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ORIGINAL RESEARCH ARTICLE

Efficacy of exogenous atrial natriuretic peptide in patients with heart failure with preserved ejection fraction: deficiency of atrial natriuretic peptide and replacement therapy

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Abstract

Aims Exogenous atrial natriuretic peptide (ANP) may be a logical treatment for heart failure (HF) patients with ANP deficiency. Lower ANP concentrations may result from HF with preserved ejection fraction (HFpEF), which also results in lower brain natriuretic peptide levels in HFpEF relative to HF with reduced ejection fraction (HFrEF), although clinical features regarding circulating ANP in HFpEF and HFrEF have not been fully investigated during acute HF. Here, we characterized the differential regulation of circulating ANP and the efficacy of exogenous ANP (carperitide) in patients with acute HF, especially HFpEF.

Methods and results Serum ANP levels before treatment and the diuretic effect of 0.0125 μg/kg/min of carperitide alone for the first 6 h were prospectively evaluated in 113 patients with acute HF who were divided into two groups: HFpEF vs. HFrEF. We mainly analysed the impact of baseline ANP levels and the presence of HFpEF on the diuretic effect of exogenous ANP. There was an inverse relationship between ANP levels and the diuretic effect of exogenous ANP ($r^2 = 0.19$, $P < 0.001$). Patients with HFpEF had lower ANP levels ($P < 0.001$) and a greater diuretic effect of exogenous ANP than patients HFrEF ($P < 0.001$). HFpEF was an independent predictor of greater diuretic effect of exogenous ANP ($P = 0.003$), as with a lower baseline ANP level ($P = 0.004$).

Conclusions Patients with HFpEF might have an aspect of ANP deficiency and represent a promising therapeutic target for modulating circulating ANP.

Keywords Acute heart failure (AHF); Carperitide; Brain natriuretic peptide (BNP); Atrial fibrillation (AF); Left atrial dysfunction

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Introduction

Atrial natriuretic peptide (ANP) is an endocrine hormone that is mainly produced in atrial granules.[1] It has been widely recognized that heart failure (HF) is a state with elevated plasma ANP due to increased left atrial (LA) pressure, whereas deficiency of circulating ANP in HF is associated with several clinical factors, such as age, gender, renal function, obesity, and atrial fibrillation (AF).[2,3] Lower serum ANP concentrations in HF may demonstrate an aspect of a deficiency in circulating ANP that contributes to difficulties in treating HF,[3,4] although this possibility and

its clinical implications have not been fully investigated.

Previous studies have suggested several clinical factors that affect natriuretic peptide concentrations in HF.[2,3] Even though there exists a clear relationship between the presence of HF with preserved ejection fraction (HFpEF) and lower brain natriuretic peptide (BNP) levels compared with HF with reduced ejection fraction (HFrEF),[5,6] the clinical implications of HFpEF with respect to the regulation of circulating ANP remain unclear. Given that serum ANP and BNP are secreted via the same pathway in response to increased cardiac stress,[7,8] HFpEF may be associated with relatively low concentrations of ANP as well as BNP. Thus, HFpEF may be a promising factor for predicting the presence of low serum ANP concentrations in patients with increased atrial pressure, that is, acute decompensated HF (ADHF), although the impact of HFpEF on the regulation of circulating ANP in patients with ADHF is not well understood.

Based on its pleiotropic physiological functions, which are typified by natriuretic effects, ANP, as with BNP, represents a rational treatment target in HF. Recently, LCZ696, which increases plasma natriuretic peptide levels according to the inhibition of neprilysin activity, was shown to have clinical benefits in the management of HF.[9] This fact was the basis of the concept of modulating natriuretic peptide levels in patients with HF. Furthermore, these benefits may rely more on ANP than BNP because neprilysin plays a significant role in the degradation of ANP rather than BNP.[3,9] Given these findings, even though baseline natriuretic peptide levels are not considered to be associated with the diuretic effect of diuretics in patients with ADHF,[10,11] administration of exogenous ANP would seem to be a logical treatment in patients with relative ANP deficiency. In addition, considering that no specific therapy has yet been shown to improve outcomes in HFpEF, it is important to consider these novel therapeutic concepts.

In the current study, we aimed to investigate (i) whether the regulation of circulating ANP differs according to the HF phenotypes in relation to whether patients have HFpEF among individuals with ADHF and (ii) whether patients with lower ANP concentrations, regardless of the presence of ADHF, benefit more from administration of exogenous ANP (carperitide).

