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Differential Regulation of Plasma Copeptin Levels in Patients with Heart Failure: A Single-Center Prospective Study

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Elevated levels of arginine vasopressin (AVP) have been reported to be involved in the pathogenesis of heart failure (HF). Recent evidence has shown the role of copeptin, the C-terminal fragment of pro-AVP, as a biomarker in patients with HF. However, the relevant information is still limited. Therefore, we evaluated 39 Japanese patients admitted for HF between 2013 and 2015 (23 males and 16 females with an average age of 79.2 years). They were treated according to the Japanese acute HF guideline. Plasma copeptin levels were measured on admission and about 1 week later. The median plasma copeptin levels on admission were 0.5 (0.1-50.6) pmol/L, higher than the normal values (0.24 ± 0.06 pmol/L). Despite the similar clinical severity on admission, the patients showed great variability in plasma copeptin levels. They were divided into three groups (13 patients/group) according to plasma copeptin levels on admission: highest (> 30.8 pmol/L), midrange, and lowest (< 0.2 pmol/L) groups. Initial treatment improved HF symptoms in 37 of 39 patients, with the two unresponsive patients in the lowest group. Notably, plasma copeptin responses to initial treatment were different, depending on admission copeptin levels. The initial treatment significantly decreased copeptin levels in the highest group, but increased copeptin levels in the lowest group. By contrast, patients in the midrange group showed no significant changes. Thus, the treatment appears to restore the plasma copeptin levels. In conclusion, HF is a complex syndrome with the differential integration of stimulatory and inhibitory inputs to the AVP/copeptin secretory system.

Keywords: brain natriuretic peptide; copeptin; heart failure; Japanese; vasopressin
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Introduction

Heart failure (HF) is a major cause of cardiovascular mortality and morbidity with an upward trend among the aging Japanese population. As HF varies greatly in etiology, severity, and response to treatment, identification of individuals at high risk for cardiovascular events is crucial (Braunwald 2008). There are several established markers used in patients with HF, including neurohormones; in particular, brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) were shown as important markers in routine clinical practice (Troughton et al. 2014).

There is increasing interest in the development of new biomarkers for HF for further improvement of risk stratification (Braunwald 2008). Arginine vasopressin (AVP) is well known for its important roles in cardiovascular regulation and pathophysiological processes (Share 1988). Importantly, elevated plasma AVP has been reported in patients with HF (Yamane 1968; Francis et al. 1990; Nakamura et al. 2006), and an advanced assay system for C-terminal pro-AVP (copeptin), a vasopressin surrogate that is more stable and easier to measure than AVP, was developed over the past decade (Morgenthaler et al. 2006). Importantly, copeptin was shown as an independent prognostic marker of cardiovascular diseases in large, prospective clinical studies (Morgenthaler 2010; Balling and Gustafsson 2014).

Plasma AVP and copeptin levels change rapidly in response to various physiological challenges (Kimura et al. 1986; Szinnai et al. 2007). However, little is known regarding changes in plasma copeptin levels during HF treatment. Given the importance of changes in these markers during follow-up of patients with HF for improving risk assessment and the lack of data on copeptin levels in Japanese

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patients with HF, we evaluated the changes in copeptin and NT-proBNP levels in response to initial treatment in patients admitted for worsening HF.

Subjects and Methods

Subjects

Written informed consent was obtained from consecutive 53 patients with worsening HF admitted to the cardiovascular unit of the Yokohama-Hodogaya Central Hospital between September 2013 and May 2015. Exclusion criteria were as follows: malignancy diagnosis, shock, acute coronary syndrome, use of non-peptide arginine vasopressin antagonists, hemodialysis, and pulmonary heart disease. The present study complied with the institutional guidelines and the Declaration of Helsinki and was approved by the ethics committees of Yokohama-Hodogaya Central Hospital and Meiji Pharmaceutical University.

Clinical evaluation and laboratory data

On admission, all patients underwent thorough clinical evaluation based on the criteria by the New York Heart Association (NYHA) and the Clinical Scenario (CS) (De Luca et al. 2007). The patients were treated based on the Guidelines for Treatment of Acute HF by the Japanese Circulation Society (JCS) 2011 (JCS Joint Working Group 2013).

Laboratory test results from routine examination were collected from all patients on admission and from the majority of subjects 7 days after admission. NT-proBNP was measured by chemiluminescent enzyme immunoassay using the Cobas e411 analyzer (Roche diagnostics, Tokyo, Japan). Creatinine clearance was calculated from the Cockcroft-Gault formula for estimated glomerular filtration rate (Cockcroft and Gault 1976).

