Treatment Strategies for Refractory Congestion

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Abstract

Worsening congestion is the main reason for hospitalization of most acute heart failure (AHF) patients. However, most patients are discharged with residual congestion, resulting in early readmissions that portend poor outcomes. Diuretics remain the mainstay of therapy. Nevertheless, these drugs stimulate the renin-angiotensin–aldosterone (RAA) axis and the sympathetic system and elicit adaptive responses in the nephron that may be counterproductive and lead to diuretic resistance. Renal failure and AHF are common and coexist in up to 40% of cases. Diuretic strategies that rely on combinations of diuretics are emphasized as a method to prevent resistance. If diuretic resistance does develop, higher-dose combination regimens, hypertonic saline solution, and mechanical ultrafiltration can be used to overcome diuretic adaptations and restore diuretic efficacy.

Introduction

Acute heart failure (AHF) accounts for 22.8% of admissions for cardiovascular causes in Brazil, according to the Ministry of Health hospital information system maintained by the Unified Health System (SUS - Sistema Único de Saúde). Despite the high cost of episodes of heart failure decompensation, rates of hospital readmission and death remain high. Intrahospital mortality from AHF in Brazil was 12.6%, according to data from the BREATHE study, which is much higher than rates in developed countries.

Hypervolemia is one of the pathophysiologic pillars of AHF, whether because of fluid retention or because of volume redistribution. Congestion was observed in 90 and 93% of patients in the BREATHE and ADHERE (The Acute Decompensated HEart Failure National REgistry) registers respectively.

Despite the near universal use of diuretics in hospitalized patients with AHF, many patients leave hospital without adequate decongestion. In the ADHERE registry, it was found that 33% of patients had lost a maximum of 2.5 kg at hospital discharge, while 20% had gained up to 5 kg while in hospital. This is even a common occurrence in clinical trials, which are situations that are far from representative of the “real world” of clinical practice. For example, 48% of participants in the classic studies DOSE-AHF (Diuretic Optimal Strategy Evaluation in Acute Heart Failure) and CARRRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure), which will be covered in detail below, still had residual congestion at hospital discharge. Concerns with worsening renal function associated with restoration of normovolemia are not justified, since it has been demonstrated that presence of congestion is a better predictor of mortality than creatinine elevation in patients discharged after AHF decompensation (Figure 1). On the other hand, elevated creatinine in conjunction with persistent signs of congestion indicates poor prognosis, because it is often associated with diuretic resistance.

Diuretic resistance is defined as incapacity to achieve decongestion despite using diuretics at appropriate doses. The lack of a consensus on specific criteria to define diuretic resistance means that its true prevalence is unknown. However, it is known to be an ominous complication of AHF that is predictive of mortality.

The pathophysiology of resistance to diuretics is complex and has not yet been fully understood. It involves a myriad of factors (Figure 2) that act in synergy to create and perpetuate the insufficient response to diuretics. Reabsorption of sodium in the distal tubules has emerged as one of its main determinants and it is known that hypertrophy of distal tubule cells is present after even a few days of treatment with loop diuretics, which results in increased sodium resorption. The “braking phenomenon” is already well known. This is a term used to designate the reduction in response after repeated doses of diuretics. It is a homeostatic mechanism that strives to prevent excessive volume depletion during continual exposure to diuretics, but which is exacerbated in patients with AHF and contributes to diuretic resistance.

The principal predictor of renal failure in patients with AHF is central venous pressure. The increased venous pressure is transmitted retrogradely to the renal vein, reducing glomerular filtration pressure and natriuresis capacity and setting up a vicious cycle that perpetuates congestion. It is essential to identify patients with diuretic resistance early, so they can be given the appropriate treatment.

Keywords

Heart Failure; Diuretics; Ultrafiltration.

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Treatment of congestion

Loop diuretics

Loop diuretics (furosemide, torsemide, and bumetanide) are essential medications in the management of hypervolemic patients, because they have greater natriuretic potential. The AHF treatment guidelines emphatically recommend use of diuretics to relieve the signs and symptoms of fluid overload.
Adequate management of these medications requires knowledge of their pharmacokinetic and pharmacodynamic properties. In contrast with the other members of this drug class, the bioavailability of furosemide is variable (10 to 90%) and is even more erratic in the presence of AHF, which generally involves loop edema. Next, furosemide is transported in the convoluted proximal tubule by the organic acids transport system and reaches Henle’s loop, where it inhibits NKCC2 cotransporter in the thick ascending limb. It also inhibits the same symport in the apical membrane of macula densa cells, blocking chloride reabsorption and stimulating renin secretion. This neurohumoral activation can contribute to perpetuation of harmful effects in patients with AHF.

