Review Article

Diuretic Combinations: Pathophysiology, Evidence, and Clinical Practice

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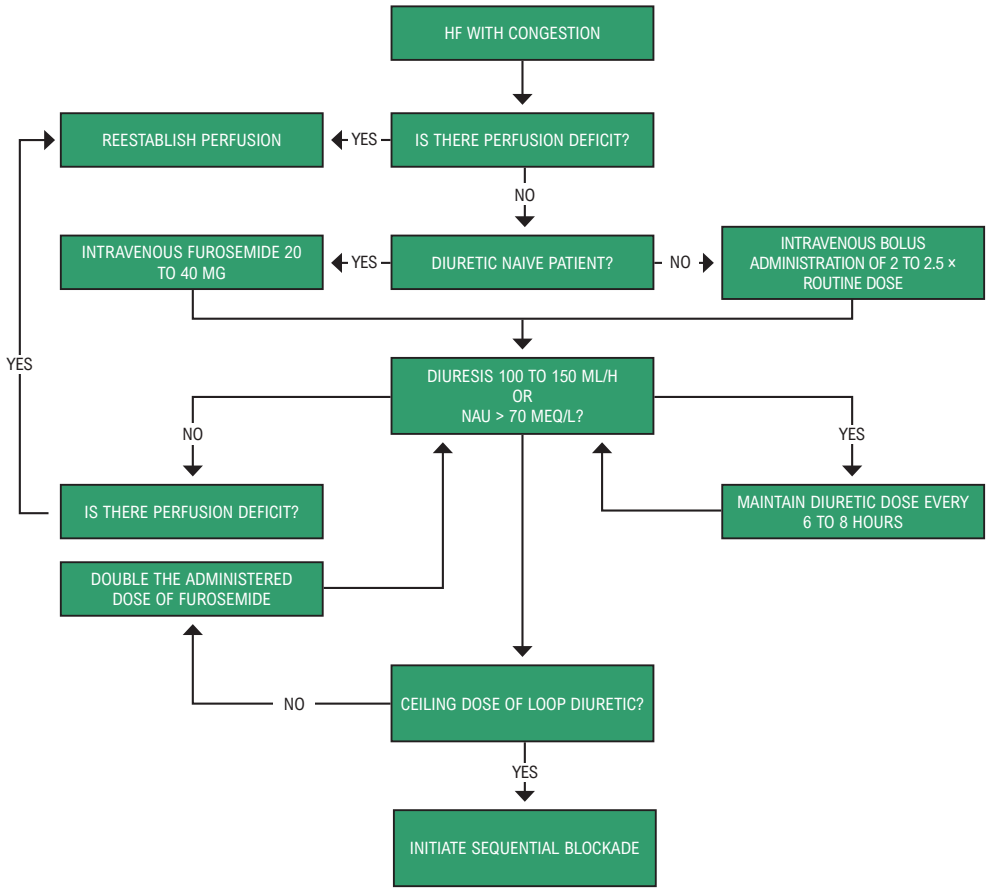
Central Illustration: Diuretic Combinations: Pathophysiology, Evidence, and Clinical Practice



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Flowchart resuming proposed diuretic management in decompensated HF with congestion. HF: heart failure; NaU: urinary sodium concentration.

Keywords

Diuretics; Pathology; Heart Failure.

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Abstract

Heart failure is a highly prevalent syndrome worldwide, including in Latin America, where prevalence rates are estimated at 1.2% to 2.1% of the population. This reality is no different in Brazil, where the syndrome is estimated to affect approximately 2% of the adult population, leading to an overwhelming financial impact of approximately 28.1 billion Brazilian reals in 2015 alone, when the total costs to society and the health system were measured. As if the broad economic impact were not enough, heart failure is

also one of the leading causes and amplifiers of morbidity and mortality, including important prognostic asymmetries when comparing different socioeconomic realities among the population.

In this context, given the unquestionable epidemiological and economic relevance of heart failure, the national BREATHE registry was carried out and published in 2015. It was able to assess that approximately 85.3% of heart failure decompensations in Brazil occurred in profiles with volume congestion, a result that remained similar in the study extension published in 2023. In this type of scenario, the use of diuretics is one of the central pillars of treatment, aiming to correct the volume status and relieve patients' symptoms.

