Sociedad Española de Nefrología

nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Brief review

Hypertonic saline and heart failure: s̈odium-centricör c̈hlorine-centric?̈

Jaime Mazón-Ruiz[a,*], *Gregorio Romero-González*[b,c], *Emilio Sánchez*[d], *Eduardo Josué Banegas-Deras*[a], *María Salgado-Barquinero*[e], *Luis Gutiérrez-de la Varga*[e], *José Joaquín Bande-Fernández*[a], *Manuel Gorostidi*[a], *Roberto Alcázar*[f]

[a] *Servicio de Nefrología, Hospital Universitario Central de Asturias, Oviedo, Spain*
[b] *Servicio de Nefrología, Hospital Universitari Germans Trias i Pujol, Badalona, Spain*
[c] *International Renal Research Institute Vicenza, Italy*
[d] *Servicio de Nefrología, Hospital Universitario de Cabueñes, Gijón, Spain*
[e] *Servicio de Cardiología, Hospital Universitario Central de Asturias, Oviedo, Spain*
[f] *Servicio de Nefrología, Hospital Universitario Infanta Leonor, Madrid, Spain*

ARTICLE INFO

Article history:
Received 7 June 2023
Accepted 19 August 2023
Available online 3 July 2024

Keywords:
Heart failure
Diuretic resistance
Hypertonic saline
Lysine chloride
PoCUS

ABSTRACT

Up to 50% of patients admitted for heart failure (HF) have congestion at discharge despite diagnostic and therapeutic advances. Both persistent congestion and diuretic resistance are associated with worse prognosis. The combination of hypertonic saline and loop diuretic has shown promising results in different studies. However, it has not yet achieved a standardized use, partly because of the great heterogeneity in the concentration of sodium chloride, the dose of diuretic or the amount of sodium in the diet. Classically, the movement of water from the intracellular space due to an increase in extracellular osmolarity has been postulated as the main mechanism involved. However, chloride deficit is postulated as the main up-regulator of plasma volume changes, and its correction may be the main mechanism involved. This c̈hloride centricäpproach to heart failure opens the door to therapeutic strategies that would include diuretics to correct hypochloremia, as well as sodium free chloride supplementation.

DOI of original article:
https://doi.org/10.1016/j.nefro.2023.08.006.

* *Corresponding author.*
E-mail address: jaimemruiz92@gmail.com (J. Mazón-Ruiz).

Suero salino hipertónico e insuficiencia cardiaca: ¿"sodio-centrista" o "cloro centrista"?

RESUMEN

Pese a los avances diagnósticos y terapéuticos, hasta un 50% de los pacientes ingresados por insuficiencia cardiaca presentan congestión al alta. Tanto la congestión persistente como la resistencia diurética se asocian con un peor pronóstico. La combinación de suero salino hipertónico y diurético de asa ha mostrado en diferentes estudios resultados prometedores. Sin embargo, continua sin lograr un uso estandarizado, en parte por la gran heterogeneidad en la concentración de cloruro sódico de la solución, la dosis de diurético o la cantidad de sodio en la dieta. Clásicamente se ha postulado el movimiento de agua del espacio intracelular gracias al aumento de la osmolaridad extracelular como el principal mecanismo implicado. Sin embargo, el déficit de cloro se postula como el principal regulador al alza de los cambios en el volumen plasmático, pudiendo ser su corrección el principal mecanismo implicado. Este abordaje "cloro centrista" de la insuficiencia cardiaca abre la puerta a estrategias terapéuticas que incluirían diuréticos que corrijan la hipocloremia, así como aporte de cloro libre de sodio.

Palabras clave:
Insuficiencia cardiaca
Resistencia diurética
Salino hipertónico
Cloruro de lisina
PoCUS

Introduction

During the last decades, we have experienced important advances in the management of heart failure (HF) and presently there are a wide range of therapeutics available thanks to the use of pharmacological groups such as beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), angiotensin receptor antagonists (ARBs) and angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (ARA-II), neprilysin inhibitors, sodium-glucose cotransporter type 2 (iSGLT2) inhibitors and mineralocorticoid receptor antagonists (MRA), among others, have been able to transform the treatment. However, HF continues to be the leading cause of hospitalization in patients over 65 years in Spain, with congestion-related symptoms being the main reason for admission. Furthermore, it is associated with in-hospital mortality rates of 4–10%, and up to 20–30% of readmissions in the first month with an estimated average cost per patient of around 15,000 euros over 5 years.[1–4]

Diuretic resistance, although lacking a uniform definition, is often described as failure to reduce congestion despite adequate and increasing doses of diuretics.