Loop diuretic dose is chosen empirically and should be guided by urinary output and clinical status. Excessive use of diuretics activates reflex neuro-hormonal mechanisms and was linked with worse outcomes in the ESCAPE study (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness). It should be remembered that patients who are chronic diuretic users will probably need higher doses. Diuretics have an S-shaped dose-response curve (Figure 3), and both AHF and renal failure shift the curve to the right, since higher doses are needed to achieve the maximum natriuretic response. In renal failure, furosemide and organic acids that accumulate in uremia compete for tubular secretion, in a situation analogous to what happens with administration of nonsteroidal anti-inflammatory drugs.

Furosemide doses and administration strategies were compared in the DOSE multicenter study (Diuretic Optimization Strategies Evaluation), which is the largest clinical trial that has been conducted to date addressing this issue. The study enrolled 308 patients with AHF and used a factorial 2x2 design to assign them to intravenous administration of furosemide at a dose 2.5 times greater than their daily dose (high dose groups) or at the same dose as their oral dose (low dose groups) and to either receive intermittent doses (twice a day) or by continuous infusion for 72 hours. The patients were given an average of 260 mg or 120 mg of furosemide (high and low dose groups, respectively). There were no differences between groups in terms of overall symptoms assessment (primary outcome). However, the high dose group had greater relief of dyspnea, greater weight loss, and greater liquid loss (secondary outcomes). Worsening renal function by 72 hours (the other primary outcome) tended to occur more frequently in the high dose group. The authors also failed to detect any difference between the continuous infusion and intermittent dose diuretic administration strategies, which was possibly related to absence of a loading dose at the start of continuous infusion.

A post hoc analysis of the DOSE study data showed that an increase in creatinine concomitant with diuretic treatment was paradoxically associated with better outcomes. This association was also observed by other authors and probably reflects changes in glomerular hemodynamics, and not tubular injury. To the extent that withdrawal, or even a decrease of the diuretic dose is not warranted in the event of renal dysfunction, if signs of hypervolemia are still present.
**Figure 2** – Mechanisms of diuretic resistance and proposed treatments. NSAIDs: non-steroidal anti-inflammatory drugs; ARB: angiotensin receptor blockers; ACEi: angiotensin-converting enzyme inhibitors; ARNI: angiotensin receptor and neprilysin inhibitors; GFR: glomerular filtration rate. Adapted from Jentzer et al.\(^{14}\)

**Figure 3** – Relationship between natriuresis and loop diuretic concentration logarithmic scale. Adapted from Ellison DH\(^{7}\)
Thiazide diuretics

Thiazide diuretics (hydrochlorothiazide, chlorothiazide, and others) and “thiazide-like” diuretics (metolazone, chlorothalidone) block the sodium and potassium cotransporter in the distal convoluted tubule and can, at least partially, counterbalance the increased sodium resorption that is associated with chronic use of loop diuretics. When used as monotherapy, they have a natriuretic effect equivalent to 30 to 40% of the effect of loop diuretics. Different members of the class basically differ in terms of their pharmacokinetic characteristics. In Brazil, only hydrochlorothiazide and chlorothalidone are available.

Combinations of thiazide and loop diuretics are often used to overcome diuretic resistance, although the evidence for doing so is not robust. While there are more than 50 publications on the subject, just 300 patients with AHF were enrolled on small studies, many without control groups, and with primary focus on physiological variables, rather than clinical outcomes. There are two ongoing clinical trials that will provide more information about the magnitude of the effect of this combination (ClinicalTrials NCT016479329 and ReBEC RBR-Sqkn8h30).

Certain concepts that are used in clinical practice, but which have not been confirmed in clinical trials merit discussion. The first is that metolazone could be more effective for combined treatment with loop diuretics, possibly because of its inhibitory effect on the proximal tubule, but there was no evidence of superiority in comparative studies. The second concept is that thiazide should be administered 30 minutes before the loop diuretic, but this has not been assessed in studies of combination use of diuretics.

Hydroelectrolytic disorders are more common with thiazide than with loop diuretics. The potential for calciuresis is greater because two to three potassium ions are lost for each sodium ion excreted. The combination of these two drug classes, in particular, greatly increases the predisposition to hypokalemia, which was present in almost two thirds of the patients in one clinical trial. The North-American AHF guidelines recommend that the combination with thiazide should be reserved for cases that do not respond well to moderate high doses of loop diuretics.

