Left Atrial Remodeling Related to Disproportionately Low B-Type Natriuretic Peptide in Acute Heart Failure Patients with Atrial Fibrillation

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The diagnostic performance of B-type natriuretic peptide (BNP) for acute heart failure (HF) is impaired in patients with atrial fibrillation (AF). Increased AF burden in HF is associated with left atrial (LA) remodeling. Recent studies have revealed that LA remodeling may affect LV filling. We hypothesized that LA remodeling affects BNP secretion in acute HF conditions. The study investigated the clinical impact of LA remodeling on admission BNP levels in acute HF patients with and without AF. Consecutive acute HF hospitalized patients (n = 899) were divided into groups with (n = 382) or without AF (n = 507) and subdivided into disproportionately low BNP (LB) (≤200 pg/ml), medium BNP (200 to 600 pg/ml) and high BNP (≥600 pg/ml) subgroups. The AF group had a higher proportion of patients with LB than the non-AF group (23.6% vs 16.6%, p = 0.009). BNP levels in both groups were positively correlated with LV end-diastolic volume and negatively correlated with LV ejection fraction in both groups. In contrast, BNP was positively correlated with LA volume index in the non-AF group, but negatively correlated in the AF group. The survival rates were significantly higher in the LB group than in the other groups in non-AF. Conversely, there were no significant differences across all groups in AF patients. In conclusion, in patients with acute HF and AF, disproportionately low BNP levels are associated with LA structural remodeling and poor prognosis. **(Am J Cardiol 2023;209:128−137)**

Keywords: acute heart failure, atrial fibrillation, atrioventricular coupling, left atrial volume, natriuretic peptide deficiency, pericardial restraint

B-type natriuretic peptide (BNP) is mainly secreted by myocytes in the left ventricle (LV) in response to volume and pressure overload. BNP is the most studied biomarker reflecting congestion and prognosis in patients with acute heart failure (HF).[1] Moreover the levels of BNP are believed to increase protectively under HF condition, given the cardioprotective roles of NP in regulating cardiovascular homeostasis and intravascular volume.[2] However, the BNP concentration known to be disproportionately low (relative BNP deficiency) in some patients with constrictive pericarditis and obesity despite acute HF conditions.[3−5] In patients with atrial fibrillation (AF), the diagnostic performance of BNP for acute HF is impaired. BNP levels are also independently influenced by both AF and HF conditions, hence it is difficulat to determine which BNP level can be used for the diagnosis of one condition in the presence of the other.[6] An increased AF burden in HF is associated with left atrial (LA) remodeling.[7] Recent studies revealed that LA remodeling may affect LV filling.[8] We hypothesized that LA remodeling affects BNP secretion under acute HF conditions. The study investigated the clinical impact of LA remodeling upon admission BNP levels in patients of acute HF with and without AF.

Methods

This study was a retrospective observational study of a small-single center. All study procedures were performed by the ethical standards of the Institutional and National Research Committee and the Declaration of Helsinki and its later amendments or comparable ethical standards. The Ethics Review Board of Osaka Medical and Pharmaceutical University approved this retrospective study and waived the requirement for informed consent (approval number 2194).

Among the 1,016 patients who required immediate treatment for acute HF or acute exacerbation of chronic HF at Osaka Medical and Pharmaceutical University Hospital between January 2015 and December 2020, a total of 889 consecutive patients were included in the study. HF was diagnosed by well-trained cardiologists based on the Framingham criteria or the universal definition of HF.[9] Moreover, an expert HF team confirmed the diagnosis. Patients

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See page 136 for Declaration of Competing Interest.

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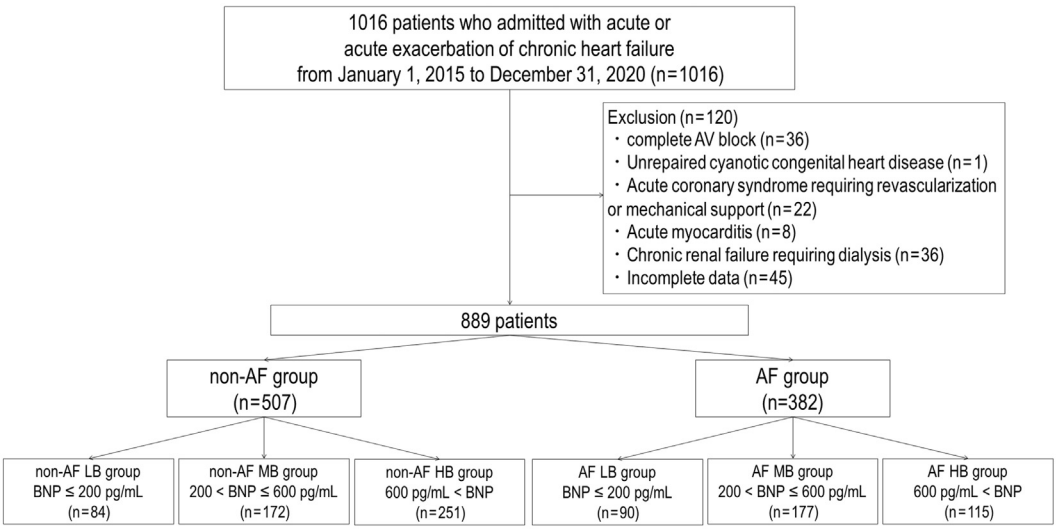

Figure 1. Study flow chart. A total of 889 patients were included in the study and categorized into the AF or non-AF groups according to their baseline heart rhythm. We further subdivided the patients into the LB, MB, and HB groups with cut-off BNP levels of 200 and 600 pg/ml at admission in each group.

with complete atrioventricular block, unrepaired cyanotic congenital heart disease, acute coronary syndrome requiring emergent revascularization or mechanical circulatory support, acute myocarditis, chronic renal failure requiring dialysis, or incomplete data were excluded. We categorized the patients according to their baseline heart rhythm on hospital admission into the with AF (n = 382) or without AF (non-AF, n = 507) groups. The groups were then subdivided into the disproportionately low BNP (LB), medium BNP (MB), and high BNP (HB) subgroups with BNP cut-off levels of 200 and 600 pg/ml (Figure 1), or into the LA volume index (LAVI) using cut-off LAVI values of 40, 80, 120, and 160 ml/m^2 in each group respectively. We extracted data from the patients' medical records on the body mass index (BMI), New York Heart Association functional classification status, vital signs, medication at admission, heart disease etiology, and risk factors.