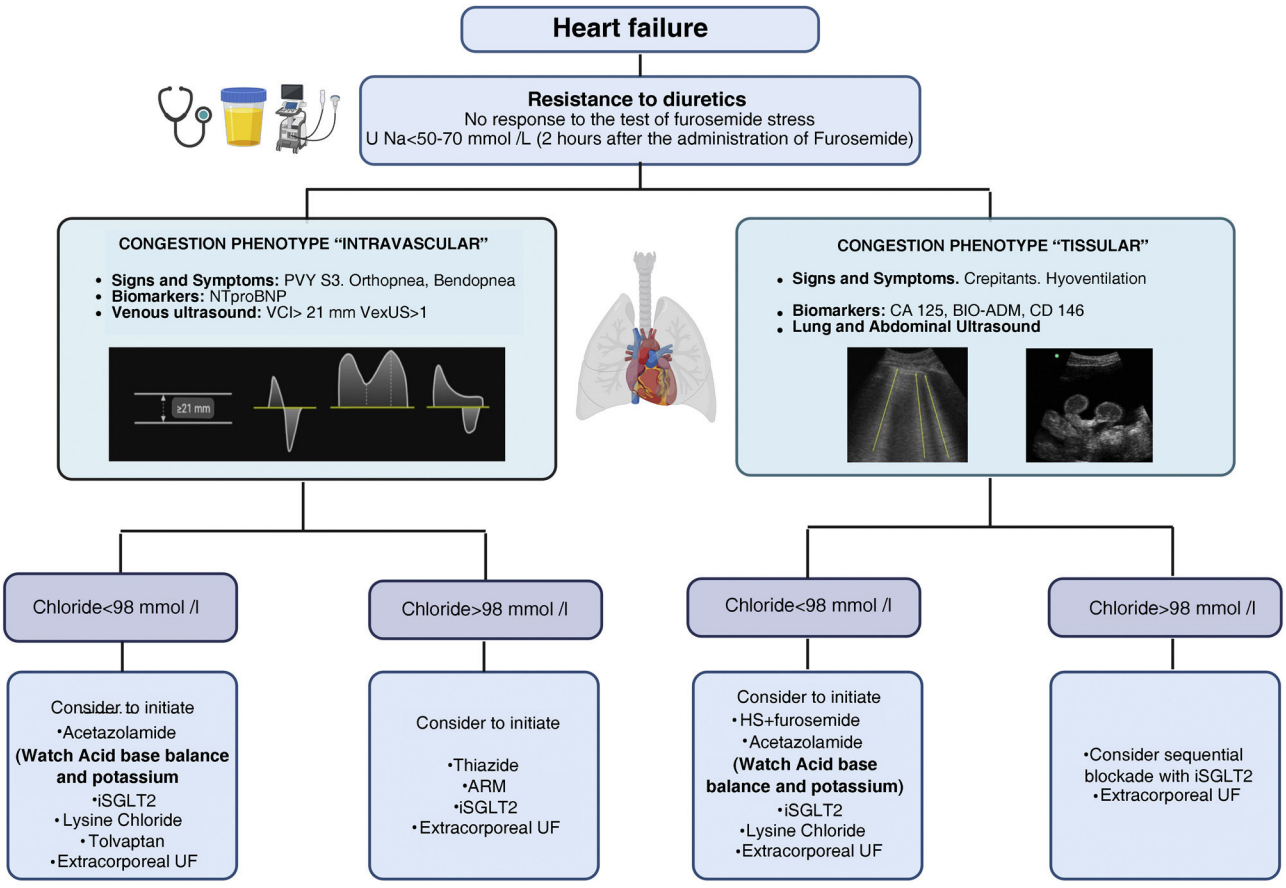
Vascular congestion and resistance to diuretic therapy are associated with poorer survival and a prolonged hospitalization, as well as higher readmission rates. Still, up to 50% of admitted patients remain congested at discharge.[5] Moreover, up to 40% of patients have pulmonary congestion as assessed by ultrasound and with the absence of symptoms, a concept recently termed "subclinical congestion" and which is associated with outcomes similar to those with clinical congestion. About 50% of this group of patients will present clinical signs of congestion during their follow -up as outpatients.[6–8]

