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PATHOPHYSIOLOGY AND MANAGEMENT OF DIURETIC RESISTANCE IN HEART FAILURE

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ABSTRACT

Acute decompensation of heart failure (HF) often presents with congestion-related signs and symptoms that are indicative of poor patient outcomes. Loop diuretics are essential in managing fluid overload and are commonly used for both acute and chronic HF treatment. However, a significant challenge arises when patients exhibit reduced responsiveness to loop diuretics, impacting their clinical progression and potentially prolonging hospital stays. This diminished response, known as diuretic resistance (DR), occurs when patients fail to decongest despite receiving appropriate and increasing doses of loop diuretics.

KEYWORDS: Heart failure, kidney disease, loop diuretics, thiazides, ultrafiltration.

1. INTRODUCTION

Heart failure (HF) leads to approximately one million hospitalizations annually in the United States[1], with this number on the rise. Fluid retention is a common issue in HF patients, and diuretics play a crucial role in managing and stabilizing the condition. Monitoring sodium and water levels, regular weight checks, and avoiding medications like non-steroidal anti-inflammatory drugs (NSAIDs) are essential in preventing salt and water retention. Diuretic resistance (DR) affects around 20%-30% of HF patients[2], with various mechanisms contributing to this resistance.

In contrast to the absence of renal injury associated with diuretic use, diuretic resistance is associated with renal failure and an increased risk of rehospitalization due to heart failure and death[3] This review aims to outline these mechanisms and provide evidence-based strategies to address DR in HF patients Diuretic resistance (DR) is usually defined as impairment of the maximal diuretic effect that ultimately limits sodium and chloride excretion and is a well-described phenomenon in the use of diuretics.[3]

There is no universally-accepted definition but the description is commonly: the failure to decongest despite receiving adequate and escalating doses of diuretics. DR is a relative term, encompassing a range of diuretic efficiency (DE), which measures how effectively a diuretic can facilitate diuresis and natriuresis, rather than the absolute dose of diuretic.[4] Only few patients are completely diuretic "non-responsive," and they represent 20–50% of hospitalized patients depending on the bar set.[5] While normal response to a diuretic has been defined as 3–4 L per 40 mg of furosemide[6], diuretic resistant individuals exhibit impaired DE of relative severity. DR in patients has been shown to contribute to worsening heart failure (WHF) during hospital stay, prolonged lengths of hospitalization, and may increased mortality and costs relative to those who respond adequately to initial diuretic administration.[6] Identifying and focusing on these individuals for personalized treatment is essential to enhance results and minimize the adverse effects of diuretic resistance on patient well-being. Diuretics play a pivotal role in acute heart failure therapy. The effectiveness of diuretics is dependent on the elimination of body sodium and fluid.

The majority of AHF admissions are linked to volume overload and treated with intravenous (IV) loop diuretics. There is, however, currently no consensus on adjustment of IV loop diuretic doses based on individual responses to initial diuretic. Actually, many patients are left inadequately treated due to the fact that diuretic dosing and response vary widely.[6] To reduce worsening of heart failure and improve treatment delivery, the individual response to diuretic therapy should be predictable so DR can be easily recognized, and intensification of therapy can be initiated.

2. Physiology of loop diuretics

Loop diuretics block ion transport directly by binding to the translocation pocket at the extracellular surface of sodium-potassium-chloride transporters (NKCCs).[7] These drugs inhibit a sodium-potassium-chloride symporter at the apical surface of thick ascending limb

cells along the loop of Henle (NKCC2, gene SLC12A1)(8) which reabsorbs about 25% of filtered salt both directly and indirectly, and this is responsible for most natriuretic effects of loop diuretics.[8] Loop diuretics also target the same symporter at the apical membrane of macula densa cells. This action disrupts tubule-glomerular feedback and promotes renin secretion.[7] These drugs also inhibit a second sodium-potassium-chloride symporter isoform, NKCC1 (Gene SLC12A2), which is expressed widely in humans. Loop diuretics through IV route have a vasodilatory effect, partially by inhibiting NKCC1 in the smooth muscle cells in vessel wall.[8] NKCC1 is also expressed in the afferent arteriole and extraglomerular mesangium in the kidney, suppressing basal secretion of renin.[8]