Blood samples were collected on admission. The BNP levels were measured using a standard radioimmunoassay (ARCHITECT BNP-JP assay; Abbott Japan Co., Ltd, Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was calculated using serum creatinine levels, age, and gender.[10]

Echocardiography was performed using standard ultrasound equipment (Vivid E9, GE Vingmed, Horten, Norway; EPIQ 7G, Philips Healthcare, Andover, Massachusetts; Artida, Canon Medical Systems, Tokyo, Japan). All patients underwent standard comprehensive 2-dimensional and Doppler echocardiography evaluations. The LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV ejection fraction (LVEF) were measured using the modified Simpson's method. The LA volume was measured retrospectively at end-systole using the biplane disk summation method.[11] The LV and LA volumes were indexed to the body surface area, to produce the LVEDV index (LVEDVI), LVESV index (LVESVI), and LAVI. We defined HF with preserved EV as an EV ≥50%. All clinical events were retrospectively obtained from the medical records. We assessed the outcomes, including all-cause death or rehospitalization for HF.

Statistical analysis

Categorical variables are presented as numbers (%) and were compared using the chi-square test or Fisher's exact test depending on the cell size category. The Shapiro−Wilk test was used to assess the normality of continuous variables. All continuous variables were expressed as means ± SD or median with interquartile ranges (IQRs). Normally distributed variables were compared between the groups using the Student's *t* tests, and non-normally distributed variables were compared using the Wilcoxon rank-sum tests. To compare multiple groups, Tukey's honestly significant difference test was used for normally distributed variables, and the Steel−Dwass test was used for non-normally distributed variables. Cumulative clinical end points were assessed using Kaplan−Meier curves with post hoc comparisons using the log-rank tests. The factors associated with disproportionately low BNP levels were investigated using univariate and multivariate logistic regression analyses. Data were analyzed using JMP Pro version 15.1.0 (SAS Institute Inc., Cary, North Carolina).

Results

AF in patients with acute HF

A total of 889 patients were included in this study: 382 (43.0%) with and 507 (57.0%) without AF. BNP was significantly higher in patients without AF (597.5 pg/ml, IQR 285.6 to 1,152.1 pg/ml) than in those with AF (436.9 pg/ml, IQR 209.9 to 695.8 pg/ml, p <0.001; Figure 2). HF patients with LB were more frequently observed in patients with AF (n = 90, 23.6%) than in those without AF (n = 84, 16.6%, p = 0.009; Figure 2). The prevalence of AF gradually increased as the degree of LA remodeling advanced (Figure 2).

As demonstrated in Table 1, the demographics and clinical characteristics of these patients according to the LB, MB, or HB group stratified by the presence or absence of

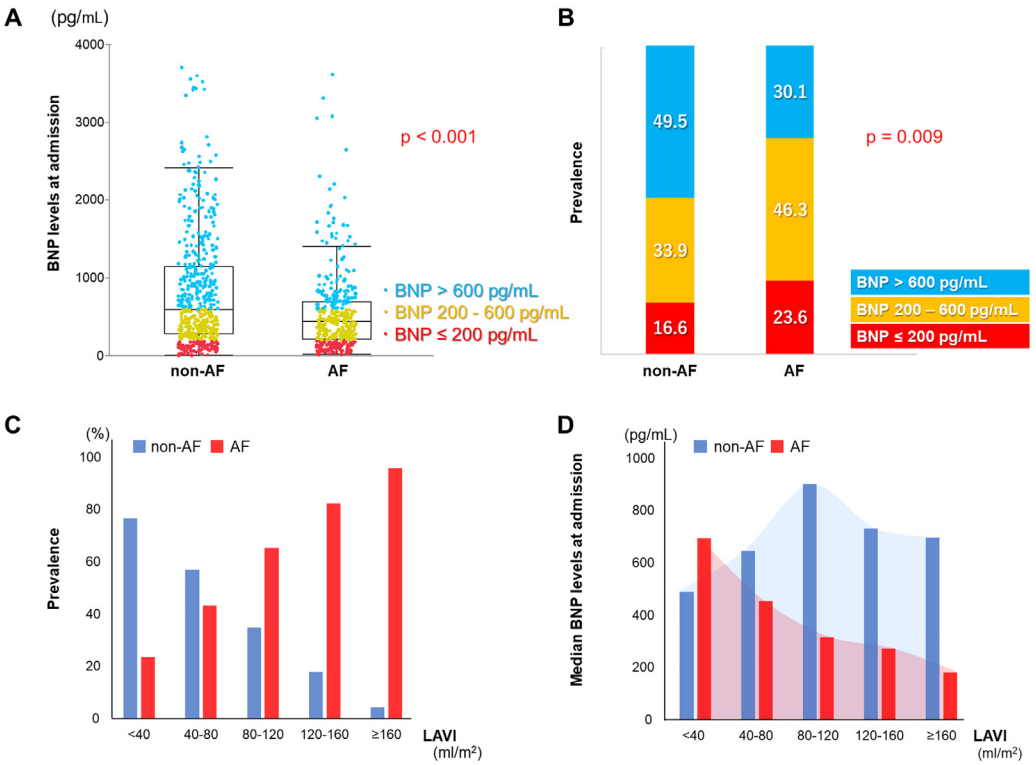

Figure 2. (*A*) Box plot BNP levels at admission in acute HF patients with and without AF. Legend: box, interquartile range; line, mean value; whiskers, upper and lower adjacent values; red plot, BNP ≤200 pg/ml; yellow plot, BNP 200 to 600 pg/ml; blue plot, BNP >600 pg/ml. (*B*) BNP category according to the cut-off value determined by BNP levels at admission in acute HF patients with and without AF. Red box, BNP ≤200 pg/ml; yellow box, BNP 200 to 600 pg/ml; blue box, BNP >600 pg/ml. (*C*) Prevalence of AF and non-AF according to the LAVI category in acute HF patients. (*D*) The difference in BNP levels based on LAVI upon admission of acute HF patients between AF and non-AF.

AF were compared. Patients with LB displayed higher BMI among patients with and without AF. The albumin levels and eGFR were also significantly higher in patients with LB in both groups.

LV or LA volume and BNP

Acute HF patients with non-AF displayed greater LAVI with increasing BNP category. However, an opposite trend was observed with increasing BNP levels in the AF groups. AF patients with LB displayed the largest LAVI among all patient groups (Table 2). A higher LAVI shifted to the descending limb of BNP levels in patients with non-AF, whereas higher LAVI led to decreased BNP levels in patients with AF, whereas the BNP levels showed an inverted U-shape in patients without AF (Figure 2).