Hypertonic saline plus furosemide: possible mechanisms of action

Several groups have studied the benefit of the association of hypertonic saline (HS) and diuretics as a treatment for patients with decompensated HF, showing promising results. However, standardized use has not been achieved, partly due to the huge heterogeneity in the concentration of sodium chloride (NaCl) used in the solution (from 1.7% to 7.5%), the dose of loop diuretic or the amount of sodium in the diet.[9,10]

One of the main hypotheses underlying the possible benefit of the association of HS and diuretic is the mobilization of fluid from the intracellular to the extracellular space due to to the increase in extracellular osmolality, thereby increasing the effective circulating volume (ECV) and suppressing renin activity.[11] In this case, its use seems more appropriate in patients with a tissue-predominant congestive phenotype demonstrated by multiparametric assessment combining physical examination (edema, crackles, pleural effusion, ascitic semiology) with biomarkers (carbohydrate antigen 125, CA 125) and bedside ultrasound (Point-of-Care Ultrasound [PoCUS]), demonstrating the presence of B-lines and/or pleural effusion in the pulmonary study.[12–15] However, none of the major published studies on the benefit of HS in HF perform a congestion phenotyping, probably including heterogeneous populations in this setting. Moreover, the theory behind the benefit of HS has been conceptually challenged in recent years following a study that demonstrated that a slow continuous infusion of HS (NaCl 1.7%), was possibly insufficient to produce water movement from the interstitial to the intravascular compartment by osmolar gradient, and consequently a significant increase in ECV, produced a benefit similar to that of bolus dosing of 3% HS.[16]

In addition, sodium-restricted diets have not shown beneficial results systematically, being even harmful in some



NaU:Urine Na; PVY: Yugular venous pressure; S3 : Third tone; NT proBNP: pro Brain Natriuretic peptide N terminal; VCI : Inferior Cave vein ; VeXUS: Venous Excess ultrasound ; CA125: carbohydrate Antigen 125; Bio -ADM: Bio Adrenomedullin; CD 146 : Cluster of differentiation 146; ISGLT2 : inhibitors of type 2 Na -glucose transporter; AMR : Antagonist of Mineralocorticoid receptor ;UF: ultrafiltration.

Fig. 1 – Therapeutic approach to the patient with HF and diuretic resistance according to the congestion phenotype and the serum chloride levels.

studies, with only a level of evidence of C.[17] The recently published trial, SODIUM-HF (Study of Dietary Intervention Under 100MMOL in Heart Failure) did not demonstrate a reduction in cardiovascular events in outpatients with HF.[18] The use of sodium infusion also seems controversial, since on the one hand most of these patients have an increase in total sodium, but not natremia, and the original studies of the use of HS plus furosemide revealed a positive net sodium balance.[19]

Chloride plays a fundamental role in the maintenance of acid-base balance through its inverse relationship with bicarbonate and in osmotic pressure homeostasis. The presence of hypochloremia, either due to dilution or absolute deficit secondary to diuretic use, dietary chloride restriction, and/or decreased absorption in the presence of intestinal wall edema, plays a key role in diuretic resistance independent of serum sodium levels, as demonstrated in a post hoc analysis of the ROSE (Renal Optimization Strategies Evaluation) study. Furthermore, it is independently associated with increased mortality in different cohorts of patients.[20–24]

The presence of hypochloremia induces the expression of the sodium-chloride cotransporter (NCC) through interaction with a family of WNK protein kinases, and favors the development and perpetuation of metabolic alkalosis (not always present) through the chloride-bicarbonate exchanger via pendrin. Furthermore, chloride, and not sodium, is the main regulator of renin production in the juxtaglomerular apparatus, causing an increase in sodium reabsorption in the presence of hypochloremia.[25] In fact, it has been postulated that chloride would have additional and different actions to those of sodium to regulate intraerythrocyte water volume. Chloride would also have an added tonicity effect that would favor the distribution of fluid from the interstitial space to the intravascular space.[26] If chloride deficit emerges as the main up-regulator of plasma volume changes, it would seem reasonable to expect a benefit from its replacement.[27] Moreover, if we take into account that approximately 90% of the chloride provided in the diet is in the form of salt, this could explain the little evidence in favor of dietary salt restriction.[28]

Chloride-centric approach to heart failure

The combination of a multiparametric and "chloride-centric" approach to congestion summarized in Fig. 1 suggests avoiding a standardized sequential nephron blockade in cases of diuretic resistance, and opens the door to therapeutic strategies that in case of hypochloremia would deliver sodium-free

Table 1 – Effect of the different pharmacological groups with diuretic effect on urinary excretion and serum concentration of the main electrolytes.