Introduction

Heart failure (HF) is a highly prevalent syndrome worldwide, including in Latin America, where prevalence rates are estimated at 1.2% to 2.1% of the population.[1] This reality is no different in Brazil, where the syndrome is estimated to affect approximately 2% of the adult population, leading to an overwhelming financial impact of approximately 28.1 billion Brazilian reals in 2015 alone, when the total costs to society and the health system were measured.[2] As if the broad economic impact were not enough, HF is also one of the leading causes and amplifiers of morbidity and mortality, including important prognostic asymmetries when comparing different socioeconomic realities among the population.[3] Other registries involving Latin America have also been able to observe that the population over 45 years of age with symptomatic HF reaches an overwhelming 9.3%.[4]

In this context, given the unquestionable epidemiological and economic relevance of HF, the national BREATHE registry[5,6] was carried out and published in 2015. It was able to assess that approximately 85.3% of heart failure decompensations in Brazil occurred in profiles with volume congestion (Figure 1), a result that remained similar in the study extension published in 2023.[6] In this type of scenario, the use of diuretics is one of the central pillars of treatment, aiming to correct the volume status and relieve patients' symptoms.[5] Therefore, given the devastating numbers of syndromic prevalence, as well as the predominant profile of clinical presentations, this review was designed to substantiate and systematize the approach to diuretic therapy in decompensated HF.

Neuroendocrine and circulatory pathophysiology of decompensated heart failure

In its genesis, HF syndrome involves increased heart cavity pressures, which trigger multiple neuroendocrine loops that culminate in hydrosaline retention, increased catecholaminergic tone, and loss of the ability to modulate systemic vascular resistance.[7] In view of this, it is also worth noting the important role that the splanchnic venous bed plays in the process of volume redistribution and systemic congestion. This system is a high-capacitance vascular bed, and its primary function is to act as a reservoir of

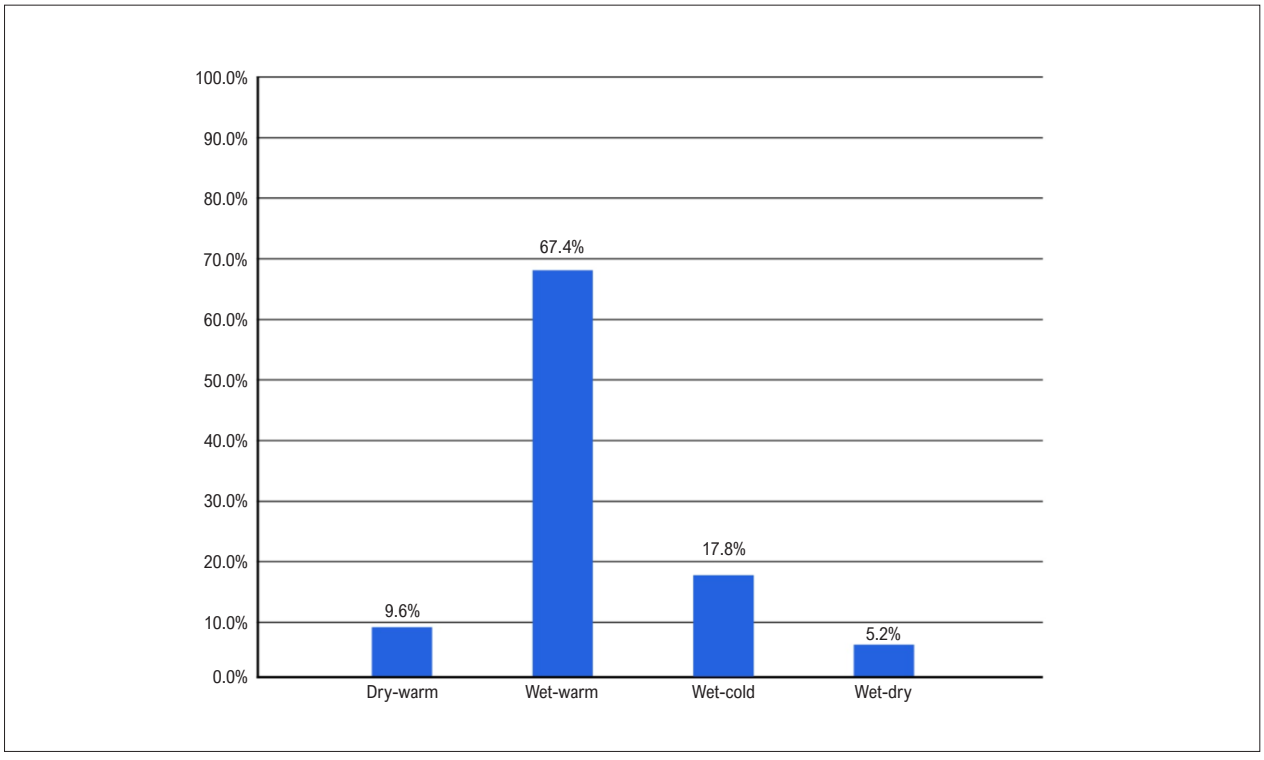

Figure 1 – *Hemodynamic profiles of heart failure decompensation in the BREATHE registry.5 Adapted by Albuquerque et al.[6]*

