The Role of Serum Chloride in Acute and Chronic Heart Failure: A Narrative Review

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Abstract

Clinical guidelines include diuretics for the treatment of heart failure (HF), not to decrease mortality but to decrease symptoms and hospitalizations. More attention has been paid to the worse outcomes, including mortality, associated with continual diuretic therapy due to hyponatremia. Studies have revealed a pivotal role for serum chloride in the pathophysiology of HF and is now a target of treatment to decrease mortality. The prognostic value of serum chloride in HF has been the subject of much attention. Mechanistically, the macula densa, a region in the renal juxtaglomerular apparatus, relies on chloride levels to sense salt and volume status. The recent discovery of with-no-lysine (K) (WNK) protein kinase as an intracellular chloride sensor sheds light on the possible reason of diuretic resistance in HF. The action of chloride on WNKs results in the upregulation of the sodium-potassium-chloride cotransporter and sodium-chloride cotransporter receptors, which could lead to increased electro-

lyte and fluid reabsorption. Genetic studies have revealed that a variant of a voltage-sensitive chloride channel (CLCNKA) gene leads to almost a 50% decrease in current amplitude and function of the renal chloride channel. This variant increases the risk of HF. Several trials exploring the prognostic value of chloride in both acute and chronic HF have shown mostly positive results, some even suggesting a stronger role than sodium. However, so far, interventional trials exploring serum chloride as a therapeutic target have been largely inconclusive. This study is a review of the pathophysiological effects of hyponatremia in HF, the genetics of chloride channels, and clinical trials that are underway to investigate novel approaches to HF management.

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Introduction

Cardiovascular disease is the most commonly diagnosed medical condition among patients aged 65 years and above and is a major global problem with an estimated worldwide prevalence of 38 million [1]. Of those, there

were 6.2 million adults in the USA who have heart failure (HF), and this number is expected to rise in the future. The high morbidity and mortality rate associated with HF make it a challenging public concern with significant financial burden on healthcare [2].

Patients with HF frequently present with multiple electrolyte abnormalities, hyponatremia, hypokalemia, and hypochloremia being the most common. This is partly due to the reduced renal perfusion from the decreased cardiac output which stimulates the renin-angiotensin-aldosterone system (RAAS) as well as arginine vasopressin and sympathetic nervous system (SNS) leading to fluid retention. While hyponatremia on admission has shown to be strongly associated with an increased risk of mortality, it is not considered a direct target for treatment since its correction does not seem to improve the outcomes [3]. On the other hand, serum chloride, an often-overlooked electrolyte, is the second most abundant electrolyte in the body, and emerging evidence points to its important role in this setting [4].

Clinical guidelines include diuretics for the treatment of HF, not to decrease mortality but to decrease symptoms and hospitalizations [5]. More attention has been paid to the worse outcomes, including mortality, associated with continual diuretic therapy due to hypochloremia. Studies have revealed a pivotal role for serum chloride in the pathophysiology of HF and is now a target of treatment to decrease mortality. The prognostic value of serum chloride in HF has been the subject of much attention [6]. In this review, we provide an overview of the currently available data on the physiologic role of serum chloride, its relevance in HF and congestive signs and symptoms, and its impact on the outcomes of these patients.

Chloride and Volume Status

Chloride concentration is regulated by the gastrointestinal tract and the kidneys [7]. As with most electrolytes, the proximal tubule is responsible for the bulk of the renal reabsorption of chloride. The thick ascending limb of the loop of Henle reabsorbs approximately 15–25% of filtered sodium chloride (NaCl) through the Na⁺/K⁺/2Cl⁻ cotransporter (NKCC) [7]. The macula densa, a region in the renal juxtaglomerular apparatus, primarily relies on chloride levels in sensing salt load and volume status. If volume status is sensed as adequate, there is decreased reabsorption of NaCl in the proximal tubule and an increased concentration of NaCl at the macula densa. This

in turn suppresses renin secretion, hence deactivating the RAAS. Interestingly, this neurohormonal effect occurs independent of sodium concentration as suggested by failure of renin suppression with administration of sodium bicarbonate compared to sodium chloride. The established role of chloride levels in regulation of renin secretion and volume status is the basis of the chloride theory for worsening HF [7].