BNP levels showed weak positive correlations with LVEDVI, LVESVI, and LV mass index in patients with and without AF (AF: $r = 0.27$, $p < 0.001$, $r = 0.35$, $p < 0.001$, and $r = 0.12$, $p = 0.016$, respectively; non-AF: $r = 0.29$, $p < 0.001$, $r = 0.32$, $p < 0.001$, and $r = 0.26$, $p < 0.001$, respectively; Figure 3) and a weak negative correlation with LVEF (AF: $r = -0.37$, $p < 0.001$; non-AF: $r = -0.34$, $p < 0.001$; Figure 3). In contrast, BNP levels showed weak positive correlation with LAVI in patients without AF but weak negative correlation with LAVI in patients with AF ($r = 0.14$, $p = 0.002$ vs $r = -0.24$, $p < 0.001$; Figure 3).

Disproportionately low BNP in patients with acute HF

The results of the univariate and multivariate logistic regression analyses for detecting LB are presented in Table 3. In patients without AF, multivariate logistic regression analysis revealed that higher BMI, higher eGFR, and lower LAVI were significantly correlated with LB. In patients with AF, multivariate logistic regression analysis revealed that higher BMI, higher eGFR, lower LVESVI, and higher LAVI were significantly correlated with LB. LAVI was also independently associated with LB after adjusting for other possible confounders; however, there was an inverse association between patients with AF (odds ratio 1.01, $p < 0.0001$) and those without AF (odds ratio 0.98, $p = 0.03$).

Furthermore, BNP levels significantly decreased after conventional HF treatment at the time of discharge compared with those at admission in all groups, including the LB groups (Figure 4).

Outcomes

During the mean follow-up of 674.4 ± 601.9 days, there were 242 cases (27.3%) of rehospitalizations for HF and 205 (23.1%) all-cause deaths (Table 1). According to the Kaplan–Meier analysis, the incidence of either HF rehospitalization or all-cause death was significantly lower in the LB group than in the HB group but only in non-AF patients; however, the incidence was not

Table 1
Demographics and clinical characteristics according to the presence of AF and comparison across BNP categories

	non-AF				AF			
Variables	non-AF LB BNP ≤ 200 pg/mL	non-AF MB BNP 200-600 pg/mL	non-AF HB BNP > 600 pg/mL	p value	AF LB BNP ≤ 200 pg/mL	AF MB BNP 200-600 pg/mL	AF HB BNP > 600 pg/mL	p value
n	84	172	251		90	177	115	
age (yrs)	72.5 ± 13.8	75.0 ± 11.2	73.7 ± 13.5	0.54	77.9 ± 8.7	77.6 ± 9.7	76 ± 10.2	0.38
male, n (%)	49 (58.3)	93 (54.1)	145 (57.8)	0.71	54 (60.0)	101 (57.1)	74 (64.4)	0.46
BMI (kg/m^2)	25.2 ± 4.7	23.6 ± 4.6*	22.4 ± 4.1*,†	<0.0001	25.1 ± 4.8	23.8 ± 4.9 *	22.6 ± 3.7*	0.0002
BMI > 25 kg/m^2	44 (52.4)	55 (32.0)*	52 (20.7) *,†	<0.0001	45 (50.0)	53 (29.9) *	25 (21.7) *	<0.0001
NYHA								
NYHAⅡ, n (%)	16 (19.3)	21 (12.2)	21 (8.5)	0.12	12 (13.3)	24 (13.6)	13 (11.3)	0.39
NYHAⅢ, n (%)	33 (39.8)	72 (41.9)	103 (41.9)		50 (55.6)	78 (44.3)	53 (46.1)	
NYHAⅣ, n (%)	34 (41.0)	79 (45.9)	122 (49.6)		28 (31.1)	74 (42.1)	49 (42.6)	
Vital signs on Admission								
systolic BP (mmHg)	140.1 ± 32.7	148.6 ± 32.9	139.6 ± 32.5 †	0.01	133.5 ± 23.5	134.6 ± 26.0	126.4 ± 27.2 †	0.04
diastolic BP (mmHg)	80.8 ± 21.2	82.1 ± 21.2	83.7 ± 21.4	0.39	75.7 ± 18.3	81.1 ± 17.8 *	79.4 ± 18.4	0.05
HR (bpm)	88.2 ± 22.3	89.0 ± 23.6	91.1 ± 19.7	0.44	85.3 ± 25.0	99.7 ± 31.8 *	97.0 ± 30.0 *	0.002
Etiologies of heart disease								
Ischemic heart disease, n (%)	20 (23.8)	61 (35.5)	100 (39.8) *	0.03	11 (12.2)	37 (20.9)	36 (31.3) *,†	0.004
Cardiomyopathy, n (%)	22 (26.2)	43 (25.0)	96 (38.3) *,†	0.008	11 (12.2)	42 (23.7) *	31 (27.0) *	0.03
Risk factors								
Hypertension, n (%)	63 (75.0)	126 (74.1)	157 (62.8) *,†	0.02	71 (78.9)	139 (78.5)	81 (70.4)	0.22
Dyslipidemia, n (%)	43 (51.8)	92 (53.8)	116 (46.4)	0.30	32 (35.6)	74 (41.8)	46 (40.0)	0.61
Diabetes Mellitus, n (%)	32 (38.6)	63 (36.8)	72 (28.8)	0.12	26 (29.2)	44 (24.9)	36 (31.3)	0.46
Smoking								
never, n (%)	39 (47.0)	94 (55.6)	127 (50.8)	0.65	50 (56.2)	94 (53.4)	66 (57.4)	0.13
past, n (%)	24 (28.9)	39 (23.1)	71 (28.4)		19 (21.4)	59 (33.5)	29 (25.2)	
current, n (%)	20 (24.1)	36 (21.3)	52 (20.8)		20 (22.5)	23 (13.1)	20 (17.4)	
Laboratory data								
Albumin (g/dL)	3.5 ± 0.6	3.4 ± 0.5	3.3 ± 0.5*	0.03	3.6 ± 0.5	3.5 ± 0.5*	3.4 ± 0.5*	0.001
estimated GFR (ml/min/1.73m^2)	55.4 ± 23.0	53.5 ± 23.5	45.2 ± 23.6*,†	<0.0001	51.8 ± 19.5	49.9 ± 21.8	41.5 ± 19.6*,†	0.0001
BNP at admission (pg/mL)	106.4 ± 49.6	386.0 ± 114.7*	1535.3 ± 1165.9*,†	<0.0001	112.3 ± 49.3	396.8 ± 119.4 *	1107.1 ± 598.9 *,†	<0.0001
BNP at discharge (pg/mL)	100.9 ± 89.6	177.4 ± 137.4	624.5 ± 1100.3*,†	<0.0001	84.8 ± 57.5	215.8 ± 187.3 *	470.3 ± 405.3*,†	<0.0001
Hematocrit (%)	36.3 ± 6.4	35.6 ± 6.9	36.5 ± 7.1	0.44	35.0 ± 6.2	36.7 ± 5.8	37.7 ± 7.3*	0.01
Medication at Admission								
ACE-inhibitor or ARB, n(%)	36 (42.9)	69 (40.4)	96 (38.4)	0.76	43 (47.8)	77 (43.5)	42 (36.5)	0.25
*β*blocker, n (%)	31 (36.9)	72 (42.1)	86 (34.4)	0.27	31 (34.4)	82 (46.3)	55 (47.8)	0.11
MRA, n (%)	8 (9.5)	27 (15.8)	34 (13.6)	0.39	31 (34.4)	47 (26.6)	29 (25.2)	0.29
loop diuretics, n (%)	26 (31.0)	54 (31.6)	93 (37.1)	0.40	58 (64.4)	93 (52.5)	73 (63.5)	0.08
loop diuretic dose (mg)	8.8 ± 16.7	10.7 ± 19.3	12.7 ± 20.1	0.29	28.3 ± 30.4	20.9 ± 27.9*	23.8 ± 25.0	0.05
Tolvapton, n (%)	3 (3.6)	2 (1.2)	12 (4.8)	0.11	13 (14.4)	12 (6.8)	7 (6.1)	0.06
Outcomes								
Heart failure rehospitalization, n (%)	11 (13.3)	39 (22.8)	65 (25.9)*	0.05	29 (32.2)	60 (34.1)	38 (33.0)	0.95
All cause death, n (%)	10 (11.9)	29 (16.9)	67 (26.7)*,†	0.004	18 (20.0)	50 (28.3)	31 (27.0)	0.33

