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Hemodynamic factors associated with serum chloride in ambulatory patients with advanced heart failure

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ABSTRACT

Background: Lower serum chloride (Cl) is associated with mortality in heart failure patients and may be more prognostically relevant than sodium. However, the association of hemodynamics and Cl levels is unknown.
Methods: 438 sequential patients with advanced chronic heart failure (ACHF) underwent invasive hemodynamic assessment with measured serum Cl levels during an evaluation for ACHF. Patients were followed for death, heart transplant (HT), or ventricular assist device placement (VAD). A backwards regression model determined hemodynamic predictors of Cl (removal, $P < 0.1$) with candidate variables: Fick cardiac index (FCI), pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), mean arterial pressure (MAP), heart rate (HR), and pulmonary artery systolic pressure (PASP). All models were also adjusted for serum sodium and bicarbonate.
Results: In this cohort, the median Cl level was 102 [98–104] meq/L (range 86–113 meq/L). Chloride was weakly correlated with FCI (rho 0.12, $P = 0.01$) and MAP (rho 0.21, $P < 0.001$); but not PCWP, RAP, HR or PASP ($P > 0.05$ for all). In the multivariable model, FCI (beta 0.73 meq/L/L/min/m^2, $P = 0.002$) but not RAP ($P = 0.3$) or MAP ($P = 0.2$), remained associated with Cl. Lower Cl was associated with increased risk of death, HT, or VAD placement (HR 0.94/meq/L, 95% CI 0.89–0.99, $P = 0.01$). However, this association was attenuated after additional adjustment for BUN ($P = 0.27$) and PCWP and FCI (0.48).
Conclusions: Lower FCI, not lower MAP or higher cardiac filling pressures, was associated with lower chloride. Although lower chloride was associated with poor long-term outcomes, this risk attenuates with adjustment for more conventional clinical parameters.

1. Introduction

Several recent analyses have shed light on the importance of serum chloride levels in heart failure. The strong link between chloride and adverse events has been shown when measured upon admission for acute decompensated heart failure [1], and when measured in the chronic stable heart failure setting [2,3]. Importantly, all of these prior findings supported a diminished prognostic role of serum sodium levels (the major electrolyte tied to adverse events in heart failure) when serum chloride levels were considered.

The reasons for this are unclear and may be explained by the broad physiological importance of maintaining chloride homeostasis in heart failure. Like serum sodium, chloride levels can be diluted in heart failure in the face of increased renally mediated free water absorption from elevated arginine vasopressin [4]. However, serum chloride also plays an important role in acid–base homeostasis, and depletion of chloride plays a major role in maintaining a contraction metabolic alkalosis [5,6]. In contrast to serum sodium, serum chloride levels are more likely depleted by loop diuretic usage — the major pharmacotherapy for decongestion in heart failure [7]. Even mutations in renal K_A chloride channels, proteins that mediate cardio-renal interactions, can predict future heart failure risk [8].

However, the biological processes mediating chloride levels in heart failure are largely hypothetical. To the best of our knowledge, there have been no direct comparisons between objective, physiological, metrics of heart failure severity and their association with serum chloride levels. Because prior reports have linked lower serum sodium levels (which correlate with serum chloride levels) with abnormal cardiac filling pressures and cardiac output [9,10], we hypothesize there will be comparable findings with serum chloride. Therefore, we aim to characterize the hemodynamic correlates of serum chloride. In addition, we

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also aim to characterize and additionally validate the prognostic value of serum chloride levels in a well-characterized cohort, with invasive hemodynamic data, of patients being evaluated for advanced heart failure.

2. Materials and methods

2.1. Study population

This cohort is comprised of ambulatory patients with advanced chronic heart failure (ACHF) seen at the Cleveland Clinic from January 1, 2000 to December 31, 2005. Medical records of all consecutive patients ≥ 18 years old with ACHF of >6 months duration who had undergone pulmonary artery catheterization (PAC) as part of an outpatient heart failure evaluation were abstracted. PAC was indicated for the assessment of disease severity often secondary to progressive signs or symptoms of heart failure. Patients who were excluded had a history of complex congenital heart disease, were on long-term inotropic drug infusions, or if their PAC placement led to direct hospitalization for management of decompensated heart failure. The Cleveland Clinic Institutional Review Board approved the study and this analysis was conducted in a manner adherent to the Declaration of Helsinki.

2.2. Data synthesis and variable definitions

Data abstraction and outcome adjudication have been previously described [11]. In the case of multiple PACs, only data from the first PAC were used. Collected data include demographic characteristics, medical history, drug and device therapy, laboratory values, and underlying heart rhythm. Serum electrolyte panels, including serum chloride levels, were checked as part of routine clinical practice on the day of PAC. Echocardiographic data were collected if performed within 1 month of the outpatient clinic visit. The left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson's method. Left ventricular end diastolic diameter was measured in the parasternal long axis view. The echocardiograms were read by board-certified cardiologists as part of routine care in accordance with the American Society of Echocardiography guidelines [12]. The strong ion difference (SID) was approximated as the absolute difference between serum sodium and chloride [13].

2.3. Assessment of hemodynamics

PAC with a balloon-tipped catheter was performed via cannulation of the internal jugular vein under ultrasound and fluoroscopic guidance with patients in the supine position. Filling pressures including right atrial pressure (RAP), pulmonary arterial pressure, and pulmonary capillary wedge pressure (PCWP) were measured at end-expiration at steady state. Mixed central venous blood gas was collected from the tip of the catheter in the pulmonary artery and cardiac output (CO) was estimated using Fick's equation and indexed to body surface area (BSA): CO/BSA = cardiac index (FCI). Mean arterial pressure (MAP) was measured non-invasively by an automated blood pressure cuff at the time of PAC.

