ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 4077–4087
Published online 31 August 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14083

ORIGINAL ARTICLE

Neuroendocrine hormone status and diuretic response to atrial natriuretic peptide in patients with acute heart failure

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Abstract

Aims Given the various effects of sacubitril/valsartan in heart failure, a deeper understanding of atrial natriuretic peptide (ANP) actions is warranted. Natriuresis is a fundamental action of ANP in acute heart failure (AHF), whereas the diuretic effect of ANP is different in each patient according to the diversity of renal response to ANP, which is affected by baseline plasma ANP status and deficiency of circulating ANP. Meanwhile, associations between other neuroendocrine hormones and the diuretic response to ANP are unclear. This study investigated the impact of pivotal neuroendocrine hormones on the diuretic effects of exogenous ANP, carperitide.

Methods and results Plasma ANP, renin, aldosterone, and vasopressin levels and the diuretic effect of 0.0125 μg/kg/min of carperitide alone for the first 6 h were prospectively evaluated in 75 patients with AHF. Lower ANP levels were significantly associated with a greater diuretic response to exogenous ANP ($r = -0.35$, $P = 0.002$). Additionally, higher vasopressin levels were significantly related to the poor diuretic effects of exogenous ANP ($r = -0.54$, $P < 0.001$). Plasma ANP and vasopressin concentrations were not significantly correlated ($r = 0.19$, $P = 0.10$). Baseline systolic blood pressure, renal function, and prior use of loop diuretics did not predict the diuretic response to exogenous ANP, whereas vasopressin levels independently predicted a diuretic response to exogenous ANP ($P < 0.001$), as well as lower plasma ANP levels ($P = 0.027$).

Conclusions Vasopressin status was significantly associated with the diuretic response to exogenous ANP in AHF, independent of plasma ANP status. The results may provide a better understanding of the actions of sacubitril/valsartan.

Keywords Atrial natriuretic peptide; Acute heart failure; Vasopressin; Plasma osmolality; Carperitide

Received: 24 February 2022; Revised: 26 June 2022; Accepted: 18 July 2022
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Introduction

Sacubitril/valsartan inhibits neprilysin, which is a key degrading enzyme *in vivo* that modulates plasma peptide concentrations and increases natriuretic peptide levels.[1–3] Because neprilysin plays a significant role in the degradation of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), ANP would primarily contribute to the efficacy of sacubitril/valsartan.[1,4] The specific treatment for heart failure (HF), through the benefits of ANP, improves clinical outcomes in patients with heart failure with reduced ejection fraction (HFrEF),[1] although the clinical benefits of sacubitril/valsartan are not consistent with those of all patients with HF.[2,5] Particularly in heart failure with preserved ejection fraction (HFpEF), a subtype of HF influences the benefits of sacubitril/valsartan.[6,7] Therefore, given the various effects of sacubitril/valsartan in HF, a deeper understanding of ANP actions is warranted.

Natriuresis of ANP improves HF, whereas patients with HF have renal resistance to natriuretic peptide, and the diuretic effect of ANP is widely different in each patient.[8] The overall mechanisms of renal resistance to ANP remain unclear, although we recently reported that the diuretic effect of exogenous ANP in acute heart failure (AHF) is strongly determined by baseline plasma ANP status.[9] Administration of exogenous ANP in patients with lower circulating ANP levels achieves greater diuretic response in AHF; that is, supplemental administration of exogenous ANP in patients with relative deficiency of plasma ANP would be a logical therapeutic option.[4,9] This result suggests that the efficacy of ANP is affected by baseline neuroendocrine hormone status and, therefore, other neurohormonal backgrounds may contribute to the diversity of ANP effects in HF. Numerous previous studies have demonstrated that increased plasma levels of pivotal neuroendocrine hormones, such as renin, aldosterone, and arginine vasopressin, play a key role in the exacerbation of HF.[10–12] However, associations between the efficacy of ANP, represented by natriuresis, and other neurohormonal backgrounds are still unclear. Further comprehension of physiological ANP actions may lead to a better understanding of the underlying mechanisms regarding the non-consistent clinical impacts of sacubitril/valsartan in each subtype of HF.[1,2]

In this study, we aimed to investigate the association between the diuretic effect of exogenous ANP and baseline characteristics of plasma neuroendocrine hormone status in patients with AHF.

Materials and methods

Ethical statement

The investigation conformed to the principles outlined in the Declaration of Helsinki. The protocol was approved by the ethics committee conformed by the Japanese Clinical Trial Act (No. CRB3180027), and all enrolled patients were provided written informed consent. Furthermore, this registry was registered by the University Hospital Medical Information Network Clinical Trial Registry, as accepted by the International Committee of Medical Journal (UMIN-ID: 000028689).

Study design and population

This study was a post hoc analysis of the database of the Beneficial Efficacy of Carperitide in Patients with Acute Decompensated Heart Failure (BEYOND) registry, which is a prospective multicentre study that evaluated the efficacy of exogenous ANP in patients with AHF.[9] To assess the relationship between the baseline concentration of plasma ANP and the first diuretic effect of exogenous ANP, plasma ANP levels before the administration of carperitide (Daiichi-Sankyo Company, Japan) and cumulative amount of urine over the first 6 h after carperitide administration were measured in all patients. The diagnosis of AHF was made based on the guidelines of the American College of Cardiology/American Heart Association.[13] Hospitalized patients according to limitation of physical activity or any worsening symptoms caused by HF were included (Stages C and D). Exclusion criteria were as follows: (i) age $<$ 20 years; (ii) occurrence of cardiogenic shock (systolic blood pressure was $<$90 mmHg); (iii) usage of catecholamines; (iv) usage of cardiac support devices; (v) dialysis; (vi) presence of acute coronary syndrome; (vii) dehydration; (viii) an allergic response to or allergies to carperitide; and (ix) pregnancy.