AF, atrial fibrillation; BNP, B-type natriuretic peptide; LB, low BNP; MB, medium BNP; HB, high BNP; BMI, body mass index; NYHA, New York Heart Association; BP, blood pressure; HR, heart rate; GFR, glomerular filtration rate; ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin Ⅱ receptor blockers; MRA, mineralcorticoid receptor antagonists;

* $p < 0.05$ vs. LB by Tukey test or Steel-Dwass test,

† $p < 0.05$ vs. MB by Tukey test or Steel-Dwass test.

Table 2
Echocardiographic characteristics according to the presence of AF and comparison across BNP categories

	non-AF				AF			
Variables	non-AF LB BNP ≤ 200 pg/mL	non-AF MB BNP 200-600 pg/mL	non-AF HB BNP > 600 pg/mL	p value	AF LB BNP ≤ 200 pg/mL	AF MB BNP 200-600 pg/mL	AF HB BNP > 600 pg/mL	p value
n	84	172	251		90	177	115	
Echogcardiographic data								
LAD (mm)	42.8 ± 8.5	44.3 ± 7.1	43.8 ± 7.5	0.37	56.0 ± 13.5	51.0 ± 9.5	49.6 ± 8.4*,†	0.005
IVSd (mm)	9.8 ± 1.5	9.7 ± 2.1	9.7 ± 2.2	0.62	10.1 ± 1.8	9.8 ± 1.8	9.3 ± 2.3*,†	0.01
PWd (mm)	10.0 ± 1.5	9.6 ± 1.8	9.6 ± 2.0	0.17	9.9 ± 1.7	9.6 ± 1.7	9.3 ± 1.9*	0.01
LVEDD (mm)	49.6 ± 9.2	51.5 ± 9.6	55.4 ± 9.9*,†	<0.0001	49.1 ± 7.9	50.1 ± 8.6	52.7 ± 8.4*,†	0.008
LVESD (mm)	35.9 ± 11.3	38.6 ± 11.8	44.7 ± 11.6*,†	<0.0001	34.1 ± 7.3	36.9 ± 10.0	41.9 ± 10.9*,†	<0.0001
LVMI (ml/m^2)	108.7 ± 34.8	115.1 ± 35.5	131.5 ± 38.5*,†	<0.0001	106.6 ± 33.5	110.1 ± 36.1	115.1 ± 33.7	0.18
LAVI (ml/m^2)	41.2 ± 19.5	47.3 ± 18.4*	53.2 ± 24.7*,†	<0.0001	102.9 ± 81.0	76.7 ± 42.3*	57.4 ± 28.0*,†	<0.0001
LAVI < 40 ml/m^2, n (%)	40 (47.6)	69 (40.1)	77 (30.7)		5 (5.6)	18 (10.2)	34 (29.6)	
LAVI 40-80 ml/m^2, n (%)	41 (48.8)	92 (53.5)	145 (57.8)*	0.01	43 (47.8)	101 (57.1)	67 (58.3)*,†	<0.0001
LAVI ≥ 80 ml/m^2, n (%)	3 (3.6)	11 (6.4)	29 (11.6)		42 (46.7)	58 (32.8)	14 (12.2)	
LVEDVI (ml/m^2)	58.0 ± 23.8	68.6 ± 31.2*	84.2 ± 36.9*,†	<0.0001	52.6 ± 20.9	58.9 ± 24.7	69.1 ± 28.1*,†	<0.0001
LVESVI (ml/m^2)	28.3 ± 19.1	36.6 ± 27.9*	53.0 ± 31.5*,†	<0.0001	23.1 ± 12.3	30.2 ± 20.0*	41.7 ± 24.4*,†	<0.0001
LVEF (%)	55.1 ± 15.3	51.3 ± 15.0	40.5 ± 14.3*,†	<0.0001	56.7 ± 11.6	51.4 ± 13.6	42.9 ± 14.2*,†	<0.0001
HFpEF, n (%)	54 (64.3)	100 (58.1)	65 (25.9)		72 (80.0)	106 (59.9)	37 (32.2)	
HFmrEF, n (%)	15 (17.9)	32 (18.6)	60 (23.9)		12 (13.3)	37 (20.9)	27 (23.5)	
HFrEF, n (%)	15 (17.9)	40 (23.9)	126 (50.2)*,†	<0.0001	6 (6.7)	34 (23.5)	51 (44.4)*,†	<0.0001
TRPG (mmHg)	27.7 ± 11.6	29.5 ± 12.3	33.5 ± 15.2*	0.006	31.8 ± 13.3	33.4 ± 13.5	32.2 ± 11.6	0.49
E (cm/s)	80.7 ± 32.4	84.2 ± 31.9	81.3 ± 31.5	0.62	109.0 ± 32.8	100.4 ± 30.6	87.6 ± 30.8†	<0.0001
E/A	1.2 ± 0.8	1.3 ± 0.7	1.4 ± 0.9	0.13				
Dct (msec)	195.8 ± 73.0	185.0 ± 59.4	164.0 ± 52.4*,†	<0.0001	186.9 ± 68.1	173.9 ± 53.9	153.7 ± 50.4*,†	0.0002
e' (septal)	5.8 ± 2.5	5.4 ± 2.2	4.7 ± 1.7*,†	0.0001	8.1 ± 2.6	6.6 ± 2.1*	5.9 ± 2.2*,†	<0.0001
s' (septal)	6.4 ± 2.0	5.8 ± 2.0*	5.1 ± 1.7*,†	<0.0001	6.6 ± 2.0	5.5 ± 1.6*	4.9 ± 1.6*,†	<0.0001
e' (lateral)	7.6 ± 2.8	7.2 ± 2.6	6.5 ± 2.6*,†	0.0004	10.5 ± 3.8	9.2 ± 3.1*	8.4 ± 2.8*	0.002
s' (lateral)	7.5 ± 2.4	6.8 ± 2.4	5.8 ± 2.0*,†	<0.0001	8.6 ± 3.1	7.0 ± 2.5*	6.3 ± 2.4*	<0.0001
E/e' (septal)	15.4 ± 6.7	16.7 ± 7.5	18.5 ± 9.3*	0.05	15.3 ± 8.0	16.4 ± 8.5	16.5 ± 8.4	0.26
E/e' (lateral)	11.9 ± 5.4	12.6 ± 6.1	13.5 ± 5.9*	0.05	11.9 ± 6.3	12.0 ± 5.7	11.6 ± 5.9	0.81
AR moderate-severe, n (%)	6 (7.1)	10 (5.8)	23 (9.2)	0.44	3 (3.3)	15 (8.5)	7 (6.1)	0.27
MR moderate-severe, n (%)	14 (16.7)	34 (19.8)	71 (28.3)*	0.03	17 (18.9)	53 (29.9)*	45 (39.1)*	0.01
TR moderate-severe, n (%)	7 (8.3)	11 (6.4)	22 (8.8)	0.66	28 (31.1)	38 (21.5)	22 (19.1)	0.10
IVCD at expiration (mm)	15.9 ± 6.1	16.1 ± 9.9	17.2 ± 12.8	0.65	20.6 ± 6.5	18.9 ± 5.8	18.6 ± 5.5*	0.04

