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ORIGINAL ARTICLE
Heart Failure

Arginine Vasopressin as an Important Mediator of Fluctuations in the Serum Creatinine Concentration Under Decongestion Treatment in Heart Failure Patients

Hajime Kataoka, MD

Background: The mechanism underlying serum creatinine (SCr) fluctuations in heart failure (HF) patients remains unclear. This study examined mediators of SCr fluctuations under diuretic treatment in HF patients.

Methods and Results: Data from 26 HF patients were analyzed. Clinical tests included measurement of peripheral blood, blood urea nitrogen, SCr, serum and urinary electrolytes, B-type natriuretic peptide (BNP), and plasma neurohormones. Among the 26 patients recovering from worsening HF, changes in SCr were negatively correlated with changes in serum Cl, and positively correlated with changes in plasma arginine vasopressin (AVP). According to the median change in SCr, patients were divided into high (range 0.16–0.79 mg/dL; n=13) and low (range −0.35 to 0.14 mg/dL; n=13) change groups. Plasma AVP concentrations after treatment decreased in the low SCr change group and increased in the high SCr change group (−1.28±2.8 vs. 2.14±4.4 pg/mL, respectively; P=0.027). In both groups, there was no change in plasma volume, plasma BNP and norepinephrine concentrations decreased, and plasma renin activity increased after treatment. Multivariate logistic regression analysis showed a tendency towards an independent association between an increase in SCr and an increase or no change in the plasma AVP after decongestion (odds ratio 4.44; 95% confidence interval 0.81–24.3; P=0.086).

Conclusions: Plasma AVP appears to be a physiologically important mediator of SCr fluctuations under decongestion treatment in HF patients.

Key Words: Antidiuretic hormone; Arginine vasopressin; Creatinine; Diuretics; Heart failure

There are complex interactions between the heart and kidney in heart failure (HF) pathophysiology.[1–3] Diuretic therapy for worsening HF frequently leads to deterioration of renal function, as determined by serum creatinine (SCr) concentrations. Many studies report that worsening renal function based on SCr concentrations and/or estimated glomerular filtration rate (eGFR) calculated from the SCr concentration after treatment for acute decompensated HF leads to recurrent episodes of worsening HF, hospitalization, and increased mortality.[4–7] Later studies, however, raised questions about the harmful effects of creatinine-based worsening renal function induced by decongestion therapy for acutely decompensated HF on long-term survival.[8–11] To determine the clinical significance of creatinine-based renal function, it is important to explore the possible intrinsic mechanism(s) underlying serial changes or fluctuations in the SCr concentration in HF patients. As yet, however, it remains unclear how SCr fluctuations are associated with change(s) in serum biochemical substances or plasma neurohormones under diuretic therapy in HF patients. Thus, the present study explored the association between changes in SCr concentrations with changes in serum solutes or plasma neurohormones after diuretic treatment in patients with acute HF.

Methods

Study Design

This study was a prospective single-center observational study that enrolled 31 consecutive patients with acute HF at Nishida Hospital (Saiki-city, Oita, Japan) who were undergoing a neurohormonal study between March 2017 and April 2018. A diagnosis of worsening of HF was established by standard clinical criteria of presentation, echocardiography, and serum B-type natriuretic peptide (BNP) concentrations.[12] Additional routine tests included thoracic ultrasound to evaluate the presence of pleural effusion[13] and monitoring changes in body weight during follow-up (HBF-352-W; Omron Healthcare, Kyoto, Japan).[12] Worsening HF was treated by conventional therapy with a combination of loop diuretics, aldosterone blockade, thiazide diuretics, an oral vasopressin antago-

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Internal Medicine, Nishida Hospital, Saiki, Japan
Mailing address: Hajime Kataoka, MD, Internal Medicine, Nishida Hospital, 2-266 Tsuruoka-Nishi-Machi, Saiki 876-0047, Japan. E-mail: hkata@cream.plala.or.jp

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nist, acetazolamide, and/or inotropic drugs administered orally and/or intravenously in the hospital or outpatient clinic. Based on follow-up examinations, the response of worsening HF to treatment and the return of the clinical presentation to a stable HF status were determined.

