Importance of Abnormal Chloride Homeostasis in Stable Chronic Heart Failure

Justin L. Grodin, MD, MPH; Frederik H. Verbrugge, MD, PhD; Stephen G. Ellis, MD; Wilfried Mullens, MD, PhD; Jeffrey M. Testani, MD, MTR; W.H. Wilson Tang, MD

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 1673 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 6772 person-years of follow-up, there were 547 deaths. Lower chloride (per standard deviation decrease) was associated with a higher adjusted risk of mortality (hazard ratio 1.29, 95% confidence interval 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 (hazard ratio 1.35, 95% confidence interval 1.08–1.69; P=0.008) or higher (hazard ratio 1.43, 95% confidence interval 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.

Key Words: chloride ■ electrolyte imbalances ■ heart failure ■ sodium

See Clinical Perspective

A low serum sodium level (hyponatremia) is a well-established adverse prognostic marker in patients with chronic heart failure. However, the pharmacological manipulation of sodium levels in patients with heart failure has yet to demonstrate consistent effects on long-term outcomes. 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. 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


Correspondence to W.H. Wilson Tang, MD, 9500 Euclid Ave, Desk F3-4, Cleveland, OH 44195. E-mail tangw@ccf.org

© 2015 American Heart Association, Inc.

Circ Heart Fail is available at http://circheartfailure.ahajournals.org

DOI: 10.1161/CIRCHEARTFAILURE.115.002453
coronary angiography from 2001 to 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 before 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 coronary artery disease (53%), preoperatively for cardiac surgery (21%), cardiomyopathy (14%), remote myocardial infarction (9%), preoperatively for noncardiac 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 Abbott Architect platform (Abbott Laboratories, Abbott Park, IL), 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 prognostic relevance or their potential to confound the chloride–risk relationship. These included age, sex, systolic blood pressure, diabetes mellitus, LVEF, angiotensin converting enzyme inhibitor or angiotensin II receptor blocker 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 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 characteristics 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.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Chloride Quartile, mEq/L (N=1673)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>&lt;101 (N=549)</td>
<td>101–102 (N=345)</td>
</tr>
<tr>
<td>Male, %</td>
<td>66 (57–74)</td>
<td>67 (59–74)</td>
</tr>
<tr>
<td>White, %</td>
<td>62.6</td>
<td>67.7</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>87.4</td>
<td>87.7</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>71.1</td>
<td>76.6</td>
</tr>
<tr>
<td>COPD, %</td>
<td>48.7</td>
<td>39.8</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>21.5</td>
<td>27 (13.4–24.7)</td>
</tr>
<tr>
<td>DASI Score</td>
<td>40 (25–55)</td>
<td>40 (25–55)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>57 (43–74)</td>
<td>62 (46–78)</td>
</tr>
<tr>
<td>Sodium, meq/L</td>
<td>137 (134–139)</td>
<td>139 (138–141)</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>22 (17–31)</td>
<td>21 (16–26)</td>
</tr>
<tr>
<td>Bicarbonate, meq/L</td>
<td>28 (25–30)</td>
<td>27 (24–29)</td>
</tr>
<tr>
<td>Red cell distribution width, %</td>
<td>14 (13.2–15.4)</td>
<td>13.8 (13.1–14.8)</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.9 (3.7–4.2)</td>
<td>3.9 (3.7–4.2)</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>327 (136–738)</td>
<td>300 (114–1,015)</td>
</tr>
<tr>
<td>ACEI or ARB, %</td>
<td>65.9</td>
<td>69.9</td>
</tr>
<tr>
<td>Beta-blocker, %</td>
<td>63.6</td>
<td>67.0</td>
</tr>
<tr>
<td>Loop diuretic, %</td>
<td>66.1</td>
<td>58.6</td>
</tr>
</tbody>
</table>

*Values expressed as either median (interquartile range) or (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide (N=811); COPD, chronic obstructive pulmonary disease; DASI, Duke Activity Status Index; eGFR, estimated glomerular filtration rate; and RDW, red cell distribution width (N=1495).

*P* value from Jonckheere–Terpstra or Cochran–Armitage trend tests.
Chloride Homeostasis in Heart Failure

Results

Baseline Characteristics

In our study cohort (see Figure I in the Data Supplement for the consort diagram), serum chloride levels were normally distributed (mean 102±4 mEq/L; median 103 mEq/L [inter-quartile 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 (β=0.81; P<0.001), bicarbonate (β=−0.47; P<0.001), age (β=0.04; P<0.001), log-transformed blood urea nitrogen (β=−0.84; P<0.001), DASI score (β=−0.02; P=0.001), RDW (β=−0.15; P=0.013), loop diuretic use (β=−0.42; P=0.026), and beta-blocker use (β=0.36; P=0.051).

Chloride and 5-Year Mortality

There were 1664 (99%) participants followed for 5-year all-cause mortality. In this group, there were 547 (33%) deaths over 6772 person-years of follow-up. Kaplan–Meier estimates for 5-year mortality stratified by whether subjects were classified by the first quartiles of chloride and sodium are shown in Figure I. The 2 lower chloride quartiles (<101 and 101–102 mEq/L) had higher cumulative mortality than the 2 higher chloride quartiles (103–104 and >104 mEq/L, log-rank χ² 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).

