Published in final edited form as:

Circ Heart Fail. 2016 January ; 9(1): e002453. doi:10.1161/CIRCHEARTFAILURE.115.002453.

The Importance of Abnormal Chloride Homeostasis in Stable Chronic Heart Failure:

Grodin et al: Chloride Homeostasis in Heart Failure

Justin L. Grodin, MD, MPH¹, Frederik H. Verbrugge, MD, PhD², Stephen G. Ellis, MD¹, Wilfried Mullens, MD, PhD², Jeffrey M. Testani, MD, MTR³, and W. H. Wilson Tang MD^{1,4}

¹Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH

²Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium

³Program of Applied Translational Research, Yale University School of Medicine, New Haven, CT

⁴Department for Cellular and Molecular Medicine, Lerner Research Institute, Cleveland Clinic, Cleveland OH

Abstract

Background—The aim of this analysis was to determine the long-term prognostic value of lower serum chloride in patients with stable chronic heart failure.

Electrolyte abnormalities are prevalent in patients with chronic heart failure. Little is known regarding the prognostic implications of lower serum chloride.

Methods and Results—Serum chloride was measured in 1,673 consecutively consented stable patients with a history of heart failure undergoing elective diagnostic coronary angiography. All patients were followed for 5-year all-cause mortality, and survival models were adjusted for variables that confounded the chloride-risk relationship. The average chloride level was 102 ± 4 mEq/L. Over 6,772 person-years of follow-up, there were 547 deaths. Lower chloride (per standard deviation decrease) was associated with a higher adjusted risk of mortality (HR 1.29, 95%CI 1.12–1.49, $P < 0.001$). Chloride levels net-reclassified risk in 10.4% ($P = 0.03$) when added to a multivariable model (with a resultant C-statistic of 0.70), in which sodium levels were not prognostic ($P = 0.30$). In comparison to those with above first quartile chloride (101 mEq/L) and sodium (138 meq/L), subjects with first quartile chloride had a higher adjusted mortality risk, whether they had first quartile sodium (HR 1.35, 95%CI 1.08–1.69, $P = 0.008$) or higher (HR 1.43, 95%CI 1.12–1.85, $P = 0.005$). However, subjects with first quartile sodium but above first quartile chloride had no association with mortality ($P = 0.67$).

Conclusions—Lower serum chloride levels are independently and incrementally associated with increased mortality risk in patients with chronic heart failure. A better understanding of the biological role of serum chloride is warranted.

Correspondence to: W. H. Wilson Tang, MD, 9500 Euclid Avenue, Desk J3-4, Cleveland, OH 44195, U.S.A. Phone: (216) 444-2121, Fax: (216) 445-6165, tangw@ccf.org.

DISCLOSURES

None.

Keywords

heart failure; sodium; chloride; electrolyte imbalances

Serum electrolyte abnormalities are common in patients with chronic heart failure, although their underlying causes are often multifactorial. Maladaptive neurohormonal responses can lead to dysregulation of arginine vasopressin-mediated free water absorption and thirst activation.^{1–3} As a result, the plasma concentration of sodium and chloride decreases. Sodium and chloride can also be lowered by chronic loop and thiazide diuretic use, which are often necessary for maintenance of euvolemia in patients with chronic heart failure.⁴ Indeed, diuretics inhibit the electrolyte reabsorption in the thick ascending limb of Henle's loop and the distal convoluted tubules.^{5, 6} As diuretics limit the kidney's ability to excrete maximally dilute urine through renal sodium and chloride wasting, their chronic use may lead to a state of electrolyte depletion.⁷

A low serum sodium level (hyponatremia) is a well-established adverse prognostic marker in patients with chronic heart failure.⁸ However, the pharmacological manipulation of sodium levels in patients with heart failure has yet to demonstrate consistent effects on long-term outcomes.⁹ Although similar mechanisms that lower sodium may also lower chloride levels, lower chloride levels may represent a broader homeostatic imbalance. Chloride plays a role in acid-base homeostasis, contributes to maintenance of urine and plasma electroneutrality, and may even effect neurohormonal activation.^{10–12} Despite this broad biological role, very little is known regarding the prognostic implications of low serum chloride in patients with chronic heart failure. Therefore, the aim of this analysis is to determine the long-term prognostic value of lower serum chloride levels, especially as they relate to lower sodium levels, in patients with chronic, stable heart failure.