	Urinary excretion			Serum concentration		
	Chloride	Sodium	Potassium	Chloride	Sodium	Potassium
Loop diuretics	↑	↑	↑	↓	↓	↓
Thiazides	↑	↑	↑	↓	↓	↓
Antialdosteronics	¿?	↑	↓	<=>	↓<=>	↑
Acetazolamide	↓	↑	↑	↑	↑	↑
Tolvaptan	<=>	<=>	<=>	↑	↑	↑
ISGLT2	↓	↑	<=>	↑	↑<=>	↓<=>

Source: Adapted from Kataoka.[25]

Table 2 – Summary of available clinical trials on the use of lysine chloride in HF patients.

Study Title	Size	Intervention	Inclusion criteria	Objectives	Status
Prospective "pre-post" pilot study on the effects of dietary chloride supplementation on neurohormonal and diuretic function in patients with heart failure	11	Lysine chloride 21 g/day for 3 days	HF on loop diuretics Dose of Furosemide >80 mg or equivalent. Stable volemia	Primary: Plasma Renin activity, levels of renin in urine and response to diuretics. Secondary: No recorded	Completed completed
Mechanism and effects of manipulating chloride homeostasis in acute heart failure[20]	125	Lysine chloride, 115 mmol vs placebo during 7 days	Decompensated HF. Chronic use of loop diuretics. Anticipated need of I.V. diuretics	Primary: Plasma volume measured by Volumex® at 7 days Secondary: NT proBNP, Serum Creatinine, Cystatin, Chloride, bicarbonate at 7 days	Patient Recruitment
Mechanism and effects of manipulating chloride homeostasis in stable heart failure[21]	20	Lysine chloride, 115 mmol vs placebo during 5 days	Stable HF[a] Maximal dose tolerated ACEI/ARA2/ARNi, BB and ARM Furosemide dose ≥40 mg or equivalent Serum chloride <102 mmol/L	Primary: Primary: plasma volume (Volumex® method) at 7 days. Secondary: NTproBNP, Serum Creatinine, Cystatin, Chloride, bicarbonate at 7 days	Patient Recruitment

Ace: angiotensin II receptor antagonists; ARM: mineralocorticoid receptor antagonist; BB: beta-blocker; LVEF: left ventricular ejection fraction; HF: heart failure; Ace: angiotensin-converting enzyme inhibitor; NTproBNP: N-terminal fragment of B-type natriuretic peptide; ARNi: angiotensin-neprilysin receptor inhibitor.

[a] Absence of hospitalization in the last 90 days or changes in diuretic doses in the last 30 days.

chloride and/or prioritize drugs with a diuretic effect that increase serum chloride,[26] as well as with a greater natriuretic or aquaretic effect depending on the congestive phenotype. It should be pointed out that regardless of the existence or not of diuretic resistance, as well as the congestive phenotype and the levels of serum chloride, the initiation of iSGLT2 is indicated in the entire spectrum of patients with HF. Table 1 summarizes the effect of the different drugs with diuretic effect on urinary excretion of the main ions (chloride, sodium, potassium) and their serum concentration. The iSGLT2 would increase serum chloride both by its aquaretic effect (osmotic diuresis) and by the activation of aldosterone, and the decrease in urinary bicarbonate reabsorption (by inhibiting the NaH3N exchanger and increasing tubular reabsorption of chloride). Acetazolamide, which also decreases tubular reabsorption of bicarbonate and increases tubular reabsorption of chloride, has demonstrated its efficacy in the treatment of acute heart failure, especially in the presence of metabolic alkalosis (the ADVOR study: Acetazolamide in Decompensated Heart Failure with Volume Overload).[29] It should be noted that in this study the use of iSGLT2 was not allowed, since during the recruitment period it was not approved for the treatment of HF. Moreover, the results of the EMPULSE study showed improvement in the combined effect on cardiovascular death and hospitalization in patients with acute HF who received empagliflozin 10 mg during admission. Certainly, additional studies are needed to demonstrate the benefit of the combined use of iSGLT2 and acetazolamide.[30] Currently, there are three ongoing randomized clinical trials evaluating the efficacy of lysine chloride (sodium-free) administration in both outpatients with HF and reduced left ventricular ejection fraction (LVEF) and in hospitalized patients with decompensated HF independently of LVEF, these trials are summarized in Table 2.[20,21] If the main benefit of HS plus furosemide is based on the correction of hypochloremia, a positive result in favor of lysine chloride would question the use of sodium chloride, and therefore HS, in patients with HF and chloride deficiency.

