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Research Article

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Clinical Significance of Spot Urinary Chloride Concentration Measurements in Patients with Acute Heart Failure: Investigation on the Basis of the 'Tubulo-Glomerular Feedback' Mechanism

Hajime Kataoka

Internal Medicine, Nishida Hospital, Oita, Japan

***Corresponding author**
Hajime Kataoka, Internal Medicine, Nishida Hospital, 2-266 Tsuruoka-Nishi-machi, Saiki-city, Oita 876-0047, Japan.

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Abstract

Urinary chloride (Cl) is the key electrolyte for regulating renin secretion at the macula densa under the 'tubulo-glomerular feedback'. Whether or not Cl filtrated into the urinary tubules actually associates with plasma renin activity (PRA) in clinical heart failure (HF) remains unclear. Data from 29 patients with acute worsening HF (48% men; 80.3±12 years) were analyzed. Blood and urine samples were immediately obtained before decongestive therapy after the patients rested in a supine position for 20-min. Clinical tests included peripheral blood tests, serum and spot urinary electrolytes, b-type natriuretic peptide (BNP), plasma neurohormones, and fractional urinary electrolyte excretion. In the 29 patients, urinary Cl concentrations inversely correlated with logarithmically transformed PRA (R^2=0.41, p=0.0002). The correlation was weaker in worsening chronic HF patients (R^2=0.32, p=0.01) compared with de novo HF patients (R^2=0.70, p=0.0026). Patients were divided into 2 groups according to the median urinary Cl concentration, a low group and a high group. Compared with the high group (100~184 mEq/L; n=14), the low group (4~95 mEq/L; n=15) exhibited more renal (serum creatinine; 1.45±0.63 vs 1.00±0.38 mg/d, p=0.029) and cardiac (log BNP; 2.99±0.3 vs 2.66±0.32 pg/mL, p=0.008 p=0.008) impairment, and higher PRA (3.42±4.7 vs 0.73±0.46 ng/mL/h, p=0.049), and lower fractional excretion of urinary Cl (1.34±1.3 vs 5.33±4.1%, p<0.0001). The present study provides clinical data on the possible functioning of urinary Cl involved in the mechanism of 'tubulo-glomerular feedback', and thus advances our understanding of the clinical meanings of the significance of urinary Cl concentration measurement.

Keywords: Acute Heart Failure, Chloride, Chloride Theory, Urinary Chloride Concentration, Tubulo-Glomerular Feedback, Plasma Renin Activity

Introduction

In the kidney, salt sensing, renin secretion, and 'tubulo-glomerular feedback' are dependent on Chloride (Cl) rather than Sodium (Na) [1-5]. Despite mounting experimental and clinical data on the neurohormonal activity occurring during heart failure (HF), actual clinical data clarifying the role of urinary Cl, which is possibly involved in 'tubulo-glomerular feedback', is lacked [6-12]. Urinary electrolyte analysis, particularly urinary Na, was recently recognized to be important for the evaluation, treatment, and prognosis of clinical HF pathophysiology [13-23]. Analysis of urinary Cl may contribute to our understanding the role of the electrolyte Cl in 'tubulo-glomerular feedback' because Cl, not Na, is the key electrolyte for regulating renin secretion. To the best of my knowledge, however, there are hardly any clinical studies examined association between urinary Cl concentration and plasma renin activity (PRA) to provide evidence for 'tubulo-glomerular feedback' actually functioning in the human body.

Thus, the present study aimed to determine the relation of the urinary Cl concentration to PRA in patients with acute HF in an effort to clarify the function of Cl in the 'tubulo-glomerular feedback'. Moreover, the clinical significance of spot urinary Cl testing in patients with acute HF was evaluated according to the urinary Cl-centered 'tubulo-glomerular feedback' model. The present study also sought to provide clinical evidence supporting the 'chloride theory' for HF pathophysiology, which states that changes in the serum Cl concentration are deeply associated with changes in plasma volume, hemodynamics, and neurohormonal activity [12, 24, 25].