METHODS

Study Population

The Cleveland Clinic GeneBank was a prospectively enrolled cohort of consecutively consenting patients undergoing elective diagnostic coronary angiography from 2001 through 2006. Detailed medical histories were obtained on all subjects upon enrollment. Blood samples were collected at the time of coronary angiography immediately after sheath placement, but prior to cardiac catheterization or any therapies were given (including anticoagulant medications). Patients with an acute coronary syndrome or a prior coronary revascularization within 30 days were excluded. Elective coronary angiography was performed for the following reasons: to rule out new or assess severity of established CAD (53%), pre-operatively for cardiac surgery (21%), cardiomyopathy (14%), remote myocardial infarction (9%), pre-operatively for non-cardiac surgery (3%), orthotopic heart transplantation evaluation (1%), and miscellaneous (2%). A clinical history of chronic heart failure was determined by the treating clinicians and confirmed by trained research personnel who enrolled patients into GeneBank. All participants gave written informed consent as approved by the Cleveland Clinic Institutional Review Board.

Study Design and Data Definitions

An estimate of glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease equation. Electrolytes, renal indices, and B-type natriuretic peptide (BNP) were measured on the Abbot Architect platform (Abbott Laboratories, Abbott Park, Illinois) and red cell distribution width (RDW) was measured by the Advia 120 hematoanalyzer (Siemens Healthcare Diagnostics, Tarrytown, NY), all by a central core laboratory. Self-reported functional status was measured by the Duke Activity Status Index (DASI) Questionnaire which the study participants completed at the time of enrollment. The DASI is a validated instrument for both functional status and prognosis in chronic heart failure.^{13, 14} Lower DASI scores are associated with a worse prognosis. Left ventricular ejection fraction (LVEF) was determined via transthoracic echocardiography by Simpson's method as part of routine clinical care and in accordance with the American Society of Echocardiography guidelines.¹⁵ Echocardiographic data and pre-angiography electrolyte levels (including chloride) were abstracted via chart review of the electronic medical record at the time of enrollment. Adjudicated outcomes were prospectively collected over the 5 years following enrollment. Death was validated by querying the Social Security Death Index.

Statistical Analysis

Continuous variables are presented as median (interquartile range) and categorical variables as percentages. Skewed variables were natural-log transformed as appropriate. The cohort was split into quartiles of serum chloride and quartiles of serum sodium levels. There was additional grouping for subjects in the first quartiles of both chloride and sodium, the first quartile of chloride only, the first quartile of sodium only, and those that were in neither. The Jonckheere-Terpstra or Cochran-Armitage tests were used to determine trends for baseline characteristic across increasing quartiles of chloride. A backwards selection linear regression algorithm was used from the baseline characteristics to determine independent correlates of serum chloride. The significance level for variable removal was $P = 0.10$ and for variable addition was $P = 0.05$. Mortality curves for chloride quartiles were generated via the Kaplan-Meier method. Cumulative mortality rates were compared by log-rank analysis. After observing no trends with time for the Schoenfeld residuals, the association of chloride and 5-year mortality was performed via a Cox-proportional hazards model. In a separate survival analysis clarifying the risk-relationship of low chloride level to low sodium level concordance or discordance, a categorical variable identifying the first quartile of chloride and/or first quartile of sodium was created. The multivariable model included covariates that were selected *a priori* either due to their prognostic relevance or their potential to confound the chloride-risk relationship. These included age, sex, systolic blood pressure, diabetes, LVEF, angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) use, beta-blocker use, loop diuretic use, and DASI score, as well as serum sodium, serum bicarbonate, and eGFR. Additional adjustments were made for a subset with both measured BNP and RDW levels. Variables with a skewed distribution were transformed. Sub-groups were divided according to loop diuretic use, diabetes, sex, diabetes, coronary artery disease, heart failure with preserved (LVEF $\geq 40\%$, HFpEF) or reduced LVEF (LVEF $< 40\%$, HFrEF), chronic obstructive pulmonary disease (COPD), and eGFR $<$ or ≥ 60

ml/min/1.73m². The discrimination (C-statistic) of the impact of chloride levels on mortality was determined as previously described.¹⁶ Category-free net-reclassification indices (NRI) and integrated discrimination improvement (IDI) were calculated for the addition of chloride to the multivariable model.¹⁷ Fractional polynomials were plotted to show the continuous association of chloride with mortality. Double-sided p-values <0.05 were considered statistically significant. Statistical analyses were performed using Stata 13.1 software (StataCorp LP, College Station, Texas).

