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Counteraction of the Natriuretic Peptide and the Renin-Angiotensin-Aldosterone Systems in Acute Heart Failure

Hajime Kataoka*

Internal Medicine, Nishida Hospital, Oita, Japan.

***Corresponding Author(s):** **Hajime Kataoka**

Internal Medicine, Nishida Hospital, 2-266 Tsuruoka-Nishi-machi, Saiki-city, Oita 876-0047, Japan.

Tel: +81-972-22-0180; Fax: +81 972 23 3053,

Email: hkata@cream.plala.or.jp

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Keywords: b-type natriuretic peptide; Renin activity; Renin-angiotensin-aldosterone system.

Abstract

Background: It is reported that the Natriuretic Peptide (NP) and Renin-Angiotensin-Aldosterone (RAA) systems counteract each other, but supporting evidence for such an interaction is lacked in clinical Heart Failure (HF).

Methods: Data from 29 patients with acute HF (48% men; 80.3±12 years of age) were analyzed. Blood and urine samples were 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, and neurohormones. Pearson's correlation was used to evaluate the linear association between log-transformed (Log) neurohormones with multiple variables.

Results: No association was detected between the Log B-type Natriuretic Peptide (BNP) and Log plasma renin activity (PRA; R^2=0.044, p=0.27). The Log BNP weakly and negatively correlated with the concentrations of urinary sodium (R^2=0.22, p=0.01) and chloride (R^2=0.28, p=0.003). The Log PRA moderately and negatively correlated with the concentrations of urinary sodium (R^2=0.53, p<0.0001) and chloride (R^2=0.41, p=0.0002).

Conclusion: Considering the physiologic actions of the NP and RAA systems, the finding that both of these systems target the same electrolytes (sodium and chloride) in the kidney may provide possible clinical evidence that these 2 systems functionally counteract each other in acute HF when considering their physiologic roles; the NP system functions in the excretion of these electrolytes, while the RAA system functions in their absorption.

Introduction

Heart Failure (HF) is a syndrome characterized by the activation of different neurohormonal systems [1,2], predominantly the Renin-Angiotensin-Aldosterone (RAA) system [3-5] and the sympathetic nervous system [1,6], but also the Natriuretic Peptide (NP) system [7,8]. The NP and RAA systems reportedly act in opposition to each other [7,8], but supporting evidence for such a counteraction between them in the pathophysiology of clinical HF remains lacked [9]. The purpose of this study was to determine whether clinical evidence exists for the presence of opposing effects of the NP and RAA systems in acute HF.

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Materials and Methods

This study was a retrospective single-center observational study enrolling 31 consecutive patients with acute HF at Nishida Hospital (Saiki-city, Oita, Japan) that participated in a neurohormonal study between March 2017 and April 2018. The Research Ethics Committee of Nishida Hospital approved the study protocol (Reference number: 201710-01), and the study was performed in accordance with the tenets of the Declaration of Helsinki.

Eligible patients had a de novo HF event or at least 1 decompensated HF episode resulting in hospitalization or outpatient treatment with cardiovascular medication. On the basis of previous studies [10], the criteria for defining an event of acute HF were the appearance of at least 2 of the following HF-related signs irrespective of the presence of symptomatic changes: physical signs (third heart sound, pulmonary crackles, and leg edema), fluid weight gain (≥1.5 kg), and pleural effusion on ultrasound [11]. 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 present study.

Physical and ultrasonographic examinations, peripheral venous blood (hematologic and neurohormonal tests), and a spot urine test were performed upon presentation of the acute HF episode immediately before the initiation of decongestive therapy. Blood and urine samples were obtained after patients rested in a supine or semi-supine position for 20 min. Peripheral blood tests were analyzed by standard techniques. The estimated plasma volume status was calculated according to Duarte's formula [12] as follows: estimated plasma volume status (dL/g) = [100 – hematocrit (%)]/ hemoglobin (g/dL)]. Plasma B-type Natriuretic Peptide (BNP) was measured by chemiluminescent immunoassay. Plasma Renin Activity (PRA) was measured by enzyme immunoassay. Plasma aldosterone and arginine vasopressin levels were measured by radioimmunoassay.

Statistical analysis

All data are expressed as mean ± SD for continuous data and percentage for categorical data. The neurohormonal values were log-transformed (Log) before statistical analysis because of their skewed distribution. Pearson's correlation was used to evaluate the linear association between 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. 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.

Pearson's correlations of Log BNP and Log PRA with multiple variables in acute HF patients (n=29) are shown in Table 2. No association was detected between the Log BNP and Log PRA (R^2=0.044, p=0.27; Figure 1a). The Log BNP weakly and negatively correlated with the concentrations of urinary sodium (R^2=0.22, p=0.01; Figure 1b) and chloride (R^2=0.28, p=0.003; Figure 1c). The Log PRA moderately and negatively correlated with the concentrations of urinary sodium (R^2=0.53, p<0.0001; Figure 1d) and chloride (R^2=0.41, p=0.0002; Figure 1e).

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)
	Acetazolamide	9 (31)
	ACE inhibitors/ARB	10 (34)
	Beta-blockers	9 (31)
	Calcium antagonists	9 (31)
	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.

Table 2: Pearson's correlation of Log BNP (pg/mL) and Log PRA (ng/mL/h) with multiple variables under acute heart failure (n=29).