Therefore inhibiting this symporter may lead to elevation of renin and consequentially angiotensin II formation.[8] The diuretic properties can alleviate congestion in heart failure patients. However, the activation of the renin-angiotensin-aldosterone system (RAAS) due to loop diuretics can further suppress tubule-glomerular feedback, resulting in a reduced glomerular filtration rate (GFR).[7]

The effects of loop diuretics on renal and systemic hemodynamics are complex and depend on dosage, administration route, and duration of use. While they activate RAAS—which typically raises systemic blood pressure and enhances sodium and water reabsorption—they also boost vasodilatory prostaglandins that elevate pressure in the proximal tubule.[7] Consequently, high-dose intravenous loop diuretics can either lower or raise arterial pressure while decreasing renal blood flow. The response to higher doses may either overcome resistance to produce a diuretic effect or continue to be ineffective.[7] Predicting which outcome will dominate for an individual patient remains challenging.

3. Causes and mechanism of diuretic resistance in HF

To achieve their effect, unbound loop diuretics have to reach the urinary lumen of the thick ascending limb of Henle loop to bind to their site of action. Thus, oral bioavailability is the first line of resistance in the outpatient setting.[3] Among different loop diuretics, bumetanide and torsemide have high oral bioavailability outperforming furosemide.[3]

Because loop diuretics are highly protein-bound (95%), hypoalbuminemia increases the distribution volume and impairs the availability of loop diuretics for facilitated diffusion.[3] Reduced kidney function and delayed peak concentration of loop diuretics are recognized contributors to diuretic resistance (DR)[7] Loop diuretics are organic anions, mostly circulate bound to proteins as mentioned above. Therefore, they do not reach tubule fluid by glomerular filtration, but necessitate secretion into the proximal tubule, via organic anion transporters and the Multidrug Resistance–Associated Protein 4.[8]

About 25% of patients with renal failure also have heart failure (HF), making it common to encounter individuals with both conditions. The delay in peak concentration is often due to an increased presence of competitive anions that bind to organic anion transporters (OAT), hindering the diuretic's ability to attach to its target site, thus diminishing its effectiveness.[7]

Non-steroidal anti-inflammatory drugs can also compete for loop diuretic secretion in a similar manner.[8] Another factor contributing to DR is the structural changes in renal cells, referred to as the "braking phenomenon".[7] Research involving rats has shown that chronic use of loop diuretics can lead to both hypertrophy and hyperplasia in the epithelial cells of the distal convoluted tubule.[7] Prolonged exposure can result in nephron remodeling, characterized by hypertrophy of distal tubular cells, which may increase sodium reabsorption and alter the response to diuretics. This phenomenon ultimately leads to lower blood sodium levels and increased resistance to diuretics over time. Thus, chronic use of diuretics increases resistance towards these diuretics.[7]

4. Diuretic braking and implications for AHF therapy

"Diuretic braking" describes the reduced effectiveness of diuretics with repeated use. While this term captures the phenomenon, it does not explain it fully; the underlying mechanisms remain unclear for both healthy individuals and those with diseases. The decreased response has not been consistently linked with significant changes in plasma volume or kidney blood flow, nor tied definitively to any specific class of diuretic.[6]

The literature on DR attributes diminished natriuretic responses during repeated furosemide administration to several potential factors. One possibility is a reduced delivery of sodium chloride (NaCl) to furosemide's action site, leading to less inhibition of NaCl reabsorption in the loop of Henle.[6] However, the relevance of these mechanisms in humans remains uncertain.

Additionally, studies on rats fed high-sodium diets have indicated that prolonged loop diuretic infusion can cause structural hypertrophy of the distal convoluted tubule, connecting tubule and intercalated cells of the collecting duct.[6] These Structural and functional adaptations in downstream nephron segments lead to increased Na-K-ATPase activity and NaCl cotransporter (NCC) expression, compensating for the heightened sodium loss from the loop of Henle caused by loop diuretics. This results in greater distal NaCl absorption, which can cause inappropriate renal sodium retention lasting up to two weeks after stopping diuretic treatment.[6]

Rao et al. demonstrated that this mechanism also applies to humans. By examining lithium's fractional excretion the gold standard for in vivo assessment of sodium handling in the proximal tubule and loop of Henle, they

found that distal compensatory sodium reabsorption significantly contributes to the diuretic-induced rise in fractional excretion of sodium (FENa), making it a key factor in diuretic resistance (DR).[9]