Acute HF patients with cardiogenic shock, a clinical diagnosis of acute coronary syndrome, or known advanced renal disease (SCr >3.0 mg/dL) were excluded from the present study.

Data Collection and Analytic Methods

Physical examination, peripheral venous blood tests, and a spot urine test for electrolytes and creatinine were performed twice (i.e., during acute HF immediately before initiation of treatment and during stable HF after successful decongestion therapy). Blood and urine samples were obtained after patients had rested in a supine or semisupine position for 20 min. Peripheral blood tests, analyzed by standard techniques, included hemoglobin [Hb], hematocrit [Hct], serum electrolytes (sodium, potassium, and chloride), blood urea nitrogen, and creatinine. The spot urine test included measurement of electrolytes and creatinine concentrations, and osmolality. Plasma BNP was measured by chemiluminescent immunoassay. Plasma epinephrine and norepinephrine were measured by HPLC. Plasma renin activity (PRA) was measured by enzyme immunoassay. Plasma aldosterone and arginine vasopressin (AVP) concentrations were measured by radioimmunoassay. The eGFR was calculated according to the revised equations for estimating the glomerular filtration rate from SCr concentrations for the Japanese population.[14] The Strauss formula was used to estimate the percentage change in plasma volume, as follows:[15]

$$\%\ \text{Change in plasma volume} = ([(Hb_1/Hb_2)\times(100-Hct_2)/(100-Hct_1)-1]\times 100$$

where superscript 1 (Hb_1, Hct_1) indicates baseline values and superscript 2 (Hb_2, Hct_2) indicates end values. Urinary osmotic pressure was measured by the freezing point depression method using an OM-6060-type automatic osmotic pressure measuring device (Arkray, Kyoto, Japan).

Statistical Analysis

All continuous data are expressed as the mean±SD and all categorical data are presented as percentages. Paired and unpaired t-tests for continuous data were used for 2-group comparisons. Pearson's correlation analysis was used to evaluate the linear association between 2 variables. Logistic regression analysis using the dichotomous dependent variables was used to determine the independent predictors of changes in SCr concentrations under recovery from worsening HF by selecting variables that demonstrated a significant linear association with changes in the SCr concentration and using iterative modeling procedures to arrive at the most efficient model. Odds ratio (ORs) and associated 95% confidence intervals (CIs) were estimated to determine the association between those variables and changes in the SCr concentration. Two-sided $P<0.05$ was considered statistically significant.

Results

Of the 31 acute HF patients, 5 were excluded from the present study because of a lack of clinical data for analysis due to cardiac death during follow-up (n=3) and insufficient data (n=2). The remaining 26 patients (50% men; mean age 81.2±12 years), including de novo acute HF patients (n=9), were enrolled in the present analysis.

Table 1. Clinical Characteristics of the Study Patients at Presentation of Worsening HF (n=26)

Age (years)	
Mean±SD	81.2±12
Range	53–97
Male sex	13 (50)
Primary cause of HF	
Hypertension	18 (69)
Valvular	4 (15)
Ischemic/cardiomyopathy	3 (12)
Arrhythmia	1 (4)
LVEF (%)	46.8±18
LVEF >50%	14 (54)
AF	13 (50)
NYHA FC at acute HF presentation	
III	5 (19)
IV	21 (81)
HF-related physical findings	
Bilateral leg edema around or above the ankle	22 (85)
Bilateral pulmonary rales beyond the basal lung	20 (77)
Pleural effusion on thoracic ultrasound	23 (88)
Third heart sound (S3)	5 (19)
No. HF signs	
Mean±SD	2.69±0.62
Range	2–4
BNP (pg/mL)	
≥2,000	1 (4)
1,000–2,000	5 (19)
500–1,000	12 (46)
200–500	6 (23)
100–200	2 (8)

Unless specified otherwise, data presented as the mean±SD or n (%). AF, atrial fibrillation; BNP, B-type natriuretic peptide; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA FC, New York Heart Association functional class.

