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RESEARCH ARTICLE

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Dynamic changes in serum chloride concentrations during worsening of heart failure and its recovery following conventional diuretic therapy: A single-center study

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Abstract

Background and aims: Few data are available regarding the dynamic changes in the serum chloride concentrations in heart failure (HF) pathophysiology. The aim of the present study was to investigate changes in the serum chloride concentration under worsening HF and its recovery following conventional diuretic therapy.

Methods: Blood test data, including measurements of serum albumin/solutes and b-type natriuretic peptide, at both worsening and recovery of HF status, were obtained from 47 patients with definite HF.

Results: Ambulatory patients with HF were enrolled and followed up at the outpatient clinic of Nishida Hospital between June 2003 and March 2009. From clinically stable to worsening HF, the serum sodium concentration increased from (mean ± SD) 139 ± 4.1 to 141 ± 5.07 mEq/L ($P < 0.05$, two-way analysis of variance) and the serum chloride concentration increased from 101 ± 5.36 to 104 ± 5.44 mEq/L ($P < 0.01$) among all patients. After resolution of worsening HF by treatment with conventional diuretics, both the serum sodium concentration and serum chloride concentration decreased significantly to 138 ± 5.12 and 99.5 ± 5.33 mEq/L, respectively ($P < 0.0001$ for each). The absolute changes in the serum sodium concentration from clinically stable HF to worsening HF appeared to be lesser than those in the serum chloride concentration (1.70 ± 4.34 vs 2.72 ± 6.02 mEq/L, $P = 0.079$, t test), but this was not statistically significant. Absolute changes in the serum sodium concentration from worsening HF to its recovery following treatment with conventional diuretics were lesser than those in the serum chloride concentration (−2.87 ± 4.38 vs −4.45 ± 5.23 mEq/L, $P = 0.0068$, t test).

Conclusion: Under conventional diuretic therapy, greater changes occur in the serum chloride concentration than in the serum sodium concentration under HF state transitions, suggesting that chloride dynamics might contribute more to HF pathophysiology under such therapeutic circumstance.

KEYWORDS

chloride, diuretics, heart failure, plasma tonicity, sodium

1 | INTRODUCTION

Chloride, despite flanking sodium as its anionic counterpart in salt, has remained largely ignored in heart failure (HF) pathophysiology.[1] Recent studies have demonstrated that changes in vascular[2-5] and red blood cell volumes[5,6] are independently associated with serum chloride concentration. Few studies, however, have evaluated the dynamic changes in serum chloride concentrations under HF pathophysiology. Therefore, the aim of this study was to investigate changes in the serum chloride concentration, including its relation to the serum sodium concentration, under worsening HF and its recovery following conventional diuretic therapy.

2 | METHODS

2.1 | Study population

The present study was a retrospective, single-center, observational study derived from a recent study[7] that examined body composition changes during follow-up of established HF patients performed in the cardiology clinic of Nishida Hospital between June 2003 and March 2009. Selected patients had at least one decompensated HF episode that resulted in hospitalization or outpatient treatment with conventional diuretics. The ethics committee at Nishida Hospital approved the study protocol. Informed consent was obtained from all patients before study enrollment.

2.2 | Data collection

The event of worsening HF was determined by the appearance of at least two of the following HF-related signs, whether or not changes in symptoms occurred: HF-related physical signs (the third heart sound, pulmonary crackles, and leg edema), fluid weight gain ($\geq$1.5 kg),[8] and ultrasound pleural effusion.[9] If multiple episodes of worsening HF existed in a single patient, the first episode was selected for the present investigation. Worsening HF was treated by conventional therapy with a combination of loop diuretics, aldosterone blockade, thiazide diuretics, and/or inotropic drugs by oral and/or intravenous routes in the hospital or outpatient clinic. HF patients with severe renal failure (serum creatinine concentration > 3.5 mg/dL at stable HF status) were excluded from the present analysis.