RESULTS

Baseline Characteristics

In our study cohort (see Supplemental Figure 1 for CONSORT diagram), serum chloride levels were normally distributed (mean 102 ± 4 mEq/L; median 103 mEq/L [interquartile ranges 101–104 mEq/L]). The full range of chloride was 89 to 115 mEq/L. There were 231 subjects (13.6%) with Cl<98 mEq/L and 101 subjects (5.9%) with Cl>107 mEq/L. Baseline characteristics across increasing chloride quartiles are shown in Table 1. Independent correlates of chloride levels in this population included sodium ($\beta=0.81$, $P<0.001$), bicarbonate ($\beta=-0.47$, $P<0.001$), age ($\beta=0.04$, $P<0.001$), log-transformed blood urea nitrogen (BUN, $\beta=-0.84$, $P<0.001$), DASI score ($\beta=0.02$, $P=0.001$), RDW ($\beta=-0.15$, $P=0.013$), loop diuretic use ($\beta=-0.42$, $P=0.026$), and beta-blocker use ($\beta=0.36$, $P=0.051$).

Chloride and 5-Year Mortality

There were 1,664 (99%) participants followed for 5-year all-cause mortality. In this group, there were 547 (33%) deaths over 6,772 person-years of follow-up. Kaplan-Meier estimates of cumulative mortality are shown in Figure 1. The two lower chloride quartiles (<101 and 101–102 mEq/L) had higher cumulative mortality than the two higher chloride quartiles (103–104 and >104 mEq/L, Log-rank χ^2 38.2, $P<0.001$).

For every standard deviation (4.1 mEq/L) decrement in chloride level was associated with 32% increase in 5-year mortality risk (HR 1.32, 95% confidence interval [95%CI] 1.22–1.43, $P<0.001$). After multivariable adjustment (Table 2), every standard deviation decrement in chloride level remained associated with a higher 5-year mortality risk (HR 1.29, 95%CI 1.12–1.49, $P<0.001$, Figure 2). After additional adjustment for natural log-transformed BNP and RDW levels (deaths, n/N=217/713), every standard deviation decrement in chloride remained associated with an increased risk of 5-year mortality (HR 1.26, 95%CI 1.03–1.55, $P=0.03$). Within the model, standard deviation (3.3 mEq/L) decrements in sodium were not associated with mortality ($P=0.30$), despite the fact that lower sodium quartiles and sodium levels within the model, but without adjustment for chloride, were associated with higher 5-year mortality risk (see Supplemental Figure 2 and 3). Within the multivariable model, there was no interaction between sodium and chloride ($P=0.15$) or between bicarbonate and chloride ($P=0.3$). This relationship is shown in Figure 3. Although there was little improvement in discrimination when chloride was added to the multivariable model (C-statistic: 0.70, 95%CI 0.68–0.72 versus 0.71, 95%CI 0.69–0.73), it reclassified risk in 10% of the cohort (NRI 10.4%, $P=0.03$ and IDI 0.3%, $P=0.03$). In a sensitivity analysis substituting natural log-transformed BUN (which was available in a

subset, deaths n/N=231/794) for eGFR in the multivariable model, the association of decreasing chloride and mortality was similar (HR 1.32, 95%CI 1.08–1.62, P=0.008). Further, the association of chloride and mortality was also relatively unchanged with the addition of COPD into the model (HR 1.30, 95%CI 1.13–1.50, P<0.001).

Kaplan-Meier estimates for 5-year mortality stratified by whether subjects were classified by the first quartiles of chloride and sodium are shown in Supplemental Figure 4. Cumulative mortality was higher for subjects in the first chloride quartile regardless of whether they were in the first sodium quartile (Log-rank, χ^2 32.5, P<0.001). Subjects with chloride levels in first quartile had a significant adjusted mortality risk if they also had sodium levels in the first quartile (HR 1.35, 95%CI 1.08–1.69, P=0.008) or higher (HR 1.43, 95%CI 1.12–1.85, P=0.005, Table 3). However, subjects with chloride levels higher than the first quartile but with sodium levels in the first quartile the adjusted mortality risk was not significant (P=0.67).