2.4. Endpoints

The time interval from the PAC to either death, heart transplantation (HT), or ventricular assist device (VAD) placement was defined as the duration of follow-up. Death was assessed by analyzing data from the electronic health record in addition to querying the Social Security Death Index. HTs and VAD placements were determined from the medical record. All endpoints were censored on December 31, 2007.

2.5. Statistical methods

Serum chloride levels were stratified into tertiles. Continuous variables were expressed as median and interquartile range (IQR) and categorical variables were expressed as number and percentage. The Jonckheere–Terpstra and Cuzick tests were used to demonstrate trends in the variables across chloride tertiles for continuous and categorical variables, respectively. Pearson's chi-square test was used to determine differences in New York Heart Association classification across chloride tertiles. Spearman's rho coefficients were calculated to determine the electrolyte and hemodynamic correlates of serum chloride. A backwards selection algorithm with bootstrap sampling (200 samples), multivariable linear regression model was used to determine the independent hemodynamic predictors of serum chloride levels. Candidate variables included heart rate, MAP, FCI, PCWP, RAP, and pulmonary artery systolic pressure (PASP) with the additional inclusion of serum sodium and serum bicarbonate, which confound serum chloride levels. Removal criterion was for $P > 0.1$. The Kaplan–Meier method was used to determine cumulative event-free survival curves across serum chloride tertiles which were compared via the Log-rank test. After observing no trends with the Schoenfeld residuals, multivariable Cox proportional hazards models were generated to determine the independent association of serum chloride with all-cause mortality, HT, and VAD placement. Three sequential multivariable models were selected with candidate variables selected based on their a priori potential to confound the chloride–risk relationship or their link with risk in ACHF. The variables in Model 1 were serum sodium and serum bicarbonate; Model 2 included the variables in Model 1 + log-transformed blood urea nitrogen; Model 3 included the variables in Model 2 + PCWP and FCI; and Model 4 included the variables in Model 1 + PCWP and FCI. All continuous variables were transformed if necessary. Two-sided P values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata 13.1 software (StataCorp LP, College Station, TX).

3. Results

3.1. Serum chloride and baseline characteristics

In our study cohort (N = 438), the median serum chloride was 102 [98–104] meq/L. Serum chloride tertiles were: tertile 1, <100 meq/L (N = 147, range 86–99 meq/L); tertile 2, 100–103 meq/L (N = 181); and tertile 3, >103 meq/L (N = 110, range 104–113 meq/L). The baseline characteristics stratified by serum chloride tertile are shown in Table 1. Increasing chloride tertiles were not associated with age, male sex, or ischemic cardiomyopathy. However, lower serum chloride tertiles were associated with more prevalent diabetes mellitus ($P = 0.002$) and lower left ventricular ejection fraction (LVEF, $P = 0.002$). While there was no association with renin–angiotensin system blocker, beta-blocker, or loop diuretic usage lower serum chloride tertiles were associated with more mineralocorticoid antagonist usage ($P = 0.013$). Otherwise, lower serum chloride tertiles were associated with lower serum sodium and higher serum bicarbonate and more renal dysfunction: higher blood urea nitrogen (BUN, $P < 0.001$) and serum creatinine ($P < 0.001$). There was no association with serum chloride and BNP. There was a modest correlation between serum chloride and BUN (rho −0.29, $P < 0.001$) and creatinine (rho −0.17, $P = 0.005$).

3.2. Serum chloride and hemodynamics

Serum chloride level was very weakly correlated with FCI (rho 0.12, $P = 0.01$) and MAP (rho 0.21, $P < 0.001$); but not PCWP (rho 0.02, $P = 0.6$), RAP (rho −0.06, $P = 0.2$), heart rate (rho −0.05, $P = 0.3$), or PASP (rho −0.03, $P = 0.06$). The hemodynamics measured via PAC stratified by serum chloride tertile are shown in Table 1. Lower serum chloride tertiles were associated with lower systemic blood pressure: lower systolic blood pressure, diastolic blood pressure, and MAP ($P < 0.001$ for all) and lower FCI ($P = 0.02$). However, there was no association between serum chloride tertile and cardiac filling pressures (RAP and PCWP) or pulmonary pressures (PASP, pulmonary artery diastolic pressure, or mean pulmonary pressure).

3.3. Hemodynamic predictors of serum chloride

In unadjusted analyses only MAP and FCI were associated with serum chloride levels ($P < 0.001$ and $P = 0.042$, respectively, Table 2). However, after entering the variables, including serum sodium and bicarbonate, into the backwards selection multivariable model, only FCI remained associated with serum chloride, but with a very low point-estimate for association (beta 0.73 meq/L/L/min/m^2, $P = 0.002$). This association persisted when serum creatinine was also forced into the model (beta 0.74 meq/L/L/min/m^2, $P = 0.002$). Without serum chloride in the multivariable model, serum sodium was associated with both RAP (beta 0.12 meq/L/mm Hg, $P = 0.003$), PCWP (beta −0.10 meq/L/mm Hg, $P = 0.03$), and MAP (beta 0.07 meq/L/mm Hg, $P < 0.001$) but not FCI ($P = 0.12$). However, the associations between serum sodium and filling pressures were attenuated when serum chloride was added in the multivariable model (RAP, $P = 0.1$ and PCWP, $P = 0.72$) and the association with MAP persisted, but with a smaller point estimate (beta 0.02 meq/L/mm Hg, $P = 0.01$).

3.4. Serum chloride and long-term outcomes

There were 105 deaths, 103 HTs, and 20 left VAD placements during 1295 person-years of follow-up. Kaplan–Meier estimates of HT- and