Peripheral hematologic and biochemical tests, except b-type natriuretic peptide measurement, were not routinely obtained for all patients of the original study because that study did not focus on the correlation between HF status and blood chemistry. Thus, the patients and blood data of the present study were not selected consecutively but were included based on the availability of complete blood data as well as simultaneous HF-related clinical data during clinically stable HF, worsening HF, and resolution of worsening HF after therapy. Findings from the follow-up examination were used to determine the optimal response (ie, resolution of at least two or more HF-related signs) to treatment for worsening HF and the clinical presentation of a return to stable HF status after therapy.

Blood tests included measurements of hemoglobin, hematocrit, total protein, albumin, electrolytes, blood urea nitrogen, creatinine, and serum b-type natriuretic peptide levels. In the present study, hyponatremia and hypochloremia were defined as a serum sodium concentration of $\leq$135 mEq/L[10] and a serum chloride concentration of $\leq$96 mEq/L.[11,12]

2.3 | Statistical analysis

All statistical analysis was performed using commercially available statistical software (GraphPad Prism 4, San Diego, CA). The data are presented as the rates and percentages for the categorical variables and as the mean ± SD or as median values and the interquartile range for the continuous data, when applicable. Continuous variables were tested for a normal distribution by Kolmogorov-Smirnov test. Normally distributed data are presented as the mean ± SD, and natural logarithmic transformation was used in the analysis of serum b-type natriuretic peptide concentration because of nonnormal distribution. Unpaired *t* test was used to compare continuous data between two groups. Three groups, baseline, worsening of HF, and recovery from HF, were compared with two-way analysis of variance (ANOVA), and post hoc

TABLE 1 Clinical characteristics of the study patients at stable heart failure status

Characteristics	n = 47
Age (y)	
Mean ± SD	78.2 ± 9.7
Range	29-93
Male	15 (32)
Primary cause of HF	
Hypertension	25 (53)
Valvular	8 (17)
Cardiomyopathy	6 (13)
Ischemic	3 (6)
Arrhythmia	3 (6)
Congenital	2 (4)
Left ventricular EF (%)	
Mean ± SD	56 ± 14
Left ventricular EF > 50%	25 (53)
Atrial fibrillation	16 (34)
NYHA-FC at stable period	
II	34 (72)
III	13 (28)
Medication	
Diuretics	46 (98)
Loop diuretics	31 (66)
Thiazide diuretics	24 (51)
Potassium-sparing diuretics	38 (81)
ACE-I/ARB	30 (64)
Calcium antagonists	21 (45)
Beta blockers	19 (40)
Digitalis	5 (11)
Nitrates	3 (6)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; EF, ejection fraction; NYHA-FC, New York Heart Failure functional class; HF, heart failure. Data are presented as number of patients (%), unless otherwise specified.

Bonferroni's correction was used for multiple comparisons. Correlations between two parameters were analyzed using Pearson's correlation and were demonstrated using scatter plots. All tests were two-tailed, and P value < 0.05 was considered statistically significant.

3 | RESULTS

Ambulatory patients with HF (n = 83) were enrolled and followed up at the outpatient clinic of Nishida Hospital between June 2003 and March 2009; of these, 47 had available data for analysis of the serum sodium and chloride concentrations at worsening of HF and its recovery. The remaining 36 patients were similarly followed up during the study period, but they did not experience an event of worsening HF, so they were not included in the present analysis. The characteristics of the 47 patients with clinical stability at study entry are summarized in Table 1. The mean (±SD) intervals between clinical stability to worsening HF and its recovery after decongestive therapy were 37.5 ± 16.3 days (range: 14-67 d) and 27.8 ± 19.8 days (range: 8-59 d), respectively.