AF, atrial fibrillation; BNP, B-type natriuretic peptide; LB, low BNP; MB, medium BNP; HB, high BNP, LAD, left atrial diameter, IVSd, interventricular septal thickness at end-diastole; PWd, posterior wall thickness at end-diastole; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; HFpEF, heart failure with preserved ejection fraction; TRPG, tricuspid regurgitation pressure gradient; E, peak early diastolic flow velocity; A, peak late atrial diastolic flow velocity; Dct, desceleration time; e', mitral annular early diastolic velocity; s', mitral annular peak systolic velocity; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; IVCD, inferior vena cava diameter.

* $p < 0.05$ vs. LB by Tukey test or Steel-Dwass test,

† $p < 0.05$ vs. MB by Tukey test or Steel-Dwass test.

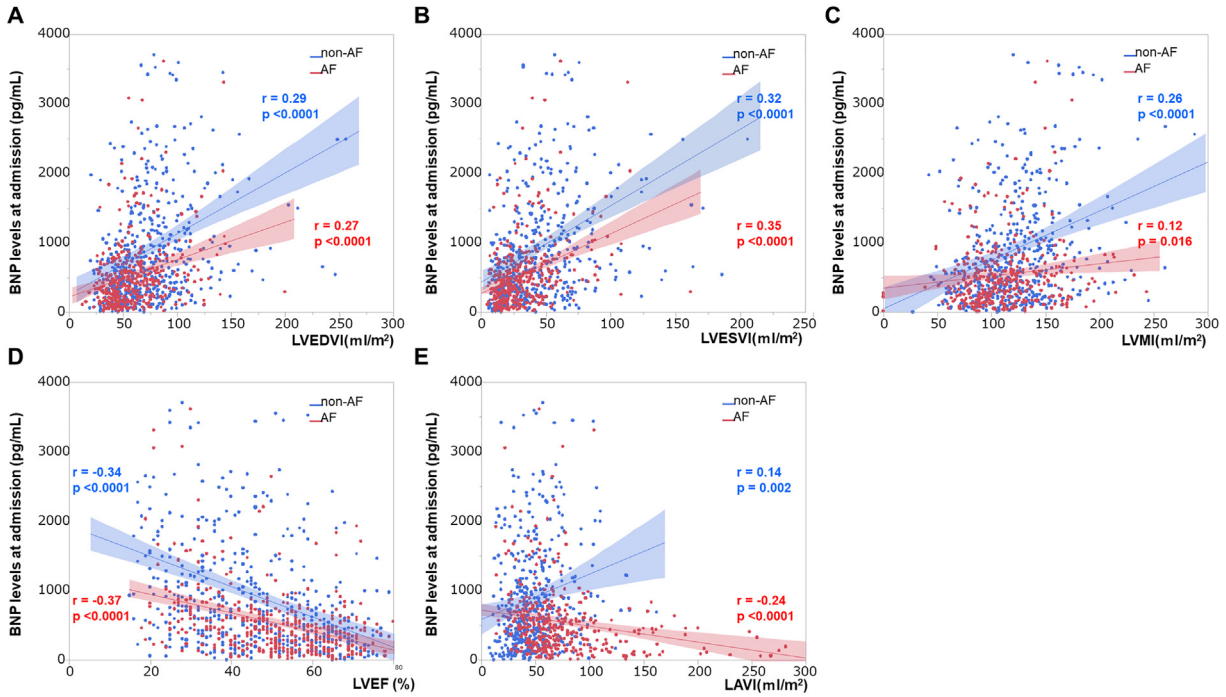

Figure 3. The comparison of correlation between BNP levels and echocardiographic parameters in acute HF patients between AF and non-AF. (*A*) LVEDVI (ml/m^2). (*B*) LVESVI (ml/m^2). (*C*) LVMI (ml/m^2). (*D*) LVEF (%). (*E*) LAVI (ml/m^2).

different between the LB, MB, and HB groups in AF patients (Figure 5). Moreover, we compared the incidence rates of HF rehospitalization and all-cause death individually according to low, medium, or high LAVI groups based on cut-off LAVI values of 40 and 80 ml/m^2 for both patients with and without AF respectively. According to the Kaplan−Meier analysis, the incidence of HF rehospitalization was significantly higher in the high LAVI group than in the low-LAVI group for patients both with and without AF (Figure 5).