Sub-group analyses revealed that lower chloride levels had relatively consistent risk of mortality across dichotomized sub-groups of: loop diuretic use, sex, diabetes, CAD, HFpEF or HFrEF, COPD, or eGFR < or = 60 ml/min/1.73m² (Figure 4). Of these, only diuretic usage significantly interacted with the chloride-risk association (P=0.02).

DISCUSSION

Our group has recently described the incremental prognostic role of serum chloride in the setting of decompensated heart failure receiving diuretic therapy that is above and beyond serum sodium levels¹⁸. Herein, we now report several key observations regarding the prognostic importance of electrolyte homeostasis in a large cohort of patients with chronic stable heart failure. First, serum chloride levels were strongly correlated to functional status (DASI Score), sodium, BUN, and loop diuretic use, while they were not closely correlated with more traditional markers of heart failure severity such as LVEF and BNP. This suggests an extra-cardiac link between abnormal chloride homeostasis with functional impairment, renal function, and decongestive therapies. Second, lower chloride was independently and incrementally associated with higher mortality even in the chronic setting, despite multivariable risk-adjustment for other electrolytes including sodium, cardio-renal biomarkers, self-reported functional status, and medication use. These findings reveal that serum chloride levels may carry important prognostic information in patients across the spectrum of heart failure, and highlight the need to better understand the potential benefits of strategies (especially for long-term diuretic strategies) that can preserve electrolyte homeostasis.

Our findings point to an association between chloride homeostasis and disease progression in heart failure whereby clinical severity may be associated with uncontrolled chloride dilution and depletion. This may be potentiated by several maladaptive mechanisms. First, neurohormonal activation and acid-base changes in chronic heart failure modulate chloride levels. For example, in combination with increased thirst,¹⁹ patients with heart failure have increased arginine vasopressin secretion, which in a mechanistically similar way to hyponatremia, causes a dilutional hypochloremia.^{1–3} Second, loop or thiazide diuretics

inhibit chloride resorption, leading to a depletion hypochloremia.^{5, 6, 20} Although the biological role of chloride is not well understood, these results highlight the clinical importance of small perturbations in chloride level, which may not be markedly abnormal. In addition, loop diuretic use did modify the risk of chloride levels, which supports the hypothesis that pharmacological effects chloride levels may have prognostic implications.

In contrast to sodium, chloride levels may represent other adversely prognostic homeostatic perturbations in heart failure. Extensive literature from murine models has demonstrated that chloride (and not sodium) in the renal tubular fluid suppresses plasma renin activity after resorption in the thick ascending limb and by direct action on the macula densa.^{11, 12} This mechanism can be suppressed with chronic loop diuretic use which blocks chloride resorption in the thick ascending limb and, over time, leads to excessive chloride loss, translating into hypochloremia. Whether depleted serum chloride levels result in increased plasma renin activity in humans with chronic heart failure remains unproven. Interestingly, recent genetic investigations into determinants of heart failure risk have pointed to loss-of-function gene variant in the CLCNKA chloride channel which affects cardiorenal interactions through salt sensitivity.²¹

The findings of the current study further support the prognostic relevance of lower chloride. Also in a retrospective analysis of CHARM, it was observed that serum chloride among other candidate variables had the strongest association with long-term mortality.²² Intriguingly, the strong inverse relationship found in this study between serum chloride levels and prognosis remained after correction for serum sodium levels, which are a well-established prognostic marker in patients with chronic heart failure.^{8, 23} Moreover, the prognostic value of serum sodium was markedly diminished within the multivariable model for mortality that included chloride levels. This finding may have broad implications for risk assignment in heart failure populations. Sodium levels are key components of many well-known chronic heart failure prognostic models,²⁴ and are one of the most commonly used and strongest correlates of death and heart failure hospitalizations in heart failure populations.^{25, 26} Importantly, analysis of chloride was absent in these models. As the current findings suggest, chloride levels may have confounded the relationship between sodium and risk and chloride may further improve risk stratification. Indeed, lower chloride levels, especially when lower relative to sodium levels, may be indicative of a state of electrolyte depletion which can be characterized by a large difference in sodium level relative to chloride level.¹⁰ As more chloride is excreted into the urine, bicarbonate anions are reabsorbed to maintain electroneutrality, which in turn, provoke alkalosis. The observation that subjects with low chloride, but not low sodium drives mortality-risk supports the importance of identifying an electrolyte-deplete phenotype. Further, making the distinction between dilutional and depletion hypochloremia is clinically relevant as it may have different therapeutic implications.²⁷