Echocardiography was performed with either Vivid E9 or Vivid 7 (GE Healthcare Japan, Tokyo, Japan). Left ventricular (LV) ejection fraction (EF) was measured using Simpson's biplane method. The ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/e') was estimated using tissue Doppler imaging of five consecutive heart beats (JCS Joint Working Group 2013).

Copeptin measurement

For copeptin measurements, heparinized blood was collected from all patients on admission and approximately 1 week later and immediately centrifuged. The plasma samples were stored at −20°C until measurements. Copeptin (pmol/L) was detected with a new sandwich immunoassay [Peninsula Laboratories International, San Carlos, California (CA), the United States of America (USA)] following the manufacturer's recommendations. Briefly, 1 mL of plasma was extracted with a C18 Sep-Column (Peninsula Laboratories International, San Carlos, CA, USA), and the eluate was lyophilized before immunoassay. Paired samples were measured in the same assay. Ambulatory plasma copeptin level in healthy volunteers was 0.24 ± 0.06 pmol/L [mean ± standard error (SE), n = 14]. Recovery rate for copeptin was 68.2 ± 4.8% (mean ± SE, n = 10). Intraassay and interassay coefficients of variation were 8.6% (n = 7) and 9.8% (n = 5), respectively.

Statistical analysis

Discrete variables were expressed as counts (%), and continuous variables were expressed as medians with interquartile ranges (1st-3rd quartile) or means ± SE. Frequency comparison was achieved by the chi-square test or Fisher's exact test. For group comparisons, Welch's *t* test, Mann-Whitney *U* test, Kruskal-Wallis test, or analysis of variance was used where appropriate. Simple linear regression and multiple regression analyses were conducted to determine the association of each variable with copeptin. The levels of copeptin and NT-proBNP were normalized by square root transformation. Statistical analyses were performed using StatFlex V6 (Artech, Osaka, Japan). A two-tailed probability value of < 0.05 was considered statistically significant.

Results

Baseline parameters

Of a total of 53 patients admitted for worsening HF, 14 were excluded based on the exclusion criteria; thus, 39 patients were included in the final analysis. Their demographic features are shown in Table 1. Valvular heart disease (43.6%) and hypertension (43.6%) were two major causes of HF. Serum sodium levels were within the normal range, whereas creatinine clearance was impaired. When patients were equally divided into three groups according to admission copeptin values, there were no differences in baseline parameters among groups (Table 1). We specified that the lowest group with admission plasma copeptin levels below 0.2 pmol/L was the first tertile, the highest group with above 30.8 pmol/L was the third tertile, and the medium group was the second tertile.

Relationship between plasma copeptin levels and serum sodium and osmolality

When we investigated the relationship between copeptin levels on admission and serum sodium and osmolality levels, we found no positive correlations in patients with HF, an outcome expected in healthy subjects (Fig. 1). These results indicated a nonosmotic copeptin release.

Patient outcomes after initial treatment

All subjects were treated to rescue and stabilize vital signs, to improve symptoms such as dyspnea, and to reduce organ congestion. Treatment was initiated as soon as possible after admission to stabilize and maintain patients using cost-effective and low-risk methods. The most commonly used drugs were furosemide (89.7%) and carperitide (87.2%), and there were no differences in medications for HF during initial treatment among tertiles.

Thirty-seven of 39 patients showed improvements in symptoms and signs with initial treatment. These clinical outcomes were similar between the second and the third tertiles. In the first tertile, one patient's condition remained unchanged, whereas another patient worsened despite treatment.

Responses of copeptin and NT-proBNP to initial treatment

Overall median (1st-3rd quartile) copeptin level in our cohort was 0.5 (0.1-50.6) pmol/L on admission and tended to decrease to 0.4 (0.2-33.0) pmol/L following initial treat-

Table 1. Baseline clinical characteristics of total patients and three groups equally divided according to admission copeptin values.