Discussion

The study demonstrated that disproportionately low BNP levels (≤200 pg/ml) were more frequently detected in patients with acute HF and AF than in those without AF. BNP levels were positively correlated with LAVI values in the non-AF group, but negatively correlated in the AF group. Furthermore, BNP levels were useful for predicting HF rehospitalization and all-cause death in the non-AF group but not in the AF group.

Table 3
Independent predictor for disproportionately low BNP (BNP≤200) in patients with and without AF

	non-AF						AF					
	Univariate			Multivariate			Univariate			Multivariate		
Variables	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
age, yrs	0.99	0.97−1.01	0.25	0.99	0.97−1.02	0.58	1.01	0.99−1.04	0.41	1.02	0.98−1.05	0.36
male	1.09	0.68−1.75	0.73		−		1.00	0.62−1.62	0.99			
BMI, kg/m^2	1.11	1.06−1.17	<0.0001	1.11	1.05−1.18	0.0003	1.08	1.03−1.14	0.002	1.13	1.06−1.19	<0.0001
systolic BP, mmHg	1.00	0.99−1.00	0.43		−		1.00	0.99−1.01	0.50			
estimated GFR, ml/min/1.73m^2	1.01	1.00−1.02	0.02	1.01	1.00−1.02	0.04	1.01	1.00−1.02	0.04	1.02	1.00−1.03	0.02
LVEDVI, ml/m^2	0.97	0.96−0.98	<0.0001				0.98	0.97−0.99	0.0004			
LVESVI, ml/m^2	0.97	0.96−0.98	<0.0001	0.98	0.95 1.01	0.10	0.96	0.94−0.98	<0.0001	0.97	0.94−1.00	0.02
LVEF, %	1.04	1.03−1.06	<0.0001	1.02	0.98−1.05	0.34	1.05	1.03−1.07	<0.0001	1.01	0.98−1.04	0.53
LAVI, ml/m^2	0.98	0.96−0.99	<0.0001	0.98	0.97−1.00	0.03	1.01	1.01−1.02	<0.0001	1.01	1.01−1.02	<0.0001
LVMI, ml/m^2	0.99	0.98−0.99	0.0002	1.00	0.99−1.01	1.00	1.00	0.99−1.00	0.19			

BNP, B-type natriuretic peptide; AF, atrial fibrillation; OR, odds ratio; CI, confidense interval; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; LVMI, left ventricular mass index.

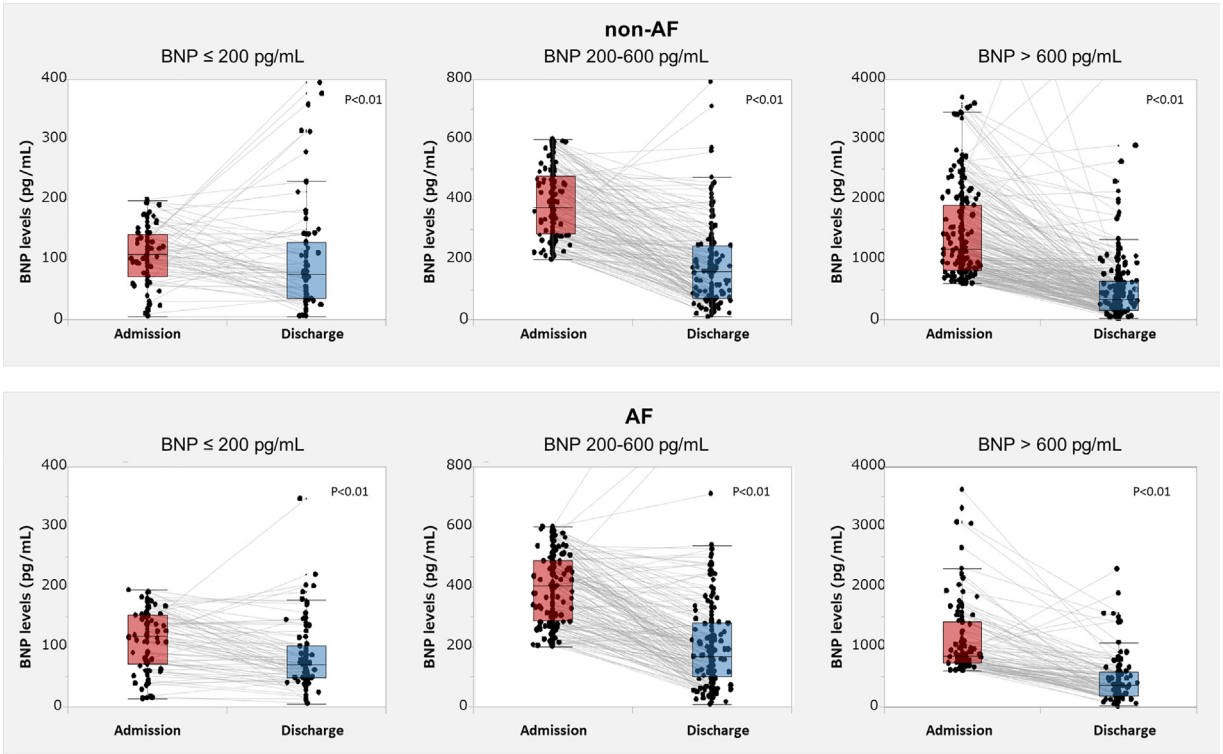

Figure 4. Changes in BNP levels at admission and discharge according to the cut-off value determined by BNP levels at admission with and without AF.

