerably limited. In addition to their diuretic effect, loop diuretics have a vasodilatory action on smooth muscle cells of vessel walls. There is also an effect on renin–angiotensin–aldosterone system activation, which has both positive aspects, such as modulation of glomerular flow in the nephron, and negative aspects, such as neurohumoral activation leading to the perpetuation of detrimental effects in patients with HF.²⁰ The efficacy of loop diuretics for decongestion depends on several factors, such as route administration, chronic use by the patients, dose, comorbidities (especially renal dysfunction), and dietary salt intake, among others.²⁰

The largest study involving diuretics in HF was the DOSE study.²² A total of 308 patients were randomized in a 2-by-2 factorial design to receive intravenous furosemide either continuously or intermittently, to maintain their outpatient dose (low-dose strategy) or to receive a 2.5-time higher dose (high-dose strategy), both applied intravenously. There was no difference in the overall assessment of symptoms by the patient and in the change in creatinine levels after 72 h, which were the primary study outcomes. In a post hoc analysis adjusted for decongestion parameters, the effect of the high dose apparently improved resolution of congestion: the higher the dose of diuretics, the greater the decongestion, and the greater the response.²³ Moreover, there was a higher number of patients with worsened renal function in the group that used higher doses of furosemide.

Diuretic resistance

Compared with healthy patients, those with HF already using loop diuretics have an attenuated response to diuretics.²⁴ Several mechanisms have been proposed to explain this process, such as reduced diuretic efficacy, salt retention, rebound effect, and nephron remodeling.^{2,20} This process generates diuretic resistance, in which diuretics do not achieve the desired decongestion, manifested by low urine sodium concentrations, despite the recommended maximum doses.²⁰ Some adjuvant treatments have been proposed to overcome the problem by maximizing diuretic response and promoting decongestion in patients with HF.

Thiazide diuretics

A strategy to “overcome” diuretic resistance is using thiazides, a class of medications that acts in the distal convoluted tubule, a site different from that where loop diuretics act, suggesting synergy in the diuretic action in the nephron and producing distal blockade of sodium reabsorption.

The most used medications in this context are hydrochlorothiazide e metolazone (considering that metolazone is not available in our setting), in addition to chlorothiazide. Studies conducted so far are promising, with increased diuresis and reduced congestion, but methodology was very limited² and there was remarkable heterogeneity, including with regard to clinical outcomes.²⁵ The doses and medications have been different (in the case of hydrochlorothiazide, the doses used in the studies range from 25 to 200 mg; in the case of metolazone, from 1.25 to 10 mg).

In patients with diuretic resistance, a study comparing metolazone, chlorothiazide, and tolvaptan (a vasopressin antagonist) identified increased diuresis with the addition of any of the three medications, with no difference between the groups, in patients receiving a high-dose of diuretics.²⁶ There was no placebo group in the trial. In a retrospective unicenter study with patients receiving intravenous furosemide, diuresis was greater in those using intravenous chlorothiazide compared to those using oral hydrochlorothiazide.²⁷

Resuming the analysis of the DOSE trial, with regard to the use of thiazides, there was a trend of higher use of thiazides in the low-dose group (23% vs 13%, $p = 0.06$), which may somehow have contributed to study neutrality.²² Furthermore, the largest study in the history of hypertension (ALLHAT) found a reduction in the incidence of HF with use of chlorthalidone,²⁸ there are no studies with the addition of chlorthalidone to loop diuretics in congested patients with HF.

In summary, thiazide diuretics are promising in the treatment of congestion in patients with HF. However, there is scarcity of more robust studies to better

Table 1 – Equipotency between loop diuretics and route of administration^{20,21}

Medication	Furosemide	Torsemide	Bumetanide
Intravenous dose	40 mg	20 mg	1 mg
Intravenous/oral conversion	1:2	1:1	1:1

define effect magnitude. Two clinical trials are currently in progress (ClinicalTrials NCT01647932²⁹ and ReBEC RBR-5qkn8h³⁰), and their results may possibly be published in the near future.

Vasopressin antagonists

The mechanism of action of vasopressin antagonists, especially of the most studied in HF, namely tolvaptan, which was developed in Japan in the 1990s, may be mainly explained by their affinity with V2 receptors located in the collecting duct, thus inhibiting free water resorption³¹ and producing aquaresis, with no electrolyte elimination. With a well defined and innovative mechanism and animal tests with favorable results, randomized clinical trials started to be conducted.³² The first multicenter study on the topic was the ACTIV in CHF,³³ a phase 2 randomized clinical trial that tested different doses of tolvaptan (30 mg, 60 mg e 90 mg) vs placebo in 319 patients with ejection fraction below 40% and decompensated HF. In the three groups, there was a weight reduction compared to the placebo group, with no worsening of renal function or electrolytic disorders. Moreover, in a post hoc analysis, there was greater benefit in more congested patients and with worse renal function. A safety analysis showed that there was a higher number of sudden deaths in the tolvaptan 60 mg group compared with placebo (6% vs 1.3%, $p < 0.01$).