	Total	1st Tertile	2nd Tertile	3rd Tertile	*P*-value
	n = 39	n = 13	n = 13	n = 13	
Age (years)	77.3 ± 2.0	73.0 ± 3.8	82.5 ± 2.7	76.2 ± 3.5	0.14
Sex (Male/Female)	23/16	10/3	7/6	6/7	0.12
NYHA class Ⅰ/Ⅱ/Ⅲ/Ⅳ	1/9/13/16	0/2/5/6	1/4/4/4	0/3/4/6	0.96
Clinical scenario (CS) CS1/CS2	19/20	6/7	8/5	5/8	0.70
Medical history					
Hypertension	31 (79.5)	10 (76.9)	11 (84.6)	10 (76.9)	1.00
Diabetes	6 (15.4)	1 (7.7)	2 (15.4)	3 (23.1)	0.28
Dyslipidemia	10 (25.6)	4 (30.8)	2 (15.4)	4 (30.8)	1.00
Atrial fibrillation/Atrial flutter	22 (56.4)	6 (46.2)	8 (61.5)	8 (61.5)	0.43
Cause of heart failure					
Coronary artery disease	12 (30.8)	4 (30.8)	4 (30.8)	4 (30.8)	1.00
Cardiomyopathy	3 (7.7)	0 (0.0)	2 (15.4)	1 (7.7)	0.47
Valvular disease	17 (43.6)	6 (46.2)	4 (30.7)	7 (53.8)	0.70
Arrhythmia	11 (28.2)	5 (38.5)	2 (15.4)	4 (30.8)	0.67
Hypertensive heart disease	17 (43.6)	5 (38.5)	6 (46.2)	6 (46.2)	0.70
Medications being taken at home					
Diuretics	16 (41.0)	4 (30.8)	7 (53.8)	5 (38.5)	0.69
β-blocker	14 (35.9)	3 (23.1)	7 (53.8)	4 (30.8)	0.69
Ca channel blocker	12 (30.8)	4 (30.8)	6 (46.2)	2 (15.4)	0.40
Angiotensin Ⅱ receptor antagonist	14 (35.9)	6 (46.2)	6 (46.2)	2 (15.4)	0.11
Angiotensin converting enzyme inhibitor	4 (10.3)	1 (7.7)	2 (15.4)	1 (7.7)	1.00
Aldosterone receptor antagonist	7 (17.9)	2 (15.4)	4 (30.8)	1 (7.7)	0.61
Aspirin	9 (23.1)	5 (38.5)	3 (23.1)	1 (7.7)	0.07
Statins	6 (15.4)	1 (7.7)	2 (15.4)	3 (23.1)	0.28
Remedy of hyperuricemia	11 (28.2)	3 (23.1)	5 (38.5)	3 (23.1)	1.00
TP(g/dL) (n = 38/13/13/12)	6.5 ± 0.1	6.5 ± 0.1	6.6 ± 0.1	6.5 ± 0.2	0.76
Serum sodium (mEq/L) (n = 38/12/13/13)	141.3 ± 0.5	141.2 ± 1.0	142.1 ± 0.7	140.8 ± 1.0	0.56
Serum creatinine (mg/dL)	1.0 (0.8-1.2)	1.0 (0.8-1.1)	1.2 (0.8-1.4)	1.0 (0.7-1.1)	0.90
Creatinine clearance (mL/min) (n = 38/13/12/13)	38.5 (28.0-56.5)	41.0 (34.8-52.3)	32.1 (26.1-39.9)	45.9 (25.4-61.4)	0.37
NT-proBNP (pg/mL) (n = 37/12/13/12)	5,974 (2,289-11,165)	4,474(1,364-8,400)	5,974(3,132-8,583)	8,185(2,271-16,962)	0.64
Copeptin (pmol/L)	0.5 (0.1-50.6)	0.07 (0.03-0.13)	0.5 (0.3-1.8)	80.5 (51.5-87.0)	< 0.0001
HR	91.4 ± 3.9	90.5 ± 7.5	87.7 ± 5.8	95.9 ± 7.2	0.69
Systolic BP (mmHg)	145.2 ± 3.4	146.0 ± 4.8	142.9 ± 5.0	146.5 ± 7.9	0.90
Diastolic BP (mmHg)	86.5 ± 3.0	88.9 ± 4.9	80.5 ± 4.2	90.1 ± 6.1	0.37
Left ventricular ejection fraction (%)	48.9 ± 2.4	47.1 ± 4.4	54.5 ± 3.9	45.0 ± 3.8	0.23
< 40%	12 (30.8)	4 (30.8)	2 (15.4)	6 (46.2)	
E/e' (n = 32/9/12/11)	15.9 (11.6-21.0)	16.4 (11.6-19.8)	12.9 (10.8-16.0)	20.2 (15.8-22.1)	0.51
8.0~15.0/ < 15.0	12/20	3/6	7/5	2/9	0.40

Data are expressed as number (percentage), mean ± standard error, or median (1st-3rd quartile).

ment (Fig. 2). Specifically, the changes in copeptin levels following initial treatment were different among three groups. In the highest (third) tertile, median copeptin levels significantly decreased from 80.5 (51.5-87.0) pmol/L to 9.4 (0.2-66.8) pmol/L ($P < 0.05$), whereas median copeptin levels significantly increased from 0.07 (0.03-0.13) pmol/L to