Methods

Study Design

This study was a retrospective single-center observational study that enrolled 31 consecutive patients with acute HF at Nishida Hospital (Saiki-city, Oita, Japan) participating in a neurohormonal study between March 2017 and April 2018. Diagnosis of worsening HF was established by standard clinical criteria according to presentation, echocardiography, and serum b-type natriuretic peptide (BNP) [26]. Additional routine tests included thoracic ultrasound to evaluate the presence of pleural effusion [27,28]. Worsening HF was treated by conventional therapy with a combination of loop diuretics, aldosterone blockade, thiazide diuretics, oral vasopressin antagonist, acetazolamide, and/or inotropic drugs by oral and/or intravenous routes in the hospital or outpatient clinic. Based on the follow-up examination, the response of worsening HF to treatment and the return of the clinical presentation to stable HF status were determined. Acute HF patients with cardiogenic shock, clinical diagnosis of acute coronary syndrome, known advanced renal disease (serum creatinine level >3.0 mg/dL) were excluded from the study.

Data Collection and Analytic Methods

Physical examination, peripheral venous blood tests (hematologic, BNP, and neurohormonal tests), and a spot urine test were performed at presentation of the acute HF episode immediately before the initiation of decongestive therapy. The blood and urine samples were obtained after patients rested in a supine or semi-supine position for 20-min. Peripheral blood tests, analyzed by standard techniques, included hemoglobin, hematocrit, serum electrolytes (Na, K, and Cl), blood urea nitrogen, and creatinine. The spot urine test included measurement of electrolyte and creatinine concentrations, and osmolality. Plasma BNP was measured by chemiluminescent immunoassay. Plasma adrenaline and noradrenaline levels were measured by high-performance liquid chromatography. Plasma renin activity was measured by enzyme immunoassay. Plasma aldosterone and arginine vasopressin (AVP) levels were measured by radioimmunoassay. Fractional electrolyte excretions were calculated as: fractional excretion of $X = (X_{urine}/X_{serum})\times(C_{rserum}/C_{rurine})\times100$ [29,30]. Urinary osmotic pressure was measured by the freezing point depression method using an OM-6060 type automatic osmotic pressure measuring device (Arkray Inc., Kyoto, Japan).

Statistical Analysis

All data are expressed as mean ± SD for continuous data and percentage for categorical data. Paired and unpaired t tests for continuous data and Fisher's exact test for categorical data were used for 2-group comparisons. Pearson's correlation was performed to evaluate the linear association between logarithmically transformed PRA and other variables. A p value of <0.05 was considered statistically significant.

Results

Of the 31 acute HF patients, 2 were excluded from the present study due to insufficient clinical data. The remaining 29 patients (48% men; 80.3±12 years), including de novo acute HF patients (n=10), were enrolled in the analysis. Clinical characteristics of the study patients at baseline are shown in Table 1. The primary causes of worsening HF varied; atrial fibrillation was observed in 14 (48%) patients. All study patients presented with 2 to 4 HF signs on the basis of physical examination and evaluation of possible pleural effusion by thoracic ultrasound. Plasma BNP levels were elevated: definitely (≥500 pg/mL) in 20 patients, moderately (200 pg/mL to <500 pg/mL) in 7, and mildly (100 pg/mL to <200 pg/mL) in 2. No diuretics were prescribed for 10 patients with de novo HF episode before current presentation to the hospital. Of the 29 patients, 24 were treated for acute HF in the hospital, and 5 were treated at the outpatient clinic.