Methods

Study design

The Beneficial Efficacy of Carperitide in Patients with Acute Decompensated Heart Failure (BEYOND) registry is a prospective multicentre observational study in which 162 patients with ADHF were enrolled and treated with low-dose continuous carperitide between June 2017 and December 2018. To assess the relationship between the baseline concentration of plasma ANP and the first diuretic effect of exogenous ANP, serum ANP levels before the administration of carperitide and cumulative amount of urine over the first 6 h after carperitide administration were measured in all patients, with the latter measured through urinary catheterization. Furthermore, to evaluate LA remodelling, the LA volume index (LAVI) was measured by echocardiography during hospitalization. The ADHF diagnosis was made based on the guidelines of the American College of Cardiology/American Heart Association.[12] 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. The investigation conforms with the principles outlined in the *Declaration of Helsinki*. The protocol was approved by the certified review board stipulated by the Japanese Clinical Trial Act (No. CRB3180027), and all enrolled patients provided written informed consent. Furthermore, this clinical trial was registered with the University Hospital Medical Information Network Clinical Trial Registry, in accordance with the International Committee of Medical Journal Editors (UMIN-ID: 000028689).

Study population

Among the 162 patients in this registry, we excluded 30 patients who were treated with intravenous furosemide or oral tolvaptan after admittance and within the first 6 h after carperitide administration, 15 patients who received 0.025 or 0.05 μg/kg/min of continuous carperitide, and four patients who were missing data for the LAVI determination (49 patients excluded in total). After these exclusions, we enrolled 113 patients who were treated with 0.0125 μg/kg/min of continuous carperitide alone during the first 6 h after admission. Subsequent treatment was determined by the responsible cardiologist in accordance with optimal treatments recommended by guidelines for HF.[13,14]

Participants were divided into two groups: those with HFrEF and with HFpEF. Differences in the baseline characteristics and clinical endpoints were analysed between the two groups. Among the characteristics, AF included patients with chronic AF and those with paroxysmal AF.

Measurement of serum atrial natriuretic peptide

Baseline blood samples on admission were collected from a vein before the administration of carperitide. Samples were

collected in tubes containing 1.25 mg/mL of ethylenediaminetetraacetic acid and the protease inhibitor aprotinin (500 KIU/mL) for measurement of ANP. The plasma was separated by centrifugation (at 2500 rpm) for 10 min and stored at −80°C until measurement. Samples from all participating hospitals were sent to SRL (Japan), where the ANP concentration was determined with the HISCL ANP immunoassay (Shionogi, Japan).

Echocardiographic variables

LAVI at end-systole and left ventricular ejection fraction were evaluated with Simpson's rule by transthoracic echocardiography during hospitalization. In the current study, HFpEF was defined as having a left ventricular ejection fraction of ≥ 40%, similar to previous studies regarding HFpEF.[15–17] Although the endocardial borders were traced in both the apical four-chamber and two-chamber views to measure LAVI, a single-plane approach was applied in cases when planimetry in both views was difficult, as defined in the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[18]

Clinical endpoints

To evaluate the specific efficacy of exogenous ANP in patients with ADHF, we set the primary endpoint as urine volume during the first 6 h after administration of carperitide. The baseline concentration of ANP and diuretic effect was analysed among the two groups.

Table 1 Patient characteristics upon admission (heart failure with reduced ejection fraction vs. heart failure with preserved ejection fraction)