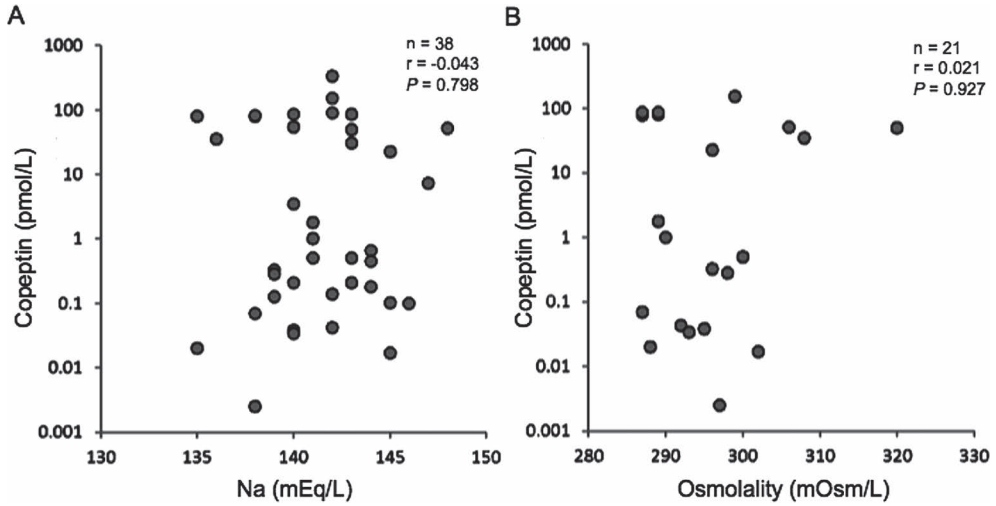

Fig. 1. Relationship between copeptin and sodium/osmolality levels.
The relationship between plasma copeptin levels and serum sodium levels (A) and serum osmolality levels (B) in patients admitted for heart failure.

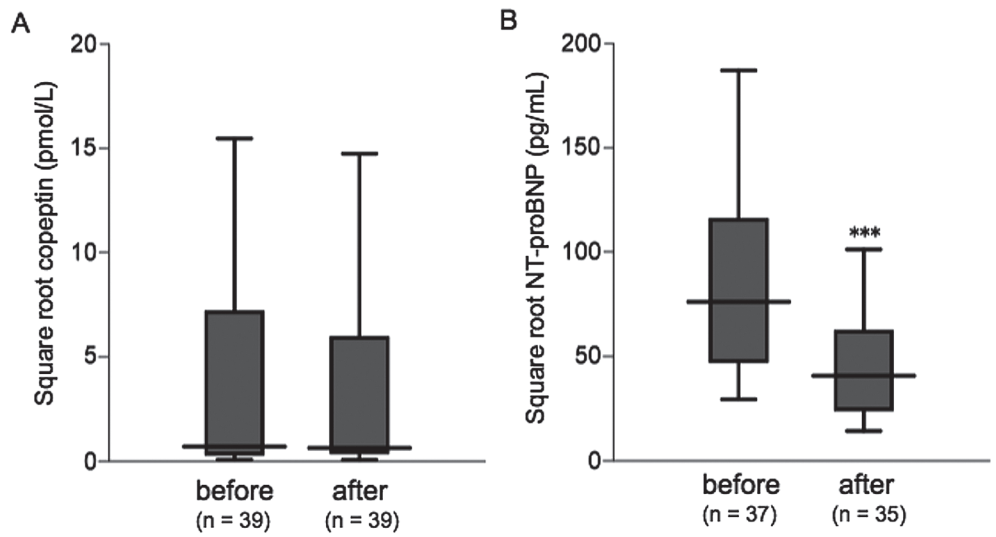

Fig. 2. Copeptin and NT-proBNP changes after initial treatment.
Changes in copeptin (A) and NT-proBNP (B) after initial treatment (after) in overall patients with heart failure. Before: before initial treatment; ***$P < 0.001$ vs. the level on admission.

0.3 (0.1-16.2) pmol/L ($P < 0.01$) in the lowest tertile. In this tertile, the copeptin levels of two patients without symptom amelioration rose after initial treatment; however, even without the values of 2 clinically unimproved patients, plasma copeptin levels significantly increased from 0.04 (0.03-0.11) pmol/L to 0.2 (0.1-8.3) pmol/L ($P < 0.01$). In the middle tertile, there was only a downward trend (not significant) (Fig. 3).

In contrast, the median NT-proBNP levels significantly decreased from 5,974.0 (2,289.0-11,165.0) pg/mL on admission to 1,826.0 (727.5-4,294.5) pg/mL after initial treatment ($P < 0.001$) (Fig. 2).