Since tolvaptan passed its initial test, the EVEREST^{34,35} studies were published 3 years later, in which 4133 patients with a profile very similar to those of the previous study, ie, ejection fraction below 40%, functional class III/IV, and decompensation within the last 48 hours, were randomized to tolvaptan 30 mg or placebo. There was no difference between the groups with regard to the primary outcome of hospitalization due to HF or cardiovascular mortality (tolvaptan 42% vs placebo 40.2%, $p = 0.55$).

In summary, these were two more neutral studies that belonged to an era when pharmacological treatment of HF seemed stagnant, with no significant advances.

In relation to diuretic resistance, however, some findings were interesting for patient's compensation: there was greater body weight reduction in 1 (-1.76 vs -0.97 kg; $p < 0.001$) and 7 days, less dyspnea, less edema and, in hyponatremic patients, greater sodium increase in the tolvaptan group. In a subsequent sub-analysis, there was reduced cardiovascular mortality or hospitalization in patients with sodium concentration below 130 mEq/L (hazard ratio: 0.6 [0.37-0.98]); $p = 0.04$), in addition to greater weight loss (0.7 kg on day 1). In another study of a population with HF in an intensive care unit, the amount of continuous furosemide was lower, the urine volume was higher, and the number of patients with worsening kidney injury was lower in the tolvaptan group than in placebo group.³⁶ Furthermore, a clinical trial of 217 patients with renal dysfunction stages 3 and 4 observed that tolvaptan resulted in higher 48-h urine volume (6464.4 ± 3173.0 vs 4997.2 ± 2101.4 mL, $p < 0.001$), with no worsening of renal function compared with placebo, in addition to greater weight loss.³⁷

However, more recently, in the TACTICS-HF³⁸ study of a population with decompensated HF, 257 patients were randomized to tolvaptan or placebo. There was worsening of renal function with tolvaptan (39% vs 27%; $p = 0.037$) and there was no greater relief of dyspnea, thus persisting the findings from previous studies of greater negative water balance. These two similar findings were reproduced in a subsequent study, in which patients with diuretic resistance were randomized,³⁹ but no worsening of renal function was observed.

With regard to diuretic resistance specifically, data are scarce: in addition to the aforementioned study, with 60 patients divided into three groups,²⁶ an open randomized study of 81 patients with HF and renal dysfunction (glomerular filtration rate < 45 mL/min/1.73 m²) showed greater urine output with tolvaptan (in agreement with previous studies in other settings), with no weight loss and with less worsening of renal function. It is worth emphasizing that the concept of diuretic resistance was not strict in this study, being defined as signs of congestion regardless of using a daily dose equal to or greater than 40 mg of furosemide.⁴⁰

In short, vasopressin antagonists did not show benefits in clinical outcomes. Is there room for their use in chronic HF? Absolutely not. Is there room for their use in acute HF? Maybe, in the scenario of patients with significant congestion, hyponatremia, loss of renal function, and actual diuretic resistance.

Nesiritide

One of the responses to situations of myocyte distention (similar to congestive presentations) is secretion of natriuretic peptides – particularly, B-type natriuretic peptide (BNP). As a consequent, there are vasodilatation, neurohumoral modulation and, in addition to other responses, natriuresis.⁴¹

Considering the vasodilatory and diuretic properties, nesiritide, a recombinant BNP, was developed. The proposal seemed interesting, which led to clinical trials. In comparison to nitroglycerin and placebo, there was a favorable hemodynamic response with nesiritide in the VMAC study, which randomized decompensated patients.⁴² However, in outpatient patients with ejection fraction below 40%, hospitalizations for HF and functional class III-IV, there was no reduction in the composite outcome of overall mortality, cardiovascular hospitalization, or hospitalization due to renal causes; thus, the idea of nesiritide was abandoned for this use.⁴³

Initially, results with nesiritide seemed favorable. Nonetheless, subsequent evidence suggested worsening of renal function and increased mortality, which led to a gradual reduction in the use of this medication in the mid-2000s.⁴⁴ As a result, larger and better-designed studies on the topic were subsequently conducted.