The clinical characteristics of the study patients at the time of presentation with acute HF are given in **Table 1**. All study patients presented with 2–4 HF signs on the basis of physical examination and evaluation of potential pleural effusion by thoracic ultrasound. Serum BNP concentrations ware definitely elevated (≥500 pg/mL) in 18 patients, moderately elevated (between 200 and <500 pg/mL) in 6, and mildly elevated (between 100 and <200 pg/mL) in 2. Treatment for acute HF was performed in hospital for 21 patients, and at an outpatient clinic for 5 patients. Decongestion therapy for 25.2±17 days (range 7–78) days led to good responses in all study patients, resulting in the disappearance of at least 2 HF-related signs in each patient; minimal residual HF-related signs remained in only 5 patients (persistent basal rales in 3 and minimal pleural effusion in 2).

As indicated in **Table 2**, of the 26 patients with recovery from worsening HF, changes in SCr concentration were negatively correlated with changes in the serum chloride concentrations (**Figure 1A**) and positively correlated with changes in the serum blood urea nitrogen and plasma AVP levels (**Figure 1B**).

Table 2. Pearson's Correlation for Changes of SCr Concentration or Plasma Arginine Vasopressin With Changes in Different Variables After Decongestion Therapy for Worsening HF

Variable	Changes in SCr		Changes in plasma AVP	
	R^2	P value	R^2	P value
SBP (mmHg)	0.007	0.67	0.0004	0.92
DBP (mmHg)	0.015	0.56	0.03	0.39
Log[BNP] (pg/mL)	0.13	0.07	0.15	0.049*
Hemoglobin (g/dL)	0.007	0.68	0.05	0.26
Hematocrit (%)	0.027	0.42	0.019	0.5
% Change in plasma volume	0.04	0.31	0.018	0.51
Serum total protein	0.005	0.74	0.006	0.7
Serum albumin	0.014	0.57	0.014	0.34
Serum electrolytes (mEq/L)				
Sodium	0.09	0.13	0.16	0.044*
Potassium	0.009	0.65	0.04	0.3
Chloride	0.17	0.04*	0.22	0.015*
Serum BUN (mg/dL)	0.3	0.004*	0.62	<0.0001*
SCr (mg/dL)	–	–	0.33	0.002*
Serum uric acid (mg/dL)	0.14	0.06	0.17	0.039*
Urinary concentrations (mEq/L)				
Sodium	0.04	0.32	0.002	0.82
Potassium	0.02	0.58	0.042	0.31
Chloride	0.04	0.33	0.001	0.88
Osmolality (mOsmol/kg H_2O)	0.018	0.51	0.007	0.67
Epinephrine (pg/mL)	0.016	0.54	0.04	0.33
Norepinephrine (pg/mL)	0.026	0.43	0.07	0.2
PRA (ng/mL/h)	0.024	0.45	0.11	0.11
Aldosterone (pg/mL)	0.001	0.86	0.0002	0.95
AVP (pg/mL)	0.33	0.002*	–	–

*P<0.05. AVP, arginine vasopressin; BUN, blood urea nitrogen; DBP, diastolic blood pressure; PRA, plasma renin activity; SBP, systolic blood pressure; SCr, serum creatinine. Other abbreviations as in Table 1.

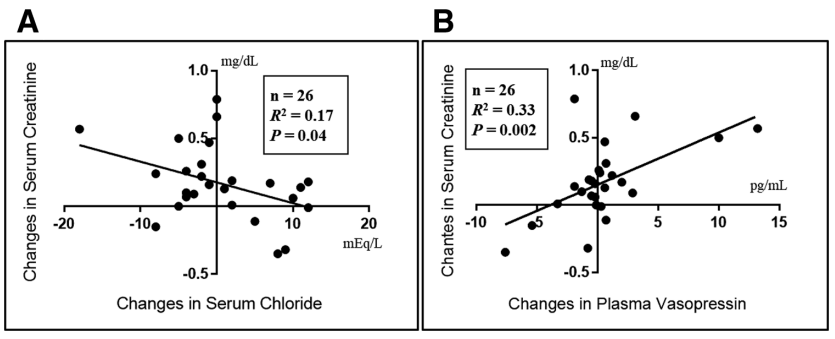

Figure 1. Relationship between changes in serum creatinine concentration and (**A**) serum chloride concentration or (**B**) plasma arginine vasopressin under treatment for worsening heart failure.