Chloride and the WNK Protein Kinases

In recent years, there has been mounting evidence on a family of serine/threonine protein kinases, with-no-lysine (K) (WNK) which play a critical role in chloride sensing, intracellular signaling, and regulation. In particular, WNKs serve as an intracellular chloride sensor; it has been shown that autophosphorylation and activation of the kinase take place in response to reduced chloride levels (shown in Fig. 1) [8]. X-ray crystallography studies on WNKs showed the presence of a chloride ion bound directly on the kinase, which established its role as a chloride-sensing protein [9]. Low intracellular chloride activates cation-chloride cotransporters such as NKCC in the thick ascending limb and sodium-chloride cotransporter (NCC) in the distal convoluted tubule through WNKs. NKCC and NCC mediate Na⁺, K⁺, and Cl⁻ influx which protects the cell against perturbations in osmotic balance. In advanced HF, hypochloremia is commonly seen and is associated with lower diuretic response and less decongestion [10]. A proposed mechanism for this is the action of chloride on WNKs resulting in the upregulation of the NKCC and NCC receptors which leads to increased electrolyte and fluid reabsorption [9, 10]. The greater amount of NKCC and NCC receptors also has a negative impact on the magnitude of the effect of diuretic therapy. Loop diuretics and thiazide diuretics, 2 first-line therapies for HF, inhibit the NKCC and NCC receptors, respectively. An increase in these receptors may be the underlying mechanism for the diminished efficacy of these medications that was observed in a number of clinical studies [8–10].

The Genomics of Chloride Channel

With the advancements in pharmacogenomics and personalized medicine, there is increasing interest in finding gene targets for HF treatment. Recent discovery of a gene which encodes a voltage-sensitive chloride

Fig. 1. WNK receptors located in distal convoluted tubule cells play a critical role in chloride sensing, intracellular signaling, and regulation. WNKs serve as an intracellular chloride sensor; when there is normal serum chloride, the WNK1 is inactivated. During low chloride rates in HF, autophosphorylation and activation of the kinase occur in response to reduced chloride levels. WNK, with-no-lysine (K); HF, heart failure; NKCC, sodium-potassium-chloride cotransporter; NCC, sodium-chloride cotransporter.

channel (CLCNKA) is potentially associated with renal sodium absorption and salt sensitive hypertension [11]. These potentially linked genetic polymorphisms might actually serve as a marker of pathologic variants of chloride channels that can have implications in HF and hence the cardiorenal axis [11].

In relation to the above findings, further studies eventually found that the potential association with HF of the above gene locus in chromosome 1p36 in HSPB7 was actually brought about in part by a polymorphism of the chloride channel gene CLCNKA itself where a glycine was substituted for the normal arginine at position 83 [11]. In those with the Gly83 variant allele, it was found that there was almost a 50% decrease in current amplitude and function of the renal chloride channel. The investigators hypothesized that individuals who carry one or more alleles encoding the variant Gly83 variant channel may develop a similar profile to a Bartter-like syndrome of hyperreninemia, which is in turn implicated in the pathogenesis of HF and cardiorenal syndrome. This also predisposes them to a higher risk of HF after a "second hit" in the form of a myocardial

infarction and volume overload since the neurohormonal mechanisms are already pathologically activated to begin with [11]. A limitation of this elegant study is the population was homogeneously white, so the effect of these genes for other race or ethnic groups needs further investigation [11].

Chloride and Fluid Retention in HF

While serum sodium is known to be a major prognosticating factor in HF, recent studies have looked more closely into its sister electrolyte, chloride. In 2015, a landmark study by Grodin et al. [6] raised the possibility that chloride may be just as, if not more, closely associated with adverse outcomes in these patients. Hypochloremia in HF patients is thought to be related to either hemodilution via the mechanisms mentioned in the previous sections, in which case it is associated with a concomitant decrease in sodium, hemoglobin, and hematocrit, or electrolyte depletion such as in diuretic-induced contraction alkalosis.