Mineralocorticoid receptor antagonists (MRA)

Spironolactone is the only mineralocorticoid receptor antagonist (MRA) available in Brazil. It has been used as part of treatment to modify the disease in heart failure with reduced ejection fraction (HFrEF) because of its pleiotropic effects. When used at high doses, it has diuretic properties. Use of spironolactone may be useful to counterbalance secondary hyperaldosteronism provoked by loop diuretics (30). High aldosterone levels have a harmful effect on the myocardium, contribute directly to diuretic resistance, and have been associated with increased rates of mortality and readmission for AHF.

These data were the basis for the ATHENA-HF study (Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure), a double-blind clinical trial that compared addition of spironolactone in high doses (100 mg) or usual doses (25 mg) to the standard treatment of 360 patients with AHF. The sample comprised patients with AHF, but without the criteria for diuretic resistance. Although this treatment was well-tolerated, administration of high doses of MRA did not result in any differences in the primary outcomes (plasma levels of N-terminal fragment of B-type natriuretic peptide [NT-proBNP]) or secondary outcomes (relief from congestive symptoms, dyspnea grade, urinary output, or weight loss). The short protocol duration (96 hours) is insufficient for the active metabolite of potassium canrenoate to accumulate and probably contributed to the null results, as did the fact that the study did not include patients with a very high severity profile.

Despite the results of ATHENA-HF, use of spironolactone in high doses is one option for avoiding hypokalemia in patients taking large quantities of potassium wasting diuretics.

Carbonic anhydrase inhibitor

From a pathophysiological point of view, strategies that target the proximal tubule could offer some benefit could offer some benefit for treatment of congestion. This segment is where the greatest quantity of sodium is reabsorbed, particularly in conditions such as AHF.

Acetazolamide blocks reabsorption of sodium bicarbonate in the proximal convoluted tubule by inhibiting the carbonic anhydrase enzyme. A greater quantity of sodium is therefore available for exchange at the level of Henle’s loop, increasing the effect of loop diuretics, particularly in renal malperfusion states. Furthermore, the greater quantity of chloride available in the macula densa can inhibit renin secretion (reducing neurohormonal activation). When administered as monotherapy, acetazolamide has very poor natriuretic activity and so its use is restricted to combined therapy. It can be useful for treatment of metabolic alkalosis induced by loop diuretics.

Some small observational studies demonstrated that acetazolamide had a positive impact on natriuresis. One of them showed that acetazolamide increased diuretic efficiency in patients with AHF, with additional excretion of 100 mmol of sodium for each 40 mg of furosemide equivalent administered. The second observed an increased diuretic response to addition of 250 mg of acetazolamide, similar to the response achieved by doubling the furosemide dose.

The ADVOR study (Acetazolamide in Decompensated Heart Failure With Volume Overload) is a double-blind randomized clinical trial that is ongoing in Belgium, with completion predicted for 2022. This study enrolled around 500 patients to test the effect of adding 500 mg of intravenous acetazolamide or placebo to a high dose loop diuretic regimen.

Tolvaptan

Arginine vasopressin antagonists (or vaptans) were developed to selectively block the V2 receptor (tolvaptan) in the collecting duct. The V2 receptors increase aquaporin-
mediated water reabsorption. Blocking it therefore increases excretion of electrolyte-free water, with no effect on excretion of electrolytes. These drugs are therefore considered aquaretics.

Tolvaptan was tested in the ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure) and EVEREST studies (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan). In both studies, there were benefits for weight loss, dyspnea, and edema, and improvements in hyponatremia, without impact on mortality or rate of readmission for AHF.

Despite the neutral results for mortality and hospital admissions, tolvaptan demonstrated some favorable effects in patients with diuretic resistance in the EVEREST trial, such as greater weight loss, less dyspnea, and less edema. Notwithstanding this result, there is scant evidence to recommend tolvaptan for treatment of diuretic resistance. It is not currently approved by the Food and Drug Administration (FDA) for treatment of AHF, but it is approved for treatment of associated hyponatremia.

Ultrafiltration

Ultrafiltration (UF) is an alternative to diuretics for treatment of hypervolemia. It consists of passing blood through hollow fibers surrounded by semipermeable membranes, subjected to a pressure gradient. The result is mechanical removal of fluid, termed the ultrafiltrate. Ultrafiltration removes sodium more effectively because whereas the ultrafiltrate is isonatremic in relation to plasma, diuretics produce hypotonic urine, with around 60 to 80 mmol of sodium per liter. Moreover, it does not trigger neuro-hormonal responses or stimulate the macula densa. In other words, the process of decongestion is physiologically different.