Based on the median change in SCr concentrations, patients were divided into 2 groups: one with a high change in SCr (range 0.16–0.79 mg/dL; n=13) and the other with a low change in SCr (range −0.35 to 0.14 mg/dL; n=13). As indicated in **Table 3**, there were no differences in SCr concentration and eGFR at baseline between the low and high SCr change groups. Cardiovascular medication at stable HF status after decongestion therapy for acute HF also did not differ between the 2 groups. There was no change in plasma volume in either group, but plasma log[BNP] and norepinephrine concentrations decreased and PRA increased after decongestion therapy in both groups. Except for log[BNP], the changes in these variables did not differ between the 2 groups. However, changes in plasma AVP concentrations differed significantly different between 2 groups, decreasing in the low SCr change group, and increasing in the high SCr change group (−1.28±2.8 vs. 2.14±4.4 pg/mL, respectively; P=0.027).

Multivariate logistic regression analysis (**Table 4**) showed a tendency towards an independent association between an increase in the SCr concentration and an increase or no change in the plasma AVP concentrations after decongestion therapy (OR 4.44; 95% CI 0.81–24.3; P=0.086).

As indicated in **Table 2**, among the 26 patients with

Table 3. Comparison of Laboratory Findings Between Groups With Low (Range −0.35 to 0.14 mg/dL) or High (Range 0.16 to 0.79 mg/dL) Changes in SCr Concentration After Diuretic Therapy

Variables	All patients (n=26)	Changes in SCr concentration		P value
		Low (n=13)	High (n=13)	
Age (years)	81.2±12	79.7±14	82.7±9.9	0.52
Basal eGFR (mL/min/1.73 m²)	45.5±19	47.7±23	43.4±14	0.58
SCr (mg/dL)				
Worsening	1.26±0.56	1.30±0.70	1.21±0.41	0.7
Recovery	1.43±0.6	1.28±0.69	1.58±0.47	0.2
ΔWorsening to recovery	0.17±0.27	−0.03±0.16	0.36±0.21	<0.0001*
P value	0.004*	0.57	<0.0001*	
SBP (mmHg)				
Worsening	135±34	130±29	141±39	0.41
Recovery	119±17	114±16	124±17	0.11
ΔWorsening to recovery	−16±25	−16.2±20	−16.6±29	0.97
P value	0.002*	0.014*	0.06	
DBP (mmHg)				
Worsening	76.3±21	75.0±22	77.7±20	0.75
Recovery	66.1±12	62.1±14	70.1±7.2	0.09
ΔWorsening to recovery	−10±20	−12.8±18	−7.62±21	0.5
P value	0.013*	0.025*	0.22	
Serum log[BNP] (pg/mL)				
Worsening	2.81±0.34	2.85±0.37	2.78±0.31	0.58
Recovery	2.25±0.31	2.16±0.32	2.34±0.28	0.14
ΔWorsening to recovery	−0.56±0.32	−0.69±0.32	−0.43±0.27	0.04*
P value	<0.0001*	<0.0001*	<0.0001*	
Hemoglobin (g/dL)				
Worsening	11.7±2.1	11.6±2.2	11.8±2.0	0.79
Recovery	12.0±2.5	11.9±2.9	12.1±2.0	0.87
ΔWorsening to recovery	0.28±1.3	0.31±1.49	0.25±1.1	0.92
P value	0.28	0.47	0.42	
Hematocrit (%)				
Worsening	35.4±6.0	34.5±6.4	36.3±5.6	0.44
Recovery	35.9±6.9	35.3±8.2	36.5±5.5	0.65
ΔWorsening to recovery	0.53±3.8	0.82±4.2	0.25±3.6	0.71
P value	0.48	0.49	0.81	
ΔChange in % plasma volume	−0.20±6.3	−0.65±6.5	0.26±6.4	0.72
Serum total protein (g/dL)				
Worsening	6.41±0.51	6.23±0.40	6.59±0.55	0.07
Recovery	6.61±0.73	6.49±0.89	6.72±0.54	0.43
ΔWorsening to recovery	0.20±0.63	0.26±0.70	0.13±0.56	0.6
P value	0.12	0.21	0.41	
Serum albumin (g/dL)				
Worsening	3.63±0.42	3.49±0.40	3.78±0.40	0.08
Recovery	3.58±0.47	3.53±0.59	3.63±0.33	0.59
ΔWorsening to recovery	−0.05±0.48	0.04±0.51	−0.15±0.45	0.34
P value	0.57	0.79	0.26	
Serum sodium (mEq/L)				
Worsening	139±5.1	137±5.8	141±3.5	0.06
Recovery	139±4.7	138±3.2	140±3.5	0.46
ΔWorsening to recovery	0.19±4.7	1.38±3.6	−1.00±4.7	0.16
P value	0.82	0.19	0.46	
Serum potassium (mEq/L)				
Worsening	4.27±0.68	4.19±0.74	4.35±0.64	0.56
Recovery	4.12±0.51	4.00±0.57	4.23±0.44	0.26
ΔWorsening to recovery	−0.15±0.73	−0.19±0.82	−0.12±0.66	0.81
P value	0.28	0.42	0.51	