Chloride has established actions on the macula densa and the RAAS. A derangement in the chloride levels may contribute further to the dysfunction of the RAAS axis in HF. In fact, as early as 1960, chloride supplementation was already known to be helpful as an adjunct treatment in diuretic-resistant fluid retention states [12]. It was postulated that the induction of a hyperchloremic acidotic state was necessary to make these patients responsive to diuretic therapy. However, as mentioned above, studies that are more recent have found that chloride plays a role in the regulation of chloride transporters (i.e., NKCC and NCC). Hypochloremia leads to an increase in these receptors, resulting in greater electrolyte and fluid reabsorption [13]. This receptor upregulation coupled with the pathologic hyperactivity of RAAS is thought to contribute to the poor prognosis of these patients.

Interaction of the Heart and Kidneys in HF

While the etiology and mechanistic processes underlying HF may be numerous, central in its pathophysiology is a disturbance in the ability of the ventricles to either pump (HF with reduced ejection fraction) or receive blood (HF with preserved ejection fraction) blood. This dysfunction results in impaired perfusion and oxygen delivery to the peripheral tissues. In compensation, various homeostatic mechanisms are activated, particularly the RAAS, arginine vasopressin system, and the SNS [14]. In the initial stages of HF, perfusion is maintained through vasoconstriction mediated by the SNS. However, the maladaptive RAAS activation will lead to expansion of the blood volume through progressive sodium and water retention. Following this increase in intravascular volume, an increase in hydrostatic pressure within the vessels will tilt the balance in favor of fluid accumulation in the interstitium. Continued increase in the circulating volume then becomes pathologic and results in the clinical signs and symptoms of congestion. In chronic HF, the interstitium can contain several liters of fluid, accounting for the gradual and usually prolonged progression of symptoms. In these patients, a precarious balance exists between the increased perfusion and significant hemodynamic overload [14].

The intrinsic link between cardiac and renal function cannot be overstated. The kidneys serve as one of the first lines of defense countering these mechanisms. However, when the renal blood flow falls below the limits of autoregulation, due to low systolic volume and blood pressure, the glomerular filtration rate (GFR) begins to decrease. Several pathophysiologic pathways have been pos-

tulated to contribute to the decline in renal function in this setting. A reduction in systolic blood pressure during admission for acute decompensated heart failure (ADHF) has been found to be significantly associated with worsening renal function [15]. This finding is independent of the cardiac output of the patient due to the unique configuration of the kidney's blood flow, wherein it is more dependent on the pressure rather than the flow or cardiac output. The reduction in systolic pressure also affects the renal baroreceptors, leading to a downstream increase in the RAAS activation further compounding the pathologic changes in circulating volume.

Aside from the arterial component (i.e., low forward flow), venous congestion is also known to be associated with worsening renal function. Damman et al. [16] found that an elevated right atrial pressure, independent of renal blood flow, was associated with a decrease in the GFR. The increased venous pressure translates to increased renal interstitial pressure (i.e., high backward pressure) and therefore interstitial hypoxia. The increased renal interstitial pressure may also compress the renal tubules leading to increased hydrostatic pressure of the Bowman's capsule, altering the Starling forces in favor of a reduction in the GFR [17]. With overfilling of the right ventricle, there is a subsequent decrease in left ventricular filling further compromising the output [17]. An increase in SNS activity modifies the renal filtration coefficient and independently causes systemic vasoconstriction, which contributes to the reduction of GFR. Likely, it is the interplay between these various factors that contribute to the full picture of cardiorenal syndrome. Figure 2 is a summary of pathophysiologic interactions in HF and renal dysfunction.