This analysis must be interpreted in the context of several limitations. We cannot exclude the presence of selection bias for undergoing diagnostic coronary angiography and treatment for chronic heart failure at a tertiary referral center. However, this cohort was relatively representative of a contemporary cohort with chronic heart failure with elevated BNP levels and a majority on beta-blocker or ACEI or ARB therapies. Because chloride levels were

only measured at one point in time, the prognostic impact of changing chloride levels could not be assessed. However, even small differences in a single chloride concentration measurement had noticeably higher mortality (Figure 1) supporting the strong prognostic value of this electrolyte. Diuretic dosage was not collected, urine electrolytes were not measured, and there were no data collected regarding physical examination findings and patient-level decision making. However, direct pharmacological manipulation of chloride levels in patients with chronic heart failure is not commonplace. There were also no formal volume status assessments, which limit the assessment of chloride distribution within the body. However, this is essential to understanding the mechanistic role chloride plays in the interstitial and intravascular spaces and should be the subject of future study. New York Heart Association Functional (NYHA) status was not prospectively collected in this cohort. Instead, the DASI was used, which is a validated, highly prognostic tool which yields a continuum of functional status assessment in patients with heart failure.^{13, 14, 28} There have been no direct conversions between NYHA class and the DASI. However, in a prospective cohort of heart failure patients who were clinically stabilized, those with an adverse 9-month prognosis had both a higher DASI (16 ± 12) and NYHA Class (2.8 ± 1.1) than those without (DASI 25 ± 17 and NYHA Class 2.3 ± 0.9).¹⁴ Although heart failure hospitalizations were not adjudicated, the large number of outcomes with minimal loss to follow-up uniquely powers this analysis to determine the prognostic role of chloride in the setting of other strong prognostic variables.

CONCLUSION

Despite relatively low prevalence of hyponatremia and hypochloremia in our cohort of patients with chronic stable heart failure, we observed that lower serum chloride level was associated with a higher 5-year mortality risk independent of renal function, self-reported functional status, medication use, loop diuretic use (and in a subset, independent of BNP and RDW). The adverse prognostic role of lower sodium levels was diminished in comparison. These findings highlight the need to describe the pathological underpinnings driving lower chloride in heart failure and explore therapies that preserve chloride homeostasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

SOURCES OF FUNDING

This research was supported by grants from the National Institutes of Health and the Office of Dietary Supplements (R01HL103931, P20HL113452). The GeneBank study has been supported by NIH grants P01HL076491, P01HL098055, R01HL103866, and the Cleveland Clinic Clinical Research Unit of the Case Western Reserve University CTSA (UL1TR 000439). Reagents for chemistry and BNP measurements were provided by Abbott Laboratories.

References

1. Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med*. 2000; 342:1581–1589. [PubMed: 10824078]