Table 1: Clinical characteristics of the study patients

Characteristics	Total (N = 29)
Age (years)	
Mean ± SD	80.3±12
Range	53-97
Male	14 (48)
Primary cause of HF	
Hypertension	19 (64)
Valvular	6 (22)
Ischemic/Cardiomyopathy	3 (11)
Arrhythmia	1 (3)
Left ventricular EF (%)	
Mean ± SD	47.8±18
Left ventricular EF > 50%	15 (52)
Atrial fibrillation	14 (48)
NYHA-FC	

III	6 (21)
IV	23 (79)
HF-related physical findings	
Bilateral leg edema around or above the ankle	24 (84)
Bilateral pulmonary rales beyond the basal lung	22 (76)
Pleural effusion on thoracic ultrasound	25 (86)
Third heart sound (S3)	5 (17)
Number of HF signs (mean ± SD; range)	2.7±0.6; 2¬–4
B-type natriuretic peptide (pg/mL)	
2000≥	1 (3)
2000 – 1000	7 (24)
1000 – 500	12 (42)
500 – 200	7 (24)
200 – 100	2 (7)
Baseline medication use	
De novo HF patients without diuretic treatment	10 (34)
Diuretics	
Loop diuretics	13 (45)
Thiazide diuretics	4 (14)
MRA	12 (42)
Tolvaptan	6 (21)
ACE inhibitors/ARB	7 (24)
Beta-blockers	9 (31)
Calcium antagonists	12 (42)
Digitalis	3 (11)
Nitrates	2 (7)

Data presented as number (%) of patients otherwise specified. ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker, EF: ejection fraction, MRA: mineralocorticoid receptor antagonist, NYHA-FC: New York Heart Association functional class, HF: heart failure.

Pearson's correlation of Log PRA (ng/mL/h) with multiple variables under acute HF (n = 29) is shown in Table 2. The urinary Cl and Na concentrations each inversely correlated well with the Log PRA in a total of 29 HF patients (Cl, R^2=0.41, p=0.0002, Figure 1A; Na, R^2=0.54, p=<0.00001). The effects of cardiovascular medication (Table 3) on the relationship between the plasma renin activity and urinary Cl concentration are shown in Figures 1B and 1C, in which the correlation between them was determined separately in worsening chronic HF patients (Figure 1B; n=19; more cardiovascular-related medication) and de novo HF patients (Figure 1C; n=10; less cardiovascular-related medication). The correlation was weaker in worsening chronic HF patients (R^2=0.32, p=0.01, Figure 1B) compared with de novo HF patients (R^2=0.70, p=0.0026, Figure 1C).

Table 2: Pearson's correlation of log PRA (ng/mL/h) with multiple variables under acute heart failure (Total N = 29)

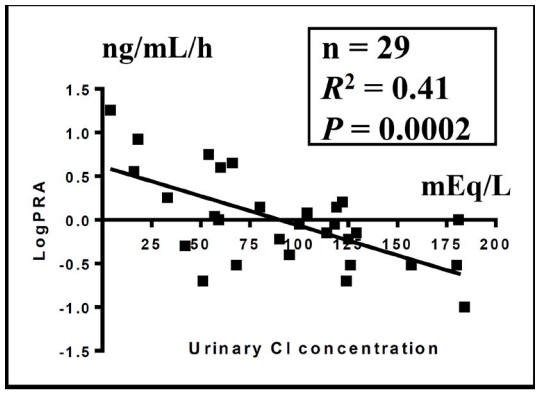
Variable	R^2	p-value
Systolic BP (mmHg)	0.07	0.17
Diastolic BP (mmHg)	0.001	0.86
Heart rate (beats/min)	0.014	0.53
Serum electrolytes		
Sodium (mEq/L)	0.024	0.42
Potassium (mEq/L)	0.0003	0.93
Chloride (mEq/L)	0.07	0.16
BUN (mg/dL)	0.096	0.1
Creatinine (mg/dL)	0.007	0.66
Log BNP (pg/mL)	0.043	0.28
Urinary concentration		
Sodium (mEq/L)	0.54	<0.0001*
Potassium (mEq/L)	0.19	0.017*
Chloride (mEq/L)	0.41	0.0002*
Osmolality (mOsm/kg H2O)	0.023	0.43
Adrenaline (pg/mL)	0.022	0.44
Noradrenaline (pg/mL)	0.21	0.013*
Aldosterone (pg/mL)	0.43	0.0001*
AVP (pg/mL)	0.02	0.46

AVP: arginine vasopressin, BNP: b-type natriuretic peptide, BP: blood pressure, BUN: blood urea nitrogen, PRA: plasma renin activity. *Statistically significant ($p < 0.05$).