Of the 162 patients enrolled in the BEYOND registry, 113 patients with AHF received only 0.0125 μg/kg/min of continuous carperitide during the first 6 h. During this period, no other diuretics were concomitantly used and the dose of carperitide was not changed. Among the 113 patients, 38 patients without measurements of renin, aldosterone, and arginine vasopressin on admission were excluded. Thus, 75 patients with AHF treated with only 0.0125 μg/kg/min of continuous carperitide were analysed. In all the 75 patients, baseline concentrations of ANP, BNP, renin, aldosterone, and arginine vasopressin were measured before the administration of carperitide. Subsequent treatment after the first 6 h was determined by the respective cardiologist in accordance with the optimal treatments recommended by the guidelines for HF.[14,15]

To assess baseline neurohormonal status behind the various diuretic effects of ANP, patients were divided into three groups based on the tertile of urine volume during the first 6 h. Baseline clinical characteristics, including plasma concentrations of ANP, BNP, renin, aldosterone, and arginine vasopressin, were evaluated in each group.

Clinical assessment

To quantify baseline plasma osmolality states, plasma osmolality was estimated as [2 × sodium (mmol/L) + glucose (mg/dL)/18 + blood urea nitrogen (mg/dL)/2.8], and the normal range was defined as being between 285 and 295 mOsm/kg.[16]

Biomarker measurements

Baseline blood samples on admission were collected from a vein before administration of carperitide. To measure ANP levels, samples were collected in tubes containing ethylenediaminetetraacetic acid and protease inhibitor aprotinin. Samples for measurement of BNP, renin, aldosterone, and

arginine vasopressin were collected in tubes containing ethylenediaminetetraacetic acid.

The plasma was separated by centrifugation at 2500 revolutions per minute (rpm), over 1500 × g, for 10 min and stored at −80°C until measurement. Samples of ANP, renin, aldosterone, and arginine vasopressin from all participating hospitals were sent to Special Reference Laboratory (SRL) Company (Japan) for the measurement. BNP levels were evaluated at each hospital. The ANP concentration was determined using a highly sensitive chemiluminescent enzyme immunoassay. The BNP, renin, and aldosterone concentrations were measured using a chemiluminescent enzyme immunoassay, and arginine vasopressin concentration was measured using radioimmunoassay. These measurements were performed using the same kind of assay for all the 75 patients.

Statistical analysis

All data are described as the presenting frequency, percentages for categorical variables, and the median value with interquartile range (Quartiles 1–3) for continuous variables. To evaluate statistical significance in the comparison of each group, Fisher's exact test was used to evaluate categorical variables, and the Mann–Whitney *U* test, the Kruskal–Wallis test, and the one-way ANOVA test were used for continuous variables. In the valuables when P value < 0.10 determined by the Fisher exact or Kruskal–Wallis tests, the Cochran–Armitage trend test for categorical variables and the Jonckheere–Terpstra trend test for continuous variables were used. The rank-order correlation of two variables was analysed using Spearman's correlation test.

Baseline patient characteristics were evaluated in the three groups based on the tertile of the diuretic response to exogenous ANP during the first 6 h. In the further analysis, to evaluate the impact of baseline neuroendocrine hormone status, patient characteristics based on the tertile of baseline plasma ANP concentrations and the tertile of plasma arginine vasopressin concentrations were evaluated. Baseline arginine vasopressin levels according to the tertiles of the diuretic effects of ANP were evaluated only in patients without tolvaptan, which is a selective V2 antagonist that increases arginine vasopressin levels in HF.[17] Log-transformed ANP and arginine vasopressin were used in the rank-order correlation and multiple regression analyses. Univariate analyses predicting the diuretic effect of exogenous ANP were performed. The impacts of arginine vasopressin levels were evaluated using multivariable analysis models adjusting for systolic blood pressure, renal function, prior use of loop diuretics, ANP levels, HFpEF, and atrial fibrillation, which are independent predictors of the diuretic effects in patients with AHF.[9,18] All analyses were performed using Stata statistical software (Version 17; StataCorp LLC, Texas, USA), and the statistically significant level was set at 5%.

Results

Patient characteristics by diuretic response to exogenous atrial natriuretic peptide

Table 1 presents the baseline patient characteristics according to the tertile of the diuretic response to exogenous ANP: ≤380 mL/6 h (Tertile 1, $N = 24$), 390–870 mL/6 h (Tertile 2, $N = 26$), and ≥890 mL/6 h (Tertile 3, $N = 25$). Overall, the median total urine volume during the first 6 h was 520 mL. Patient characteristics were not significantly different among the tertiles of the diuretic response to exogenous ANP, although patients with higher diuretic response (Tertile 3) had a higher rate of atrial fibrillation (Tertile 1 vs. Tertile 2 vs. Tertile 3: 16.7% vs. 42.3% vs. 76.0%, $P < 0.001$) (*Table 1*). Prior medications, including diuretics, were not associated with the diuretic response to exogenous ANP.