Intertertile changes of patients with HF during initial treatment

Following initial treatment for HF, several patients changed from one tertile on admission to another tertile, based on copeptin and NT-proBNP levels. The distribution of patients according to tertiles categorized before and after initial treatment is shown in two contingency tables (Tables 2 and 3). The chi-square test detected a shift in the distribution of patients in the NT-proBNP tertiles ($P = 0.0008$) (Table 2) but not in the copeptin tertiles ($P = 0.520$) (Table 3).

Changes of copeptin and NT-proBNP levels in patients with HF classified according to the NYHA and CS criteria

The levels of copeptin on admission in patients with worsening HF showed a stepwise upward trend with

increasing NYHA classification scores. Median copeptin levels were 0.6 (0.2-25.0) and 0.5 (0.1-55.1) pmol/L in class I-II and in class III-IV patients, respectively; however, no significant difference was detected between the two groups.

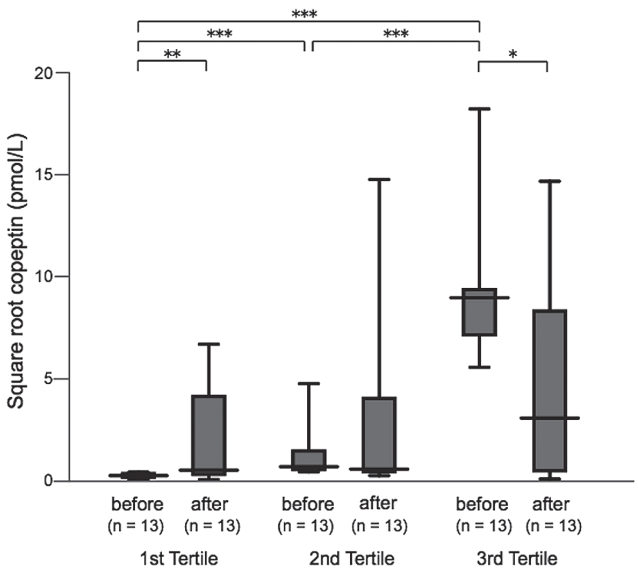

Fig. 3. Copeptin changes in low-, middle-, and high-copeptin groups.
Changes in copeptin after initial treatment (after) in each 3 groups divided by admission copeptin values. Before: before initial treatment; *$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

After treatment, median copeptin level decreased to 0.3 (0.2-0.6) in class I-II patients, with a significant difference from 1.0 (0.2-44.9) observed in class III-IV patients ($P < 0.01$) (Fig. 4). Furthermore, median NT-proBNP values were 2,769.0 (1626.8-6527.3) and 5974.0 (2,372.5-16,001.0) pg/mL in class I-II and class III-IV patients, respectively; these values were significantly different ($P < 0.05$). Further, in class III-IV patients, the levels of NT-proBNP decreased significantly with initial treatment ($P < 0.001$) (Fig. 4).

In CS1 patients, median copeptin level on admission was 0.4 (0.2-26.8) pmol/L, which tended to be lower than that in CS2 patients [1.1 (0.1-80.0) pmol/L]. After initial treatment, median copeptin level was 0.3 (0.2-40.0) pmol/L in CS1 patients and tended to decrease to 0.5 (0.2-17.1) pmol/L in CS2 patients (Fig. 5). Median NT-proBNP values were 6670.0 (2,414.3-12,136.0) and 4,078.0 (1,787.0-12,778.0) pg/mL in CS1 and CS2 patients, respectively; there was no significant difference between the two patient groups. However, in both CS1 and CS2 patients, the NT-proBNP levels significantly decreased after initial treatment ($P < 0.001$) (Fig. 5).

Copeptin and cardiac functions

Copeptin tended to be higher in patients with systolic LV dysfunction. Median plasma copeptin levels were 26.2 (0.1-82.9) pmol/L in patients with EF < 40% (n = 12) and 0.5 (0.2-26.8) pmol/L in those with EF ≥ 40% (n = 27).

Table 2. Distribution of patients with heart failure on the tertiles according to NT-proBNP values on admission (Before) and after initial treatment (After).

			Before		
			1st Tertile (n = 11)	2nd Tertile (n = 11)	3rd Tertile (n = 11)
After	1st	Tertile (n = 11)	8	2	1
	2nd	Tertile (n = 11)	3	6	2
	3rd	Tertile (n = 11)	0	3	8

$P = 0.0008$, by Chi-square test.

Table 3. Distribution of patients with heart failure on the tertiles according to copeptin values on admission (Before) and after initial treatment (After).

			Before		
			1st Tertile (n = 13)	2nd Tertile (n = 13)	3rd Tertile (n = 13)
After	1st	Tertile (n = 13)	6	4	3
	2nd	Tertile (n = 13)	3	6	4
	3rd	Tertile (n = 13)	4	3	6

$P = 0.520$, by Chi-square test.