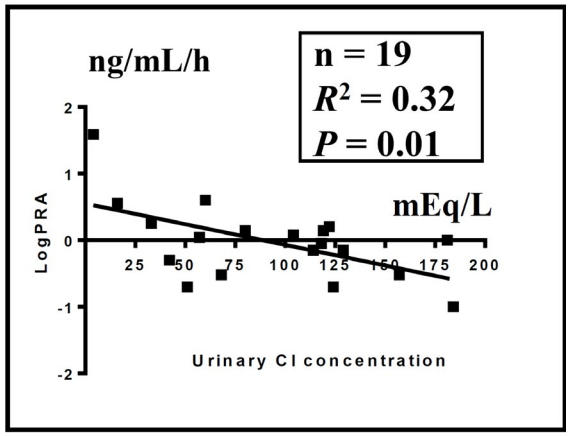
Table 3: Comparison of the baseline medication use between worsening chronic HF patients and de novo HF patients (Total N = 29)

		Worsening chronic HF patients (n = 19)	De novo HF patients (n = 10)	p-value
Diuretics		19 (100)	0	<0.0001*
Loop diuretics		13 (68)	0	<0.0001*
Thiazide diuretics		4 (21)	0	0.27
MRA		12 (63)	0	0.001*
Tolvaptan		6 (32)	0	0.07
Acetazolamide		9 (47)	0	0.01*
Neurohormonal blockades		13 (68)	2 (20)	0.01*
ACE inhibitors/ARB		5 (26)	2 (20)	1
Beta-blockers		8 (42)	1 (10)	0.1
	1 drug of above	13 (68)	1 (10)	0.005*
	2 drugs of above	0	1 (10)	0.34

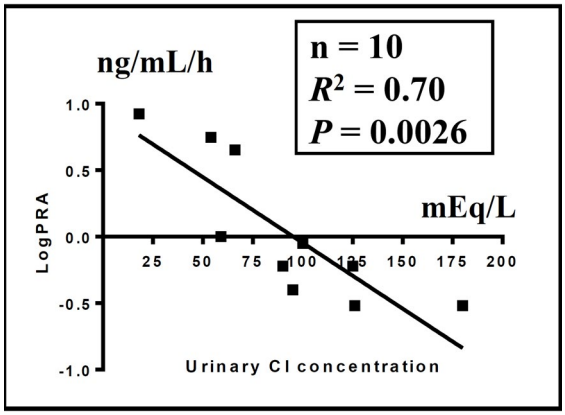
Data presented as number (%) of patients. ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker, MRA: mineralocorticoid receptor antagonist. *Statistically significant ($p < 0.05$, Fisher's exact test).



A) a total of HF patients (n=29),



B) worsening chronic HF patients (n=19),



C) de novo HF patients (n=10). Cl: chloride, HF: heart failure, PRA: plasma renin activity.

When divided into 2 groups according to the median serum Cl concentration (Table 4), the low (88~104 mEq/L; n=15) and the high (105~114 mEq/L; n=14) serum Cl concentration groups showed similar trends of the urinary Cl concentration, i.e., the low serum Cl concentration group had a low urinary Cl concentration compared with the high serum Cl concentration group, which had high urinary Cl concentrations (76.6±50 vs 109±45 mEq/L; p=0.077). All the laboratory blood and spot urinary data, except the serum Na concentration, were similar between the 2 groups.