non-stressed volume. This non-stressed volume is primarily a large volume reservoir, and its recruitment is through the stimulation of alpha-adrenergic receptors, which are abundant in this bed.

In patients with HF, activation of adrenergic loops leads to hyperstimulation of these receptors, redistributing volume that, under normal conditions, would not be stressed to the systemic circulation, causing congestion. Accordingly, when proposing the use of vasodilators, such as nitrates, the aim is to reestablish capacitance closer to the original one of the venous bed and to favor the outflow of systemic congestion. As illustrated in Figure 2, in a model of vasculocentric circulatory compression, by reducing central venous pressures, it is possible to optimize venous return, which allows better flow from the periphery to the heart. In this model, the mean systemic filling pressure governs the venous system, so that the determinants of flow optimization (Q) are the amount of stressed volume and right atrial pressure. Therefore, recovering capacitance is equivalent to reducing the systemic outflow point, making it more efficient.[8]

Once the compartmental volumes have been redistributed, it is also necessary to readjust the volume content to the vascular and tissue structures, which is achieved through diuretic-induced natriuresis.

Treatment of congestion

The use of diuretics is extremely common in HF treatment, and they are the most widely used class of drugs prescribed to hospitalized patients (Figure 3).

This approach becomes especially important in view of the therapeutic targets for hospitalized patients with HF, as put forth by the Brazilian Society of Cardiology,[9] which involve the following:

- Diuresis of 1.5 to 2.5 ml/kg within the first 6 hours;
- Absence of orthopnea and heightened respiratory effort within the first 24 hours;
- Absence of dyspnea upon minimal effort within 72 hours;
- Oxygen saturation greater than 90% on room air;
- Heart rate less than 100 beats per minute;
- Respiratory rate less than 22 breaths per minute;
- Systolic pressure below 110 to 130 mmHg.

Diuretic classes

Loop diuretics

Loop diuretics are the most widely used class in the decongestion process in HF due to their great potential to induce natriuresis and negative fluid balance. Their mechanism of action (Figure 4), involves blocking the sodium-potassium-chloride cotransporter (NKCC) in the ascending limb of the loop of Henle, leading to dilution of the medullary gradient and reducing hydrosaline reabsorption capacity in the functional units of the kidney.[10]

The main representatives of the loop diuretic class are furosemide, bumetanide, and torsemide; the latter is not yet available in Brazil. Routinely used dosages and intervals are displayed in Figure 5. It is important to note that the dose spectrum of loop diuretics is quite broad, and the decision regarding the doses applied in the decongestion process for each patient can be better elucidated by understanding