Changes in body weight, b-type natriuretic peptide level, peripheral blood test, and blood chemistry under transition of HF status are shown in Table 2, and changes in serum sodium and chloride concentration are shown in Figure 1A,B, respectively. From clinically stable to worsening HF, the mean serum sodium concentration increased from 139 ± 4.1 mEq/L (range: 129-146 mEq/L) to 141 ± 5.07 mEq/L (range: 119-148 mEq/L, P < 0.05, two-way ANOVA) and the mean serum chloride concentration increased from 101 ± 5.36 mEq/L (range: 85-110 mEq/L) to 104 ± 5.44 mEq/L (range: 84-113 mEq/L, P < 0.01, two-way ANOVA). After resolution of worsening HF by conventional diuretic therapy, the mean serum sodium concentration significantly decreased to 138 ± 5.12 mEq/L (range: 120-145 mEq/L) and the mean serum chloride concentration significantly decreased to 99.5 ± 5.33 mEq/L (range: 87-103 mEq/L, P < 0.0001 for each, two-way ANOVA).

The relation of the absolute changes (Δ) from clinically stable to worsening HF and its recovery following conventional diuretic therapy in the 47 study patients is shown in Figure 2. Overall, changes in the serum sodium (r = −0.612, P < 0.0001, Pearson's correlation; Figure 2A) or chloride (r = −0.55, P < 0.0001; Figure 2B) concentrations from stable HF to worsening HF and its recovery after therapy were negatively correlated. Absolute changes in the serum chloride concentration from clinically stable to worsening HF (2.72 ± 6.02 mEq/L) appeared to be greater than those in the serum sodium concentration (1.70 ± 4.34 mEq/L), but this was not statistically significant (P = 0.079, t test). Absolute changes in the serum chloride concentration from worsening HF to its recovery following treatment with conventional diuretics were greater than those in the serum sodium concentration (−4.45 ± 5.23 vs −2.87 ± 4.38 mEq/L, P = 0.0068, t test).

The distribution of the serum sodium and chloride concentrations at worsening of HF and its recovery by conventional diuretic therapy in the 47 study patients is shown in Figure 3. Among a total of 47 worsening HF events, serum sodium concentrations were positively correlated with serum chloride concentrations at worsening of HF (r = 0.822, P < 0.0001, Pearson's correlation; Figure 3A) and its recovery following conventional diuretic therapy (r = 0.840, P < 0.0001; Figure 3B). The incidence of hyponatremia was 11% (five patients), and that of hypochloremia was 9% (four patients) (Figure 3A). After decongestive therapy, the incidence of hyponatremia increased to 23% (11 patients) and that of hypochloremia increased to 26% (12 patients) (Figure 3b). Coexistence of hyponatremia and hypochloremia was observed in three patients (6%) at worsening of HF and in 10 (21%) following conventional diuretic therapy.

TABLE 2 Changes in peripheral blood biochemistry and hematologic values in worsening and recovery of heart failure status (n = 47)

Variable	Stable	Worsening	Recovery	*P* Value Stable vs Worsening	*P* Value Stable vs Recovery	*P* Value Worsening vs Recovery
Body weight (kg)	49.8 ± 11.8	52.3 ± 12.0	48.9 ± 11.5	<0.01	NS	<0.01
Serum log b-type natriuretic peptide (pg/mL)	2.08 ± 0.39	2.57 ± 0.34	2.03 ± 0.41	<0.001	NS	<0.001
Peripheral blood						
Red blood cell count ($\times 10^{12}$/L)	36.3 ± 5.9	34.4 ± 5.9	37.3 ± 6.4	<0.001	<0.05	<0.001
Hemoglobin (g/dL)	11.9 ± 1.64	11.2 ± 1.64	12.1 ± 1.85	<0.01	NS	<0.01
Hematocrit (%)	34.8 ± 4.72	33.0 ± 4.77	35.2 ± 5.3	<0.01	NS	<0.01
Blood chemistry						
Serum total protein (g/dL)	6.55 ± 0.54	6.17 ± 0.53	6.65 ± 0.47	<0.05	NS	<0.01
Serum albumin (g/dL)	3.88 ± 0.35	3.60 ± 0.38	3.91 ± 0.33	<0.05	NS	<0.01
Serum sodium (mEq/L)	139 ± 4.1	141 ± 5.07	138 ± 5.12	<0.05	NS	<0.001
Serum potassium (mEq/L)	4.23 ± 0.58	4.1 ± 0.69	4.29 ± 0.5	NS	NS	NS
Serum chloride (mEq/L)	101 ± 5.36	104 ± 5.44	99.5 ± 5.33	<0.01	NS	<0.001
Blood urea nitrogen (mg/dL)	27.1 ± 14.4	20.4 ± 7.97	30.2 ± 12.8	NS	<0.05	<0.01
Serum creatinine (mg/dL)	1.19 ± 0.47	1.02 ± 0.39	1.20 ± 0.46	<0.05	NS	<0.01