Table 4: Comparisons of low and high groups stratified on the basis of the serum chloride concentration, urinary chloride concentration, or plasma renin activity in 29 patients with acute heart failure

	Total (N=29)	Serum Chloride Concentration (mEq/L)			Urinary Cl Concentration (mEq/L)			Plasma Renin Activity (ng/mL/h)		
		Low (n=15)	High (n=14)	p-value	Low (n=15)	High (n=14)	p-value	Low (n=15)	High (n=14)	p-value
		88 ~ 104	105 ~ 114		4 ~95	100 ~ 184		0.1 ~ 0.9	1.0 ~ 18	
Vital signs										
Systolic BP (mmHg)	137±35	136±31	139±39	0.86	144±36	130±33	0.3	144±37	130±32	0.29
Diastolic BP (mmHg)	79±19	77±18	81±25	0.56	79±17	79±21	0.98	78±20	80±18	0.75
Heart rate (beats/min)	86.5±21	84.3±18	88.8±25	0.58	87.5±20	85.3±23	0.78	81.9±25	91.3±15	0.24
Laboratory blood data										
Hemoglobin (g/dL)	11.8±2.1	11.9±2.2	11.8±2.2	0.91	11.8±2.2	11.9±2.1	0.92	11.8±2.1	11.9±2.2	0.89
Hematocrit (%)	35.9±6.4	35.8±6.9	35.9±6.2	0.95	35.7±6.8	36.0±6.2	0.92	35.6±6.2	36.2±6.9	0.8
Serum electrolytes										
Sodium (mEq/L)	139±4.8	136±4.6	142±3.1	0.0007*	138±4.9	139±4.8	0.37	138±6.0	139±3.3	0.66
Potassium (mEq/L)	4.27±0.6	4.33±0.6	4.20±0.7	0.61	4.30±0.7	4.23±0.6	0.77	4.25±0.6	4.29±0.7	0.87

Chloride (mEq/L)	103±6.2	98.8±4.8	108±3.5	<0.0001*	102±7.1	104±5.1	0.38	103±6.1	103±6.6	0.99
BUN (mg/dL)	27.0±13	26.4±14	27.6±11	0.8	31.4±13	22.2±10	0.047*	24.3±12	29.8±13	0.25
Creatinine (mg/dL)	1.23±0.56	1.24±0.53	1.23±0.62	0.99	1.45±0.63	1.00±0.38	0.029*	1.18±0.58	1.29±0.56	0.6
Log BNP (pg/mL)	2.83±0.35	2.88±0.40	2.77±0.29	0.42	2.99±0.30	2.66±0.32	0.008*	2.81±0.26	2.85±0.43	0.76
Neurohormonal test										
Adrenaline (pg/mL)	0.08±0.07	0.077±0.07	0.087±0.08	0.74	0.095±0.08	0.067±0.06	0.31	0.068±0.06	0.096±0.08	0.31
Noradrenaline (pg/mL)	1.02±0.67	1.15±0.69	0.88±0.63	0.28	1.24±0.78	0.78±0.43	0.72	0.76±0.38	1.29±0.8	0.03*
Renin activity (ng/mL/h)	2.12±3.6	2.96±4.8	1.23±1.4	0.2	3.42±4.7	0.73±0.46	0.049*	0.47±0.26	3.90±4.6	0.008*
Aldosterone (pg/mL)	128±106	146±119	109±90	0.36	158±121	96.4±79	0.19	86.2±71	174±120	0.023*
AVP (pg/mL)	3.55±3.5	3.15±2.7	3.97±4.2	0.53	4.17±4.1	2.89±2.6	0.11	2.95±2.6	4.19±4.2	0.34
Laboratory urinary data (spot urine)										
Concentration of urinary electrolytes										
Sodium (mEq/L)	90.8±46	80.1±48	102±43	0.21	56.7±30	127±30	<0.0001*	113±37	66.9±44	0.005*
Potassium (mEq/L)	30.8±18	31.5±20	30.1±16	0.84	36.7±22	24.5±9.2	0.006*	26.3±14	35.6±21	0.17
Chloride (mEq/L)	92.3±50	76.6±50	109±45	0.077	52.9±27	135±29	<0.0001*	114±41	70.0±49	0.01*
% excretion of urinary electrolytes										
Sodium (%)	2.45±2.6	2.47±2.5	2.42±2.8	0.95	1.15±1.3	3.83±3.0	<0.0001*	2.94±2.8	1.92±2.3	0.3
Potassium (%)	16.4±9.5	17.6±11	15.1±8.3	0.49	14.0±8.9	19.1±9.7	0.006*	15.7±7.4	17.2±12	0.69
Chloride (%)	3.27±3.6	3.28±3.5	3.25±3.7	0.98	1.34±1.3	5.33±4.1	<0.0001*	3.83±3.8	2.67±3.4	0.39
Osmolality (mOsm/kg H2O)	470±183	443±167	498±202	0.43	487±198	451±171	0.014*	465±180	474±194	0.9