Characteristic	HFrEF $n = 53$	HFpEF $n = 60$	*P*-value
Age (years)	71.4 ± 14.2	76.5 ± 10.9	0.03
Male	41 (77.4%)	32 (53.3%)	0.01
BMI (kg/m^2)	24.1 ± 6.2	25.0 ± 4.9	0.39
Obesity (BMI ≥ 30)	5 (9.4%)	6 (10.0%)	0.92
Medical history			
Hypertension	28 (52.8%)	48 (80.0%)	0.003
Diabetes mellitus	22 (41.5%)	23 (38.3%)	0.85
Dyslipidaemia	14 (26.4%)	19 (31.7%)	0.68
Hospitalization for HF	29 (54.7%)	26 (43.3%)	0.26
OMI	13 (24.5%)	6 (10.0%)	0.04
Stroke/TIA	6 (11.3%)	11 (18.3%)	0.43
Chronic lung disease	9 (17.0%)	8 (13.3%)	0.61
AF	20 (37.7%)	35 (58.3%)	0.04
PAF	4 (7.5%)	8 (13.3%)	0.37
CAF	16 (30.2%)	27 (45.0%)	0.12
PMI	5 (9.4%)	8 (13.3%)	0.57
CRT-D	7 (13.2%)	3 (5.0%)	0.19
Medication[a]			
Furosemide	30 (56.6%)	27 (45.0%)	0.26
Spironolactone	18 (34.0%)	14 (23.3%)	0.30
Tolvaptan	10 (18.9%)	8 (13.3%)	0.45
ACE-I or ARB	29 (54.7%)	28 (46.7%)	0.45
Beta-blocker	24 (45.3%)	29 (48.3%)	0.85
Ca-blocker	7 (13.2%)	29 (48.3%)	<0.001
Physical examination			
NYHA 3 or 4	52 (98.1%)	57 (95.0%)	0.62
Heart rate	99.1 ± 27.0	88.7 ± 23.3	0.03
Systolic BP	142.8 ± 33.3	149.5 ± 26.7	0.24
Diastolic BP	86.9 ± 20.2	80.1 ± 22.2	0.09
Orthopnoea	37 (69.8%)	48 (80.0%)	0.28
JVD	42 (79.2%)	48 (80.0%)	0.99
S3 gallop	33 (62.3%)	37 (61.7%)	0.99
Coarse crackles	35 (66.0%)	48 (80.0%)	0.14
Leg oedema	42 (79.2%)	58 (96.7%)	0.006
Cold extremity	9 (17.0%)	7 (11.7%)	0.43

ACE-I, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; Ca, calcium; CAF, chronic atrial fibrillation; CRT-D, cardiac resynchronization therapy; HF, heart failure; JVD, jugular venous distension; NYHA, New York Heart Association classification; OMI, old myocardial infarction; PAF, paroxysmal atrial fibrillation; PMI, pacemaker implantation; TIA, transient ischaemic attack.
[a]Prescribed before admission.

Table 2 Examination findings upon admission (heart failure with reduced ejection fraction vs. heart failure with preserved ejection fraction)

	HFrEF $n = 53$	HFpEF $n = 60$	*P*-value
Laboratory findings			
ANP (pg/mL)	406.0 (308.0–636.0)	216.5 (134.0–306.5)	<0.001
BNP (pg/mL)	1204.0 (684.0–1815.0)	501.8 (311.8–844.0)	<0.001
Hb (g/dL)	12.8 ± 2.3	11.0 ± 2.4	<0.001
Ht (%)	39.6 ± 6.4	34.0 ± 6.9	<0.001
eGFR (mL/min/1.73 m^2)	47.1 ± 21.9	46.3 ± 20.2	0.84
Cr (mg/dL)	1.41 ± 0.76	1.30 ± 0.76	0.44
BUN (mg/dL)	27.0 ± 14.2	27.3 ± 25.8	0.94
Echocardiographic findings			
LVEF (%)	30.9 ± 5.6	56.2 ± 9.9	<0.001
LAVI (mL/m^2)	52.3 ± 27.0	60.7 ± 36.6	0.18
RAVI (mL/m^2), $n = 109$	29.6 ± 15.2	37.3 ± 24.6	0.06
LAD (mm)	41.7 ± 9.7	44.8 ± 8.5	0.08
LVDd (mm)	61.5 ± 9.8	49.7 ± 8.3	<0.001
LVDs (mm)	51.0 ± 8.5	33.9 ± 7.6	<0.001
LVEDV (mL)	160.0 ± 62.9	92.1 ± 35.0	<0.001
LVESV (mL)	110.2 ± 44.9	41.6 ± 20.6	<0.001
DCT (ms)	167.5 ± 69.9	186.6 ± 47.9	0.09
E/e′	18.2 ± 8.0	17.8 ± 11.2	0.86
Significant MR[a]	20 (37.7%)	23 (38.3%)	0.99
Significant TR[a]	13 (24.5%)	20 (33.3%)	0.41
Significant AR[a]	5 (9.4%)	11 (18.3%)	0.28

ANP, atrial natriuretic peptide; AR, aortic regurgitation; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; DCT, discrete cosine transform; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HFpEF, heart failure with preserved ejection fraction; Ht, haematocrit; LAD, left atrial diameter; LAVI, left atrial volume index; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; RAVI, right atrial volume index; TR, tricuspid regurgitation.
[a]Moderate and severe valvular disease.