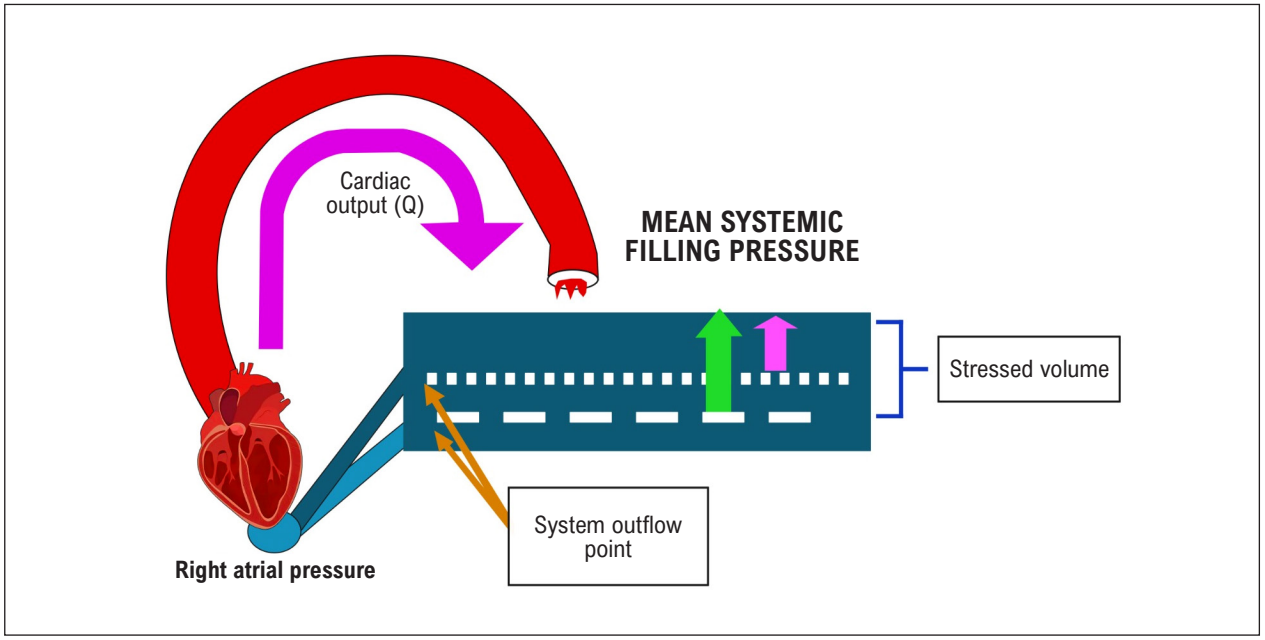

Figure 2 – *Schematic example demonstrating that increasing the capacitance of the venous bed results in optimized venous return and, therefore, outflow of vascular and tissue congestion. Adapted Magder.[8]*

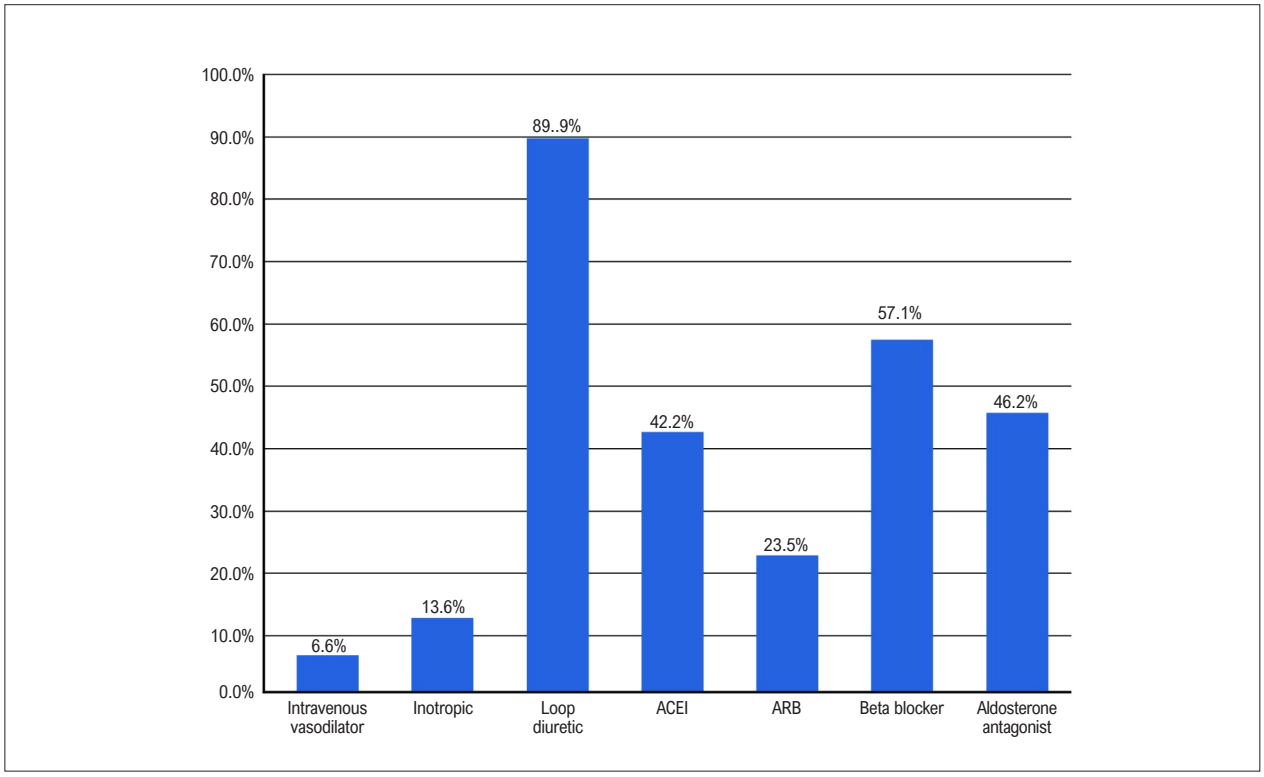

Figure 3 – *In-hospital medications prescribed for the treatment of acute heart failure. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker. Adapted by Rohde et al.*[9]