The first large clinical trial on nesiritide in acute patients was ASCEND-HF, in which 7141 patients with HF were randomized.⁴⁵ The result was a neutral study, with no effect on mortality or new hospitalization for HF, but perhaps with a better response with regard to dyspnea. As a furosemide

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potentiator, a mechanism that could be interesting in the case of patients with diuretic resistance, the result was also neutral.⁴⁶

The next study on the topic focused on patients with renal dysfunction stages 3 and 4. The ROSE-AHF study compared low-dose dopamine, nesiritide, and placebo.⁴⁷ There was no difference in decongestion or in improvement of renal function between the groups. In 2018, the production of nesiritide was discontinued in the United States.

Mineralocorticoid receptor antagonists

Spironolactone and eplerenone are representative of aldosterone antagonists and of the path of diuretics in HF, promoting reduced mortality in combination with other well-established therapies.⁴⁸⁻⁵⁰ They act on the distal convoluted tubule, and thus have both neurohumoral and diuretic actions. Based on the latter action, it was possible to build the rationale for the use of these antagonists in patients with ADHF.

In ADHF, the first data on the use of de spironolactone in diuretic dose were favorable: less signs of congestion and lower levels of natriuretic peptides.⁵¹ Subsequently, the ATHENA-HF study was published, which involved 460 patients and compared spironolactone 100 mg vs placebo.⁵² The results were neutral, thus failing to show the benefit of spironolactone in ADHF.

Therefore, mineralocorticoid receptor antagonists still have a major role in the treatment of chronic HF, but with no apparent benefit in the context of ADHF.

Sacubitril/valsartan

Sacubitril/valsartan, a combination of an angiotensin blocker with a neprilysin inhibitor, had its effect compared with that of enalapril in the largest study ever performed in patients with chronic HF, the PARADIGM-HF.⁵³ In this study, sacubitril/valsartan promoted a 20% reduction in a primary composite outcome of cardiovascular death or hospitalization for HF (relative risk [RR] 0.80; confidence interval [CI] 0.73-0.87; $p = 0.000002$). There was also a statistically significant reduction of similar magnitude in cardiovascular mortality (RR 0.80 CI 0.71-0.89; $p = 0.00004$) and overall mortality (RR 0.84 CI 0.76-0.93; $p = 0.0001$). The mechanism of action of this drug may be explained by inhibition of BNP degradation, promoted by neprilysin, associated with renin-angiotensin-aldosterone system blockade, promoted by valsartan. As a result, there is an increase in BNP serum levels and, respectively, in its endogenous effects of vasodilatation and natriuresis, both of which are desirable in the treatment of patients with HF.

Based on the foregoing, we may consider sacubitril/valsartan as another medication that may potentially add knowledge in the study of diuretics. In a sub-analysis of the PARADIGM-HF study, there was a decrease in the use of furosemide (or equivalent) in the sacubitril/valsartan arm compared with the enalapril arm: around 2% in 6 months, 4.1% in 12 months, and 6.1% in 24 months.⁵⁴ There are controversies whether reduced diuretic requirement results from improvement in clinical-hemodynamic parameters in patients with HF or from a direct diuretic effect.⁵⁵

In the context of ADHF, the sacubitril/valsartan was again compared with enalapril in the PIONEER-HF study.⁵⁶ Patients hospitalized with ADHF were followed for up to 8 weeks. There was a statistically significant decrease in the primary outcome of serum levels of NT-ProBNP, an outcome replacing clinical improvement in this population. Additionally, there was a 44% decrease in the relative risk of hospitalization for HF.

Furthermore, an additional finding may suggest a clinically relevant diuretic effect: a higher level of hypotension was observed in patients receiving sacubitril/valsartan compared with those receiving enalapril, which may have been caused by a diuretic effect.⁵⁷ However, there is still scarcity of larger studies for a better understanding of the eventual diuretic effect of sacubitril/valsartan.

SGLT-2 inhibitors

More than 150 years have gone from the discovery of the first non-selective sodium-glucose cotransporter inhibitors up to the emergence of current medications. The sodium-glucose cotransporter 2 (SGLT-2) is predominantly located on proximal convoluted tubule and is responsible for absorbing nearly 90% of the glucose filtered by the kidney through a sodium-dependent channel. Natriuresis induced by transporter blockade leads to greater sodium load to the macula densa and, through glomerular feedback, causes afferent arteriole constriction, reducing intraglomerular pressure and proteinuria. Osmotic natriuresis promoted by SGLT-2 inhibitors reduces blood pressure and blood volume, leading to lower pre- and afterload, with consequent reduction in ventricular filling pressures.^{58,59}

The exact mechanism responsible for the beneficial effect of SGLT-2 inhibitors in HF is unknown; however, several of their effects may have a positive impact on this condition, such as blood pressure reduction, blood volume reduction, renin-angiotensin-aldosterone axis blockade, and weight loss.