Clinical Trials – Chloride in Chronic HF

The study that instigated interest in the role of serum chloride in HF was the post hoc analysis of the Beta-Blocker Evaluation of Survival (BEST) trial [18] by Tesani et al. [19]. In the univariate model, both serum sodium and serum chloride were strongly associated with mortality, whereas the bicarbonate level was not. Interestingly, only serum chloride remained strongly associated with mortality in the multivariate model. The investigators found that hypochloremia, in the absence of hyponatremia, was a negative prognostic indicator in patients with HF [19]. In this study, hypochloremia was also found to be associated with a greater loop diuretic dose and higher serum bicarbonate.

Fig. 2. Bidirectional pathways linking HF, renal dysfunction, and congestion in cardiorenal syndrome. Decomensation of HF can lead to deterioration in renal function via exacerbated neurohormonal activity (i.e., low forward flow) or through fluid overload and renal venous congestion (i.e., high backward pressure). HF, heart failure; LVEDP, left ventricular end-diastolic pressure. Adapted with permission from Kazory A. Clin J Am Soc Nephrol 2016;11:1463-71.

Similar findings were seen in the study by Grodin et al. [20]. They found that every standard deviation decrease in chloride levels (4.1 mEq/L) at admission to the hospital was associated with a 32% increase in 5-year mortality risk even after multivariable adjustment for other factors including serum sodium, cardiorenal biomarkers, self-reported functional status, and medication use. It was noted that serum chloride levels had strong associations with functional status, sodium, BUN, and loop diuretic use, but did not correlate with more traditional markers of HF severity such as left ventricular ejection fraction and B-type natriuretic peptide. Notable in this study is that subgroup analysis revealed that loop diuretic use significantly decreased the association of chloride and mortality. Similar to the study by Testani et al. [19], this implies that the use of loop diuretics contributes significantly to chloride depletion.

The prospective cohort study by Cuthbert et al. [21] showed congruent findings. Low serum chloride was strongly and independently associated with increasing mortality and all-cause mortality or HF hospitalization. The prognosis of patients with hypochloremia, whether from dilution or depletion associated with diuretics, was similar. Grodin et al. [22] analyzed data from the TOPCAT trial which studied patients with HF with preserved ejection fraction. Results were similar to previous studies in that lower serum chloride was associated with an increased risk for cardiovascular death, all-cause death, and HF hospitalizations. Hypochloremia was also associated with loop and thiazide diuretic use which implicates these medications in chronic chloride depletion.

However, different disease states and patient population may affect these results. Ferreira et al. [23] analyzed