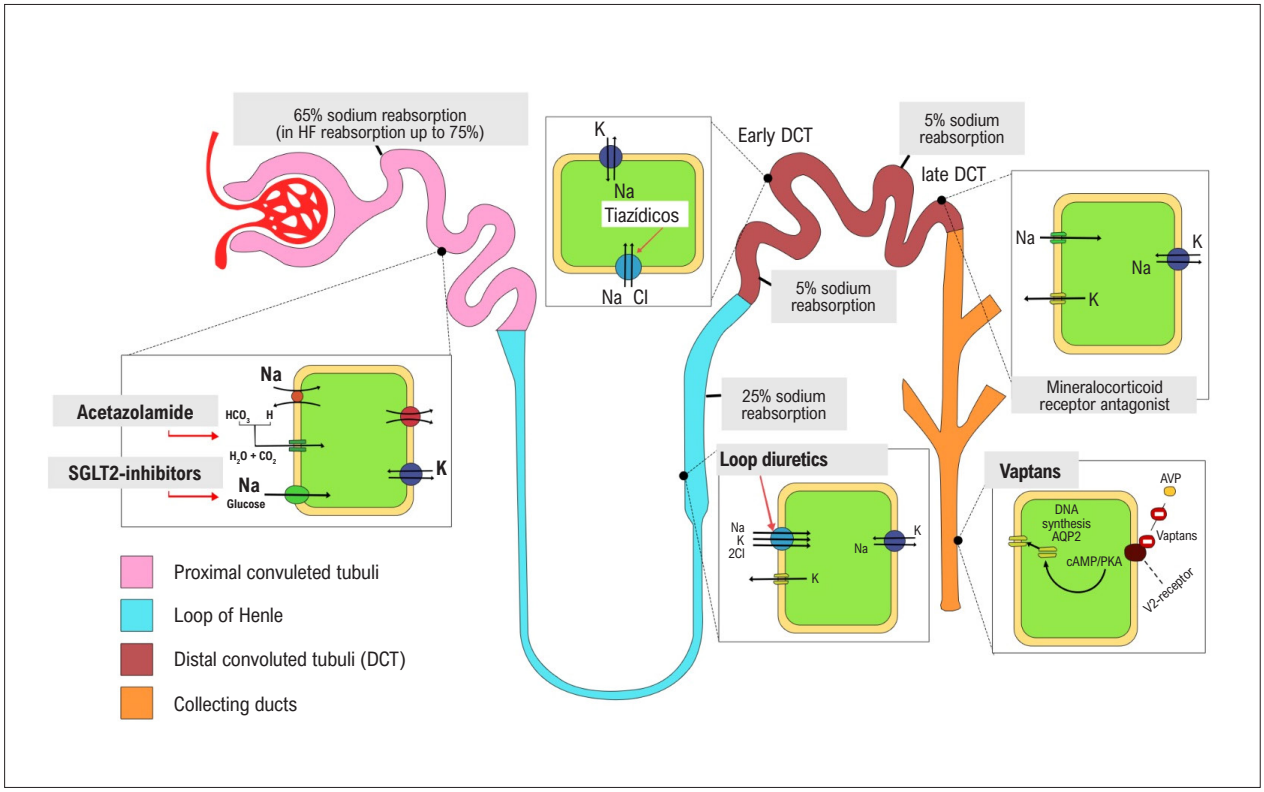

Figure 4 – *Mechanisms of action of diuretics used in the decongestion process. Adapted by Mullens et al.11 DCT: distal convoluted tubuli; HF: heart failure.*

Dosages and intervals of diuretics

Diuretics	Route	Initial dose (mg)	Interval (hours)	Maximum dose (mg)
Loop diuretics				
Furosemide	IV	20	4-4/6-6	240
Bumetanide	IV	0.5 to 2.0	6-6	10
Thiazides				
Hydrochlorothiazide	Oral	25	24-24/12-12	100
Chlorthalidone	Oral	12.5	24-24/12-12	50
Indapamide	Oral	2.5	24-24	5.0
Potassium-sparing agents				
Spironolactone	Oral	25	24-24/12-12	50
Amiloride	Oral	2.5	24-24	20
Triamterene	Oral	2.5	24-24	100

IV: intravenous.