Figure 1 The increase in diuretic response of exogenous ANP was inversely correlated with the baseline levels of circulating ANP (scatter and fractional polynomial plot: correlation between the baseline ANP levels and urine volume during the 6 h after the administration of exogenous ANP). ANP, atrial natriuretic peptide.

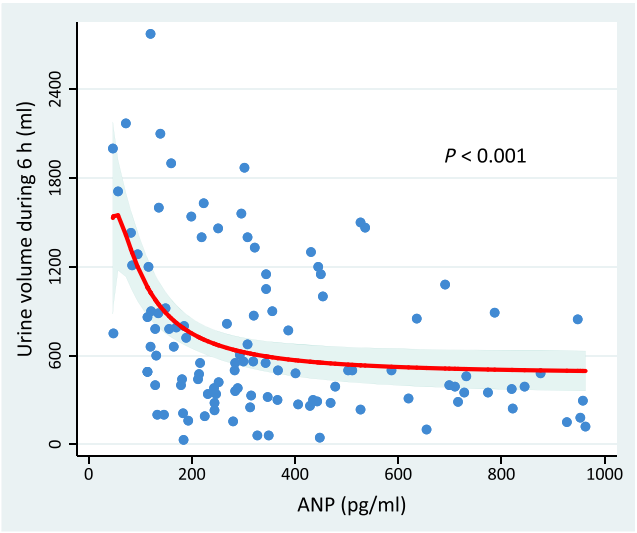
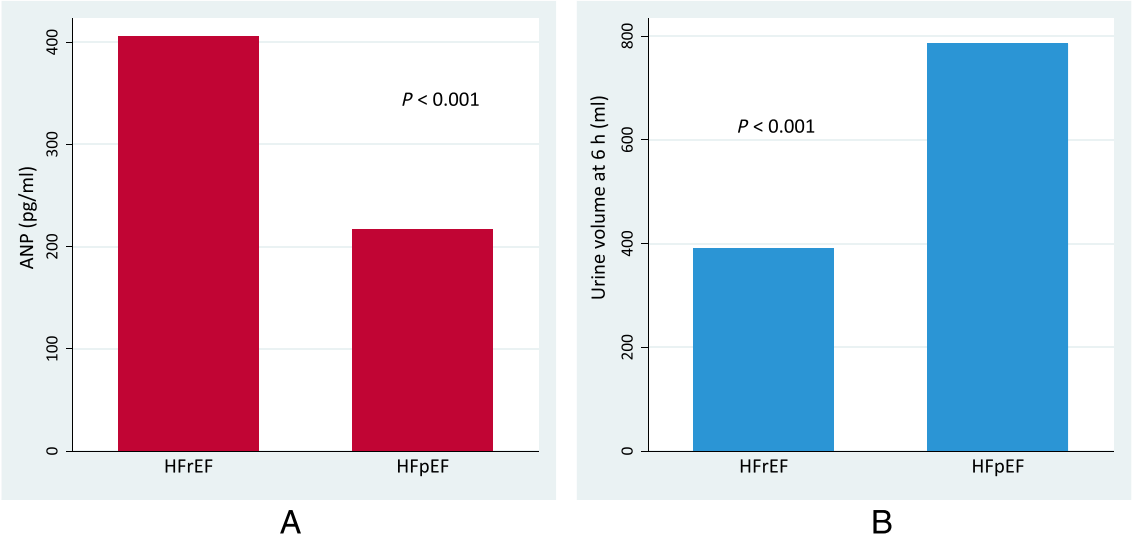


Figure 2 Comparison of median values of (A) baseline ANP levels and (B) urine volume at 6 h between the two groups (HFrEF vs. HFpEF). ANP, atrial natriuretic peptide; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



Statistical analysis

All data are described as the presenting frequency, percentages for categorical variables, and the mean value (±standard deviation) or median value with inter-quartile range (Quartile 1–3) for continuous variables. To evaluate statistical significance in comparisons between groups, the Fisher exact test was used to evaluate categorical variables, and the Student *t*-test or Mann–Whitney test was used for continuous variables. Statistical tests for continuous variables among more than two groups consisted of the one-way ANOVA and the Kruskal–Wallis test. Linear correlation of two variables was analysed by the Spearman correlation test. To evaluate the relationship between the baseline ANP levels and the diuretic effect of exogenous ANP, we used a fractional polynomial analysis. We also analysed multivariate fractional polynomial analysis models to assess if the ANP levels in addition to demographics were associated with a diuretic effect of

exogenous ANP when adjusting for other multiple factors including BNP levels, renal function, blood pressure, and the use of diuretics before admission. Furthermore, we analysed additional models to evaluate the statistical independence of the ANP levels from other well-known factors that influence serum ANP levels, such as the presence of obesity and AF.[2,3] In the multivariate regression analyses, log-transformed urine volume was used as the objective variable. All analyses were performed by using Stata software, version 15 (StataCorp), and the significance level was set at 5%.