(**Table 3** continued the next page.)

Variables	All patients (n=26)	Changes in SCr concentration		P value
		Low (n=13)	High (n=13)	
Serum chloride (mEq/L)				
Worsening	104±5.8	103±6.1	104±5.5	0.51
Recovery	104±5.8	106±3.9	103±7.2	0.26
ΔWorsening to recovery	0.54±7.2	2.62±7.0	−1.54±7.1	0.15
P value	0.71	0.2	0.45	
BUN (mg/dL)				
Worsening	26.6±11	26.2±12	26.9±12	0.87
Recovery	38.6±20	31.2±13	46.0±23	0.05*
ΔWorsening to recovery	12.0±17	5.00±8.9	19.1±20	0.027*
P value	0.001*	0.07	0.004*	
Serum uric acid (mg/dL)				
Worsening	6.38±2.4	6.30±2.8	6.45±2.0	0.87
Recovery	7.43±2.1	7.25±1.6	7.62±2.6	0.67
ΔWorsening to recovery	1.05±2.2	0.95±2.4	1.16±2.1	0.81
P value	0.023*	0.18	0.07	
Epinephrine (pg/mL)				
Worsening	0.085±0.08	0.079±0.05	0.091±0.10	0.69
Recovery	0.048±0.05	0.046±0.04	0.050±0.05	0.84
ΔWorsening to recovery	−0.04±0.06	−0.03±0.05	−0.04±0.07	0.74
P value	0.005*	0.03*	0.068	
Norepinephrine (pg/mL)				
Worsening	0.96±0.63	0.86±0.61	1.05±0.66	0.45
Recovery	0.52±0.33	0.41±0.19	0.64±0.39	0.07
ΔWorsening to recovery	−0.44±0.6	−0.45±0.54	−0.41±0.67	0.86
P value	0.001*	0.01*	0.047*	
PRA (ng/mL/h)				
Worsening	1.64±2.0	2.10±2.4	1.18±1.4	0.25
Recovery	5.48±6.1	4.66±5.3	6.30±6.9	0.5
ΔWorsening to recovery	3.84±5.6	2.55±3.9	5.12±6.9	0.25
P value	0.0018*	0.035*	0.02*	
Aldosterone (pg/mL)				
Worsening	117±90	114±102	120±81.4	0.88
Recovery	209±257	158±114	260±346	0.32
ΔWorsening to recovery	92.1±215	43.8±110	140±282	0.26
P value	0.039*	0.18	0.1	
Vasopressin (pg/mL)				
Worsening	3.54±3.4	3.28±2.4	3.80±4.3	0.71
Recovery	3.97±6.1	2.00±1.6	5.94±8.2	0.1
ΔWorsening to recovery	0.43±4.0	−1.28±2.8	2.14±4.4	0.027*
P value	0.59	0.12	0.1	
Urine osmolality (mOsmol/kg H_2O)				
Worsening	473±184	482±214	463±156	0.8
Recovery	452±155	456±163	449±153	0.91
ΔWorsening to recovery	−20.3±163	−26.3±188	−14.4±141	0.86
P value	0.53	0.62	0.72	
Medication use when status stable after decongestion therapy for acute HF				
Loop diuretics	22 (85)	11 (85)	11 (85)	1
Thiazide diuretics	4 (15)	1 (8)	3 (23)	0.59
MRA	22 (85)	9 (69)	13 (100)	0.1
Tolvaptan	6 (23)	2 (15)	4 (30)	0.64
Acetazolamide	17 (65)	9 (69)	8 (60)	1
ACEI/ARB	10 (38)	6 (46)	4 (30)	0.69
β-blockers	12 (46)	4 (30)	8 (60)	0.24
Calcium antagonists	10 (38)	5 (38)	5 (38)	1