Figure 5 – *Classes, dosages, and intervals of diuretics routinely used in the decongestion process. Adapted Rohde et al.*[9]

the concepts of bioavailability, drug half-life, and diuretic threshold. The bioavailability of orally administered furosemide is extremely limited and variable, making the intravenous route preferable for administration during the decongestion process. Nevertheless, the drug's half-life is approximately 6 hours. During this period, the plasma concentration of the drug must be able to exceed the patient's diuretic threshold. Therefore, administrations at shorter intervals (4 to 6 hours for each dose) are preferable, as long as the doses administered at each time are capable of inducing a urinary output compatible with what is desired for the decongestion process.[10]

Specifically in HF, the activation of neurohumoral axes that result in hydrosaline retention are substantially amplified, and the induction of natriuresis and negative fluid balance may require high doses of furosemide.[10] To better elucidate the approach to dosage and results of decongestion, the DOSE Trial[12] evaluated 308 patients in a 2-by-2 factorial randomized, placebo-controlled design for continuous versus intermittent infusion in high-dose groups (defined as 2 to 2.5 times the previously used oral diuretic dose) versus low-dose groups. Although the study was negative regarding the primary outcome of subjective symptom improvement, different pre-specified secondary outcomes, such as objective improvement in dyspnea, weight loss, and negative fluid balance, were achieved in a consistent and statistically significant manner in the group that received higher doses of diuretics. It is also important to underscore that there was no difference between the continuous and intermittent infusion groups, with a greater number of adverse effects in worsening renal function in the continuous administration group. These findings rationalize the proposals that, during the decongestion process, high doses of loop diuretics should be applied and continuous or intermittent administration is not relevant, provided that each patient's intervals and diuretic thresholds are respected. Worsening renal function during the decongestion process occurs in 30% to 50% of patients hospitalized for HF, and this incidence varies substantially depending on the definition of worsening renal function applied.[13]

A final observation on the use of diuretics in the decongestion process is the concern regarding hypotension associated with the use of high doses of diuretics. This issue has been evaluated in multiple studies, including the DOSE Trial itself,[12] in addition to studies with models of patients using substantial doses of vasopressors and lung injury associated with sepsis,[14] and they did not observe greater incidence of hypotension in the arms of patients exposed to high doses of loop diuretics. In this context, it is necessary to propose that the use of loop diuretics, ideally in high doses, is the centerpiece in treatment of congestion and does not depend on absolute blood pressure levels, although it may depend on perfusion parameters, which are often dissociated from one other in patients with HF.[10]

Mechanisms of resistance to loop diuretics and their clinical implications

A significant proportion of patients hospitalized for HF with congestion are unable to achieve decongestion targets despite the use of high doses of loop diuretics.[15] This occurs due to several mechanisms, including the following: low chloride concentration in the NKCC pump, generally present in more advanced stages of the decongestion process; hypoalbuminemia, since this is the serum protein that carries furosemide from the plasma to its effector site; poor perfusion states in which correction

of the perfusion deficit is a priority, including in relation to decongestion itself, and which can be resolved with the use of inotropic agents.[16]

In the case of hypochloremia, it is intuitive to conclude that its occurrence is due to rarefaction of the substrate necessary for the NKCC cotransporter, inhibited by the diuretic, resulting in reduced efficacy of the drug. In these situations, it is possible to consider providing chloride in high concentrations, for example, by means of 3% saline solution concomitantly with diuretic therapy, to achieve the desired natriuresis. Furthermore, furosemide is carried by albumin in plasma, and severe hypoalbuminemia impairs the delivery of the drug to its effector site. Thus, the administration of albumin solution may also be able to maximize diuretic-mediated urinary output.[10,11,15] There is still room for debate as to whether this increase in diuresis mediated by albumin delivery is due to greater availability of the carrier or to the inexorable delivery of chloride, since the concentration of this ion is high in the majority of commercially available albumin solutions.[17]

Thiazides

Even in view of the aforementioned corrective measures, it is possible that patients are unable to establish negative balances compatible with the treatment goals, making it necessary to combine diuretics with the aim of blocking sequential segments of the nephron, as shown in Figure 4.[15] This is because the activity of distal tubular sodium reabsorption seems to be supplanted by the blockade of different parts of the nephron.[17] Thus, they are used in conjunction with loop diuretics according to the dosages explained in Figure 5. It is also worth noting that the use of thiazide diuretics in monotherapy is not encouraged, seeing that their isolated natriuretic potential is lower than that of loop diuretics.[11]

It is necessary to consider that sequential nephron blockade with the combined use of thiazides and loop diuretics necessarily involves a greater risk of serious hydroelectrolytic disorders, such as hyponatremia and hypokalemia,[18] which require caution and monitoring of concentrations in order to correct their plasma concentrations.