The P value indicates the difference across all three groups. Differences between three groups were tested by two-way analysis of variance, followed by a multiple comparison post hoc test.

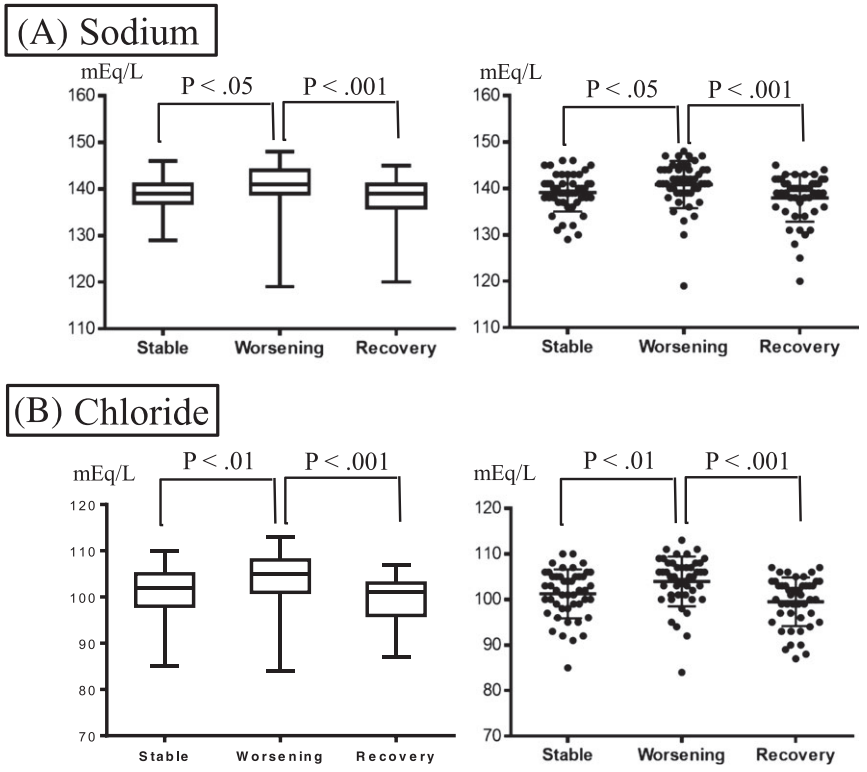

FIGURE 1 Serial changes in A, serum sodium and B, chloride concentrations under transition of heart failure (HF) status. Data are presented as box plots (left) and dot plots (right). In the boxplots, the box contains values between 25th and 75th percentiles, with the median value indicated by the horizontal line. Vertical lines represent 10th and 90th percentiles. In the dot plots, horizontal lines indicate mean with standard deviation. Differences between three groups were tested by two-way analysis of variance, followed by Bonferroni multiple comparison post hoc test (Table 2). All data points are shown in the range plotted