Table 2 shows the laboratory and echocardiographic findings of the tertile of the diuretic response to exogenous ANP. The baseline haemoglobin and haematocrit levels were significantly lower in patients with a higher diuretic response (Tertile 3). Baseline renal function and plasma osmolality were comparable between the three groups, whereas urinary osmolality was significantly lower in Tertile 3.

In the echocardiographic findings, a higher left ventricular ejection fraction (LVEF), a higher rate of HFpEF, and larger left and right atrial volumes were significantly associated with better diuretic response to exogenous ANP (*Table 2*).

Neuroendocrine hormone status and the diuretic response to exogenous atrial natriuretic peptide

Baseline plasma ANP, BNP, renin, renin activity, aldosterone, and arginine vasopressin status according to the diuretic response to exogenous ANP were evaluated (*Figure 1*). Among the pivotal neuroendocrine hormones, renin, renin activity, and aldosterone levels were not associated with the diuretic response to exogenous ANP. Otherwise, baseline ANP and arginine vasopressin levels were significantly different between the tertiles of the diuretic response to exogenous ANP (*Figure 1A* and *1F*). Lower baseline ANP values were significantly associated with a higher diuretic response to exogenous ANP (*Figure 1A*). Additionally, baseline arginine vasopressin concentrations were significantly different between the tertiles; patients with poor diuretic response had higher baseline vasopressin levels on admission (*Figure 1F*). In the further analysis focusing on patients without the use of tolvaptan ($N = 66$), similar associations between baseline vasopressin levels and the diuretic response to exogenous ANP were observed (Supporting Information, *Figure S1*, $P < 0.001$). Supporting Information, *Figure S2* shows correlations between the diuretic effect of exogenous ANP and (A) plasma

Table 1 Baseline patient characteristics by diuretic response of atrial natriuretic peptide

	Diuretic response during the first 6 h				
	Tertile 1 (N = 24) ≤380 mL/6 h	Tertile 2 (N = 26) 390–870 mL/6 h	Tertile 3 (N = 25) ≥890 mL/6 h	P value	P value for trend[a]
Age (years)	74.9 ± 12.9	72.9 ± 12.6	75.6 ± 11.3	0.72	—
Male	15 (62.5%)	18 (69.2%)	14 (56.0%)	0.66	—
BMI (kg/m^2)	23.2 ± 4.7	24.4 ± 5.6	25.4 ± 5.1	0.33	—
HF hospitalization	9 (37.5%)	13 (50.0%)	10 (40.0%)	0.67	—
Medical history					
Hypertension	18 (75.0%)	13 (50.0%)	20 (80.0%)	0.05	0.69
Diabetes mellitus	11 (45.8%)	12 (46.2%)	18 (72.0%)	0.32	—
Dyslipidaemia	11 (45.8%)	5 (19.2%)	6 (24.0%)	0.10	—
Atrial fibrillation	4 (16.7%)	11 (42.3%)	19 (76.0%)	<0.001	<0.001
Chronic lung disease	1 (4.2%)	5 (19.2%)	3 (12.0%)	0.31	—
Medication					
ACEI/ARB	12 (50.0%)	12 (46.2%)	16 (64.0%)	0.44	—
Beta-blocker	10 (41.7%)	14 (53.8%)	15 (60.0%)	0.42	—
MRA	4 (16.7%)	8 (30.8%)	6 (24.0%)	0.56	—
Loop diuretics	7 (29.2%)	15 (57.7%)	13 (52.0%)	0.11	—
Tolvaptan	2 (8.3%)	4 (15.4%)	3 (12.0%)	0.90	—
Ca-blocker	7 (29.2%)	5 (19.2%)	14 (44.0%)	0.17	—
Baseline physical examination					
NYHA III or IV	24 (100%)	25 (96.2%)	24 (96.0%)	0.99	—
Orthopnea	18 (75.0%)	15 (57.7%)	19 (76.0%)	0.31	—
JVD	19 (79.2%)	22 (84.6%)	20 (80.0%)	0.87	—
Coarse crackles	16 (66.7%)	17 (65.4%)	20 (80.0%)	0.46	—
S3 gallop	20 (83.3%)	15 (57.7%)	18 (72.0%)	0.15	—
Oedema	21 (87.5%)	22 (84.6%)	25 (100%)	0.13	—
Heart rate	95 ± 24	90 ± 25	84 ± 18	0.20	—
Systolic BP	159 ± 31	144 ± 36	144 ± 22	0.16	—
Diastolic BP	90 ± 21	87 ± 22	77 ± 17	0.06	0.03

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; Ca, calcium; HF, heart failure; JVD, juggler vein distension; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association functional classification.
[a]The Cochran–Armitage trend test for categorical variables and the Jonckheere–Terpstra trend test for continuous variables.

renin concentrations, (B) plasma renin activity, and (C) plasma aldosterone concentrations. In this further analysis, baseline renin concentration, renin activity, and aldosterone concentration did not have significant relationship with the diuretic effect of exogenous ANP.

Figure 2 shows that baseline ANP levels had weak correlation with the total urine volume at 6 h after the administration of exogenous ANP (r = −0.35, P = 0.002). In addition, there was moderate correlation between arginine vasopressin levels and total urine volume during the first 6 h (r = −0.54, $P < 0.001$) (*Figure 2*). In the further analysis focusing on only patients without tolvaptan (N = 66), there were similar trends that baseline ANP and vasopressin concentrations were significantly correlated with the diuretic effects of exogenous ANP (ANP: r = −0.44, $P < 0.001$ and vasopressin: r = −0.54, $P < 0.001$) (Supporting Information, *Figure S3*).