2. Goldsmith SR, Francis GS, Cowley AW Jr, Levine TB, Cohn JN. Increased plasma arginine vasopressin levels in patients with congestive heart failure. *J Am Coll Cardiol.* 1983; 1:1385–1390. [PubMed: 6343460]
3. Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, Kubo SH, Rudin-Toretsky E, Yusuf S. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the studies of left ventricular dysfunction (solv'd). *Circulation.* 1990; 82:1724–1729. [PubMed: 2146040]
4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology F, American Heart Association Task Force on Practice G. 2013 accf/aha guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *J Am Coll Cardiol.* 2013; 62:e147–239. [PubMed: 23747642]
5. Greger R, Schlatter E. Properties of the basolateral membrane of the cortical thick ascending limb of henle's loop of rabbit kidney. A model for secondary active chloride transport. *Pflugers Arch.* 1983; 396:325–334. [PubMed: 6844137]
6. Mastroianni N, De Fusco M, Zollo M, Arrigo G, Zuffardi O, Bettinelli A, Ballabio A, Casari G. Molecular cloning, expression pattern, and chromosomal localization of the human na-cl thiazide-sensitive cotransporter (slc12a3). *Genomics.* 1996; 35:486–493. [PubMed: 8812482]
7. Verbrugge FH, Dupont M, Steels P, Grieten L, Swennen Q, Tang WH, Mullens W. The kidney in congestive heart failure: 'Are natriuresis, sodium, and diuretics really the good, the bad and the ugly?'. *Eur J Heart Fail.* 2014; 16:133–142. [PubMed: 24464967]
8. Rusinaru D, Tribouilloy C, Berry C, Richards AM, Whalley GA, Earle N, Poppe KK, Guazzi M, Macin SM, Komajda M, Doughty RN, Investigators M. Relationship of serum sodium concentration to mortality in a wide spectrum of heart failure patients with preserved and with reduced ejection fraction: An individual patient data meta-analysis(dagger): Meta-analysis global group in chronic heart failure (maggic). *Eur J Heart Fail.* 2012; 14:1139–1146. [PubMed: 22782968]
9. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C. Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan I. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The everest outcome trial. *JAMA.* 2007; 297:1319–1331. [PubMed: 17384437]
10. Galla JH, Gifford JD, Luke RG, Rome L. Adaptations to chloride-depletion alkalosis. *Am J Physiol.* 1991; 261:R771–781. [PubMed: 1928424]
11. Kirchner KA, Kotchen TA, Galla JH, Luke RG. Importance of chloride for acute inhibition of renin by sodium chloride. *Am J Physiol.* 1978; 235:F444–450. [PubMed: 31796]
12. Lorenz JN, Kotchen TA, Ott CE. Effect of na and cl infusion on loop function and plasma renin activity in rats. *Am J Physiol.* 1990; 258:F1328–1335. [PubMed: 2186635]
13. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, Cobb FR, Pryor DB. A brief self-administered questionnaire to determine functional capacity (the duke activity status index). *Am J Cardiol.* 1989; 64:651–654. [PubMed: 2782256]
14. Parissis JT, Nikolaou M, Birmpa D, Farmakis D, Paraskevaidis I, Bistola V, Katsoulas T, Filippatos G, Kremastinos DT. Clinical and prognostic value of duke's activity status index along with plasma b-type natriuretic peptide levels in chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol.* 2009; 103:73–75. [PubMed: 19101233]
15. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the american society of echocardiography and the european association of cardiovascular imaging. *J Am Soc Echocardiogr.* 2015; 28:1–39 e14. [PubMed: 25559473]
16. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 1996; 15:361–387. [PubMed: 8668867]

17. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011; 30:11–21. [PubMed: 21204120]
18. Grodin JL, Simon J, Hachamovitch R, Wu Y, Jackson G, Halkar M, Starling RC, Testani JM, Tang WH. Prognostic role of serum chloride levels in acute decompensated heart failure. *J Am Coll Cardiol*. 2015; 66:659–666. [PubMed: 26248993]
19. Sica DA. Sodium and water retention in heart failure and diuretic therapy: Basic mechanisms. *Cleve Clin J Med*. 2006; 73(Suppl 2):S2–7. discussion S30–33. [PubMed: 16786906]
20. Verbrugge FH, Nijst P, Dupont M, Penders J, Tang WH, Mullens W. Urinary composition during decongestive treatment in heart failure with reduced ejection fraction. *Circulation Heart failure*. 2014; 7:766–772. [PubMed: 25037309]
21. Cappola TP, Matkovich SJ, Wang W, van Booven D, Li M, Wang X, Qu L, Sweitzer NK, Fang JC, Reilly MP, Hakonarson H, Nerbonne JM, Dorn GW 2nd. Loss-of-function DNA sequence variant in the *clnka* chloride channel implicates the cardio-renal axis in interindividual heart failure risk variation. *Proc Natl Acad Sci U S A*. 2011; 108:2456–2461. [PubMed: 21248228]
22. Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, Swedberg K, Wang D, Yusuf S, Michelson EL, Granger CB, Investigators C. Red cell distribution width as a novel prognostic marker in heart failure: Data from the charm program and the duke databank. *J Am Coll Cardiol*. 2007; 50:40–47. [PubMed: 17601544]
23. Deubner N, Berliner D, Frey A, Guder G, Brenner S, Fenske W, Allolio B, Ertl G, Angermann CE, Stork S. Dysnatraemia in heart failure. *Eur J Heart Fail*. 2012; 14:1147–1154. [PubMed: 22820314]
24. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The seattle heart failure model: Prediction of survival in heart failure. *Circulation*. 2006; 113:1424–1433. [PubMed: 16534009]
25. Ouwerkerk W, Voors AA, Zwiderman AH. Factors influencing the predictive power of models for predicting mortality and/or heart failure hospitalization in patients with heart failure. *JACC Heart Fail*. 2014; 2:429–436. [PubMed: 25194294]
26. Rahimi K, Bennett D, Conrad N, Williams TM, Basu J, Dwight J, Woodward M, Patel A, McMurray J, MacMahon S. Risk prediction in patients with heart failure: A systematic review and analysis. *JACC Heart Fail*. 2014; 2:440–446. [PubMed: 25194291]
27. Verbrugge FH, Steels P, Grieten L, Nijst P, Tang WH, Mullens W. Hyponatremia in acute decompensated heart failure: Depletion versus dilution. *J Am Coll Cardiol*. 2015; 65:480–492. [PubMed: 25660927]
28. Grodin JL, Hammadah M, Fan Y, Hazen SL, Tang WH. Prognostic value of estimating functional capacity with the use of the duke activity status index in stable patients with chronic heart failure. *J Card Fail*. 2015; 21:44–50. [PubMed: 25175697]