Results

Patient characteristics

Table 1 presents the baseline characteristics of the two groups of patients (n = 113 in total). There were several differences in characteristics between individuals with HFpEF and with HFrEF. HFpEF patients were older, were more likely to be women, and more frequently had hypertension and AF. The use of diuretics, angiotensin-converting-enzyme inhibitor, angiotensin II receptor blocker, and beta-blocker was comparable among patients with HFrEF and HFpEF, whereas a Ca-blocker was more frequently prescribed for HFpEF patients. An increased heart rate and higher incidence of leg oedema upon admission were noted in patients with HFrEF. Systolic and diastolic pressure did not significantly differ between the two groups. The medical history for rates of hospitalization for HF was similar between the two groups. Among the 55 (48.7%) patients with AF, 43 (38.1%) had chronic AF and 12 (10.6%) had paroxysmal AF. Body mass index (BMI) levels and the proportion of patients with obesity were not significantly different between the two groups.

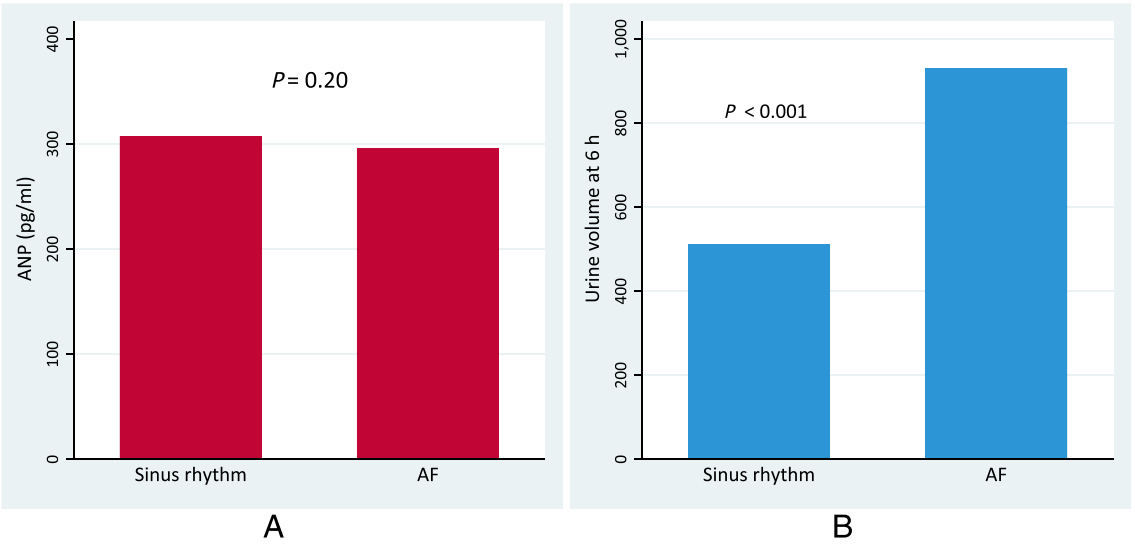
Serum atrial natriuretic peptide and laboratory findings

The baseline serum ANP concentration did not follow a normal distribution (*Figure S1*). The median ANP concentration of the cohort was 300.0 pg/mL (inter-quartile range, 181.0–454.0 pg/mL). Baseline levels of ANP and BNP had similar relationships between the two groups, and individuals with HFpEF did show significantly lower ANP and BNP levels (*Table 2*, *Figure 2A*). Patients with HFpEF were more likely to have lower haemoglobin and haematocrit levels than those with HFrEF.

Echocardiographic findings

Echocardiographic findings showed several differences (*Table 2*). Patients in the HFpEF group were more likely to have a larger atrial volume and diameter than those in the HFrEF group, but these differences were not significant. Left ventricular volume and diameter were significantly larger in patients with HFrEF than those with HFpEF for both diastolic and systolic phases. The value of E/e′ was comparable regardless of the presence of HFpEF. There were no significant differences between the two groups with respect to the presence of valvular diseases.