Univariate analyses suggested that lower arginine vasopressin concentrations, lower ANP concentrations, and the presence of HFpEF and atrial fibrillation predicted greater diuretic response to exogenous ANP. Otherwise, baseline systolic blood pressure, renal function, and prior use of loop diuretics did not predict the diuretic response to ANP (*Table 3A* and *3B*). In a multivariable analysis models adjusting for the clinical confounding factors, lower arginine vasopressin levels independently predicted a greater diuretic response to exogenous ANP (*Table 3A* and *3B*). Lower ANP concentrations, HFpEF, and atrial fibrillation were also independent predictors of a better response to ANP (ANP: P = 0.029, HFpEF: P = 0.019, and atrial fibrillation: P = 0.008) (*Table 3B*), despite systolic blood pressure, renal function, and loop diuretic use were not (*Table 3A*).

Patient characteristics by the baseline atrial natriuretic peptide and arginine vasopressin levels

Baseline neuroendocrine hormone statuses and clinical characteristics based on the tertile of the ANP and arginine vasopressin concentrations are summarized in *Figure 3* and Supporting Information, *Table S1A* and *S1B*. Lower baseline ANP concentrations (ANP: 47–214 pg/mL, N = 25) were significantly associated with a higher value of LVEF (*Figure 3A*) and a higher rate of HFpEF (tertile of ANP, 47–214 pg/mL vs. 219–367 pg/mL vs. 387–963 pg/mL: 60.0% vs. 40.0% vs. 12.5%, P = 0.002) (Supporting Information, *Table S1A*). Baseline neuroendocrine hormone status, without BNP, was not related to baseline ANP levels (Supporting Information, *Table S1A*). In

Table 2 Examination findings by diuretic response of atrial natriuretic peptide

	Diuretic response during the first 6 h				
	Tertile 1 (N = 24) ≤380 mL/6 h	Tertile 2 (N = 26) 390–870 mL/6 h	Tertile 3 (N = 25) ≥890 mL/6 h	P value	P value for trend[a]
Baseline laboratory findings					
Haemoglobin (g/dL)	12.9 (10.2–13.9)	12.6 (10.3–14.2)	11.2 (9.2–12.0)	0.044	0.03
Haematocrit (%)	39.7 (32.8–42.7)	37.0 (32.8–43.7)	33.9 (28.9–37.2)	0.046	0.03
Albumin (g/dL)	3.6 (3.2–3.8)	3.4 (3.1–3.7)	3.3 (3.1–3.7)	0.35	—
Na (mEq/L)	143 (139–145)	142 (138–145)	143 (140–144)	0.76	—
eGFR (mL/min/1.73 m^2)	47.4 (25.4–59.5)	39.8 (31.3–60.9)	45.7 (30.9–59.5)	0.89	—
BUN (mg/dL)	24 (19–34)	21 (17–34)	18 (14–25)	0.13	—
Glucose (mg/dL)	129 (115–168)	129 (106–142)	119 (99–139)	0.19	—
Plasma osmolality (mOsm/kg)	302 (296–307)	299 (293–302)	299 (294–302)	0.32	—
Baseline urinary findings					
U-Na (mEq/L)	82 (53–132)	95 (73–129)	88 (71–127)	0.72	—
U-Cl (mEq/L)	79 (42–109)	92 (70–122)	77 (58–109)	0.42	—
U-osmolality (mOsm/kg)	508 (398–701)	423 (348–612)	390 (308–505)	0.08	0.03
Echocardiographic findings					
LVDd (mm)	54.4 ± 9.9	55.3 ± 12.2	54.2 ± 11.9	0.94	—
LVEF (%)	40.7 ± 13.6	44.6 ± 19.4	52.3 ± 13.2	0.04	0.03
HF subtype				0.008	—
HFrEF	15 (62.5%)	13 (52.0%)	5 (20.0%)	0.008	0.003
HFmrEF	6 (25.0%)	3 (12.0%)	7 (28.0%)	0.32	—
HFpEF	3 (12.5%)	9 (36.0%)	13 (52.0%)	0.01	0.005
LAD (mm)	38.8 ± 9.9	44.4 ± 9.9	44.6 ± 7.8	0.049	0.06
LAV (mL)	69.3 ± 26.7	104.2 ± 89.6	100.6 ± 41.2	0.09	0.008
LAVI (mL/m^2)	43.8 ± 16.3	62.6 ± 53.9	60.8 ± 23.0	0.13	0.02
RAV (mL) (N = 73)	42.4 ± 25.2	54.4 ± 29.5	69.0 ± 51.8	0.05	0.01
RAVI (mL/m^2)	26.9 ± 16.2	33.2 ± 18.9	41.6 ± 29.7	0.08	0.02

BUN, blood urea nitrogen; Cl, chloride; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAD, left atrial diameter; LAV, left atrial volume; LAVI, left atrial volume index; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; Na, sodium; RAV, right atrial volume; RAVI, right atrial volume index; U, urinary.
[a]The Cochran–Armitage trend test for categorical variables and the Jonckheere–Terpstra trend test for continuous variables.

contrast to left ventricular status, left and right atrial volume indices were not associated with baseline ANP levels, as with atrial fibrillation status.