Clinical Perspective

While hyponatremia and cardio-renal compromise have long been considered therapeutic challenges in the management of heart failure especially at its advanced stages, the role of chloride homeostasis have largely been overlooked despite insightful early mechanistic work suggesting that chloride is an important component for maintaining plasma electroneutrality. Specifically, extensive literature from murine models has demonstrated that chloride (and not sodium) in the renal tubular fluid suppresses plasma renin activity after resorption in the thick ascending limb and by direct action on the macular densa. Almost all large randomized trials did not capture chloride levels in their case report forms, and population-based observational studies also ignored them. Herein, we observed that serum chloride levels were strongly correlated not only to standard cardio-renal indices (sodium, urea, loop diuretic use) as well as functional status, but did not correlate with more traditional markers of heart failure severity such as ejection fraction and natriuretic peptide levels. Furthermore, lower chloride was independently and incrementally associated with higher mortality, despite multivariable risk-adjustment for all above parameters, and when chloride was incorporated sodium levels lost its prognostic value. These findings highlight the need to better understand the potential benefits of strategies to preserve electrolyte homeostasis with an added focus to achieve chloride homeostasis.

Figure 1.

Title: Kaplan-Meier Estimated of 5-Year Mortality Across Chloride Quartiles

Figure 2.

Title: Predicted 5-Year Mortality Risk by Chloride Level

Caption: The risk-relationship has been plotted as a fractional polynomial. Multivariable adjustment was for sodium, bicarbonate, estimated glomerular filtration rate, 10-year increase in age, systolic blood pressure, male sex, diabetes, ejection fraction, ACEI or ARB use, beta-blocker use, loop diuretic use, and 5-point decrease in DASI score.

Figure 3.

Title: The Risk-Adjusted Probability of 5-Year Mortality of Various Chloride Levels for a Given Sodium Level

Caption: Multivariable adjustment for bicarbonate, estimated glomerular filtration rate, 10-year increase in age, systolic blood pressure, male sex, diabetes, ejection fraction, ACEI or ARB use, beta-blocker use, loop diuretic use, and 5-point decrease in DASI score.

Figure 4.

Title: 5-Year Mortality Risk of Chloride Levels Across Sub-Groups

Caption: The standard deviation of chloride is 4.1 meq/L. For loop diuretic use, P-interaction=0.02 and for all other sub-groups the P-interaction>0.05.