Figure 3 Comparison of median values of (A) baseline ANP and (B) urine volume at 6 h between the two groups (sinus rhythm vs. AF). AF, atrial fibrillation; ANP, atrial natriuretic peptide.



Study endpoint

In univariate analysis models that used the ANP levels to predict the diuretic effect of exogenous ANP, the best-fitting model was the first-degree fractional polynomial model (*Table S1*).

Figure 1 shows the fractional polynomial plots, which indicate the impact of the baseline ANP levels on the diuretic effect of exogenous ANP. As shown in this plot, there is an inverse relationship between these two variables (r^2 = 0.19, $P < 0.001$).

In contrast to the lower ANP levels in patients with HFpEF compared with HFrEF (*Table 2*, *Figure 2A*), the diuretic effect of exogenous ANP during the first 6 h after administration was significantly higher in patients with HFpEF (HFrEF vs. HFpEF, median [inter-quartile range]: 390 [260.0–605.0] mL vs. 785 [415–1307.5] mL, $P < 0.001$) (*Figure 2B*). In a univariate analysis, obesity was not significantly associated with the diuretic effect of exogenous ANP (no obesity vs. obesity: 500.0 [322.5–915.0] mL vs. 490 [387.5–905.0] mL) (*Figure S2*). In contrast, the presence of AF predicted a significantly greater diuretic effect of exogenous ANP (sinus rhythm vs. AF: 390.0 [272.5–705.0] mL vs. 845.0 [457.5–1400.0] mL, $P < 0.001$) (*Figure 3A*), even though ANP levels did not differ between patients with sinus rhythm and those with AF (sinus rhythm vs. AF: 307.5 [195.8–512.5] pg/mL vs. 296.0 [142.5–446.5] pg/mL) (*Figure 3B*).

In multivariate analysis models that predicted the diuretic effect of exogenous ANP (*Table 3*), the statistical independence of the ANP level and the presence of HFpEF was preserved when the models were adjusted for several factors including BNP levels, systolic pressure, renal function, and the use of furosemide (ANP level: P = 0.004, HFpEF: P = 0.003, respectively). In an additional multivariate analysis model (*Table 4*), the presence of AF was also an independent predictor of the diuretic effect of exogenous ANP (P = 0.001).

Table 3 Multivariate fractional polynomial regression analysis model predicting the urine volume during the initial 6 h after administration of exogenous atrial natriuretic peptide (n = 113)

	Standardized coefficients	95% CI lower boundary	95% CI upper boundary	*P*-value	VIF
ANP level	2 113 033	672 451	3 553 615	0.004	1.21
BNP level	−0.073	−0.172	0.025	0.14	1.32
Age	−1.36	−9.64	6.91	0.74	1.35
Male	169.6	−29.9	369.1	0.10	1.12
Systolic BP	−0.70	−4.18	2.78	0.69	1.33
eGFR	0.094	−5.15	5.34	0.97	1.47
Furosemide use	−6.37	−218.8	−206.0	0.95	1.38
HFpEF	317.1	107.6	526.5	0.003	1.21

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

Table 4 Multivariate fractional polynomial regression analysis model predicting the urine volume during the initial 6 h after administration of exogenous atrial natriuretic peptide (including the presence of AF, n = 113)

	Standardized coefficients	95% CI lower boundary	95% CI upper boundary	*P*-value	VIF
ANP level	40 724	12 796	68 652	0.005	1.44
BNP level	−0.019	−0.117	0.078	0.70	1.46
Age	−3.24	−11.11	5.83	0.42	1.37
Male	158.6	−29.7	346.9	0.10	1.11
Systolic BP	0.54	−2.56	3.64	0.73	1.18
eGFR	−0.14	−4.64	4.93	0.95	1.36
HFpEF	248.3	44.9	451.6	0.017	1.41
AF	325.1	140.8	509.4	0.001	1.16

AF, atrial fibrillation; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; VIF, variance inflation factor.