Table 1. Summary of studies of hyponatremia in chronic HF

First author	Study design	Patients, <i>n</i>	Study population	Main inclusion criteria	Objective	Main findings
Testani et al. [19]	Post hoc analysis of cohort from BEST trial	2,699	Chronic HF	NYHA class III or IV, LVEF of $\leq 35\%$, use of an ACE inhibitor for ≥ 1 month	To determine the prognostic importance of hyponatremia in patients with HF	Low serum Cl is associated with increased mortality (HR 1.3 per standard deviation decrease, 95% CI: 1.18–1.42, $p < 0.001$)
Grodin et al. [20]	Prospective cohort	1,673	Chronic stable HF undergoing elective diagnostic coronary angiography	Clinical history of chronic HF diagnosed by clinicians and confirmed by trained research personnel	To determine the prognostic value of hyponatremia in chronic stable HF	Low serum Cl levels are independently associated with increased mortality (HR 1.29, 95% CI: 1.12–1.49, $p < 0.001$)
Hanberg et al. [13]	Prospective cohort	162	Chronic HF receiving loop diuretics	Patients with home loop diuretic dose of ≥ 80 mg oral furosemide equivalents	To probe the relationship and physiology bridging chloride levels and diuretic resistance	Lower Cl levels are associated with lower loop diuretic response (odds ratio, 7.3; 95% CI: 3.3–16.1; $p < 0.001$)
Ferreira et al. [23]	Post hoc analysis of EPHEUS and CAPRICORN trials	7,195	High-risk MI complicated by reduced LVEF and HF	LV systolic dysfunction and HF from 12 h to 21 days after acute MI	To determine association between Na and Cl, prognostic value of Cl in high-risk MI populations, and prognostic value of Cl in addition to Na	Low serum Cl (< 100 mmol/L) is associated with mortality in this population if with low Na (≤ 138 mmol/L; adjusted HR [95% CI] for all-cause mortality = 1.42 [1.14–1.77]; $p = 0.002$)
Cuthbert et al. [21]	Retrospective cohort	4,705	Chronic HF	Ambulatory patients with clinical signs and symptoms of HF (HFpEF or HFrEF)	To determine prevalence of hypo- and hypernatremia and its association with mortality and mortality or hospitalization with HF	Decrement in Cl is associated with mortality (HR 1.04, 95% CI: 1.02–1.06, $p < 0.001$) and mortality or hospitalization with HF (HR 1.03, 95% CI: 1.02–1.05, $p < 0.001$) with decrement in Cl, independent of other variables
Grodin et al. [22]	Post hoc analysis of TOPCAT trial	942	Chronic HFpEF	Natriuretic peptide stratum with recorded serum Cl levels from the Americas, VEF $\geq 45\%$, controlled systolic blood pressure, serum potassium < 5 mmol/L	To determine association between serum Cl with clinical outcomes in HFpEF patients	Every standard deviation decrease in serum chloride (4.05 mmol/L) is independently associated with increased risk for cardiovascular death (HR 1.51, 95% CI: 1.11–2.06, $p = 0.008$) and all-cause death (HR 1.29, 95% CI: 1.02–1.62, $p = 0.04$) in HFpEF
Zhang et al. [24]	Retrospective cohort	905	Chronic HF	Clinically diagnosed CHF confirmed by echocardiography and X-ray	To explore the association between admission serum Cl concentrations and mortality risk	Decrement in Cl is associated with mortality (HR 0.89 [0.863–0.918]; $p < 0.001$); however, on adjusting for Na, no independent association was seen. Combined lower Na and Cl is associated with higher mortality (HR 4.334 [2.716–6.916], $p < 0.001$)

HF, heart failure; BEST, Beta-Blocker Evaluation of Survival Trial; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; HR, hazard ratio; CI, confidence interval; EPHEUS, Eplerenone Post-AMI Heart Failure Efficacy and Survival Study; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Study; MI, myocardial infarction; LV, left ventricle; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; HFpEF, heart failure with preserved ejection fraction; VEF, ventricular ejection fraction.