In the analysis based on arginine vasopressin concentrations, baseline arginine vasopressin levels were not associated with LVEF status (*Figure 3B*). Otherwise, patients with higher arginine vasopressin levels had significantly higher plasma osmolality (tertile of arginine vasopressin, 0.4–2.0 pg/mL vs. 2.1–5.7 pg/mL vs. 5.8–61 pg/mL: 294 [292–300] mOsm/kg vs. 300 [296–307] mOsm/kg vs. 301 [298–308] mOsm/kg, P = 0.02) (*Figure 3D*). Additionally, the low arginine vasopressin group showed a statistical trend towards lower urinary osmolality (352 [306–525] mOsm/kg vs. 419 [341–695] mOsm/kg vs. 494 [389–646] mOsm/kg, P = 0.07; P for trend = 0.03) (*Figure 3F* and Supporting Information, *Table S1B*). Of the neuroendocrine hormones, renin activity was associated with baseline arginine vasopressin status (Supporting Information, *Table S1B*).

Supporting Information, *Figure S4* demonstrates the relationship between baseline plasma ANP levels and plasma arginine vasopressin levels. There were no statistically significant correlations between ANP and arginine vasopressin concentrations (r = 0.19, P = 0.10).

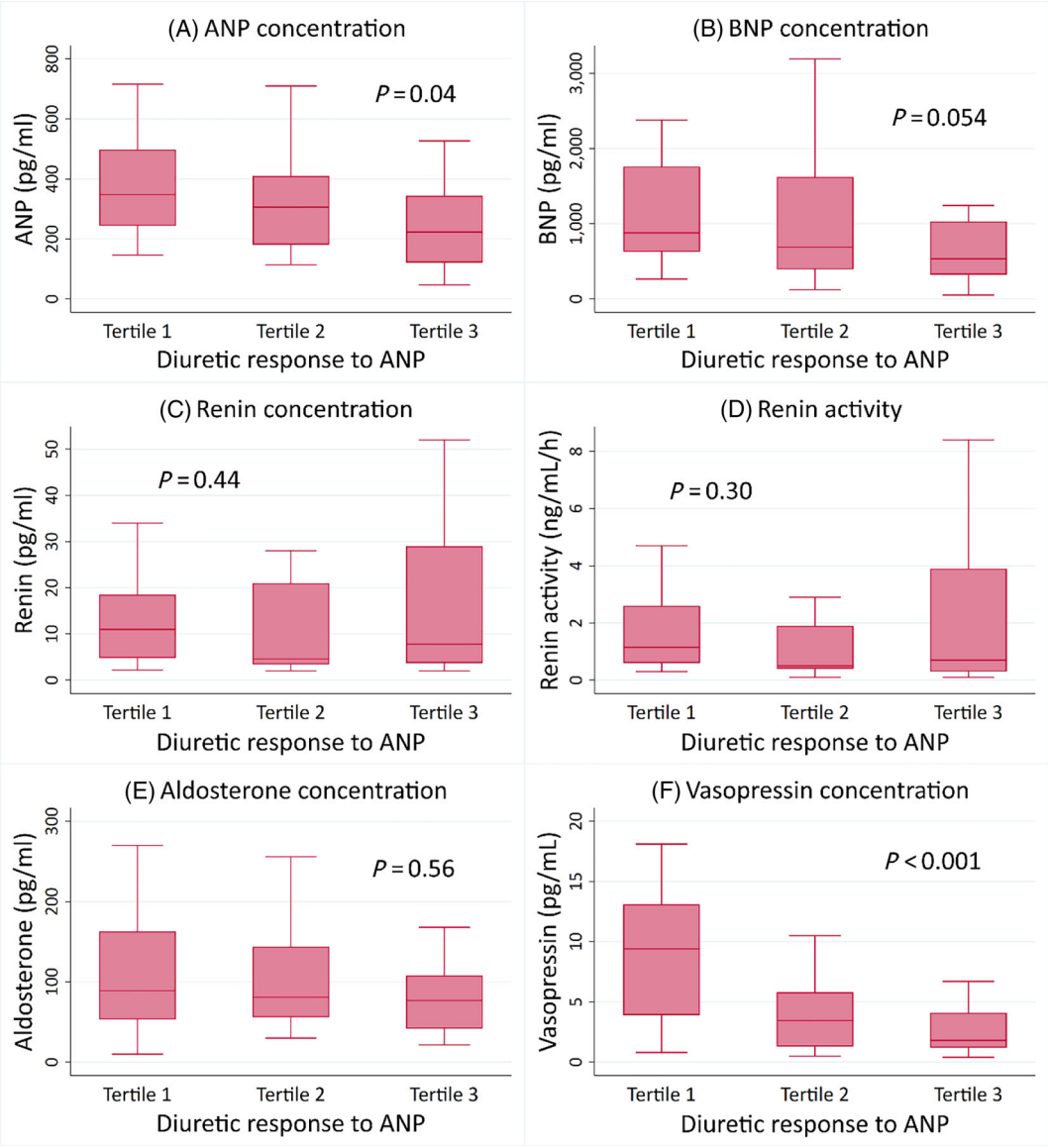
Discussion

This was the first study, to the best of our knowledge, to investigate the association between the pure efficacy of exogenous ANP and baseline neurohormonal status, including renin, renin activity, aldosterone, and arginine vasopressin in patients with AHF. In addition to lower ANP levels, higher baseline arginine vasopressin concentrations were independently associated with poor diuretic response to exogenous ANP. Given the no significant correlation between baseline ANP and arginine vasopressin levels and the results of multivariable analysis models, arginine vasopressin may independently play a key role regarding the diuretic resistance to ANP in patients with AHF.

