Review Article

Hypertonic Saline Solution: How, Why, and for Whom?

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Abstract

The administration of hypertonic saline (HS) in decompensated heart failure (HF) seems counterintuitive, given the concept that sodium is universally harmful for these patients. However, increasingly, strict sodium restrictions have been questioned due to the lack of proven benefits. On the other hand, we know that in acute HF complicated with diuretic resistance, there is hyperactivation of the renin-angiotensin-aldosterone system (RAAS), resulting in a state of excessive increase in renal avidity for sodium, hindering the action of loop diuretics. In this sense, HS would have the potential to attenuate the hyperactivation of RAAS and provide a supply of sodium to the renal tubules, enabling the action of loop diuretics. Several studies have consistently demonstrated that the association of HS with loop diuretics results in greater diuresis, weight loss, and possibly improved renal function. Therefore, despite being underused, we believe that HS is an effective, low-cost, and widely available strategy whose mechanism of action addresses one of the central points in the pathophysiology of diuretic resistance.

Introduction

According to the conventional paradigm for managing heart failure (HF), sodium is seen as harmful because it is associated with fluid retention, symptoms of congestion, and, consequently, a greater risk of hospitalizations.[1] From this view, administration of hypertonic saline (HS) to patients presenting with decompensated HF with signs of hypervolemia seems counterintuitive. However, strict dietary sodium restrictions have been increasingly questioned, with some studies even demonstrating worse outcomes.[2] Recently, the Randomized trial SODIUM-HF failed to demonstrate a reduction in death or cardiovascular hospitalizations in patients with HF receiving a sodium-restricted diet (<1500mg/day).[3] On the other hand, we know that in decompensated HF, hyperactivation of the renin-angiotensin-aldosterone system (RAAS), resistance to diuretics, progressive worsening of renal function, and hyponatremia can occur, which can be attenuated by HS.

Keywords

Heart Failure; Diuretics; Acute Kidney Injury; Hyponatremia.

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Manuscript received November 10, 2023, revised manuscript November 14, 2023, accepted November 14, 2023

DOI: https://doi.org/10.36660/abchf.20230078

We will describe here the mechanism and rationale behind the use of HS in acute HF, the clinical evidence that supports its use, and how to prescribe it in clinical practice.