Table 2. Summary of studies of hyponatremia in ADHF

First author	Study design	Patients, <i>n</i>	Study population	Main inclusion criteria	Objective	Main findings	Comment
Grodin et al. [6]	Retrospective study with 2 cohorts	2,194 (1,318 and 876)	ADHF	Patients admitted for ADHF with a documented prior cardiac implantable electronic device	To determine the prognostic significance of serum Cl levels in relation to serum Na levels in patients with ADHF	Admission serum Cl levels during hospitalization for ADHF are independently and inversely associated with long-term mortality (HR per unit change: 0.94; 95% CI: 0.92–0.95; $p < 0.001$)	Serum Na is no longer associated with mortality when serum Cl is added to the multivariable model
Ter Maaten et al. [12]	Post hoc analysis of PROTECT trial	2,033	Acute HF with mild to moderate renal dysfunction	History of HF ≥ 14 days for which diuretic therapy had been prescribed Hospitalized for HF within 24 h with signs of fluid overload, impaired renal function, high BNP or NT-proBNP plasma levels	To determine whether hyponatremia is associated with reduced diuretic response and decongestion and evaluate changes in serum Cl and the prognostic significance of these changes	Low serum Cl at AHF hospital admission is strongly associated with impaired decongestion New-onset or persistent hyponatremia 14 days later is independently associated with reduced survival (HR: 3.11 [2.17–4.46]; $p < 0.001$)	Hypochloremia that resolved is not associated with reduced survival
Grodin et al. [27]	Post hoc analysis of ROSE-AHF trial	360	Acute HF with prior diagnosis of HF identified within 24 h of hospital admission	Clinically diagnosed HF eGFR >15 but <60 determined via MDRD formula Anticipated hospitalization of at least 72 h	To determine the short-term clinical response and postdischarge outcomes associated with serum Cl levels in acute HF	Serum Cl levels in acute HF are inversely associated with loop diuretic response ($p < 0.001$) and are inversely associated with 60-day death (HR 0.86, $p = 0.029$), 60-day death and rehospitalization (HR 0.90, $p = 0.01$), and 180-day death (HR 0.91, $p = 0.049$)	Changes in Cl levels are associated with parameters of decongestion, but not with clinical outcomes
Kondo et al. [29]	Prospective cohort	293	ADHF	ADHF patients admitted emergently	To explore the relationship between Cl and HF death, noncardiovascular death, and all-cause death	Persistent hyponatremia (HR 9.13 [2.56–32.55], $p < 0.0001$) and progressive hyponatremia (HR 4.65 [1.61–13.4], $p = 0.002$) have increased risk for HF death Persistent hyponatremia (HR 3.63 [1.58–8.32], $p = 0.001$) and progressive hyponatremia (HR 2.10 [1.14–3.90], $p = 0.016$) is associated with increased all-cause mortality	Low Na has no prognostic value in predicting HF death after adjustment for low Cl
Marchenko et al. [28]	Retrospective study	1,504	Patients with ADHF requiring IV diuretics	Primary diagnosis of ADHF Use of IV diuretics	To study the correlation between low serum Cl and 30-day hospital readmission in patients with ADHF	Lower serum Cl is associated with higher 12-month mortality (31.4 vs. 20.2%, $p = 0.015$) and higher 30-day readmission (OR: 1.35, 95% CI: 1.02–1.77, $p = 0.033$)	The association seems to be weak with Cl demonstrating low predictive value as a potential biomarker

ADHF, acute decompensated heart failure; HR, hazard ratio; CI, confidence interval; PROTECT Study, ProBNP Outpatient Tailored CHF Therapy; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro b-type natriuretic peptide; eGFR, estimated glomerular filtration rate; ROSE-AHF, Renal Optimization Strategies Evaluation in Acute Heart Failure trial; MDRD, modification of diet in renal disease.

the prognostic value and association of serum chloride with adverse outcomes in subjects with acute myocardial infarction complicated by reduced left ventricular function and HF. Serum chloride was independently associated with all-cause mortality and cardiovascular mortality but only in patients with the lower serum sodium tertile ($\text{Na} < 138 \text{ mmol/L}$). Zhang et al. [24] studied the prognostic value of serum chloride in a Chinese Han population in China. The study found that each unitary decrease in chloride was associated with an 11% increase in risk of mortality. In both of these studies, the association between mortality and hyponatremia was independent of the use of loop diuretics.

Two studies on the association of hyponatremia and mortality were presented at the American College of Cardiology in March 2020. One study found that hyponatremia was a strong independent predictor of mortality and that an abnormal serum chloride on admission is associated with increased short- and long-term mortality [25]. A study of 289 patients undergoing left ventricular assist device placement found that hyponatremia was associated with decreased survival at 1 year [26].

There seems to be a strong association among serum sodium, serum chloride, and mortality; however, as seen above, the precise relationship and the potential confounding elements still remain elusive. Table 1 is a summary of clinical trials for patients with chronic HF.