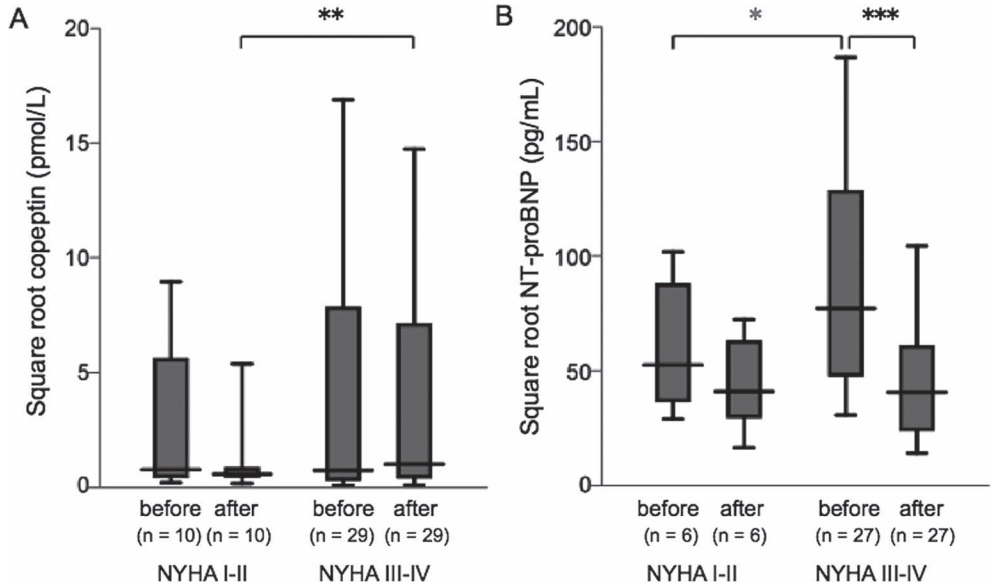

Fig. 4. Copeptin and NT-proBNP in NYHA stratification.
Changes in copeptin (A) and NT-proBNP (B) after initial treatment (after) in patients with heart failure, stratified according to the New York Heart Association (NYHA) functional classes. Before: before initial treatment; *$P < 0.05$, **$P < 0.01$, *** $P < 0.001$.

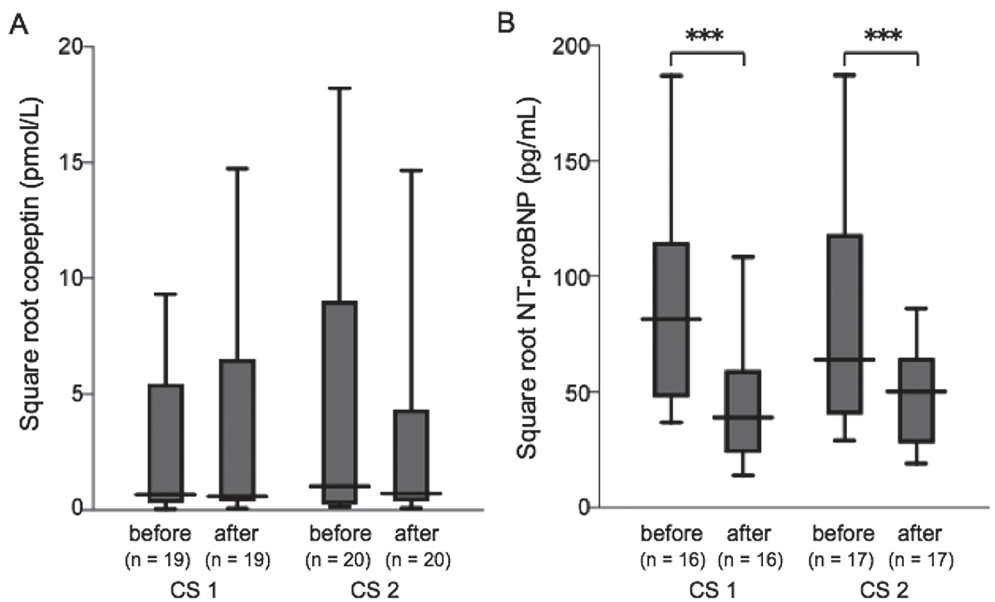

Fig. 5. Copeptin and NT-proBNP in Clinical Scenario stratifiction.
Changes in copeptin (A) and NT-proBNP (B) after initial treatment (after) in patients with heart failure, stratified according to the Clinical Scenario (CS) criteria. Before: before initial treatment; *** $P < 0.001$.

The initial treatment for worsening HF did not change copeptin levels in either group. Finally, the levels of copeptin on admission were similar in patients with different diastolic LV dysfunctions, as determined by E/e′ (n = 32).