To date, seven clinical trials have been published comparing UF with pharmacological treatment in patients with AHF, five of which examined clinical outcomes. The largest of these enrolled 224 patients, highlighting the difficulty of recruiting participants for studies evaluating invasive methods of treatment.

The first clinical trial was the RAPID-CHF (Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure), with just 40 patients randomized to UF or pharmacological therapy. The study observed that UF improved symptoms and provoked greater loss of liquid, but with no differences in weight.

The first large study was published in 2007, randomizing 188 patients for a single UF session or standard treatment with diuretics within 24 hours of admission for AHF: the UNLOAD study (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure). The results were positive, since there was a 52% reduction in unplanned visits after hospital discharge, a 44% reduction in hospital admissions for AHF, and a 63% reduction in days in hospital after readmission. Some limitations of UNLOAD should be noted, such as that it was sponsored by industry and did not have an independent events committee.

The CARRESS-HF study was published next, enrolling 188 patients on a randomized clinical trial, funded by the National Heart, Lung, and Blood Institute. This study compared the effects of UF at a fixed velocity of 200 mL/h with goal-paced drug treatment (loop diuretics, thiazide, vasodilators, and inotropics). No significant differences were observed in outcomes including weight loss (5.7 ± 3.9 vs. 5.5 ± 5.1 kg, respectively, p = 0.58), degree of dyspnea, and wellbeing rating, rated on a visual analog scale. There were no differences in mortality, emergency visits, or readmissions for heart failure by 60 days. However, the UF group had a higher rate of complications (7.2% vs. 5.7%, p = 0.03), represented by bleeding and dialysis catheter infection. Strangely, while the group on pharmacological treatment had a reduction in creatinine levels, the UF group had creatinine elevation of 0.23 mg/dL.

Certain details of the CARRESS-HF study merit mention because they could have contributed to the null result. First, the group on pharmacological treatment were given medication at doses titrated to maintain daily urinary output at 3 to 5 liters, whereas the UF group were given a fixed rate of 200 mL/hour of UF, which was not individualized. Second, the mean duration of intervention was much longer in the drug treatment group (92 hours) than in the UF group (40 hours). Another important limitation of this study was the high rate of cross-over, because 30% of the patients in the UF group were given diuretics after the end of the protocol and 10% of the patients allocated to UF did not receive it for a range of reasons. These results should therefore be treated with caution.

It should also be noted that the CARRESS-HF study cannot be considered a counterpoint to the UNLOAD study, since there were significant differences in the inclusion criteria and study protocols (Table 1).

The CUORE study (Continuous Ultrafiltration for Congestive Heart Failure) was a smaller study that assessed UF and pharmacological treatment in 56 patients at two centers. As in the UNLOAD study, patients were also randomized within 24 h of admission to flexible UF strategies (rate and duration) or conventional unguided pharmacological therapy. In contrast with other trials, the UF group was also given pharmacological treatment. There was no difference in weight at hospital discharge between the two groups, but the UF group had a lower rate of readmission and mortality (combined) at 1 year.

The AVOID-HF study (Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure) was designed to compare guided UF strategies and pharmacological treatment. It was designed to enroll 810 patients with AHF, but was unfortunately terminated early by the study sponsor, because of budget problems and slow recruitment. Although it did not achieve sufficient statistical power, analysis of the outcomes of the 224 patients recruited was favorable to UF, with a lower rate of occurrence of a first AHF-related event by 90 days (25% in the UF group vs. 35% in the pharmacological treatment group). The primary study outcome, time to first event, was longer in the UF group (62 days) than in the pharmacological treatment group (34 days), although without statistical significance (p = 0.106). At 30 days after
hospital discharge, fewer patients in the UF group had been readmitted for AHF ($p = 0.034$).

Due to the inconsistent results, the majority of centers reserve UF as a salvage strategy for patients whose hypervolemia cannot be resolved with pharmacological treatment. Figure 4 depicts a proposed algorithm for refractory congestion. Use of both methods (UF and pharmacological treatment) in synergy can also be considered.

The AHF treatment guidelines recommend UF in cases of refractory hypervolemia, but diverge on the degree of recommendation and level of evidence. According to the Brazilian guidelines, this indication is class I with level of evidence B, whereas the European guidelines give it a class IIb recommendation and level of evidence C. The recently-published American guidelines do not contain any specific recommendations on UF in patients with AHF.