AVP: arginine vasopressin, BNP: b-type natriuretic peptide, BP: blood pressure, BUN: blood urea nitrogen. *Statistically significant difference between before and after treatment ($p < 0.05$, unpaired t test).

When divided into 2 groups based on the median urinary Cl concentration (Table 4), the low urinary Cl concentration group (4~95 mEq/L; n=15) exhibited more renal (serum creatinine; 1.45±0.63 vs 1.00±0.38 mg/d, p=0.029) and cardiac (log BNP; 2.99±0.30 vs 2.66±0.32 pg/mL, p=0.008) impairment compared with the high urinary Cl concentration group (100~184 mEq/L; n=14). The low urinary Cl concentration group also exhibited higher PRA (3.42±4.7 vs 0.73±0.46 ng/mL/h, p=0.049), and a lower fractional excretion of urinary Cl (1.34±1.3 vs 5.33±4.1%, p<0.0001), Na (1.15±1.3 vs 3.83±3.0%; p<0.0001), and K (14.0±8.9 vs 19.1±9.7%; p=0.006). The plasma AVP level tended to be high in the low urinary Cl concentration group compared with the high urinary Cl concentration group (4.17±4.1 vs 2.89±2.6 pg/mL, p=0.1). Urine osmolarity was higher in the low urinary Cl concentration group than in the high group (487±198 vs 451±171 mOsm/kgH2O, p=0.014).

When divided into 2 groups according to the median PRA (Table 4), the high PRA group (1.0~18 ng/mL/h; n=14) had high serum values of noradrenaline (1.29±0.8 vs 0.76±0.38 pg/mL, p=0.03) and aldosterone (174±120 vs 86.2±71 pg/mL, p=0.023), and low spot urinary Cl (70.0±49 vs 114±41 mEq/L, p=0.01) and Na (66.9±44 vs 113±37 mEq/L, p=0.005) concentrations compared with the low PRA group (0.1~0.9 ng/mL/h; n=15).

Discussion

The present study, in which acute HF patients were analyzed immediately before initiating decongestive treatment (pre-treatment phase), provides clinical data on the possible functioning of 'tubulo-glomerular feedback' by evaluating the relation of spot urinary Cl concentration with PRA, which should advance our understanding of the clinical significance and utility of urinary electrolyte analysis, and also provides data supporting the concept of the 'chloride theory' of HF pathophysiology [12,24,25].

Function of 'Tubulo-Glomerular Feedback' in Acute HF

Many experimental studies have demonstrated the central role of urinary Cl in the 'tubulo-glomerular feedback' mechanism, through which absorption and excretion of urinary electrolytes and water along the urinary tubules are integrated for maintaining body fluid dynamics [1-4]. It remains unclear, however, whether the urinary Cl concentration regulates PRA in clinical HF pathophysiology of human body. Although the urine content, including electrolyte Cl, should be modified by the process of glomerular filtration of plasma running through the renal tubules to the bladder, the present study revealed a modest correlation between the spot urinary Cl concentration and PRA (Figure 1), confirming the possible functioning of 'tubulo-glomerular feedback' in the human body. Indeed, the scatter plot of individual HF patients in the pres-

ent study shown in Figure 1 is consistent with the findings reported by He et al, in which the relationship between the macula densa Cl concentration and renin secretion was evaluated in an isolated perfused rabbit juxtaglomerular apparatus preparation [3]. Of course, the Cl concentration in the urine coming into the macula densa is not the only factor affecting the release of plasma renin.