Univariate and multivariate analyses

Linear regression analysis revealed that copeptin levels on admission were loosely correlated with NT-proBNP levels ($P = 0.023$) (Fig. 6). The net copeptin and NT-proBNP values before and after initial treatment were also correlated ($P = 0.013$) (Fig. 6). In multivariate regression analysis, copeptin was associated with NT-proBNP levels using total protein and potassium as covariables ($r = 0.495$, $P = 0.012$). Among patients in the highest tertile according to admission copeptin levels, serum creatinine was strongly associated with copeptin using age, EF, and NT-proBNP as covariables ($r = 0.931$, $P = 0.001$).

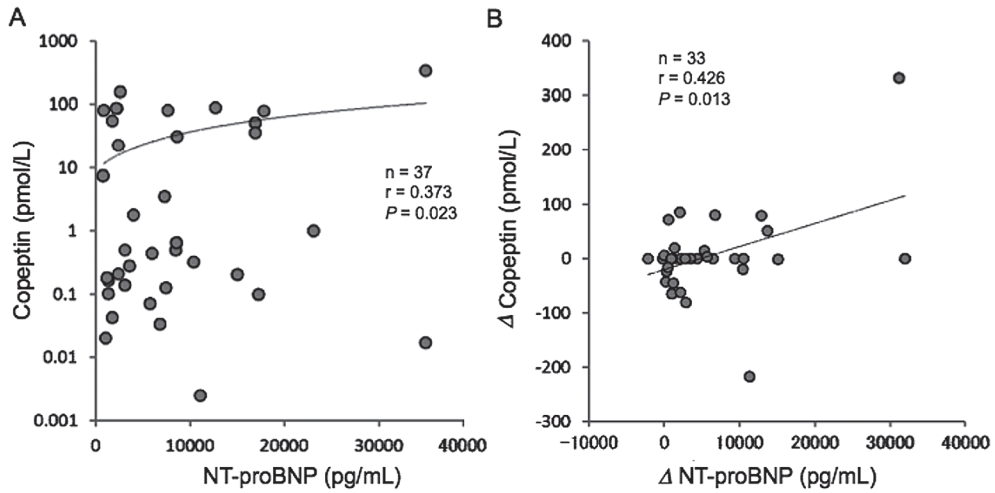

Fig. 6. Correlation between copeptin and NT-proBNP.
Correlation between copeptin and NT-proBNP levels on admission (A) and correlation between changes in copeptin and NT-proBNP during initial treatment (B) in patients admitted for heart failure.

Discussion

Our findings clearly demonstrated that overall copeptin levels on admission were elevated above the expected physiological range and that changes in copeptin levels in response to initial therapy positively correlated with those observed in NT-proBNP levels upon treatment. Further, multiple regression analysis showed NT-proBNP as an independent predictor of plasma copeptin level. These findings lend further support to previous studies suggesting AVP and copeptin as neurohormonal markers for HF (Schrier and Abraham 1999; Neuhold et al. 2008; Alehagen et al. 2011; Maisel et al. 2011), similar to BNP and NT-proBNP. Copeptin is simultaneously released with AVP from the neurohypophysis in response to osmotic as well as nonosmotic stimuli. Morgenthaler et al. (2006) reported that copeptin values in healthy subjects were below 13.8 pmol/L, whereas Neuhold et al. (2008) showed that plasma copeptin levels were strongly and independently correlated with all-cause mortality in a 24-month follow-up study of patients with HF. Specifically, they showed that the mortality rate in patients with copeptin values higher than 21.7 pmol/L was above 50% and with copeptin values less than 5.75 pmol/L, less than 12%. Furthermore, Voors et al. (2009) demonstrated that copeptin levels higher than 25.9 pmol/L was associated with increased mortality of approximately 40% during the follow-up of 33 ± 7 months in patients with HF after acute myocardial infarction. These risk-associated copeptin values were observed in the highest tertile of patients categorized according to copeptin levels on admission in the present study. Although copeptin is biologically inactive, elevated AVP can accelerate cardiac dysfunction through increased water retention via V_2 receptors in the kidney and arteriolar vasoconstriction via V_{1a} receptors in the vascular smooth muscle cells (Share 1988; Torres 2015). Furthermore, AVP is suggested to be involved in the progression of LV dysfunction by aggravating wall stress, stimulating ventricular hypertrophy, and myocardial remodeling (Fukuzawa et al. 1999; Fan et al. 2007). These roles of AVP may be reflected in the increased copeptin levels that were observed in clinically worse patients in the present cohort.