Future lines of research

New studies are needed to determine the usefulness of the combination of HS plus diuretic in HF and clarify the pathophysiological basis that explains its benefit. It is important to pursue specific patient profiles avoiding its generalized use in patients refractory to diuretic treatment. This requires the inclusion of more homogeneous populations, randomizing patients according to serum chloride and congestive profile using new tools such as PoCUS.

The evidence generated could imply a shift from a "sodium-centric" paradigm to a "chloride-centric" approach for the management of congestion.

Funding

This work has not received any funding.

Conflict of interest

The authors declare that they have no conflicts of interest.

Key concepts

- Congestion and resistance to diuretic therapy in HF are associated with increased morbidity and mortality. Despite this, up to a 40% of patients admitted with this diagnosis present at discharge a subclinical congestion, undetectable without the implementation of bedside ultrasound.
- Chloride deficiency, a factor in refractoriness to diuretic treatment and mortality in patients with HF, emerges as the possible main upward regulator of plasma volume changes.
- The association of HS and loop diuretic as a treatment for patients with decompensated HF has not achieved a standardized use, partly due to the great heterogeneity of the population included, the concentration of NaCl in the solutions used, the dose of loop diuretic and/or the amount of sodium in the diet.
- Correction of hypochloremia may be the main beneficial mechanism of HS treatment, rather than the movement of water into the extracellular space by osmotic processes.
- In patients with HF and resistance to diuretic treatment, we suggest to bring together a multiparametric assessment of congestion with the concentration of serum chloride, both to optimize the therapeutic approach and aiming the design new studies to assess the usefulness of the association of HS and loop diuretic.

REFERENCES

1. Costanzo MR. Verdict In: congestion guilty. JACC Hear Fail. 2015;3(10):762–4.
2. Stokes MB, Chan WPA, Worthley MI, Coates PT. Acetazolamide—another tool in the congestion battle? Kidney Int. 2023;103(6):1012–4.
3. Escobar C, Varela L, Palacios B, Capel M, Sicras A, Sicras A, et al. Costs and healthcare utilisation of patients with heart failure in Spain. BMC Health Serv Res. 2020;20(1).
4. Butt JH, Fosbøl EL, Gerds TA, Andersson C, McMurray JJV, Petrie MC, et al. Readmission and death in patients admitted with new-onset versus worsening of chronic heart failure: insights from a nationwide cohort. Eur J Heart Fail. 2020;22(10):1777–85.
5. Lala A, McNulty SE, Mentz RJ, Dunlay SM, Vader JM, AbouEzzeddine OF, et al. Relief and recurrence of congestion during and after hospitalization for acute heart failure. Circ Hear Fail. 2015;8(4).
6. Rivas-Lasarte M, Maestro A, Fernández-Martínez J, López-López L, Solé-González E, Vives-Borrás M, et al. Prevalence and prognostic impact of subclinical pulmonary congestion at discharge in patients with acute heart failure. ESC Hear Fail. 2020;7(5):2621–8.
7. Gargani L, Pang PS, Frassi F, Miglioranza MH, Dini FL, Landi P, et al. Persistent pulmonary congestion before discharge predicts rehospitalization in heart failure: a lung ultrasound study. Cardiovasc Ultrasound. 2015;13(1):40.
8. Coiro S, Rossignol P, Ambrosio G, Carluccio E, Alunni G, Murrone A, et al. Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. Eur J Heart Fail. 2015;17(11):1172–81.
9. Paterna S, Fasullo S, Parrinello G, Cannizzaro S, Basile I, Vitrano G, et al. Short-term effects of hypertonic saline solution in acute heart failure and long-term effects of a moderate sodium restriction in patients with compensated heart failure with New York heart association class III (class C) (SMAC-HF study). Am J Med Sci. 2011;342(1).
10. Griffin M, Soufer A, Goljo E, Colna M, Rao VS, Jeon S, et al. Real world use of hypertonic saline in refractory acute decompensated heart failure: a U.S. center's experience. JACC Hear Fail. 2020;8(3).
11. Torres Sanabria M, Aguilera Agudo C, Baena Herrera J, Restrepo Córdoba A, García-Pavía P, Cobo Marcos M. Estrategias en congestión refractaria: efectos del suero salino hipertónico en insuficiencia cardiaca aguda. REC CardioClinics. 2019;54(1):55–7.
12. de la Espriella R, Santas E, Zegri Reiriz I, Górriz JL, Cobo Marcos M, Núñez J. Cuantificación y tratamiento de la congestión en insuficiencia cardíaca: una visión clínica y fisiopatológica. Nefrología. 2022;42(2):145–62.
13. Mazón Ruiz J, Banegas EJ, Pérez Canga JL, Bravo González-Blas L, Menéndez García N, Cavada Bustamante A, et al. Medicina de precisión: «Point of Care Ultrasound» (PoCUS) en el abordaje diagnóstico del paciente con hiponatremia. Nefrología. 2023.
14. Koratala A, Reisinger N. Venous excess doppler ultrasound for the nephrologist: Pearls and Pitfalls. Kidney Med. 2022;4(7):100482.
15. Núñez J, de la Espriella R, Rossignol P, Voors AA, Mullens W, Metra M, et al. Congestion in heart failure: a circulating biomarker-based perspective. A review from the Biomarkers Working Group of the Heart Failure Association, European Society of Cardiology. Eur J Heart Fail. 2022;24(10):1751–66.
16. Okuhara Y, Hirotani S, Naito Y, Nakabo A, Iwasaku T, Eguchi A, et al. Intravenous salt supplementation with low-dose furosemide for treatment of acute decompensated heart failure. J Card Fail. 2014;20(5).
17. Mahtani KR, Heneghan C, Onakpoya I, Tierney S, Aronson JK, Roberts N, et al. Reduced salt intake for heart failure: a systematic review. JAMA Intern Med. 2018;178(12).
18. Ezekowitz JA, Colin-Ramirez E, Ross H, Escobedo J, Macdonald P, Troughton R, et al. Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an international, open-label, randomised, controlled trial. Lancet. 2022;399(10333).
19. Licata G, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, et al. Effects of high-dose furosemide and