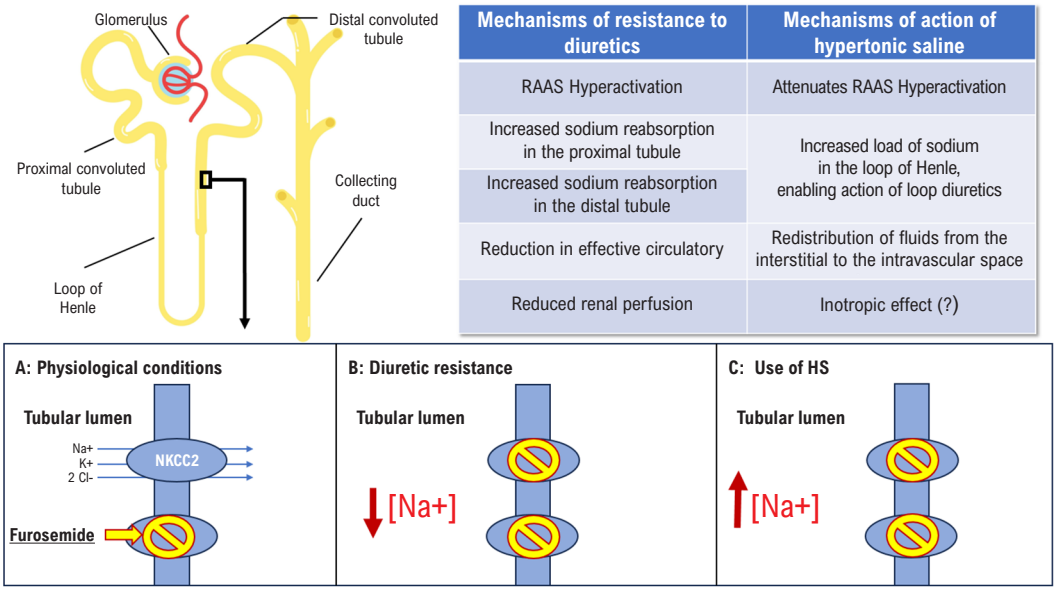
Diuretic resistance mechanisms

The treatment of congestion in HF and in other states of hypervolemia, is fundamentally based on the use of loop diuretics, which prototype is furosemide. This class of medications works by blocking the sodium-potassium-chloride co-transporter (NKCC2) in the thick ascending portion of the Loop of Henle.[4] This co-transporter is responsible for the reabsorption of up to 25% of sodium chloride present in the renal tubules, explaining the natriuretic effect of furosemide.[4] However, a subgroup of patients may develop resistance to diuretics, characterized by low urinary volume and low urine sodium concentration despite increasing doses of furosemide.[4] This situation is often associated with progressive renal dysfunction (cardiorenal syndrome) and presents high mortality.[1] The central mechanism that explains diuretic resistance is the increase in renal sodium reabsorption capacity after chronic use of high doses of loop diuretics.[4] This process occurs through a series of complex cell signaling pathways that generate nephron adaptations. As an example, we can mention the hypertrophy of the distal segments of the nephron, resulting in an increase in its sodium reabsorption capacity. Loop diuretics also stimulate the release of renin in the afferent arteriole, resulting in greater activation of the RAAS and consequently also increasing the capacity for sodium and water reabsorption by the renal tubules.[4,5] Due to the pathophysiology of decompensated HF, there is a strong activation of the RAAS, which is then potentiated by the use of increasing doses of loop diuretics, inducing a state of enormous "avidity" for sodium.[4,5] Finally, there is also an increase in the sodium reabsorption capacity in the proximal tubules, which results in the arrival of less sodium load in the Loop of Henle.[5] Considering that loop diuretics depend on the presence of sodium in the renal tubules to exert their effect by blocking the NKCC2 co-transporter, this results in lower diuretic efficiency.[5] The alternatives commonly used to overcome diuretic resistance are: escalating the dose of loop diuretics, sequential nephron blockade, i.e., use of multiple classes of diuretics in combination, or ultrafiltration. However, none of these alternatives is capable of attenuating the excessive increase in sodium avidity that occurs in decompensated HF complicated with diuretic resistance.[1]

Mechanism of action of HS

HS solutions have been studied in various pathological conditions for over 100 years with several proposed mechanisms.[6] In decompensated HF, one of the most plausible mechanisms is the increased sodium supply in the

Central Illustration: Hypertonic Saline Solution: How, for What, and for Whom?



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Representation of nephron segments, mechanisms of diuretic resistance and mechanisms of action of HS. The panel below demonstrates apical membrane of tubular cells of the thick ascending portion of Loop of Henle. A: under physiological conditions, the NKCC2 cotransporter is responsible for reabsorption of up to 25% of filtered sodium. Loop diuretics block this receptor, resulting in natriuretic effect. B: in situations of high diuretic resistance, there is an increase in sodium reabsorption in different segments of the nephron, resulting in lower concentration of this ion in the tubular lumen of Loop of Henle. Therefore, despite the use of loop diuretics, the result is less sodium excretion in urine and consequently less diuretic effect. C: with the use of HS, there is an increase in sodium concentration in the tubular lumen, which associated with loop diuretics, results in increased natriuresis, reversing diuretic resistance. HS: hypertonic saline.

renal tubules, facilitating the pharmacological action of loop diuretics.[7] This mechanism becomes particularly relevant when there is a high degree of diuretic resistance, which results in an excessive increase in renal sodium reabsorption capacity and hyperactivation of the RAAS. Still, in this sense, sodium load would have the theoretical potential to attenuate the hyperactivation of the RAAS. Furthermore, due to its high osmolarity, HS has the ability to quickly move fluids from the interstitial space to the intravascular space, enabling the maintenance of adequate venous return and renal perfusion.[6,7] Finally, a possible positive inotropic mechanism induced by hypertonicity has also been proposed.[6] Central Illustration demonstrate mechanisms of diuretic resistance and mechanisms of action of HS.