Table 2. Cox-Proportional Hazards Models for the Association of Chloride and 5-Year Mortality

<table>
<thead>
<tr>
<th>Model</th>
<th>HR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.32 (1.22–1.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted Model 1†</td>
<td>1.29 (1.12–1.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted Model 2‡</td>
<td>1.26 (1.03–1.55)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; BNP, B-type natriuretic peptide (N=811); DASI, Duke Activity Status Index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; and LVEF, left ventricular ejection fraction.

*Hazard ratio for chloride is standardized for a 4.1 mEq/L decrease.
†Adjustment for age (10 y increments), male sex, history of diabetes mellitus, 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=217/794).
by guest on June 19, 2017 http://circheartfailure.ahajournals.org/Downloaded from

Clinical severity may be associated with uncontrolled chloride homeostasis and disease progression in heart failure, whereby strategies (especially for long-term diuretic use) that can preserve electrolyte homeostasis. Our group has recently described the incremental prognostic information in patients across the spectrum of heart failure severity, such as LVEF and BNP. This suggests an extracardiac 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 stable heart failure. First, serum chloride levels were strongly correlated to functional status (DASI Score), sodium, blood urea nitrogen, and loop diuretic use, whereas they were not closely correlated with more traditional markers of heart failure severity, such as LVEF and BNP. This suggests an extracardiac 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 use) 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, patients with heart failure have increased arginine vasopressin secretion, which in a mechanistically similar way to hyponatremia causes a dilutional hypochloremia. Second, loop or thiazide diuretics inhibit chloride resorption, leading to a depletional hypochloremia. 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 on 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 macular densa. 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.

The findings of the current study further support the prognostic relevance of lower chloride. Also in a retrospective analysis of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) Program, it was observed that serum chloride among other candidate variables had the strongest association with long-term mortality. 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 markers 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 models24 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 depletional hypochloremia is clinically relevant because 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 angiotensin converting enzyme inhibitor or angiotensin II receptor blocker 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 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 New York Heart Association class and the DASI. However, in a prospective cohort of heart failure patients who were clinically

<table>
<thead>
<tr>
<th>Chloride Grouping, mEq/L</th>
<th>Sodium Grouping, mEq/L</th>
<th>Unadjusted</th>
<th>Adjusted‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;101</td>
<td>&lt;138</td>
<td>1.69 (1.38–2.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;101</td>
<td>≥138</td>
<td>1.60 (1.27–2.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥101</td>
<td>&lt;138</td>
<td>1.17 (0.85–1.61)</td>
<td>0.34</td>
</tr>
<tr>
<td>≥101</td>
<td>≥138</td>
<td>Reference</td>
<td>...</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; DASI, Duke Activity Status Index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; and LVEF, left ventricular ejection fraction.

*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.
‡Adjustment for age (10 y 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.

Figure 4. 5-Year mortality risk of chloride levels across subgroups. The standard deviation of chloride is 4.1 meq/L. For loop diuretic use, P interaction =0.02, and for all other subgroups, the P interaction >0.05. CAD indicates coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with preserved ejection fraction; and HFpEF, heart failure with reduced ejection fraction.
stabilized, those with an adverse 9-month prognosis had both a higher DASI (16±12) and New York Heart Association Class (2.8±1.1) than those without (DASI 25±17 and New York Heart Association Class 2.3±0.9).  

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.

Conclusions

Despite a 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 RWD). 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.

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 National Institutes of Health (NIH) grants P01HL076491, P01HL098055, and 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.

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Although 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 has 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 lose 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.
Importance of Abnormal Chloride Homeostasis in Stable Chronic Heart Failure
Justin L Grodin, Frederik H Verbrugge, Stephen G Ellis, Wilfried Mullens, Jeffrey M Testani
and W.H. Wilson Tang

_Circ Heart Fail_. 2016;9:e002453
doi: 10.1161/CIRCHEARTFAILURE.115.002453
_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/9/1/e002453

Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2015/12/31/CIRCHEARTFAILURE.115.002453.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Heart Failure_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
thttp://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Heart Failure_ is online at:
thttp://circheartfailure.ahajournals.org//subscriptions/
Supplemental Figure 1. CONSORT diagram for study population

N=8,987
prospectively enrolled into the
Cleveland Clinic GeneBank Study

N=1,781
with a history of chronic heart failure

N=1,673
with measured chloride levels

N=1,664
with follow-up for all-cause mortality at 5-years

N=7,206
with no history of chronic heart failure

N=108
without measured chloride levels

N=9
were lost to follow-up

N=713
with measured BNP and RDW levels
Supplemental Figure 2.

Title: Kaplan-Meier Estimated of 5-Year Mortality Across Sodium Quartiles
Supplemental Figure 3.
Title: Predicted 5-Year Mortality of Sodium Level with and without Adjustment for Chloride

Caption: The risk-relationships have been plotted as fractional polynomials. Multivariable adjustment was 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.
Supplemental Figure 4.

Title: Kaplan-Meier Estimates of 5-Year Mortality Stratified by Chloride and Sodium Level Relationship

Caption: Quartiles for chloride in meq/L are: Q1, <101; Q2, 101-102; Q3, 103-104; and Q4, >104 and quartiles for sodium in meq/L are: Q1, <138; Q2, 138-139; Q3, 140-141; and Q4, >141.