The 4 main stimuli for renin release are:
(1) decreased baroreceptors stretch in afferent arterioles,
(2) decreased Na and Cl delivery to the macula densa,
(3) activation of renal sympathetic nerves and stimulation of b-adrenergic receptors, and (4) decreased negative feedback signaling through angiotensin II [5,31].

The present study provides important information regarding the effects of cardiovascular medication on the PRA and 'tubulo-glomerular feedback' mechanism. As shown in Figure 1, the urinary Cl concentration was not well correlated with PRA in worsening chronic HF patients (Figure 1B) compared with de novo HF patients (Figure 1C). The different correlation strengths between them would be influenced by the different types of cardiovascular medications in each population: no diuretic medication and fewer neurohormonal blockers (angiotensin-converting enzyme, angiotensin II receptor, or beta blockers) in de novo HF patients, and vice versa in worsening chronic HF patients (Table 3). Indeed, it is well known that cardiovascular medications greatly affect renin-angiotensin-aldosterone system activity. Loop diuretics can stimulate renin release by inhibiting macula densa Na/Cl transport in the kidney, which mimics a situation of low sodium/chloride delivery to the macula densa and thus elicits renin secretion [5,32]. Angiotensin-converting enzyme and angiotensin II receptor blockers inhibit angiotensin II-negative feedback, leading to an increase in PRA. In contrast, beta-blockers reduce renin levels by suppressing beta-adrenergic stimulation of the kidney [33]. Therefore, extreme caution is needed when evaluating the tubulo-glomerular feedback mechanism in patients receiving diuretics and neurohormonal blockers.

Clinical Significance of the Spot Urinary Cl Concentration Measurement

Many recent clinical studies, except several reports that examined urinary Na concentration before initiation of acute HF treatment (pre-treatment), have focused on investigating the characteristics of urinary electrolytes after diuretic treatment, particularly the urinary Na concentration or excretion, as an early marker for predicting diuretic responsiveness and a long-term prognostic marker in patients with acute HF [13-23]. Almost exclusively, these studies found that a low urinary Na concentration or excretion either pre- or post-diuretic treatment for worsening HF is associated with a poor short-term diuretic response and a high risk of long-term mortality. Most of these previous studies, however, did not consider urinary electrolyte levels as useful clinical information for understanding the complex HF pathophysiology and clarifying different HF profiles. Among these studies, Martens et al, examine serial urinary Na concentrations before and after an acute HF episode, and offered novel insight into the potential mechanisms contributing to the developing of acute HF [23]. Similar to the study by Martens et al, in that the urinary Na concentration was investigated, the present study demonstrated heterogenous distribution of the spot urinary Cl concentration and ability to phenotype acute HF status on the basis of this information, as described below [23].

Given the possible evidence for the actual functioning of 'tubulo-glomerular feedback' in acute HF patients reported here, it is expected that information obtained from a spot urinary Cl concentration can integrate the separate HF elements comprising individual HF status (e.g., neurohormonal activities, electrolytes status, and renal and cardiac functions) into construction of systematic and reasonable linkages among them. As such, a pre-treatment spot urinary Cl test in acute HF patients would provide useful clinical data toward characterizing each acute HF phenotype before de novo diuretic treatment or adjustment of a recent diuretic regimen. That is, when acute HF patients were stratified into 2 groups on the basis of the median value of the pre-treatment urinary Cl concentration, the low group exhibited more compromised renal and cardiac functions than the high group. More importantly, spot urinary Cl analysis provides data on differential activation of neurohormonal systems between groups under acute HF pathophysiology, including renin and AVP hormones (i.e., high neurohormonal activation in acute HF patients with a low urinary Cl concentration vs low neurohormonal activation in those with a high urinary Cl concentration), and provides essential information for dynamic movement of urinary Cl (also including Na, K, and water) [i.e., low (or high) urinary excretion of Cl in groups with low (or high) urinary Cl concentration under high (or low) levels of neurohormonal activation]. The observed neurohormonal changes in renin and aldosterone were analogous to the study by Honda et al, that showed lower urinary Na concentration was associated with increased neurohormonal activities [22].