Mineralocorticoid receptor antagonists

The use of aldosterone receptor antagonists is highly recommended in the subgroup of patients with HF with reduced ejection fraction.[19-21] However, their use as diuretic adjuvants in the decongestion process has been little studied, and the largest study that concluded their efficacy and safety for this purpose was the ATHENA-HF Trial.[22] In this publication, the authors randomized patients to high doses (100 mg/day of spironolactone) versus low doses or placebo (12.5 to 25 mg/day of spironolactone) with the evaluation of the surrogate endpoint of NT-proBNP levels at baseline and 96 hours after randomization, concluding that there was no difference regarding the primary endpoint or intermediate endpoint, including urinary output, decongestion time, diuretic doses used, or improvement in subjective dyspnea scores, between the groups that received low doses or high doses of spironolactone. However, the study concluded that high doses of spironolactone were widely safe in terms of the occurrence of hyperkalemia, hypotension, or worsening renal function, leaving open the possibility of future studies evaluating even higher doses, such as 200 to 400 mg of spironolactone per day, which are usually used in patients with liver cirrhosis. In any case, guidelines for the management of acute HF still recommend low to intermediate doses.[9,23,24]

Carbonic anhydrase inhibitors

Acetazolamide is a carbonic anhydrase inhibitor that acts on the proximal convoluted tubule, reducing sodium absorption in this nephron territory.[25] Its use in the decongestion process was evaluated in the ADVOR Trial,[25] a multicenter, double-blind, placebo-controlled study that evaluated the addition of intravenous acetazolamide to the diuretic regimen of hospitalized patients with congestive HF. In this study, there was greater success in decongestion (defined as the absence of signs of volume overload assessed by a trained cardiologist) in the acetazolamide group, thus making it possible to conclude that it plays a role as a natriuretic adjuvant in this population. It is also interesting to note that, in the ADVOR Trial, the dosage of acetazolamide used was 250 to 500 mg per day of the intravenous formulation, which is not available in Brazil.

Vasopressin receptor antagonists

The neurohumoral regime in HF reaches the common point of hydrosaline retention, and the consequent positive fluid balance with symptoms of congestion is also mediated by the arginine-vasopressin (AVP) pathway. [26]

In light of this knowledge about the AVP system, a new class of diuretics was created, namely, vasopressin receptor antagonists, also known as "vaptans." They act at the level of the collecting duct, inhibiting V2 receptors and promoting "aquaresis" by inhibiting aquaporins, which are channels that promote water reabsorption in this nephron territory.[27] Their mechanism of action gives the class the specific potential to act directly on one of the major pathways that result in hyponatremia, an isolated prognostic marker in HF.[28] There are several representatives of the vaptans class, but tolvaptan is especially interesting for patients hospitalized with HF, as the EVEREST Trial[29] compared tolvaptan versus placebo as a diuretic adjuvant in the decongestion process. The study was negative for its primary outcome of reduced all-cause mortality and for the combined outcome of reduced mortality and hospitalization for HF. However, it was positive for several intermediate outcomes that are highly relevant to the decongestion process, such as weight loss, improved dyspnea, and resolution of hyponatremia and edema. Although they have exhibited an excellent hemodynamic profile with good decongestion results, the use of vaptans is limited by their high cost, so that they are currently considered a cost-effective treatment only in the subpopulation of patients with high doses of furosemide and hyponatremia.[30] Furthermore, tolvaptan is not currently available in Brazil.