Clinical Trials – Chloride in Acute HF

The first landmark study that looked at the role of chloride in ADHF was the retrospective cohort study of Grodin et al. [6]. The study was composed of patients with a history of chronic HF and cardiac implantable electronic device who were admitted for ADHF. Interestingly, serum sodium levels did not correlate with increased mortality after multivariate adjustment. Instead, the authors reported that lower levels of chloride on admission and hyponatremia on discharge were associated with increased all-cause mortality, independent of sodium levels. Similar findings were observed in a post hoc analysis of the data from the ROSE-AHF (Renal Optimization Strategies Evaluation in Acute Heart Failure) trial. The authors found that baseline chloride levels did not correlate with worsening or persistent HF but had a negative association with response to diuretics and diuretic efficiency, increased 60-day and 180-day mortality, and rehospitalization rate [27]. The use of diuretics lowered serum chloride levels during admission. However, this

acute change in chloride was not associated with increased mortality. Adjustment for prehospital diuretic use also decreased the association of baseline chloride levels and mortality. These findings imply that while loop diuretics can deplete chloride, its impact on mortality is less pronounced compared with other causes of hyponatremia in HF (i.e., dilution).

Further investigation on the association between hyponatremia and rehospitalization was done by Marchenko et al. [28]. In their study, hyponatremia on either admission or discharge was found to be independently associated with a greater 30-day readmission rate. However, the predictive value of chloride for readmission was found to be low. Mortality at 12 months was also observed to increase in this setting. While the study grouped those with hyponatremia on either admission or discharge as one during the analysis, it is notable that the number of patients with hyponatremia at discharge was greater than those on admission and that only a small portion of the patients were hyponatremic from admission to discharge. This change likely reflects the effect of decongestive therapy during admission. Hence, the magnitude of the effect of therapy-related hyponatremia on prognosis is unknown in this study.

The value of baseline chloride as a reliable prognostic marker was challenged by Ter Maaten et al. [12]. In their analysis of a cohort from the PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) trial, they found that baseline serum chloride was not significantly associated with mortality at 180 days when adjusted for baseline sodium. Instead, patients with persistent hyponatremia until day 14 and patients with new-onset hyponatremia at day 14 had the strongest association with mortality [12]. This study raises the possibility that treatment-related hyponatremia may lead to worse outcomes. The association with serial changes in chloride and mortality was also seen by Kondo et al. [29]. Those patients with persistent hyponatremia and progressive hyponatremia were at increased risk of mortality due to progressive HF. Of note, the dose of loop diuretics and thiazides during hospitalization was associated with progressive hyponatremia and therefore with poorer outcomes. Table 2 is a summary of clinical trials for patients with acute HF.

Table 3. Common diuretics used in HF and its effects on chloride

Diuretic	Typical maintenance dose, mg PO (maximum dose, mg, IV)	Effect on serum chloride
<i>Loop diuretics [35]</i>		
Furosemide	40–240 (600)	Decreases serum chloride by preventing reabsorption in the ascending loop of Henle
Bumetanide	1–5 (10)	
Torsemide	10–20 (200)	
<i>Thiazide and thiazide-like diuretics [36]</i>		
HCTZ	12.5–100 (200)	Decreases serum chloride by blocking electroneutral NaCl absorption at the distal convoluted tubule, connecting tubule, and early collecting duct [32]
Metolazone	2.5–10 (20)	
Chlorthalidone	25–200 (100)	
Chlorothiazide	500–100 (1000)	
<i>Mineralocorticoid receptor antagonists [37]</i>		
Spirolactone	25–50 (50–100)	No significant effect [38]
Eplerenone	25 (50)	
<i>Vasopressin antagonist</i>		
Tolvaptan	30 (60)	No significant effect
<i>Other mechanisms</i>		
Acetazolamide [32]	250 (500 mg 3×/day)	A potential chloride-regaining diuretic [32] Possesses a “non-reabsorbable anion-like effect” Brings about excretion of bicarbonate into the urinary tubules with interchangeable absorption of filtrated chloride into the blood and concurrent excretion of potassium into the urine [32]

HF, heart failure; mg, milligrams; PO, per ore; IV, intravenous; HCTZ, hydrochlorothiazide; NaCl, sodium chloride.