Baseline atrial natriuretic peptide status and the diuretic response to atrial natriuretic peptide

Few previous studies have demonstrated the pure diuretic efficacy of exogenous ANP (or BNP) in AHF. Consistent with our recent report,[9] baseline plasma ANP levels independently

Figure 1 Baseline neuroendocrine hormone status by diuretic response to exogenous ANP: (A) ANP, (B) BNP, (C) renin, (D) renin activity, (E) aldosterone, and (F) arginine vasopressin.

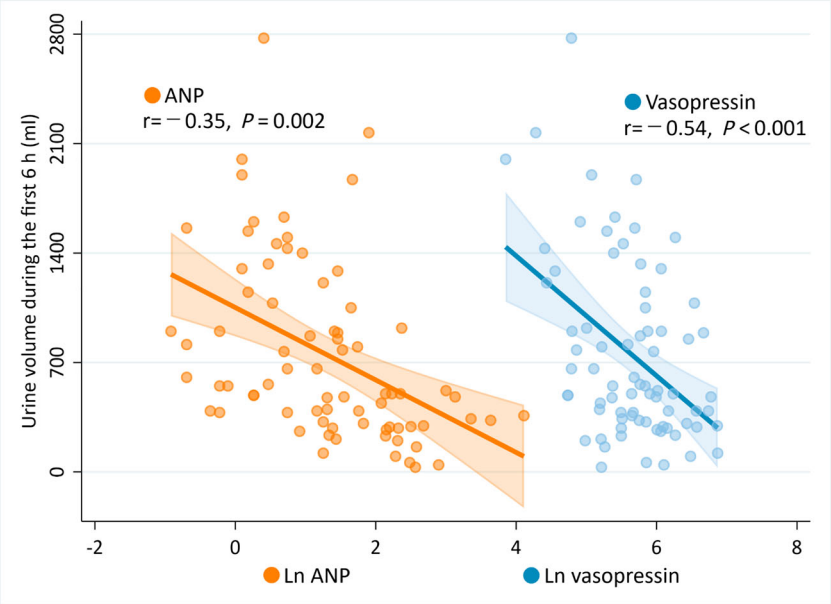


vasopressin

Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide

predicted the diuretic response to exogenous ANP. This finding supports the recent emerging paradigm that ANP deficiency is a useful therapeutic target for ANP replacement therapy in HF,[19–21] similar to hormonal deficiency in other organs. The diuretic response or resistance to diuretics in the setting of AHF is mainly determined by renal function, blood pressure, and prior use of diuretics,[18,22] although these factors were not associated with a higher diuretic response to exogenous ANP. A unique mechanism of ANP leading to natriuresis is an increase in renal blood flow through vasodilation of the afferent arteriole in the kidney, which is a specific effect of ANP distinguished from other diuretic drugs.[23] The renal hyporesponsiveness of ANP is mainly determined by the down-regulation of renal natriuretic peptide receptor-A,[8,24] resulting in the particular mechanisms of diuretic response and resistance to ANP, unlike other diuretics, which only contribute to the inhibition of tubular fluid absorption.

Figure 2 Relationships between baseline plasma ANP levels and diuretic response to exogenous ANP (red, *N* = 75), and baseline plasma arginine vasopressin levels and diuretic response to ANP (blue, *N* = 75).



Abbreviations: ANP, atrial natriuretic peptide

Table 3 Multivariable linear regression analysis models to estimate the impact of arginine vasopressin levels on the diuretic effect of exogenous ANP adjusting for (A) baseline blood pressure, renal function, and loop diuretics use before admission (*N* = 75) and (B) baseline ANP levels, HFpEF, and atrial fibrillation (*N* = 75)

(A)

	Univariate analysis model to predict diuretic effect of exogenous ANP				Multivariable analysis model to predict diuretic effect of ANP				
	Standardized coefficients	Lower 95% CI	Higher 95% CI	*P* value	Standardized coefficients	Lower 95% CI	Higher 95% CI	*P* value	
Ln vasopressin	−232	−340	−123	<0.001	−236	−355	−116	<0.001	1.17
Systolic BP	−1.63	−5.93	2.67	0.45	1.12	−3.42	5.66	0.62	1.11
eGFR	2.62	−3.58	8.82	0.40	0.29	−5.75	6.33	0.92	1.14
Loop diuretics	92.3	−173.9	358.5	0.49	75.5	−203.3	354.3	0.59	