*P<0.05. Unless specified otherwise, data are presented as the mean±SD or as n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist. Other abbreviations as in Tables 1,2.

Table 4. Multivariate Predictors of Changes in SCr Concentration Under Decongestion Therapy

Change after treatment	Changes in SCr after decongestion treatment				
	Low group (n=13)	High group (n=13)	Wald X^2	OR (95% CI)	P value
Serum chloride					
Increase/no change	8	5	0.61	0.51 (0.09–2.79)	0.4
Decrease	5	8			
Antidiuretic hormone					
Increase/no change	4	9	2.95	4.44 (0.81–24.3)	0.086
Decrease	9	4			
Blood urea nitrogen					
Increase/no change	10	12	0.08	1.35 (0.16–11.8)	0.78
Decrease	3	2			

Based on the median change in serum creatinine (SCr) concentrations, patients were divided into 2 groups: one with a high change in SCr (range 0.16–0.79 mg/dL) and the other with a low change in SCr (range −0.35 to 0.14 mg/dL). CI, confidence interval; OR, odds ratio.

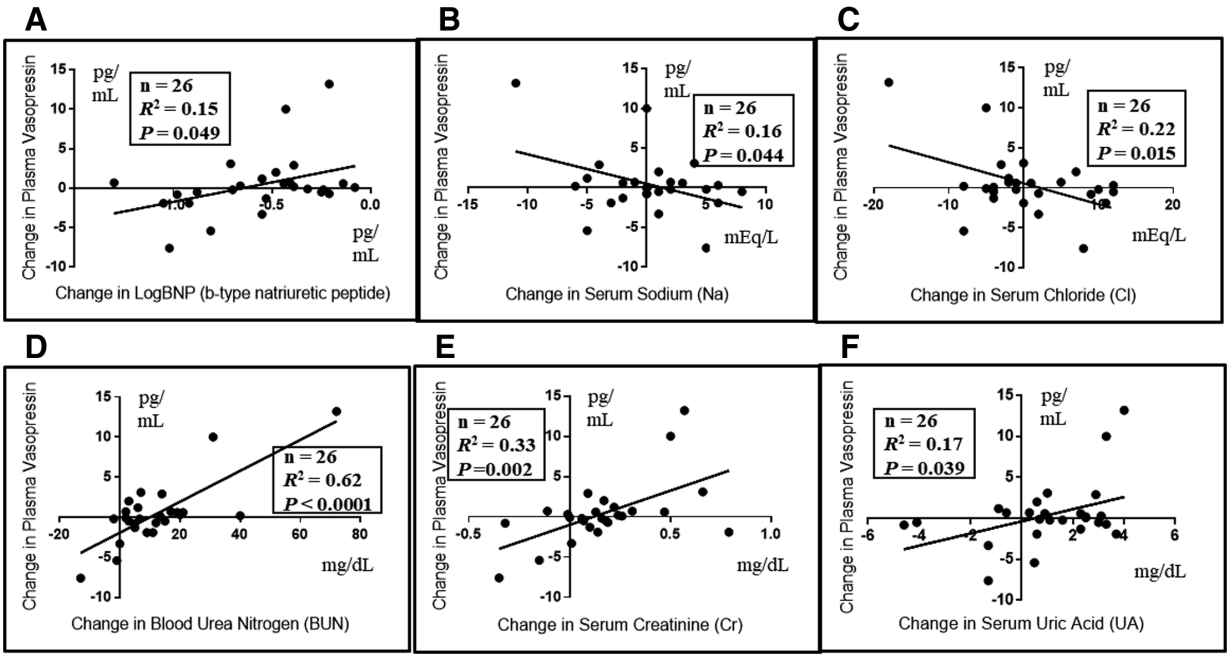

Figure 2. Relationship between changes in plasma arginine vasopressin concentrations and changes in (**A**) plasma log B-type natriuretic peptide (BNP), (**B**) serum sodium, (**C**) serum chloride, (**D**) blood urea nitrogen, (**E**) serum creatinine, and (**F**) serum uric acid concentrations.