Common Diuretics Used in HF

Based on the latest position statement of the European Society of Cardiology on the use of diuretics in HF with congestion, the use of loop diuretics is still the first-line treatment of congestion followed by thiazide and acetazolamide if the desired urine output is not achieved. Loop and thiazide diuretics can potentially deplete serum chloride primarily by preventing its reabsorption [30–32]. On the other hand, acetazolamide which has been considered as a potential chloride-regaining diuretic increases serum chloride levels, independent of sodium, through inhibition of intracellular and luminal carbonic anhydrase in the proximal tubules [33, 34]. Other diuretics used in HF like spironolactone and tolvaptan has no significant effect on the serum chloride. Table 3 is a summary of common diuretics used in HF and their effects on serum chloride.

Serum Chloride as a Treatment Target

Given the aforementioned findings, several studies have attempted to investigate the therapeutic impact of chloride supplementation. The isolated increase in serum chloride can be achieved either by supplementation of sodium-free chloride or by administration of an agent or medication that increases serum chloride without affecting serum sodium (i.e., acetazolamide). As early as the 1960s, an interventional trial by Rubin et al. [35] studied the effect of sodium-free chloride (i.e., lysine monohydrochloride) supplementation on patients with refractory congestion. The results showed that it enhanced fluid and electrolyte excretion in patients previously resistant to diuretics. Based on that concept, Hanberg et al. [13] performed their experiment on 10 patients (pilot study) which had inconsistent results; instead of reducing renin level, it increased it. However, the metrics of decongestion were improved implying increased efficiency of the diuretics. There is an ongoing randomized controlled trial [36] on the effect of lysine chloride supplementation in acute and chronic HF patients on the change in blood volume and other endpoints.

Fig. 3. Important findings of the clinical trials looking at the role of serum chloride among patients with acute and chronic HF. Several studies have shown significant association of hypochloremia with mortality with varying results depending on disease states and study population. Intracellular chloride sensors play a role in diuretic resistance, and these sensors may be treatment targets. An amino acid substitution in the CLCNKA gene affects the renal chloride channels and is associated with increase in HF regardless of myocardial damage. HF, heart failure.

The impact of acetazolamide administration has also been investigated by several studies. Kataoka et al. [37] used acetazolamide in patients with ADHF and chronic HF to determine if its use can increase and sustain chloride levels. The study found that chloride concentrations improved within 10 days and were sustained for at least 60 days. On the other hand, a randomized controlled trial by Verbrugge et al. [38] looked at acetazolamide's effect

on improving natriuresis in HF. Acetazolamide was added to low-dose loop diuretics in the treatment arm, which showed a similar impact on urine sodium excretion and metrics of decongestion that high-dose loop diuretics had (i.e., it increased their efficiency). Another ongoing larger clinical trial, ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) [39], will use the same hypothesis to determine whether adding acetazol-

amide will improve decongestion when combined with loop diuretics in ADHF, potentially leading to improved clinical outcomes.

Conclusion

Because the macula densa relies on chloride levels in sensing salt load and volume status, chloride plays a significant role in fluid homeostasis in HF. Also, by serving as an intracellular chloride sensor, the WNK pathway probably plays a role in diuretic resistance. Genetic studies have shown that in a Caucasian population, an amino acid substitution in the CLCNKA gene affects the renal chloride channels and is associated with increase in HF regardless of myocardial damage. While several studies in both acute and chronic HF populations have demonstrated the prognostic value of hypochloremia, interventional clinical trials that explored serum chloride as a therapeutic target have so far been inconclusive. Prospective randomized controlled studies are underway which may elucidate the role of serum chloride as a therapeutic target to improve outcomes in patients with HF. These studies should shed light on whether serum chloride should be integrated into current models for prediction of HF prognosis. Figure 3 is a summary of the findings of this review.

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Frederick Rivera, Pia Alfonso, and Jem Marie Golbin made the first draft. Additional inputs on the renal physiology and cardio-renal interaction were added by Dr. Kozary, Dr. Lo, and Dr. Lerma. The manuscript was edited by Dr. Volgman and worked with Caroline Volgman to create Figures 1 and 3.

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