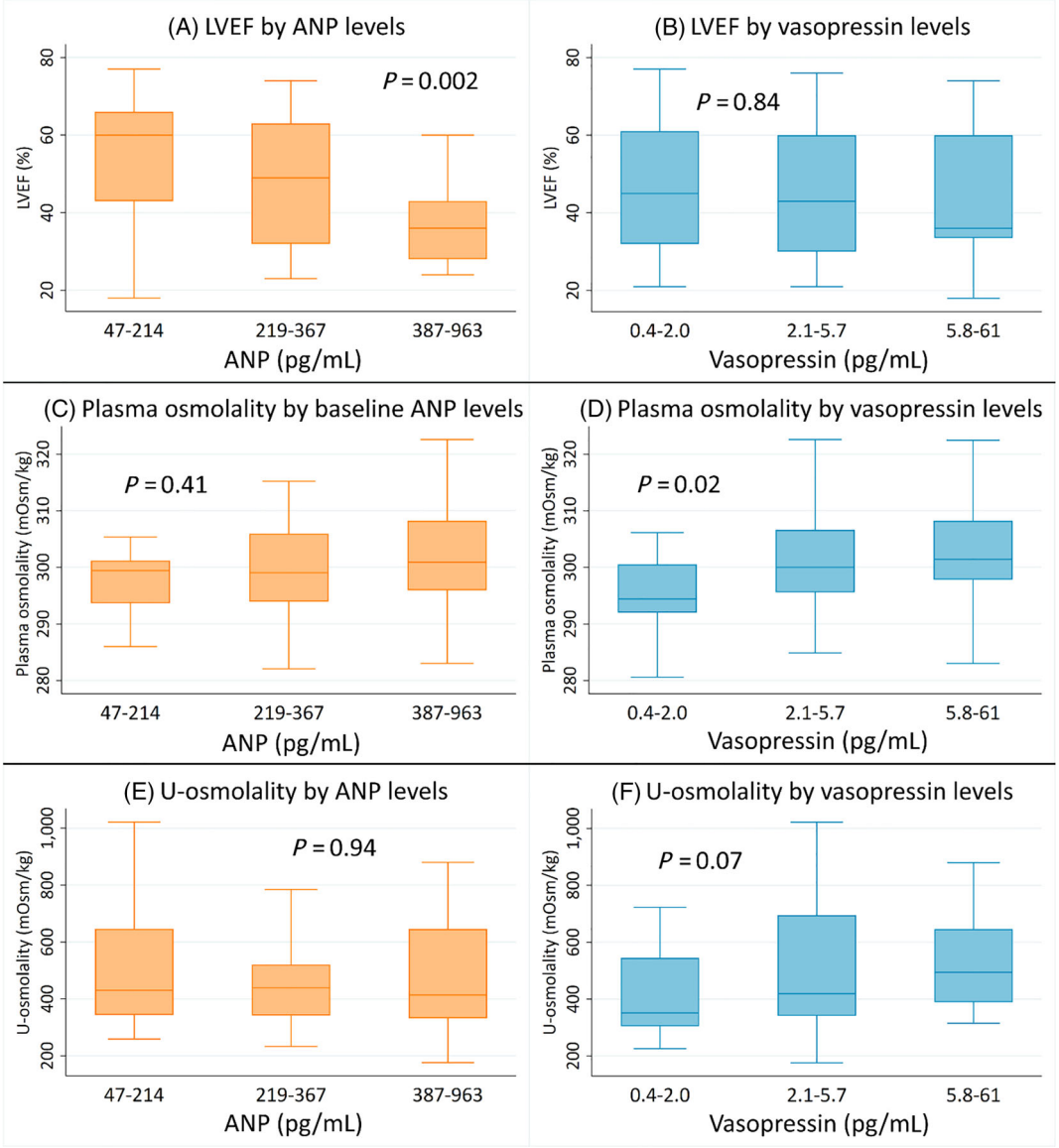
(B)

	Univariate analysis model to predict diuretic effect of exogenous ANP				Multivariable analysis model to predict diuretic effect of ANP			
	Standardized coefficients	Lower 95% CI	Higher 95% CI	*P* value	Standardized coefficients	Lower 95% CI	Higher 95% CI	*P* value
Ln vasopressin	−232	−340	−123	<0.001	−186	−283	−89	<0.001
Ln ANP	−384	−568	−199	<0.001	−196	−373	−20	0.029
HFpEF	481	227	735	<0.001	286	48	524	0.019
Atrial fibrillation	481	238	724	<0.001	293	79	507	0.008

ANP, atrial natriuretic peptide; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction.

DOI: 10.1002/ehf2.14083

Figure 3 LVEF, plasma osmolality, and urinary osmolality by baseline ANP and arginine vasopressin levels (*N* = 75). ANP, atrial natriuretic peptide; LVEF, left ventricular ejection fraction; U, urinary.



Abbreviations: ANP, atrial natriuretic peptide; LVEF, left ventricular ejection fraction; U, urinary

Baseline arginine vasopressin status and the diuretic response to atrial natriuretic peptide

We demonstrated that renin, renin activity, and aldosterone levels were not significantly associated with the diuretic response to ANP. Meanwhile, higher arginine vasopressin concentrations were significantly associated with the poor diuretic response to ANP, and the impact of arginine vasopressin was statistically independent from other clinical confounders including baseline ANP status.

Previous study demonstrated that higher arginine vasopressin levels are associated with lower ANP concentrations in patients with chronic HF, particularly in HFpEF.[25] Otherwise, in this study, which focused on patients with AHF, there were no significant correlations between baseline plasma arginine vasopressin and ANP concentrations. In addition, clear

differences were observed between patient characteristics according to the baseline ANP and arginine vasopressin levels. Given the distinct patient backgrounds behind the baseline ANP and arginine vasopressin statuses and the lack of statistical correlation between ANP and arginine vasopressin levels, ANP and arginine vasopressin levels may clinically have low correlation in patients with AHF.