small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. Am Heart J. 2003;145(3):459–66.
20. Grodin JL, Sun JL, Anstrom KJ, Chen HH, Starling RC, Testani JM, et al. Implications of serum chloride homeostasis in acute heart failure (from ROSE-AHF). Am J Cardiol. 2017;119(1).
21. Grodin JL, Verbrugge FH, Ellis SG, Mullens W, Testani JM, Tang WHW. Importance of abnormal chloride homeostasis in stable chronic heart failure. Circ Hear Fail. 2016;9(1).
22. Cuthbert JJ, Pellicori P, Rigby A, Pan D, Kazmi S, Shah P, et al. Low serum chloride in patients with chronic heart failure: clinical associations and prognostic significance. Eur J Heart Fail. 2018;20(10):1426–35.
23. ter Maaten JM, Damman K, Hanberg JS, Givertz MM, Metra M, O'Connor CM, et al. Hypochloremia, diuretic resistance, and outcome in patients with acute heart failure. Circ Hear Fail. 2016;9(8).
24. Valga F, Monzon T, Vega-Diaz N, Santana A, Moscol G, Ruiz-Santana S, et al. Serum chloride as a marker of cardiovascular and all-cause mortality in chronic hemodialysis patients: 5-year follow-up study. Nefrología. 2023.
25. Kataoka H. The "chloride theory", a unifying hypothesis for renal handling and body fluid distribution in heart failure pathophysiology. Med Hypotheses. 2017;104:170–3.
26. Kataoka H. Chloride in heart failure syndrome: its pathophysiologic role and therapeutic implication. Cardiol Ther. 2021;10.
27. Arora N. Serum chloride and heart failure. Kidney Med. 2023;5(4):100614.
28. Paterna S, Parrinello G, Cannizzaro S, Fasullo S, Torres D, Sarullo FM, et al. Medium term effects of different dosage of diuretic, sodium, and fluid administration on neurohormonal and clinical outcome in patients with recently compensated heart failure. Am J Cardiol. 2009;103(1).
29. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al. Acetazolamide in acute decompensated heart failure with volume overload. N Engl J Med. 2022;387(13):1185–95.
30. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022;28(3):568–74.