Hypertonic saline solution

In the elegant work by Issa et al., the infusion of 7.5% HSS twice daily for three days prevented renal dysfunction in patients with decompensated heart failure. During the study protocol, the increase in serum creatinine (0.3mg/dl or above) occurred in 2 (10%) of the HSS arm and 6 (50%) of the placebo arm. (relative risk 0.3; confidence interval 0.09 to 0.98; $p = 0.01$). Relative to baseline, serum creatinine and cystatin C levels were lower in HSS compared to placebo.

Administration of hypertonic saline solution (HSS) has been used as a treatment option in cases of resistance to diuretics and refractory hypervolemia for more than two decades. Much of what is known about use of HSS comes from experimental models of hemorrhagic and septic shock. Infusion of hypertonic NaCl solution results in a sudden increase in plasma osmolarity, immediately displacing fluid from the interstitium to the vascular space as a consequence of the increased tonic pressure, expanding plasma volume, and increasing renal flow. After infusion of HSS, a loop diuretic is administered in bolus. Over 20 years of experience, infusion of HSS has proven to be a safe and well-tolerated treatment.

One of the first studies with HSS was observational, in a sample of 30 patients who were given 150 mL of NaCl solution (at 1.4 to 4.6%) administered twice a day, followed by furosemide (250-2,000 mg) over 6 to 12 days. There were improvements in dyspnea, edema, and disease severity, according to functional class.

Later, the same authors conducted a single-blind randomized study that recruited 60 patients to compare furosemide (500-1,000 mg) combined with HSS (1.4 to 4.6% NaCl, depending on natremia) or placebo. This study observed that the HSS group had greater urinary output and greater natriuresis and improvements in creatinine and New York Heart Association functional class.

Finally, a larger clinical trial with 107 patients tested the effect of HSS on rates of hospital readmission and mortality. The same protocol as above was applied and resulted in a lower rate of hospital readmission in the HSS group (25 patients out of a total of 53) than in the placebo group (43 patients out of a total of 54) over the 31 ± 14 months of follow-up. Additionally, mortality was significantly lower in the HSS group (24 patients vs. 47, $p < 0.001$) than in the placebo group. Another large clinical trial (NCT05298098), with a double-blind and randomized design, is ongoing and will recruit 600 patients to test the effect of an even more concentrated solution (NaCl 10%), with results predicted for 2023.

The Brazilian guidelines recommend HSS in patients with refractory congestion (class IIa, level of evidence B). While the European guidelines do mention HSS, they do not make any specific recommendations.

Albumin

Loop diuretics are organic acids that circulate firmly bonded to albumin. Albumin increases secretion of furosemide in Henle’s loop and therefore hypoalbuminemia may reduce bioavailability of furosemide in Henle’s loop. However, there are no studies of use of albumin in AHF and its role in the genesis of diuretic resistance may be irrelevant. There is little evidence suggesting that infusion of albumin increases the natriuretic response, as long as serum albumin is above 2 mg/dL. There is scant evidence on the role of albumin in AHF, limited to case reports and the experience of centers specialized in AHF.

Conclusions

Adequate management of congestion in patients with advanced AHF remains a challenge. Over the last two decades, several clinical trials in AHF patients have been published, but unfortunately without yielding significant advances in treatment for these patients. Better understanding...
Figure 4 – Therapeutic flow diagram illustrating treatment of congestion in acute heart failure. UO: urinary output; SGLT2i: sodium-glucose cotransporter 2 inhibitors. Adapted from Mullens et al.36

Persistent congestion

Assess 24h urinary output

UO < 3-4 L

Double dose of loop diuretic up to maximum dose

Assess for 6 hours

< 100 mL diuresis per hour

Diuretic at maximum dose?

Yes

Combined diuretic therapy:
First line: thiazide
Second line: acetazolamide or amiloride
Third line: consider SGLT2i

Persistent congestion

UO > 3-4 L

Continue at current dose until decongestion

Repeat up to maximum loop diuretic dose

No

Consider reducing loop diuretic dose until UO > 5 L per day

Persistent congestion

Ultrafiltration

Assess decongestion prior to hospital discharge

Persistent congestion

Assess for 6 hours

< 100 mL diuresis per hour

Diuretic at maximum dose?
of the mechanisms of diuretic resistance can contribute to appropriate treatment and better outcomes.

**Author Contributions**

Writing of the manuscript and Critical revision of the manuscript for intellectual content: Linhares GP, Souza-Neto JD.

**Potential Conflict of Interest**

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

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