Baseline Characteristics

Table 1

Clinical Characteristics	Chloride Quartile, mEq/L (N=1,673)				P-value*
	<101 (N=549)	101–102 (N=345)	103–104 (N=366)	>104 (N=413)	
Age, y	66 (57–74)	67 (59–74)	68 (60–75)	69 (61–76)	<0.001
Male, %	62.6	67.7	68.6	59.3	0.30
White, %	87.4	87.7	90.6	85.4	0.71
Coronary artery disease, %	77.1	76.6	72.0	76.4	0.45
Diabetes, %	48.7	38.9	35.6	29.3	<0.001
COPD, %	36.1	28.5	23.5	21.5	<0.001
Systolic BP, mm Hg	127 (112–142)	130 (117–150)	128 (116–143)	132 (120–147)	<0.001
DASI Score	21.5 (12.7–34.7)	27 (13.4–42.7)	29.7 (18.7–42.7)	30.2 (18–42.7)	<0.001
Ejection fraction, %	40 (25–55)	40 (25–55)	40 (30–55)	40 (30–55)	0.09
eGFR, mL/min/1.73m ²	57 (43–74)	62 (46–78)	60 (47–76)	58 (45–73)	0.49
Sodium, meq/L	137 (134–139)	139 (138–141)	140 (139–142)	141 (140–143)	<0.001
Blood urea nitrogen, mg/dL	22 (17–31)	21 (16–26)	21 (16–27)	20 (15–26)	0.004
Bicarbonate, meq/L	28 (25–30)	27 (24–29)	26 (24–28)	24 (22–27)	<0.001
Red cell distribution width, %	14 (13.2–15.4)	13.8 (13.1–14.8)	13.6 (13–14.4)	13.6 (13–14.4)	<0.001
Albumin, g/dL	3.9 (3.7–4.2)	3.9 (3.7–4.2)	4.0 (3.7–4.1)	3.9 (3.7–4.1)	0.43
BNP, pg/mL	327 (136–738)	300 (114–1,015)	309 (109–670)	310 (127–636)	0.41
ACEI or ARB, %	65.9	69.9	65.9	69.5	0.42
Beta-Blocker, %	63.6	67.0	66.7	71.9	0.01
Loop diuretic, %	66.1	58.6	53.6	51.8	<0.001

* P-value from Jonckheere-Terpstra or Cochran-Armitage trend tests.

Values expressed as either median (interquartile range) or (%).

Abbreviations: COPD, chronic obstructive pulmonary disease; DASI, Duke Activity Status Index; eGFR, estimated glomerular filtration rate; RDW, red cell distribution width (N=1,495); BNP, B-type natriuretic peptide (N=811); ACEI, angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker

Table 2

Cox-Proportional Hazards Models for the Association of Chloride and 5-Year Mortality

Model	HR* (95%CI)	P-value
Unadjusted	1.32 (1.22–1.43)	<0.001
Adjusted Model 1 [†]	1.29 (1.12–1.49)	<0.001
Adjusted Model 2 [‡]	1.26 (1.03–1.55)	0.027

* Hazard Ratio for chloride is standardized for a 4.1 mEq/L decrease.

[†] Adjustment for age (10y increments), male sex, history of diabetes, LVEF, loop diuretic use, beta-blocker use, ACEI or ARB use, DASI score (per 5 point drop), eGFR, serum sodium, and serum bicarbonate.

[‡] Adjustment with the variables in Model 1 plus red cell distribution width and ln[BNP] (deaths n/N=217/723).

Table 3

Cox-Proportional Hazards Models for the Association of Chloride and Sodium Level Concordance and 5-Year Mortality

Chloride and Sodium Grouping		Unadjusted		Adjusted *	
Chloride, mEq/L [†]	Sodium, mEq/L [‡]	HR (95%CI)	P-value	HR (95%CI)	P-value
<101	<138	1.69 (1.38–2.08)	<0.001	1.35 (1.08–1.69)	0.008
<101	138	1.60 (1.27–2.02)	<0.001	1.43 (1.12–1.85)	0.005
101	<138	1.17 (0.85–1.61)	0.34	1.07 (0.77–1.58)	0.67
101	138	Reference	–	Reference	–

* Adjustment for age (10y increments), male sex, history of diabetes, LVEF, loop diuretic use, beta-blocker use, ACEI or ARB use, DASI score (per 5 point drop), eGFR, serum sodium, and serum bicarbonate.

[†] Quartiles for chloride in mEq/L are: Q1, <101; Q2, 101–102; Q3, 103–104; and Q4, >104. Values correspond to Q1 or Q2–4.

[‡] Quartiles for sodium in mEq/L are: Q1, <138; Q2, 138–139; Q3, 140–141; and Q4, >141. Values correspond to Q1 or Q2–4.