Discussion

This was the first study to investigate the association between the pure efficacy of the administration of an ANP-based drug alone and baseline regulation of circulating ANP in patients with ADHF. The current study showed that (i) the diuretic effect of exogenous ANP was significantly associated with baseline ANP levels; (ii) in HFpEF patients, where the HF phenotype was closely associated with lower ANP levels, there was a greater diuretic response to exogenous ANP relative to the response in HFrEF patients; and (iii) lower baseline ANP levels and the presence of HFpEF were independent predictors of the diuretic effect of exogenous ANP. Furthermore, the presence of AF is also an independent predictor of the greater diuretic effect of exogenous ANP in a multivariate analysis model including ANP level and the presence of HFpEF.

Deficiency of atrial natriuretic peptide and atrial natriuretic peptide replacement therapy

In this study, lower ANP levels were significantly associated with a greater diuretic efficacy of exogenous ANP. This finding supports the recent emerging paradigm that ANP deficiency, which is associated with several clinical factors including age, gender, renal function, obesity, and AF,[2,3] is a useful therapeutic target for ANP replacement therapy in HF,[2,19,20] similar to hormonal deficiency in other organs.

Even though the baseline ANP level alone was a strong predictor of the beneficial efficacy of exogenous ANP, which supports the hypothesis that lower serum ANP concentrations

reflect an aspect of ANP deficiency in ADHF, there were certain patients who did not gain the greater diuretic effect of exogenous ANP regardless of their lower ANP levels (*Figure 1*). Several factors previously shown to contribute to the diuretic effect in patients with ADHF, such as renal function, blood pressure, and prior use of diuretics,[10,21] were not observed to do so in the present study. Further research is warranted to investigate the other pathophysiologic basis that is associated with the diuretic response to exogenous ANP in patients with ADHF.

Heart failure with preserved ejection fraction and atrial natriuretic peptide replacement therapy

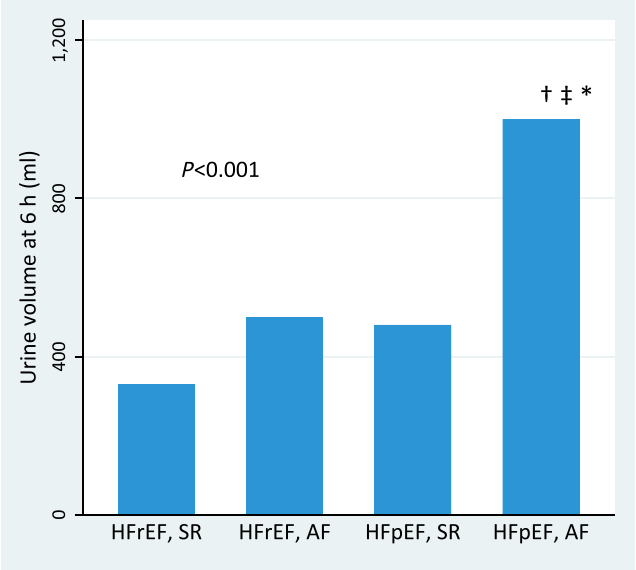
Given that serum BNP levels in patients with HFpEF are relatively low as compared with levels in patients with HFrEF[5,6] and that the synthesis and clearance of ANP and BNP are mediated by similar pathways,[7,8] the presence of HFpEF may contribute to a lack of elevation in circulating ANP levels, similar to the effect on BNP. Indeed, our data suggested that patients with HFpEF had significantly lower ANP levels as compared with patients with HFrEF, which was similar to their relative BNP levels. In addition, we found that HFpEF was a strong predictor of a greater diuretic effect of exogenous ANP. These data suggest that this phenotype of HF may be associated with a state of ANP deficiency and support the beneficial therapeutic use of exogenous ANP in these patients.

Other subtypes of heart failure and atrial natriuretic peptide replacement therapy

As noted above, age, gender, renal function, obesity, and AF independently influence serum natriuretic peptide levels in patients with HF.[2,3] Obesity is known to contribute to deficiency in circulating natriuretic peptide,[22] although obesity did not influence the diuretic effect of exogenous ANP in our study. As shown in *Figure 3B* and *Table 4*, AF did predict a greater diuretic response to exogenous ANP, independently of lower ANP concentrations and the presence of HFpEF.