The present study suggests that acute HF patients with a low urinary Cl concentration in the pre-treatment test may be expected to have loop diuretic resistance because such an acute HF phenotype already exhibits compromised renal and cardiac functions under a highly activated neurohormonal system, as was similarly reported by Hanberg et al. [20]. Urinary Cl-centered information linked to the 'tubulo-glomerular feedback' model may be useful for deciding therapeutic options, because loop diuretic-resistant acute HF patients with a low urinary Cl concentration may respond well to treatment with Cl-regaining diuretics, such as acetazolamide, vasopressin receptor antagonist, and sodium-glucose cotransporter-2 inhibitor [34]. Acute HF patients with low urinary Cl concentration might be candidates for treatment by renin-angiotensin-aldosterone system blockade if there are no contraindications, such as coexisting renal dysfunction, hypotension, and HF with preserved ejection fraction [35].

Clinical Proof of the 'Chloride Theory' for HF Pathophysiology

Several years ago, a unifying hypothesis of the 'chloride theory' for HF pathophysiology was proposed, that states that changes in the serum Cl concentration is the primary determinant of changes in the plasma volume and neurohormonal activity under worsening HF and its resolution [24,25]. The proposed hypothesis is based on assumed interactions between changes in the serum Cl concentration and neurohormonal systems, but it has remained unclear whether this hypothesis is truly applicable to clinical real-world HF pathophysiology because previous clinical studies

examined, without exception, the association of Na (not Cl) and water to the neurohormonal system [12]. Observations in the present study support the 'chloride theory' for HF pathophysiology on the basis of interactions between urinary Cl concentration and neurohormonal activities during worsening HF, i.e., renin activity becomes depressed in acute HF patients with an increased serum Cl concentration and renin activity becomes enhanced in those with a decreased serum Cl concentration [24,25]. Importantly, the present study clearly demonstrates that, in acute HF patients with a decreased urinary Cl concentration, excretion of Cl into the renal tubules is depressed, or, alternatively, their absorption from the renal tubules is enhanced, under high renin activation, but the serum Cl concentration does not increase effectively, probably due to insufficient supply of enough amount of Cl into the vascular or extracellular space, owing to yet unknown mechanisms. These observations have demonstrated the potential real-world applicability of the 'chloride theory' to clinical HF pathophysiology.

Study Limitations

This study was performed in a relatively small number of patients comprising a clinically heterogeneous population (e.g., both HF with preserved and reduced left ventricular ejection fraction; both established and de novo HF; and both pre-existing diuretic therapy and diuretic naive), was a single-center observational study, and should be considered hypothesis-generating. The present results were derived from a population of patients with moderate HF. Therefore, the results of this study cannot be generalized to patients with more advanced HF. Further studies including a larger number of HF patients with various HF conditions are needed to better assess the clinical implications of measurements of urinary Cl concentration in HF pathophysiology.

Conclusion

The present study provides the data on possible actual working of the 'tubulo-glomerular feedback' in the human body by evaluating the relation between spot urinary Cl concentration and PRA. In this study, it appears that the association of urinary Cl and Na with many variables was highly similar, but strictly speaking, this does not mean that electrolyte Na can be substituted for electrolyte Cl when evaluating HF pathophysiology because renin secretion and 'tubulo-glomerular feedback' are dependent on Cl rather than Na [1-5], and their prognostic significance and pathophysiologic roles are quite different [36-39]. Thus, it is reasonable to closely investigate the serum and urinary Cl dynamics, as well as the serum and urinary Na dynamics, in HF pathophysiology in future clinical studies.

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