AF and BNP

Several studies have demonstrated that BNP levels are elevated in patients with AF even in the absence of HF.[12] Conversely, the diagnostic performance of BNP is impaired by AF in the presence of HF.[12] When the BNP thresholds for diagnosing acute HF in patients without AF were applied to those with AF, the sensitivity was preserved, but a marked decrease in specificity (from 80% to 30%) was observed,

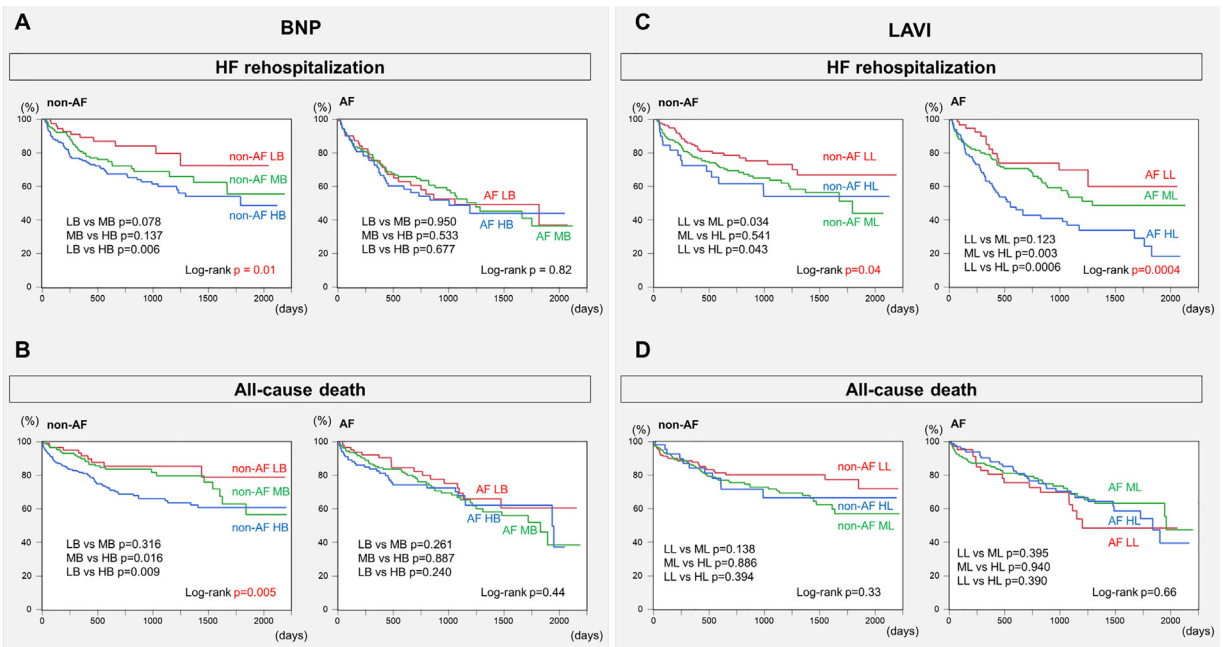

Figure 5. (*A, B*) Kaplan−Meier analysis for all-cause death and rehospitalization for HF in patients in the LB (BNP ≤200 pg/mL), MB (BNP 200-600 pg/mL), and HB (BNP >600 pg/mL) groups and the differences between AF and non-AF baseline heart rhythms (AF and non-AF). (*C, D*) Kaplan−Meier analysis for all-cause death and rehospitalization for HF in patients with LL (LAVI ≤40 ml/m^2), ML (LAVI 40-80 ml/m^2) versus HL (LAVI >80 ml/m^2), and the differences between AF and non-AF. LL, low-LAVI; ML, medium-LAVI.

leading to an increase in the false-positive rate.[12] Most recent clinical trials have used higher BNP cut-off values to include patients with AF than those without AF to avoid false positives.[13,14] Therefore, we demonstrated the clinical characteristics in acute HF patients with disproportionately low BNP levels and AF to prevent underdiagnosis of HF.

LA remodeling and BNP

Generally, BNP levels and the LAVI have been proposed to reflect elevated LV filling pressure.[15] Unexpectedly, in the study, AF modified the association between LA remodeling and BNP levels, with a significant inverse association observed in patients with acute HF and AF. Although these mechanisms were not clarified in the study, we hypothesize the following mechanisms.

BNP was mainly synthesized in the ventricular myocardium, and stimulation of its secretion may be explained by ventricular wall stress.[16] BNP release was suppressed in patients with constrictive pericarditis despite the presence of markedly elevated filling pressures because of the inhibition of myocardial stretch by the thickened and constricted pericardium.[5,17] Moreover, patients with obesity have lower BNP concentrations than those without obesity despite having higher filling pressures,[3,18,19] possibly as a result of increased fat deposition, resulting in enhanced pericardial restraint.[8,19] The findings are consistent with the relation between BMI and BNP levels observed in the study (Table 3). Recent studies have revealed that an increase in pericardial restraint not only result from pericardial abnormalities but also from enlarged epicardial heart volume (enlarged ventricle or atria).[8] Moreover, LA systole might contribute up to 20% to 30% of the LV filling in healthy individuals.[20] The absence of LA contractions is associated with decreased LV filling (atrioventricular uncoupling), resulting in limited cardiac output. Advanced LA remodeling might be associated with marked limitations in LV preload, through the loss of atrioventricular coupling and pericardial restrain, resulting in reduced secretion of NP from the ventricular myocytes.

The endocrine function of the heart mainly occurs in the atria, particulary in patients with AF.[21,22] Previous studies have suggested that LAVI values, as indicators of LV filling pressure, are positively correlated with BNP levels in patients without AF but with chronic HF.[23] However, the studies included patients with chronic HF with less advanced LA remodeling (median LAVI 34 [28 to 42] ml/m^2) when compared with our study. Fibrotic atrial remodeling may contribute to reduced secretion of NP (NP deficiency) from atrial myocytes.[24] Hence, the positive association between the BNP level and LAVI value might be explained in patients without AF (mostly with less advanced LA remodeling) and the negative association in those with AF (mostly with advanced LA remodeling) in the present study (Figure 6). We suggest that advanced LA remodeling leads to pericardial restraint and atrial fibrosis, resulting in BNP deficiency because of impaired ventricular and atrial secretion of BNP despite high LV filling pressure.[23,25]