5. Prediction of diuretic resistance in HF patients

Anticipating DR before it becomes clinically significant could improve outcomes for heart failure (HF) patients. A natriuretic response prediction equation (NRPE) can be utilized to track natriuretic responses by measuring urinary sodium output (NAout) based on urine samples collected two hours post-loop diuretic administration.[7] Since creatinine has limited reabsorption and secretion in the tubule, the serum creatinine to urine creatinine (CrS/CrU) ratio indicates sodium concentration levels in the tubules, allowing for calculation of urine formation rates. Therefore, the rapid rate of urine formation (ml/min) can be calculated from the serum to urine creatinine ratio and the estimated GFR (eGFR) product. Sodium excretion (mmol/min) can be derived from multiplying this result by the urine sodium concentration (NaU). The equation is, NAout = eGFR x (BSA/1.73) x (CrS/CrU) x 60 min x 2.5 hours x (NaU/1000 ml), where BSA is the body surface area.[7]

Most natriuresis occurs shortly after IV loop diuretics are given, and natriuresis is accomplished in six hours. By multiplying by 2.5 hours, we can get a cumulative sodium output where the time of 2.5 was chosen hours in this equation since most natriuresis occurs soon after IV diuretic administration. The 1.73 m2 constant normalizes BSA to normal.[7] when patients who don't have a satisfactory respond to diuretics within a short period of an hour or two after loop diuretic administration are detected, repeat dosing could be started early, which grants positive effects concerning outcomes ranging from faster alleviation of symptoms to perhaps a reduction in hospital stay length or enhancement of general decongestion.[7]

6. Prognosis of diuretic resistance in HF

In heart failure management, assessing mortality risk and disease severity is essential for effective treatment strategies. Diuretic resistance has been associated with worsened HF during hospital stays, longer admissions, and potentially higher mortality rates compared to those who respond well initially.[7] Addressing this resistance may require higher dosages or medication combinations, underscoring the need for evaluating congestive heart failure severity alongside treatment intensity.

Neuberg et al retrospectively evaluated 1,153 patients with advanced heart failure to shed light on how diuretic resistance (defined as the need for a high dose) relate to mortality outcomes. The study revealed that high doses of loop diuretics—specifically furosemide over 80 mg or bumetanide over 2 mg daily—were independent predictors of total and cause-specific mortality in this population. These findings suggest that recognizing diuretic resistance as a marker for prognosis is crucial in managing chronic CHF patients effectively.[10]

7. Management of diuretic resistance

7.1 Increased Dose

First strategy for managing diuretic resistance involves increasing the dose to ensure adequate levels of diuretics reach the target site in the kidneys. One study demonstrated the efficacy and safety of high-dose furosemide (250–4000 mg/day, orally or intravenously) in 35 patients with severe congestive heart failure and poor renal function. No significant side effects were reported, but all patients experienced weight loss and symptomatic improvement.[7] However, the efficacy of furosemide in patients with renal failure is hampered by decreased activity of organic anion transporters (OATs) and decreased renal blood flow, which may result in decreased concentrations in the renal tubules. Thus, in most cases, increasing the dose can effectively treat diuretic resistance in heart failure patients, although it may not alleviate resistance in individuals with poor renal function.[7]

7.2 Continuous Infusion of Loop Diuretics

When comparing IV bolus therapy with continuous infusion of diuretics, it is clear that the latter provides a more consistent and prolonged delivery of the drug, thus preventing sodium retention after diuretic administration. The DOSE trial compared the efficacy and safety of continuous versus intermittent furosemide therapy in acute heart failure and found no difference in symptom control or net fluid loss after 72 hours in either group.[11] Some other studies have shown greater diuresis with continuous infusion compared with a similarly dosed IV bolus regimen.[12] At this stage, there is a lack of conclusive clinical evidence to support the routine implementation of continuous IV infusion therapy with loop diuretics.