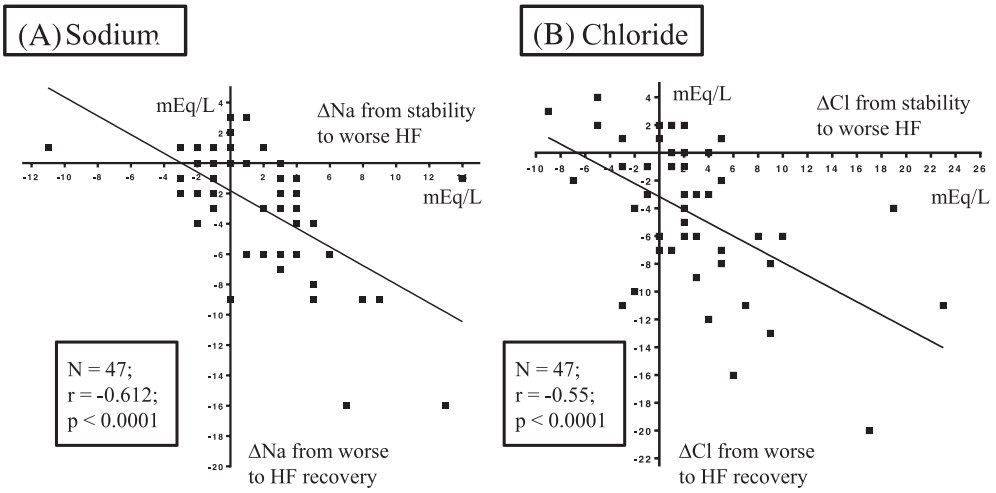

FIGURE 2 Relationships of absolute changes in the A, serum sodium and B, chloride concentrations from clinically stable to worsening heart failure and its recovery following conventional diuretic therapy. Changes in the serum sodium (r = −0.612, P < 0.0001, Pearson's correlation) or chloride (r = −0.55, P < 0.0001) concentrations from stable HF to worsening HF and its recovery after therapy are negatively correlated

4 | DISCUSSION

In the last several years, the important role of chloride in the field of HF pathophysiology has been recognized. Some studies have strongly and independently noted the prognostic importance of hypochloremia in patients with chronic HF.[11,12] Recent studies have revealed that chloride is a key electrolyte that regulates plasma volume during worsening HF[2,3] and its recovery following treatment with conventional diuretics,[4] leading to propose a unifying hypothesis, the "chloride theory" for HF pathophysiology,[3,13] which states that changes in serum chloride concentration are primarily associated with changes in plasma volume and renin-angiotensin-aldosterone system activity in HF pathophysiology.

To date, most studies have investigated the body fluid dynamics in HF through the control of sodium, potassium, and water balance in the body.[14-16] Few data are available, however, regarding the dynamic changes in serum chloride concentrations under HF pathophysiology. Sodium and chloride concentrations are highly correlated at both worsening of HF and its recovery (Figure 3). Important differences, however, exist among individuals. Namely, under worsening of HF, discordant movement of chloride and sodium appeared in as many as nine of 47 patients (19% of study patients); increased sodium and

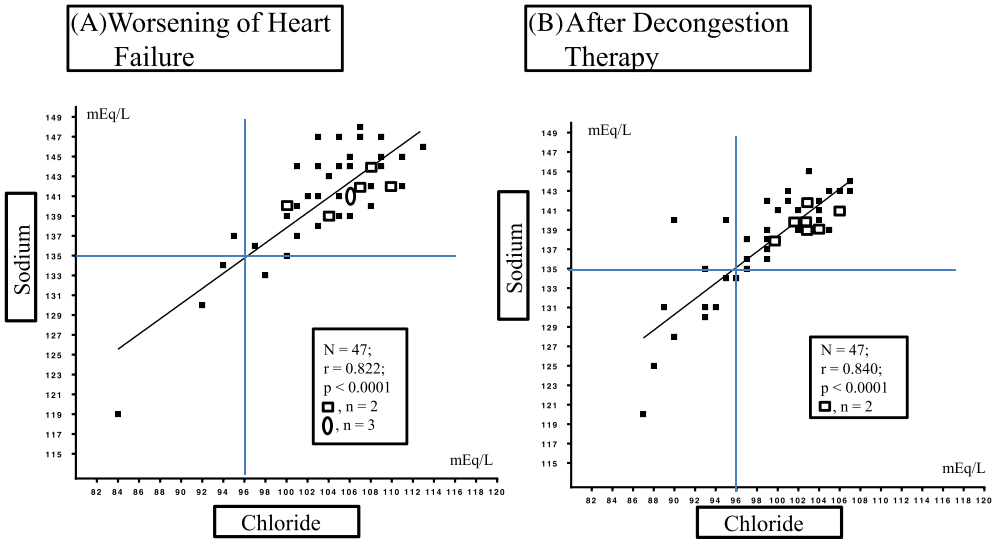

FIGURE 3 Scatterplot of individual serum sodium and chloride concentrations at A, worsening of heart failure and B, its recovery after conventional diuretic therapy. A symbol is used when two or three data points overlap. All data points are shown in the range plotted