recovery from worsening HF, changes in plasma AVP concentrations were positively correlated with changes in plasma log[BNP] (**Figure 2A**) and kidney-related solutes (i.e., blood urea nitrogen [**Figure 2D**], SCr [**Figure 2E**], and serum uric acid [**Figure 2F**]), and negatively correlated with changes in serum sodium (**Figure 2B**) and chloride (**Figure 2C**) concentrations.

Discussion

Interpretation of the Present Study

SCr concentrations could be affected by changes in handling and metabolism, such as creatinine production in the muscle and diffusion into the plasma, excretion of plasma creatinine by glomerular filtration and/or tubular excretion into the urine, and tubular reabsorption of urinary creatinine.[16–19] More importantly, SCr fluctuations could be significantly affected by body fluid status rather than intrinsic kidney injury during the clinical course of HF.[20,21] To date, however, limited clinical data are available regarding the association between serial changes in SCr with regulatory neurohormonal agent(s) and their role in regulating body fluid status under decongestion therapy for HF patients. The present study revealed an important role for AVP as a possible determinant of SCr changes or fluctuations in individual HF patients under decongestion therapy.

Previous Studies on Creatinine-Based Renal Function in Cardiorenal Syndrome

The pathophysiology of renal dysfunction under HF status is multifactorial and associated with decreased renal perfusion,[22–24] venous congestion,[22,24–27] higher renal interstitial pressure,[28] atherosclerosis and inflammation, endothelial dysfunction, and neurohormonal activation.[1,3,29] Decongestion therapy for worsening HF patients may resolve congestion but worsen renal function by excessive diuretic-related hypovolemia[8,10,30,31] and/or a drop in blood pressure[5,6,32–34] accompanied by enhanced activation of the sympathetic and renin-angiotensin-aldosterone systems, leading to Type 1 cardiorenal syndrome.[2,3,31,35] As to creatinine-based worsening renal function induced by decongestion therapy, of particular interest is a report by Metra et al,[9] who demonstrated that worsening renal function under decongestion therapy was not associated with worse outcomes, but that worsening renal function in the context of persistent congestion was an independent predictor of post-discharge morbidity and mortality. Subsequently, achieving individualized optimal plasma volume and resolution of congestion, despite the occurrence of creatinine-based worsening renal function, are the 2 main purposes of diuretic therapy for controlling HF.[8,36,37]

Previous Studies on AVP Activity in HF Pathophysiology

The antidiuretic hormone AVP is a potentially important neurohormone in HF pathophysiology for the regulation of body fluid status. This hormone affects free water reabsorption in the kidney, body fluid osmolality, blood volume, vasoconstriction, and myocardial contractile function.[38] The dominant stimulus for AVP secretion is serum osmolality, but non-osmotic factors (e.g., cardiac filling pressure, arterial pressure, and the effects of adrenergic stimuli and angiotensin II in the central nervous system) can modulate the osmotic control of AVP to varying degrees.[39] However, in the present study, changes in plasma AVP activity were not correlated with changes in the plasma neurohormonal activity after decongestion therapy for acute HF patients (**Table 2**).

Lanfear et al[40] reported that an elevated AVP concentration in patients hospitalized for worsening chronic systolic HF was independently associated with longer-term outcomes, including death. In the clinical setting, AVP activity is ordinarily elevated in HF patients compared with normal subjects.[41–44] However, there are some controversies regarding the correlation between AVP activity and hemodynamic parameters, with some studies reporting a positive association with right-sided cardiac pressure,[42] a significant correlation between baseline AVP concentrations and an increase in systemic vascular resistance after vasopressin antagonist infusion,[45] a weak association with differences in the left ventricular ejection fraction,[41] and an unclear association between AVP activity and hemodynamic parameters.[43] Interestingly, Imamura et al[44] reported a definite association between elevated AVP concentrations and advanced HF patients with low cardiac output, and a reversal of this association following an improvement in cardiac function with surgical treatment.