7.3 Combination Diuretic Therapy

Sequential nephron blockade with diuretic combination therapy is a very important therapeutic approach in the treatment of diuretic resistance. It is the next course of action when the desired diuretic response is not achieved with high-dose loop diuretic monotherapy.[13]

7.3.1 Thiazides

Thiazide diuretics are not successful as monotherapy in the treatment of decompensated heart failure; however, the addition of 25–100 mg of thiazide to high-dose intravenous furosemide in 20 patients with NYHA grade 3 and 4 heart failure and 4 patients with diuretic resistance resulted in increased weight loss and increased urine output.[13]

The most common combination is a loop diuretic plus a thiazide, although large-scale placebo-controlled trials have not been conducted.[13] Metolazone (a thiazide-like diuretic) is commonly used because of its low cost and availability. Metolazone also inhibits sodium

reabsorption in the proximal tubule, which may contribute to its synergistic effect. Chlorothiazide is available in an intravenous formulation that is faster in onset of action than metolazone. However, studies have failed to find benefits of one over the other. However, a recent propensity analysis found that in patients with heart failure with diuretic resistance, increasing the dose of loop diuretics is a preferable strategy over routine early addition of thiazide diuretics when diuresis is inadequate.[13]

7.3.2 Aldosterone Antagonists

A number of studies have explored the potential benefits and safety of adding spironolactone, particularly to loop diuretics. The first major double-blind RALES study in which spironolactone was added to a treatment regimen for patients with EF ≤35% that included an ACE inhibitor, a loop diuretic, and in most cases digoxin, was stopped early because an interim analysis showed a 30% reduction in mortality in the spironolactone group, attributable to a reduction in mortality due to both progression of heart failure and sudden cardiac death, and a reduction in hospitalization for worsening heart failure and a significant improvement in heart failure symptoms with spironolactone. Importantly, the incidence of serious hyperkalemia was low in both groups of patients.[14]

After the RALES results were reported, an early single-center survey and later a large epidemiological survey reported a significant increase in hospitalization for hyperkalemia associated with a significant increase in mortality in the aldosterone antagonist group.[13] In the ATHENA-HF trial, the addition of high-dose spironolactone (100 mg/day) was compared with standard treatment for acute heart failure, which included low-dose spironolactone (12.5–25 mg/day) or placebo. The primary endpoint was the change in NT-proBNP from baseline levels to 96 hours. Secondary endpoints were clinical congestion score, respiratory distress, net urine output, and net weight change. The result showed that the addition of spironolactone to standard care was well tolerated, with no significant difference in potassium levels and estimated glomerular filtration rate between the two groups, but it did not improve the primary or secondary efficacy endpoints over the time period.[15]

7.3.3 Acetazolamide

Acetazolamide is a new and old agent used to relieve congestion in patients with decompensated heart failure. It is a carbonic anhydrase inhibitor that facilitates sodium reabsorption in the proximal tubule and is previously known for its use in the treatment of pulmonary edema and glaucoma.[7]

A meta-analysis of nine studies (three randomized trials and six cohort studies) through mid-2017 with a total of 229 patients with heart failure concluded that, when compared with placebo, acetazolamide lowered blood pH, significantly increased sodium excretion, and reduced the apnea-hypopnea index (and central apnea index) among patients with heart failure.[16]

Results from an observational study and a small prospective randomized trial indicate that adding acetazolamide (500 mg given intravenously once daily) to intravenous loop diuretic therapy increased urinary sodium excretion in patients with acute decompensated heart failure.[13] Mullens et al recently published the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) study, a multicenter, placebo-controlled study in which 519 patients with heart failure received loop diuretics at standard doses (equivalent to twice the oral maintenance dose) and were randomized to once-daily intravenous acetazolamide (500 mg) versus placebo. The combination of acetazolamide and loop diuretic resulted in greater clinically complete decongestion than placebo at 3 days (42% versus 31%), with associated benefits of shorter hospital stay. The incidence of renal deterioration, hypokalemia, hypotension, and adverse events was similar in both groups, while death from any cause or readmission for heart failure at 3 months occurred in 29.7% of patients in the acetazolamide group versus 27.8% in the placebo group.[17] One limitation of this trial was the exclusion of patients receiving SGLT2 inhibitors from the trial, which in contemporary clinical care would likely be added to the treatment of acute decompensated heart failure (ADHDF).