The decrease of “hard” cardiovascular outcomes (cardiovascular death, infarction, and stroke) related to atherosclerosis in clinical trials was small and limited to patients with established disease, whereas the reduction in hospitalizations for HF and in renal disease progression was robust and not limited to patients with atherosclerotic disease or history of HF.⁶⁰

It is believed that the benefit of SGLT-2 inhibitors in reducing rates of hospitalization for HF results predominantly from their diuretic effect, since patients in clinical trials showed fewer hospitalizations during the first months after randomization.^{61,62} Furthermore, a sub-analysis found a decrease in mortality and in hospitalizations for HF in patients with diabetes and HF, with no phenotypical distinction.⁶³ It is unlikely that the effect on death, HF, and nephroprotection may result from better glycemic control, since the decrease in glycated hemoglobin was slight compared with placebo.⁵⁹ Moreover, SGLT-2 inhibitors have the advantage of not activating neurohumoral mechanisms.⁶⁴

In the DAPA-HF study,⁶⁵ 4744 patients with class III-IV HF and an ejection fraction of 40% or less were assessed. There was

a significant reduction in worsening HF (hospitalization or need for intravenous diuretics), regardless of the presence or absence of diabetes. These results represent an advance in the treatment of HF, being the first clearly demonstrated a reduced mortality in HF with the use of an antidiabetic drug.

Empagliflozin was tested in the EMPEROR-Reduced study,⁶⁶ which randomized 3730 patients with class III-IV HF and an ejection fraction of 40% or less. In this study, there was a reduction in the composite outcome of cardiovascular mortality or hospitalization due to HF worsening on account of reduced hospitalizations.

More recently, sotagliflozin was assessed in patients with diabetes and recent hospitalization due to worsening HF. In the SOLOIST-WHF study,⁶⁷ 1222 patients were evaluated, of which nearly 79% had an ejection fraction below 50% — median 35%. Similar to what was observed in the EMPEROR-Reduced study,⁶⁶ the primary composite outcome of cardiovascular mortality or hospitalizations for IC was lower in the intervention group on account of reduced hospitalizations. The study ended early because of loss of funding from the sponsor. In short, SGLT-2 inhibitors are a promising class in the treatment of HF, with a decrease in hospitalizations and possibly in cardiovascular mortality, without definite data so far in patients with ADHF.

Hypertonic saline

Over the last 20 years, hypertonic saline has been studied with greater interest in the management of congestion in patients with ADHF. Its main rationale is based on the concept of relative hypovolemia, relative to IC, or absolute, due to the use of diuretics. As a response, glomerulus causes a decrease in glomerular filtration rate; by administering hypertonic saline, this glomerular effect may be attenuated or even eliminated, leading to greater diuresis when used in association with furosemide.⁶⁸

First data on hypertonic saline showed increased diuresis, reduced length of hospital stay and BNP levels, improved renal function, and reduced mortality, thus encouraging the continuity of studies.⁶⁹⁻⁷³ However, there is considerable heterogeneity between the studies,^{74,75} and an episode of duplicate data in publications, leading to the retraction of one meta-analysis on the topic.⁷⁶ Furthermore, despite body weight reduction, doubts remain with regard to the actual benefit of hypertonic saline in the resolution of pulmonary congestion.⁷⁷

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Finally, a systematic review and meta-analysis about hypertonic saline that assessed studies with 2.4 to 4.6% saline associated with 500 mg of furosemide administered intravenously twice a day showed that saline improved weight loss, preserved renal function, and decreased hospitalizations for HF, length of hospital stay, and mortality.⁷⁸

Fluid and sodium restriction

Fluid and sodium restriction in congested patients with HF is a very ancient practice, being recommended in the main HF guidelines. However, evidence supporting this recommendation is scarce.⁷⁹ Moreover, there is considerable heterogeneity both in the tested interventions and in the recommended interventions. Generally speaking, the results of the best studies so far in patients with ADHF were neutral and failed to show the benefits of fluid and sodium restriction on weight loss and clinical stability; furthermore, they showed that this restriction increased thirst perception in patients randomized to fluid and sodium restriction.⁸⁰⁻⁸² Hence, there is no evidence recommending routine fluid and sodium restriction in congested patients hospitalized with ADHF and receiving contemporary treatment.

Conclusion

There have been many advances in the study of diuretics, especially during the last 50 years. In possession of current knowledge, clinical physicians can choose from a wide range of options for the best management of congestion in patients with ADHF. There are several open knowledge gaps on the best strategy for congest patients with ADHF, especially with regard to the study of thiazide diuretics, sacubitril/valsartan, and SGLT-2 inhibitors. This may be interpreted as an opportunity window in knowledge, with the combination of diuretics being a reality as an effective therapy in the management of congestion in ADHF, which may occur as evidence advances.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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