Evidence

Although the use of HS is still restricted to few centers, a series of studies have already been carried out evaluating its effectiveness.[7-9] In 2021, Liu et al. published a meta-analysis of randomized studies evaluating the role of HS associated with furosemide in decompensated HF.[8]

Eleven studies with a total of 2,987 patients were included. One study was multicenter with 1,927 patients, and the others were single-center with less than 100 patients. Overall, the risk of bias was considered moderate to high. HS concentrations between 1.4 and 7.5% were used, and no major adverse events were observed. The use of HS associated with furosemide was associated with greater diuresis, weight loss, serum sodium level, and natriuresis. Regarding clinical outcomes, HS was related to lower mortality, hospital readmission rates, and length of hospital stay. [8] A possible limitation of the meta-analysis is that of the 11 studies evaluated, 6 of them were carried out by the same group, raising the possibility of data duplication. However, a sensitivity analysis was carried out to remove these works, and the result was maintained. Regarding the clinical outcomes of mortality and hospital readmissions, the study with the greatest weight in the meta-analysis was published by Paterna et al.[10] In this study, the patients were randomized to receive 250 mg furosemide associated with HS and moderate sodium restriction (120 mmol/day) versus 250 mg furosemide and strict sodium restriction (80 mmol/day). Both groups had fluid restrictions of 1000 mL/day, and after hospital discharge, patients maintained their respective sodium restrictions (120 versus 80 mmol/day). The mortality and re-hospitalization outcomes were assessed after an average of 57 months of follow-up, making it unlikely that they could

be attributed solely to interventions carried out during the hospitalization period. Therefore, we view with some caution the impact of HS on the outcomes of reducing mortality and readmissions and believe that further confirmatory studies are necessary.

In a Brazilian randomized study, 34 patients hospitalized for decompensated HF were randomized to receive 100 mL of 7.5% HS twice a day for three days versus placebo. HS was associated with a lower incidence of renal dysfunction (defined as an elevation in creatinine of at least 0.3 mg/dL), lower cystatin C levels, and improvements in markers of tubular function. The result suggests the potential of HS to attenuate or prevent the occurrence of kidney injury during HF decompensation.[6]

More recently, the experience of an American academic center with the use of HS in acute refractory decompensated HF was also published.[1] Fifty patients were retrospectively evaluated, showing resistance to diuretics, a tendency to hyponatremia, and worsening renal function. The use of HS 3% associated with loop diuretics was related to increased urinary volume, weight loss, improved kidney function, and increased serum sodium levels. No respiratory or neurological adverse effects were detected.

How to prescribe HS

In our practice, we use HS in hospitalized patients with decompensated HF, presenting diuretic resistance. The patient profile that probably have the greatest benefit is: severe hypervolemia refractory to high doses of loop diuretics, tending to hyponatremia and already presenting renal dysfunction (cardiorenal syndrome). A practical approach is to dilute 20 mL of 20% sodium chloride in 130 mL of 0.9% sodium chloride, resulting in a final concentration of approximately 3.5%. The solution is administered intravenously over 30-60 minutes, twice a day, followed by bolus intravenous furosemide. There is no pre defined dose of furosemide to be applied after HS. We usually calculate it based on the previous dose of loop diuretics which the patient was using before starting HS. Kidney function, electrolytes, weight, and urine output should be monitored at least once a day.

Conclusion

In short, HS has already been tested in several studies, demonstrating an adequate safety and tolerability profile, with no major adverse effects reported. Furthermore, the results of these studies are quite consistent demonstrating that the use of HS associated with loop diuretics increases urinary volume and weight loss and reduces creatinine values, outcomes of great relevance for patients with decompensated HF complicated with resistance to diuretics and cardiorenal syndrome. Therefore, despite being underused, HS is an elegant, low-cost, and widely available strategy whose mechanism of action addresses one of the central points in the pathophysiology of diuretic resistance.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Murad CM, Marcondes-Braga FG.

Potential conflict of interest

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

Sources of funding

There were no external funding sources for this study.

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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