decreased chloride were observed in two patients, and decreased sodium and increased chloride were observed in seven patients. Therefore, it is optimal to evaluate the changes in serum sodium and chloride concentrations under transition of HF status separately first and in combination after considering the possible role of each electrolyte in different HF states.[3]

In the present study, absolute changes in serum chloride concentration from clinically stable to worsening HF and its resolution after conventional diuretic treatment were greater than those of the sodium concentration, indicating that chloride has greater effects on the serum osmolality or tonicity.[17] Mechanisms for this differential movement between serum sodium and chloride are unclear, but the handling of $Na^+/K^+/2Cl$ through cotransporters in the nephrons may contribute to the greater changes observed in serum chloride concentration than in sodium concentration in HF pathophysiology.[18] Alternatively, recent insights suggest that sodium is not distributed in the body solely as a free cation but that it is also bound to large interstitial glycosaminoglycan networks in different tissues, which may have an important regulatory function for maintaining the serum sodium concentration by refilling sodium from the interstitial network into the blood.[19] Also, it should be kept in mind that changes in serum electrolytes may be multifactorial and interrelated, resulting from neurohormonal activation, renal dysfunction, medications, and dietary intake.[20] Further studies are required to clarify the mechanisms of differential changes in serum sodium and chloride concentrations under different situations of HF status.

Considering that HF-associated hypochloremia is an important prognostic marker for life expectancy,[11,12] manipulation of the serum chloride concentration could be an attractive therapeutic target for HF treatment, particularly in patients with refractory and residual congestive HF with persistent or progressive hypochloremia even after higher doses of diuretic treatment. In such situations, the "chloride theory"[3,13] would allow for rational decision making and a better understanding of the HF pathophysiology based on the changes in the serum chloride concentration. Examples of therapeutic options include (1) reducing the quantity and concentration of serum chloride using conventional diuretics[21] for worsening HF patients with a higher concentration and retention of serum chloride and (2) enhancing serum chloride concentration for worsening HF patients with hypochloremia using a V_2 receptor antagonist,[5,17,22] supplementing chloride by lysine chloride administration[12] or hyperosmotic saline infusion,[23] or usage of acetazolamide.[24,25] Additional studies are required to clarify the consequence of serum chloride modulation treatments in HF pathophysiology.

5 | LIMITATIONS

First, this study was performed with the use of a relatively small number of patients and was a single-center observational study and should thus be considered to be hypothesis generating. Second, the present results were derived from a population of mild-to-moderate HF patients. Therefore, the results of this study cannot be generalized to more advanced HF patients. Thus, a study including a larger number of HF patients is needed to better assess the dynamics of chloride in HF pathophysiology.

6 | CONCLUSION

Dynamic changes are observed in both serum sodium and serum chloride concentrations under HF state transitions. Under conventional diuretic therapy, greater changes occur in serum chloride concentration than in serum sodium concentration under HF state transitions, suggesting that chloride dynamics might contribute more to HF pathophysiology under such therapeutic circumstance. Additional studies are required to clarify the effects of different diuretics other than conventional diuretics on serum chloride dynamics[24,25] and subsequent consequence in HF pathophysiology.

CONFLICTS OF INTEREST

There is no relationship with industry and financial associations that might pose a conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Dr Hajime Kataoka
Formal analysis: Dr Hajime Kataoka
Investigation: Dr Hajime Kataoka
Methodology: Dr Hajime Kataoka
Project administration: Dr Hajime Kataoka
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