Furthermore, when we divided the individuals into four groups according to the presence of HFpEF and AF, the urine volume at 6 h was significantly greater in HFpEF patients with AF than in patients with the other subtypes of HF (*Figure 4*). Because patients with AF had similar ANP levels as compared with patients with sinus rhythm, our current findings do not suggest why patients with AF experienced a greater diuretic effect of exogenous ANP. This may have been a result of the multifactorial causes of the diuretic effect of exogenous ANP in the setting of ADHF in addition to baseline ANP levels. However, these easily determined criteria—that is, the presence of HFpEF and AF—are more applicable to daily clinical practice than the measurement of ANP levels and could improve the management of HF using an ANP-based drug. Future research should focus on other pathophysiological bases including the hypothesis that a deficiency in circulating ANP caused by atrial endocrine dysfunction subsequent to LA marked fibrosis in patients with AF may be associated with diuretic effects of exogenous ANP.[3]

Figure 4 Comparison of median values of urine volume at 6 h across the four patient groups (HFrEF with sinus rhythm vs. HFrEF with AF vs. HFpEF with sinus rhythm vs. HFpEF with AF). Significant comparisons are as follows: †, significantly different from HFrEF with sinus rhythm; ‡, significantly different from HFrEF with AF; *, significantly different from HFpEF with sinus rhythm.



Clinical perspectives

The results of this study were consistent with the emerging concept that modulating natriuretic peptide concentrations is a beneficial therapeutic target in HF. Recently, studies of LCZ696, which consists of sacubitril/valsartan, have suggested its clinical benefit in the management of chronic HF.[9,23] As ANP is the principal natriuretic peptide elevated by LCZ696,[3] the relative deficiency of ANP should be the focus of additional studies, along with analysis of ANP replacement therapy for HF. Furthermore, as both ANP and BNP bind to natriuretic peptide receptor-A (NPR-A),[24,25] exogenous BNP (nesiritide) may be a promising drug in patients with relative ANP or BNP deficiency. Further studies are needed to determine whether the use of exogenous BNP in place of ANP could have an effect similar to the results of our study.

There were a couple of limitations to this study. Given the small sample size of this study, the number of patients was statistically insufficient to evaluate any association between ANP deficiency and each clinical endpoint such as in-hospital death (there were only 10 in-hospital deaths among these patients, and there were no significant associations between in-hospital deaths and either ANP concentration or the presence of HFpEF; data not shown). Similarly, we may need more participants to evaluate clinical impacts of obesity ($<$10% of patients had a BMI $\geq$ 30 in our cohort) (*Table 1*). Next, although the measurement of circulating ANP may be challenging, we did not present the reference for validation of ANP analysis. Further research is warranted to confirm whether the results of this study are reproducible in a larger cohort. In addition, because this study did not include long-term follow-up after discharge, the impact of ANP deficiency on long-term clinical outcomes remains unclear. The marginal change in haemodynamic status during the first 6 h after the administration of exogenous ANP was not measured, and thus we could not assess the associations between changes in haemodynamic parameters and the diuretic effect of exogenous ANP. We analysed the association between the baseline ANP levels and the efficacy of exogenous ANP in the setting of ADHF, and thus it remains unclear whether these results can be generalized to stabilized ambulatory patients with chronic HF. In addition, we focused on only synthesis dysfunction with respect to the regulation of circulating ANP. Patients with HF have impaired ANP activity according to several key mechanisms, such as the down-regulation of NPR-A and renal cyclic guanosine monophosphate dysfunction, both of which induce a reduced natriuretic response to acute volume expansion.[26] Furthermore, clearance of ANP, which also has a key role in regulating circulating ANP,[8] was not evaluated in this study. Finally, the most important limitation of this study was that it did not fully clarify the reason why patients with HFpEF had lower ANP levels than patients with HFrEF, in addition to reduced BNP levels. These limitations should be considered in future research.

Conclusions

HFpEF was significantly associated with lower ANP concentrations and the greater diuretic effect of exogenous ANP in ADHF; that is, this HF phenotype may have an aspect of deficiency of circulating ANP. The current study supports the emerging concept that relative natriuretic peptide deficiency is a promising therapeutic target in HF and the hypothesis that HFpEF is a compatible phenotype with response to treatment to modulate the level of circulating natriuretic peptide. Furthermore, the presence of AF is also a considerable predictor of the greater diuretic effect of exogenous ANP in patients with ADHF.

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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. Distribution of baseline serum ANP concentration among the patients in this study.
Figure S2. Comparison of median urine volume at 6 hours between patients classified as non-obese and obese (i.e., BMI $\geq$ 30).
Table S1. Comparisons of univariate linear and nonlinear (fractional polynomial regression) models predicting the log-transformed urine volume during the initial 6 hours after administration of exogenous ANP.

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