7.3.4 Multi-Nephron Segment Diuretic Therapy (MSDT)

Multiple-nephron segment diuretic therapy (MSDT) is defined as the simultaneous use of four classes of diuretics with effects along the entire nephron length, and is a potential method for overcoming severe diuretic resistance in acute heart failure.[13] A retrospective analysis of a study of 167 hospitalized patients with acute heart failure and diuretic resistance showed that MSDT was associated with an increase in mean 24-hour urine output on the first day of treatment compared with the previous day (2.16 L to 3.08 L) in the total cohort and in the severe diuretic resistance group (0.91 L to 2.08 L). The mean cumulative weight loss on day 7 or at discharge from the hospital was 7.4 kg (15.3 to 3.4 kg). There were no changes in serum chemistry or renal function. Further prospective studies of MSDT in AHF and diuretic resistance are clearly needed.[13]

7.3.5 Sodium-glucose transporter 2 (SGLT2) inhibitors

The diuretic effect of SGLT-2 inhibitors occurs in the proximal convoluted tubule (PCT), where the sodium-glucose transporters 2 (SGLT2s) is located. SGLT-2 inhibitors reduce sodium reabsorption by causing constriction of the proximal arteriole and dilation of the distal arteriole, leading to a decrease in glomerular filtration rate. SGLT-2 inhibitors also reduce protein in the urine.[18]

Since the majority of sodium is reabsorbed in the loop of Henle and the distal tubule, SGLT-2 inhibitors have minimal diuretic effects, but can enhance the diuretic response when combined with other classes of diuretics by improving the response to atrial natriuretic peptide.[18] According to a pilot study, randomized, double-blind, placebo-controlled, multicenter study of the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPARESPONSE-AHF), empagliflozin did not affect diuretic response (weight change per 40 mg furosemide), respiratory rate, hospitalization time, or NT-proBNP levels. However, it was safe and reduced both mortality and rehospitalization at 60 days after discharge.[19] Wilcox et al evaluated the diuretic synergy between dapagliflozin and bumetanide in healthy subjects, where the diuretic effect and sodium excretion were enhanced when one of the two treatments was added to the other after 1 week of treatment with one drug, and the combination therapy reversed the hyperuricemia caused by bumetanide.[20] In a small retrospective study of 31 patients with acute heart failure, 58% of whom had type 2 diabetes, who received SGLT-2 inhibitors as adjunctive therapy, weight loss, urine volume, and diuretic efficacy improved 24 h after initiation of treatment, without worsening renal function, potassium, or blood pressure.[21]

The role of SGLT2 inhibitors as adjunctive therapy to diuretic therapy in diuretic resistance remains to be determined; however, their mechanism of action as a diuretic and the preliminary results described above make further clinical investigations necessary. When diuretic resistance precludes effective decongestion 21reatment in patients who have not previously taken SGLT2 inhibitors, it is recommended that these drugs be added to loop diuretics. In patients previously treated with SGLT2 inhibitors, additional doses of acetazolamide may increase the effectiveness of decongestion management.[13]

7.3.6 Aquaretics

Tolvaptan is a selective vasopressin receptor V2 antagonist which causes aquaresis without loss of sodium.[3] In patients with hyponatremia with congestive heart failure, tolvaptan acutely increases serum sodium and reduces body weight but does not improve long-term morbidity or mortality in congestive heart failure.[13]

7.4 Co-administration of diuretics with albumin

Low plasma protein levels due to chronic loss or decreased production impede plasma refill from the interstitial space and thus the delivery of loop diuretics to the kidney. In this case, increasing the dose of loop diuretics before correction of hypoproteinemia would be futile.[22] Albumin administration may enhance sodium excretion. However, studies have yielded mixed results. A meta-analysis concluded that this approach suggests transient effects of modest clinical significance.[13] Some guidelines continue to suggest the use of albumin infusion as a supplement to diuretics when renal patients appear to be volume depleted (or appear to be "underfilled").[13]

7.5 Ultrafiltration

Ultrafiltration is carried out by passing blood through semipermeable hollow fibers with negative pressure applied to the surrounding space which causes isotonic fluid to be removed out of the intravascular space with a higher sodium content compared to the very low urine sodium produced by loop diuretics.[3] However, ultrafiltration has not proven superior in decongestion over diuretic therapy in randomized trials of acute heart failure and has been associated with more complications.[13]

8. CONCLUSION

Diuretic resistance is common among heart failure patients with a significant impact on outcomes. Identifying and focusing on these individuals is essential to enhance results and reducing negative effects on patient health and possibly life. High doses of loop diuretics and combination therapy are the currently available treatment strategies.

Conflicts of Interest

There is no conflicts of Interest.

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