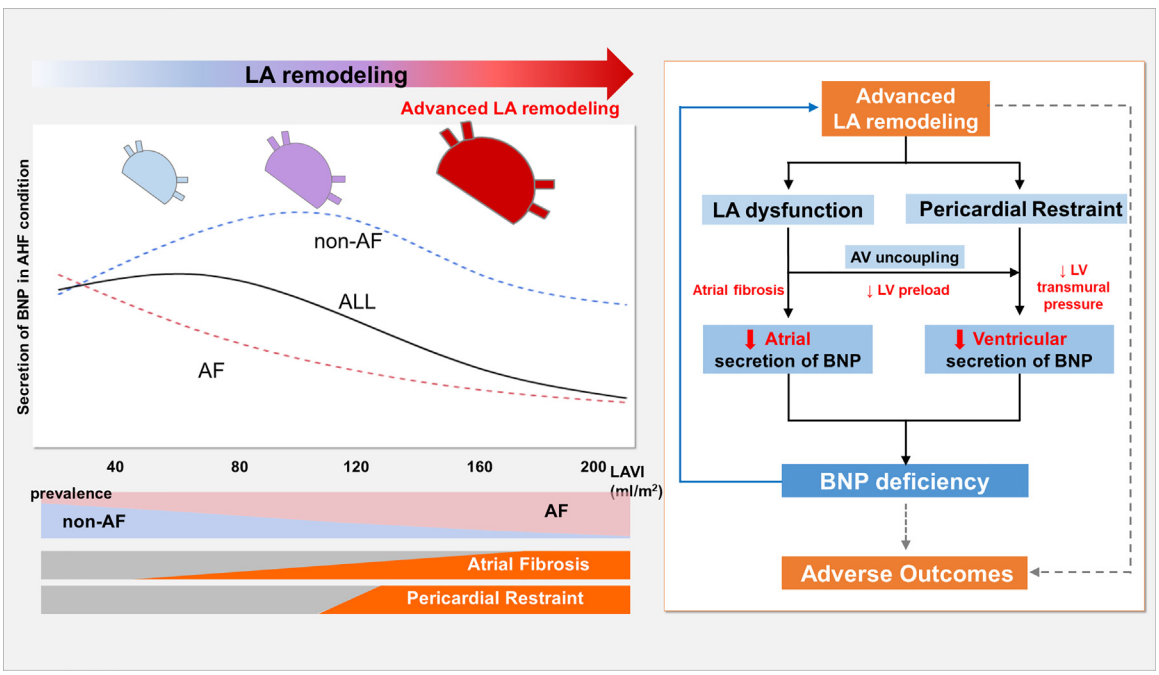

Figure 6. Different BNP secretion patterns are observed as a result of progressive LA remodeling in patients with acute HF with and without AF. Increased AF prevalence in patients with acute HF is associated with the worsening of LA remodeling. A positive association between BNP levels and LAVI in non-AF patients without advanced LA remodeling and a negative association in AF patients and non-AF with advanced LA remodeling were observed. Advanced LA remodeling may lead to atrioventricular uncoupling, pericardial restraint and atrial fibrosis, resulting in BNP deficiency because of the impaired ventricular and atrial secretion of natriuretic peptides. BNP deficiency may lead to atrial remodeling, given the significant role of natriuretic peptides. AV = uncoupling, atrioventricular uncoupling.

BNP is believed to increase protectively under conditions of HF, given the cardioprotective roles of NP in regulating cardiovascular homeostasis and intravascular volume.[2] Recently, it has been proposed that BNP deficiency causes HF because of the inability to secrete BNP despite high LV filling pressure.[26] BNP deficiency might lead to increased blood pressure, increased fluid volume, and increased adipose tissue, possibly resulting in LA remodeling (Figure 6).

Low BNP and prognosis

Previous studies suggested that BNP levels are associated with the risk of adverse outcomes in AF patients without HF.[27] In contrast, a previous large-scale analysis of the Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure trial and The Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure trial have revealed that BNP levels have prognostic value in AF patients with HF and NT-pro BNP levels >400 pg/ml.[14] However, patients with AF and low NT-pro BNP (<400 pg/ml) levels had a significantly higher event rate than those without AF.[14] We demonstrated that the presence of LB was related to a favorable prognosis in the non-AF group, but not in the AF group, in line with the findings of a previous study.[14] Furthermore, in the study, high LAVI values were associated with a poor prognosis in patients with and without AF. The current data on the inverse correlation between BNP levels and LAVI in the AF group might explain the unexpected result that the presence of LB was an indicator of poor prognosis.

Clinical implications

Current clinical guidelines provide class I recommendations for the use of BNP measurements to support HF diagnosis and assess HF severity or prognosis.[28] The diagnosis of HF in the context of AF is challenging because AF is associated with changes in the echocardiographic parameters and circulating BNP levels that confound HF diagnosis.[29] Our observations that LB in patients with AF was related to higher LAVI values and poor prognosis calls into question why a higher BNP cut-off value was employed in most clinical HF trials for the inclusion of patients with AF. Patients with disproportionately low BNP levels and high LAVI values should be carefully monitored to avoid underestimation of HF diagnosis and thus its severity. Our study identified important knowledge gaps in the management of patients with acute HF and AF.

BNP-guided therapy using a standard BNP concentration target threshold may be inappropriate for patients with advanced LA remodeling and BNP deficiency, even in acute HF conditions. Our results showed that BNP levels significantly decreased before and after conventional HF treatment in all groups, including the LB group. However, BNP-guided therapy using an individualized BNP concentration target threshold may be useful for patients with acute HF and BNP deficiency.

Limitations

Our study has some limitations. First, this was a retrospective observational study of a small-single center cohort with a limited follow-up period. Second, the study could not confirm the causal relation between LA remodeling and BNP deficiency owing to its retrospective nature. However, we believe that BNP deficiency could be a cause or result of atrial remodeling. Future studies may be required to elucidate the existing evidence on LA remodeling and BNP deficiency. Third, HF was diagnosed by well-trained cardiologists based on the universal definition of HF diagnosis[9] and confirmed by an expert HF team. However, despite this, established diagnostic criteria are lacking for HF diagnosis. Fourth, the assignment of the AF group was based on the electrocardiogram returned to baselines at hospital admission, and some patients in the non-AF group may have experienced an AF episode before or after the evaluation. Fifth, the LA remodeling was a complex phenomenon. Beyond the utilization of the atrial size (LA diameter) and volume (LAVI), multiple additional indexes are imperative for its comprehensive evaluation.[30]

Conclusions

We demonstrated that LA remodeling in patients with AF was associated with disproportionately low BNP levels and poor prognosis, which should be considered in clinical practice. These complex relations should be carefully considered in patients with acute HF and AF to avoid the underestimation of HF diagnosis and prognosis. Further investigation is needed to test the hypothesis that LA remodeling affects cardiac filling and BNP secretion.

Lay summary

Generally, both BNP levels and the LAVI have been proposed to reflect elevated LV filling pressure and poor prognosis. Unexpectedly, in the study, AF modified the association between LA remodeling and BNP levels, with a significant inverse association observed in patients with acute HF and AF. The complex relations should be carefully considered in patients with acute HF and AF to avoid the underestimation of HF diagnosis and prognosis. Further investigations are needed to test the hypothesis that LA remodeling affects BNP secretion, or that BNP deficiency affects LA remodeling.

Declaration of Competing Interest

The authors have no competing interests to declare.

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