With regard to the correlation between AVP activity and serum sodium concentrations, 1 study did not demonstrate a significant association between them,[43] although many other studies have confirmed AVP elevation in HF patients with hyponatremia.[44–47] A positive association between AVP concentrations and PRA was reported by Goldsmith et al,[43] but not by Creager et al.[45] There is a scant clinical data on the association between changes in SCr and AVP activity under resolution of worsening HF after decongestion treatment.

Association Between SCr Fluctuations and AVP Activity in HF Pathophysiology

Serial SCr changes or fluctuations ordinarily occur during the clinical course of HF, and often seem to be associated with changes in body fluid status,[20,21] possibly due to the effects primarily of dietary fluid intake and the use of diuretics. As mentioned above, the antidiuretic hormone AVP is significantly associated with HF pathophysiology, but its association with serial changes in SCr under decongestion treatment has not been well evaluated. The present study demonstrated the possible underlying neurohormonal circumstances for fluctuations in SCr concentrations during the clinical course of HF, during which an as yet unknown, but potentially causal, relationship may exist among changes in SCr, AVP secretion, and body fluid status in individual HF patients, as hypothesized below.

As shown in the present study, plasma AVP concentrations were inversely correlated with changes in serum sodium and chloride concentrations (**Table 2**; **Figure 2B**,**C**). Conversely, changes in plasma AVP concentrations were positively correlated with the change in the SCr concentration under sufficient diuresis following diuretic use (**Table 2**; **Figures 1B**,**2E**). Considering these facts together, it is conceivable that, under HF pathophysiology, a change to a low (or high) serum sodium or chloride concentration after decongestion treatment would be accompanied by paradoxically high (or low) AVP secretion (**Figure 2B**,**C**), thus favoring more water absorption (excretion), despite presumed low (high) serum osmolality due to a decrease (increase) in sodium and chloride electrolytes. Under the conditions of forced diuresis by the use of medical diuretics, such antidiuretic actions of high (or low) AVP may be insufficient or maladapted to ensure lowering (enhancing) of the SCr concentration (**Figure 2E**) via a hemodilution (or concentration) mechanism, probably owing to inadequate water absorption (excretion) in the urinary tubules. As such, many episodes of creatinine-based worsening renal function under diuretic treatment would reflect hemodynamic or functional changes in glomerular filtration (pseudo-worsening renal function).[48] Therefore, changes in SCr would not be an appropriate measure for determining intrinsic renal injury in HF patients. Other biomarkers are more suitable for identifying intrinsic kidney injury in HF patients under decongestion therapy.[49] The concept described above is hypothetical, and further detailed studies are required to precisely assess the interactions among changes in SCr, AVP secretion, and body fluid status in HF pathophysiology.

Study Limitations

This study is a cross-sectional observational study and should be considered as hypothesis generating, and to have some limitations. The present study was performed on a population of patients with mild-to-moderate HF. Therefore, the findings of the present study cannot be generalized to patients with more advanced HF. Further, this study was a small-sized retrospective observational study with a selection bias due to data availability. Thus, studies including a larger number of HF patients are needed to better assess the association of changes in SCr concentra-

tions with changes in serum solutes or plasma neurohormones in HF patients.

Conclusions

The antidiuretic hormone AVP appears to be a physiologically important mediator of serial SCr changes or fluctuations under decongestion therapy in HF patients.

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Disclosures

The author has no conflicts of interest to declare.

IRB Information

The Research Ethics Committee of Nishida Hospital approved the study protocol (Reference no. 201710-01). This study was performed in accordance with the Declaration of Helsinki. The study involved only diagnostic standard data and thus individual consent for inclusion was waived, but an oral explanation of the need for blood and hormone tests was provided.

Data Availability

The deidentified participant data will not be shared.

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