		Log BNP		Log PRA	
Variable		**R2**	**p value**	**R2**	**p value**
Systolic BP (mmHg)		0.003	0.77	0.07	0.17
Diastolic BP (mmHg)		0.016	0.51	0.001	0.86
ePVS (dL/g)		0.023	0.43	0.023	0.43
Serum electrolytes					
	Sodium (mEq/L)	0.002	0.98	0.024	0.42
	Potassium (mEq/L)	0.048	0.25	0.0003	0.93
	Chloride (mEq/L)	0.027	0.4	0.07	0.16
BUN (mg/dL)		0.085	0.12	0.1	0.1
Creatinine (mg/dL)		0.036	0.33	0.007	0.66
Urinary concentration					
	Sodium (mEq/L)	0.22	0.01*	0.54	<0.0001*
	Potassium (mEq/L)	0.044	0.27	0.19	0.02*
	Chloride (mEq/L)	0.28	0.003*	0.41	0.0002*
Serum minus urinary concentration					
	Sodium (mEq/L)	0.22	0.01*	0.53	<0.0001*
	Potassium (mEq/L)	0.048	0.25	0.2	0.016*
	Chloride (mEq/L)	0.28	0.003*	0.4	0.0002*
% urinary excretion of electrolyte					
	Sodium	0.032	0.36	0.13	0.057
	Potassium	0.009	0.63	0.013	0.55
	Chloride	0.06	0.19	0.1	0.09
Log BNP (pg/mL)		–	–	0.044	0.28
Log PRA (ng/mL/h)		0.044	0.28	–	–
Log Aldosterone (pg/mL)		0.068	0.17	0.31	0.002*
Log AVP (pg/mL)		0.014	0.54	0.016	0.51

*Statistically significant (p<0.05). AVP: Arginine Vasopressin; BNP: B-type Natriuretic Peptide; BP: Blood Pressure; BUN: Blood Urea Nitrogen; ePVS: Estimated Plasma Volume Status; PRA: Plasma Renin Activity.

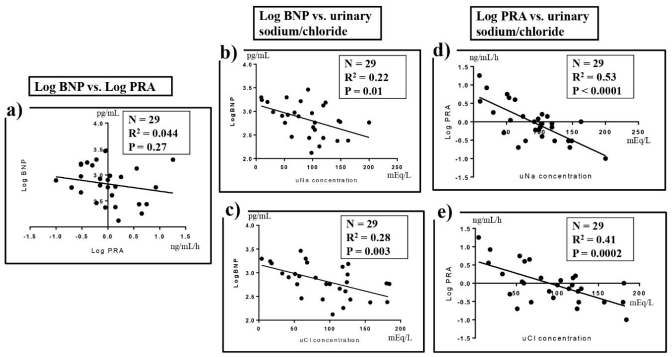

Figure 1: Inter-relationships between; **(A)** Log BNP vs. Log PRA, **(B)** Log BNP vs. urinary sodium (Na) concentration, **(C)** Log BNP vs. urinary chloride (Cl) concentration, **(D)** Log PRA vs. Na concentration, and **(E)** Log PRA vs. urinary Cl concentration.

Discussion

In HF pathophysiology, the NP system acts as an ideal counter-regulatory mechanism to the RAA system [3-5], influencing renal blood flow and sodium excretion through direct renal actions or by inhibiting the release or actions of other vasoconstrictive agents [7,8]. However, there are few clinical studies investigating the interaction between the RAA and NP systems. In the present study, no significant linear correlation was detected between the plasma levels of PRA (representative of the RAA system) and BNP (representative of the NP system), but a significant negative linear correlation was detected between plasma levels of both BNP and PRA, and the urinary sodium and chloride concentrations. These observations suggest that the RAA and NP systems similarly target the same electrolytes in the kidney, but functionally act opposite to each other when considering their different physiologic roles. Namely, it is conceivable that the RAA system induces the re-absorption of sodium, chloride, and water, whereas the NP system acts to excrete these electrolytes and water in the kidney. Less diuretic requirement in HF patients with sacubitril/valsartan treatment would be related to its possible diuretic effect through the activation of the NP system [13].

Then, how are plasma BNP and urinary sodium and chloride concentrations significantly and negatively correlated? A causal relationship between BNP and urinary electrolyte concentrations could not be determined in the present study, but their association seems to be an indirect phenomenon mediated by hemodynamics. Namely, considering that several studies have shown a positive association of the serum chloride level with cardiac output [14,15] or the estimated plasma volume status [16], the various BNP levels observed among HF patients in the present study would reflect a different cardiac burden

promoted by chloride-associated hemodynamic changes, and subsequent differential BNP secretion would affect the uresis of sodium, chloride, and water in the kidney, thus inducing the corresponding change in urinary sodium and chloride concentrations.

Limitations

The present study had a lot of limitations. First, 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. Second, only a correlation analysis between BNP and PRA with multiple variables was performed in the present study, and therefore the detailed causality and confounders remain unknown. Lastly, one third of eligible patients took RAA inhibitors and/or beta blockers, but these pharmacologic effects were not taken into account in the present analysis. However, acutely decompensated HF status would greatly attenuate these pharmacologic effects on RAA system. Further studies including a larger number of HF patients with various HF conditions are needed to better assess the association of the NP system with the sodium and chloride electrolytes, and water in HF pathophysiology.

Conclusion

Considering the physiologic actions of the NP and RAA systems, the finding of the present study that both of these systems target the same urinary electrolytes (sodium and chloride) provides indirect clinical evidence that these 2 systems functionally counteract each other in the kidney under acute HF. Future studies are needed to clarify the renal processing of urinary electrolytes separately in the NP and RAA systems.

Author declarations

Statement of Ethics

The Research Ethics Committee of Nishida Hospital approved the study protocol (Reference number: 201710-01), and the study was performed in accordance with the tenets of the Declaration of Helsinki.

Conflict of interest statement

The author reports no relationships that could be construed as a conflict of interest.

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Author contributions

This is the work of one author.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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