Our results clearly demonstrated that in patients with HF, copeptin secretion was induced by nonosmotic stimuli as there was no association between copeptin and serum sodium/osmolality levels on admission in patients with HF. The activation of carotid baroreceptors during HF has been implicated in nonosmotic AVP release during arterial underfilling (Schrier and Abraham 1999). In addition, angiotensin II, as a potent stimulant of AVP, may also play a partial role in nonosmotic AVP release (Shoji et al. 1986); it was increased in most patients with HF (Schrier and Abraham 1999). Moreover, inflammatory cytokines, such as interleukin 1, were reported to stimulate AVP release (Yamamoto et al. 1994; Szczepanska-Sadowska et al. 2010), and AVP is a well-known stress-sensitive hormone (Katan and Christ-Crain 2010). Renal impairment was also reported to correlate with plasma copeptin levels (Balling and Gustafsson 2014); similarly, we observed renal impairment in patients in the highest copeptin tertile in the current study. Conversely, several inhibitory mechanisms exist to control AVP secretion. First, an increase in arterial pressure is expected to trigger the Henry-Gauer atrial reflex, leading to AVP suppression (Schrier and Abraham 1999). Indeed, the management of acute HF depends on the increase in systolic blood pressure to over 140 mmHg, as observed in CS1 patients. Second, glucocorticoids (Shoji et al. 1999; Katan and Christ-Crain 2010) and BNP (Miller et al. 2009) were also reported to suppress AVP secretion. These complicated mechanisms of AVP and copeptin secretion might at least partially reflect the variations in copeptin levels found in patients stratified according to the NYHA and CS criteria

and the LV function such as EF and E/e' in the present study. Thus, overall, our results suggested that increased copeptin levels in patients with HF in our study resulted from overriding inhibitory signals triggered by nonosmotic stimulation.

Copeptin response to treatment in patients with HF has been less clear (Yandle and Troughton 2010). In the current study, response of plasma copeptin to initial treatment varied depending on copeptin levels on admission. Namely, copeptin levels decreased after initial treatment in patients in the highest copeptin tertile, but increased in the lowest tertile. These results suggested that stimulatory input was dominant for copeptin release in the highest tertile and inhibitory input in the lowest tertile on admission. Further, initial treatment was likely to restore copeptin levels, suggesting that plasma copeptin levels might be negatively regulated in the lowest tertile. The differential integration of stimulatory and inhibitory inputs to AVP/copeptin secretory system could impact individual copeptin responses.

The copeptin level in the lowest tertile was indistinguishable from healthy subjects. Clinical severity and cardiac function on admission were not different between the highest and lowest tertiles. Therefore, it does not necessarily follow that a patient is free from HF just because he/she happens to have low plasma copeptin levels.

Compared with copeptin, our patient cohort presented a less complicated profile of NT-proBNP response. On admission, NT-proBNP level was increased more in the NYHA class III-IV patients than in the NYHA class I-II patients. Furthermore, initial treatment led to significant decreases in NT-proBNP levels in the NYHA class III-IV patients. These results were in strong agreement with a previous study which demonstrated that NT-proBNP was an excellent indicator of clinical severity and improvement in HF (Troughton et al. 2014). The increase in LV end-diastolic pressure is a dominant stimulant of BNP and NT-proBNP release (Braunwald 2008). In addition, BNP levels were shown to be strongly correlated with pulmonary capillary wedge pressure (Nakamura et al. 2006). Distinct control of copeptin and NT-proBNP secretion could have potentially contributed to their additive effect on risk stratification. Indeed, Khan et al. (2007) reported that NT-proBNP and copeptin showed similar accuracy in predicting death or HF in acute myocardial infarction; however, this combination in a multimarker risk stratification approach provided greater predictive accuracy.

One additional finding in our study was the intertertile changes of patients following treatment. Two-thirds of the patients remained within the same tertile after patients were divided with corresponding NT-proBNP values. In contrast, dynamic changes were found across copeptin tertiles. These results suggest that copeptin levels might be more variable than NT-proBNP.

Our study was a small-scale, prospective, single-center study including older Japanese patients; thus, the results could not be directly extended to larger and younger populations or to other ethnic groups. In addition, Swan-Ganz catheterization was not performed in this study; therefore, we were not able to directly assess the hemodynamic status of patients. Finally, we limited copeptin measurements to two times, one at the start and the other after 7 days, which may have led to failure to more comprehensively detect changes in copeptin levels.

In conclusion, we confirmed high levels of plasma copeptin in overall patients with HF and further found differential responses of plasma copeptin levels to initial treatment depending on copeptin level on admission. These results have further confirmed that HF is a complex clinical syndrome with great variations in etiology and pathophysiology.

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Conflict of Interest

The authors declare no conflict of interest.

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