Among the differences in patient characteristics according to baseline ANP and arginine vasopressin status, it was noteworthy that lower ANP levels were significantly associated with higher LVEF and higher rate of HFpEF, although arginine vasopressin concentrations were not associated with LVEF status. LVEF is significantly associated with the diuretic effect of exogenous ANP in AHF,[9] whereas arginine vasopressin status was not associated with LVEF in this study. Meanwhile, higher plasma arginine vasopressin levels were linked to higher plasma osmolality and were also associated with a trend towards higher urinary osmolality. Furthermore, several factors previously shown to contribute to the diuretic effect in patients with AHF, such as renal function, blood pressure, and prior use of diuretics, were not observed to do so in this study.[18] These findings support that specific triggers independent of ANP regulation may elevate plasma arginine vasopressin concentrations in AHF and that higher arginine vasopressin levels may play an important role in the poor diuretic effects of ANP.

Numerous studies have demonstrated that plasma arginine vasopressin concentrations are elevated in patients with HF due to multifactorial causes and increased regardless of plasma osmolality and sodium concentrations.[10,26–28] Especially in the setting of AHF, which is a state with systemic haemodynamic changes, arginine vasopressin regulation cannot be explained by osmoregulation alone,[29,30] and arginine vasopressin concentrations can be modulated by non-osmotic factors, such as stimulated baroreceptors subsequent to reduced arterial pressure.[29] The dominant regulator of arginine vasopressin secretion is serum osmolality.[10] When plasma osmolality increases over 142 mEq/L of serum sodium, plasma arginine vasopressin concentrations exceed 5.0 pg/mL and urine volume becomes maximally concentrated (1200 mOsm/kg water) according to renal effects on the V_2 receptor in the collecting duct of the nephron.[29] The findings of this study suggested that baseline arginine vasopressin levels were not related to baseline blood pressure and were significantly associated with higher plasma osmolality. Increased secretion of arginine vasopressin might lead to higher urinary osmolality due to water reabsorption in collecting ducts; therefore, increased arginine vasopressin might cause renal hyporesponsiveness to ANP, which is unrelated to the regulation of ANP status. These results suggest that the arginine vasopressin antagonist, tolvaptan, may provide a reasonable effect in patients with hyporesponsiveness to ANP, especially in AHF.

Limitations

Because of the small sample size of this study, the number of patients might be insufficient to fully evaluate the clinical endpoints such as in-hospital death or hypotension during the treatment. Similarly, more patients may be needed to evaluate the clinical impact of patient characteristics on plasma ANP and arginine vasopressin concentrations. The marginal change in haemodynamic status during the first 6 h after the administration of exogenous ANP was not measured; thus, the associations between changes in haemodynamic parameters and the diuretic effect of exogenous ANP could not be estimated. This study did not perform long-term follow-up after discharge; therefore, the effects of ANP and other neuroendocrine hormone statuses on long-term clinical outcomes were unclear. Because the association between baseline ANP and arginine vasopressin levels and the efficacy of exogenous ANP in the setting of AHF were analysed, it remains unclear whether these results can be generalized to stabilized ambulatory patients with chronic HF. In the current study, we did not have the information of dosage of loop diuretics before admission. Therefore, the impact of prior use of loop diuretics was not fully evaluated. This study did not include sufficient sample size of patients with tolvaptan (N = 9), which is a vasopressin V2-receptor antagonist. Thus, we could not focus on particularly the association between the diuretic effect of exogenous ANP and baseline arginine vasopressin status in patients treated with tolvaptan. Further research is warranted to focus on the limitations.

Conclusions

Lower baseline ANP concentrations were significantly associated with a greater diuretic response to exogenous ANP; hence, supplemental administration of exogenous ANP in patients with relative deficiency of circulating ANP would be a beneficial therapeutic strategy in AHF. Higher baseline arginine vasopressin levels were significantly associated with a lack of a diuretic response to exogenous ANP. Arginine vasopressin may be an independent key contributor to the diuretic efficacy of ANP. Further studies to contribute to a better understanding of the clinical effects of ANP in patients with AHF are warranted, which is the underlying mechanism shared with the effect of sacubitril/valsartan.

Acknowledgements

The authors would like to acknowledge financial support from Daiichi-Sankyo.

Conflict of interest

Yuji Ikari has received a research grant from Daiichi-Sankyo, and Takanori Ikeda has received a research grant and remuneration from Daiichi-Sankyo. The other authors have no conflict of interest.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Baseline vasopressin levels according to the tertile of the diuretic response to exogenous ANP in patients without tolvaptan on admission (N = 66). Abbreviations: ANP, atrial natriuretic peptide.

Figure S2-A. Relationships between baseline plasma renin concentrations and the diuretic effect of exogenous ANP (N = 75). Abbreviations: ANP, atrial natriuretic peptide.

Figure S2-B. Relationships between baseline plasma renin activity levels and the diuretic effect of exogenous ANP (N = 75). Abbreviations: ANP, atrial natriuretic peptide.

Figure S2-C. Relationships between baseline plasma aldosterone concentrations and the diuretic effect of exogenous ANP (N = 75). Abbreviations: ANP, atrial natriuretic peptide.

Figure S3. Relationships between baseline plasma ANP levels and diuretic response to ANP (orange), and baseline plasma arginine vasopressin levels and diuretic response to ANP (blue) in patients without tolvaptan (N = 66). Abbreviations: ANP, atrial natriuretic peptide.

Figure S4. Relationships between baseline plasma ANP levels and plasma arginine vasopressin levels (N = 75). Abbreviations: ANP, atrial natriuretic peptide.

Table S1. Main patient characteristics by (A) baseline ANP and (B) arginine vasopressin status.

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