SGLT2 Inhibitors

Inhibitors of the sodium-glucose cotransporter in the proximal convoluted tubule play an established role in

populations with diabetes and high cardiovascular risk,[31-33] patients with HF with reduced ejection fraction,[34,35] and patients with HF with preserved ejection fraction.[36,37] The benefits offered to specific populations are so broad and compelling that Eugene Braunwald went so far as to consider them the statins of the twenty-first century.[38] Despite their well-deserved fame, SGLT2 inhibitors do not yet appear to play a central role as diuretics in the treatment of acute HF with congestion, seeing that their natriuretic effect is limited and short-lived, and their benefits are attributed to other characteristics of modulation of myocardial energy metabolism and systemic metabolism.[39] Even so, they are safe to introduce in this scenario,[40] and they add medium-term benefits when introduced during hospitalization[40,41] or on an outpatient basis in patients who are experiencing clinical worsening.[40]

Decongestion process and renal function

During the decongestion process, up to three quarters of patients may present worsening renal function, which may or may not be permanent.[12] In this context, it is natural to conclude and possible to observe that those who present persistent dysfunction tend to have worse prognosis; however, it is interesting to highlight that those who recover renal function after hospitalization have similar prognosis to those whose renal function remained unchanged.[12] Furthermore, during the decongestion process, some serum components tend to concentrate, such as hematocrit. In the ESCAPE Trial,[42] patients who presented hemoconcentration were strongly associated with worsening renal function, but they were also the group with the best survival after hospitalization.[42] Accordingly, it is possible to infer that complete decongestion is a priority for protecting renal function during the process of volume correction, since hospital discharge with residual congestion is strongly correlated with early readmission and increased mortality.[43]

In addition to volume and hydrostatic considerations that concern the maintenance of renal filtration and secretion capacity, the perfusion status of patients hospitalized with HF must also be routinely assessed. This is because up to 23% of hospitalizations occur in so-called "cold" profiles,[5,6] and, when a perfusion deficit is present, the priority is to correct it, to the detriment of resolving fluid intoxication, since other key organs, such as the brain and heart, may also be at risk of perfusion. Finally, the analysis of biomarkers that indicate tubular injury in patients undergoing aggressive diuretic therapy for decongestion in HF in the ROSE Trial[44] allowed the conclusion that worsening serum markers of renal function was not accompanied by indicators of tubular injury,[44] thus reinforcing the current concept that fluctuations in urea and creatinine are mostly benign findings resulting from a phenomenon of water redistribution, to the detriment of the impression of kidney injury with long-term complications.[44]

Achieving Euvolemia

Assessing bedside volume is extremely challenging, to the point that trained examiners, when guided exclusively by physical examination findings, demonstrate much lower accuracy than would be desired.[17] Accordingly, it is necessary to assess multiple variables in a serial manner in order to obtain greater accuracy. For this purpose, it is possible to use, for example, daily body weight measurement, radiological instruments such as chest X-ray, volume assessment with point-of-care ultrasound, laboratory measurements such as NT-proBNP at discharge in relation to admission, and invasive measurements such as pulmonary artery catheter or transpulmonary thermodilution measurements. A possible approach to the decongestion process is shown in the Central Illustration, where the points always revolve around ensuring adequate perfusion and aggressive choice of diuretic therapy dose.

Conversion to outpatient care

While they are still in the hospital, patients with HF must demonstrate clinical and volume stability for 24 hours on the oral drug regimen in order for discharge to be considered safe.[17] It is possible that discharge may be necessary while still on sequential blockade, especially in patients who require high doses of furosemide. In addition to hydrosaline management, it is necessary to ensure that patients are using the maximum dose tolerated during the hospital stay of the four classes of medications capable of altering their prognosis in the short, medium, and long term.[9,17,23,24] Finally, in the outpatient setting, it is important for these patients to be monitored with a regimen of more frequent visits in the post-discharge period, given that this is a period of greater fragility and risk of readmission, in addition to aggressive titration of disease-modifying doses.[45]

Take-home messages

- The vast majority of patients with decompensated HF are found to be in volume overload at the time of decompensation;
- The aggressive pursuit of euvolemia is a priority to the preservation of nitrogenous waste;
- The combination of more than one diuretic class has proven to be an effective strategy to achieve decongestion;
- Patients' perfusion status and urinary output should be reassessed at all times;
- Resolving congestion is as important as initiating treatment, even before discharge, with medications that are capable of impacting the medium- and long-term prognosis of patients with HF.

Conclusion

HF is a globally relevant problem, with major economic and human impacts. During its treatment, whether in-hospital or not, it is highly likely that the use of diuretics will be necessary for better volume management, and it is essential to understand the particularities of each class in order for the management of cases to be as assertive as possible, always aiming to minimize the chances of hospitalization and improve quality of life.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Mourilhe-Rocha R, Ribeiro PF; Critical revision of the manuscript for content: Mourilhe-Rocha R, Ribeiro PF, Sales ALF, Spinetti PPM, Albuquerque FN, Bittencourt MI.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

This study is not associated with any thesis or dissertation work.

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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