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ORIGINAL ARTICLE

Lower B-type natriuretic peptide levels predict left ventricular concentric remodelling and insulin resistance

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Abstract

Aims Natriuretic peptides have reportedly been associated with cardiac hypertrophy and insulin resistance; however, it has not been established if B-type natriuretic peptide (BNP) is associated with either insulin resistance or cardiac remodelling in a population with normal plasma BNP levels. We investigated the relationship among plasma BNP levels, insulin resistance, and left ventricular (LV) remodelling in a population with normal physiological plasma BNP levels.

Methods and results Among 1632 individuals who participated in annual health checks between 2005 and 2008 in Arita-cho, Saga, Japan, 675 individuals [median (interquartile range) for age 62 (51–69) years; 227 men (34%)] with LV ejection fraction 50% and BNP level $<$35 pg/mL were enrolled in this study. Insulin resistance was assessed using homeostatic model assessment of insulin resistance (HOMA-IR). LV geometry, including LV concentric remodelling, was classified based on relative wall thickness (RWT) and LV mass index values derived from echocardiographic findings. Factors associated with insulin resistance and LV geometry were investigated using multiple logistic regression analysis. Tertiles of BNP were inversely associated with HOMA-IR [1st tertile, 1.33 (0.76–1.74); 2nd tertile, 1.05 (0.72–1.59); 3rd tertile, 0.95 (0.66–1.58), P = 0.005]. Lower BNP was associated with the prevalence of insulin resistance, defined as HOMA-IR $\geq$1.37, even after full multivariate adjustment [1 SD increment in BNP = adjusted odds ratio (aOR) 0.740; 95% confidence interval (CI) 0.601–0.912; P = 0.005]. LV concentric remodelling (RWT $>$0.42; LV mass index $\leq$115 g/m^2 in men and $\leq$95 g/m^2 in women) was observed in 107 (16%) participants, while normal LV geometry (RWT $\leq$0.42; LV mass index $\leq$115 g/m^2 in men and $\leq$95 g/m^2 in women) was seen in 423 (63%), and LV hypertrophy (LV mass index $>$115 g/m^2 in men and $>$95 g/m^2 in women) in 145 (21%). Both low BNP level and higher insulin resistance were independently linked to LV concentric remodelling after multivariate adjustment (1 SD increment in BNP = aOR 0.714, 95% CI 0.544–0.938, P = 0.015; HOMA-IR $\geq$ 1.37 vs. $<$1.37: aOR 1.694, 95% CI 1.004–2.857, P = 0.048, respectively).

Conclusions Lower BNP levels are linked to either insulin resistance or LV concentric remodelling in a population with normal plasma BNP levels, suggesting that participants with lower natriuretic peptide level might be vulnerable to the development of metabolic disorders and LV morphological abnormalities.

Keywords B-type natriuretic peptide; Insulin resistance; Left ventricular remodelling

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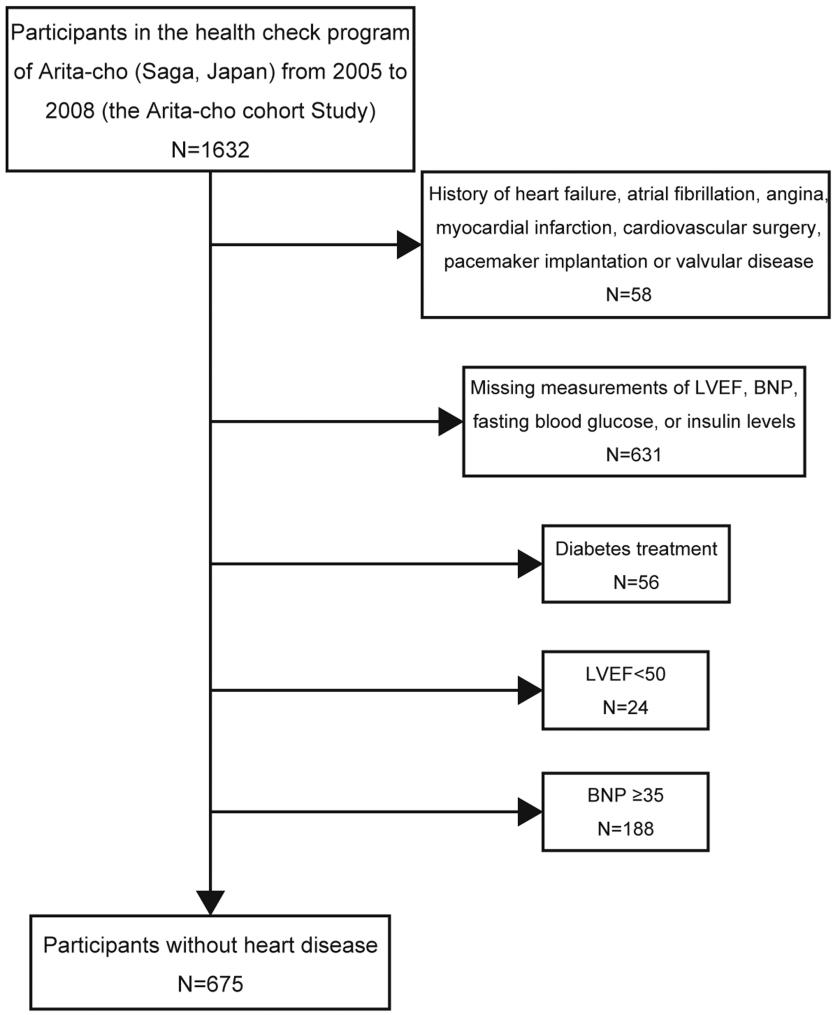
Introduction

Both atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), encoded by *Nppa* and *Nppb* genes, respectively, are synthesized predominantly in the cardiac myocytes and released into the systemic circulation in response to myocardial wall stretching.[1,2] Natriuretic peptides (NPs) exert pleiotropic effects, such as the excretion of both electrolytes

and water from the kidneys, reducing vascular tone, and demonstrating anti-hypertrophic and anti-fibrotic effects in the heart.[1] Indeed, genetic variation in or near *Nppa*, *Nppb*, and *Npra* genes encoding natriuretic peptide receptor A (NPRA) are associated with regulation of either blood pressure or cardiac hypertrophy.[3,4] In addition, lower basal NP levels were shown to predispose the development of cardiac hypertrophy in a mouse model.[5] Clinically, NPs serve as not only therapeutic agents and biomarkers for heart failure (HF) but are also a major mediator in the regulation of metabolic processes.[6] By binding to NPRA, NPs generate intracellular cyclic guanosine monophosphate (cGMP) and activate the cGMP-dependent protein kinase cascade, which promotes mitochondrial biosynthesis and fat oxidation of skeletal muscle, and has actions such as insulin resistance, improved glucose metabolism, and enhanced energy metabolism in mice.[7] In humans, log BNP levels are inversely correlated with homeostatic model assessment of insulin resistance (HOMA-IR) in patients with HF.[8] Also, higher NP levels predict lower prevalence of insulin resistance, and thus, diabetes mellitus (DM).[9,10]

Heart failure with preserved ejection fraction, a common type of HF characterized by abnormal left ventricular (LV) diastolic function,[11] is a heterogenous syndrome associated with underlying comorbid conditions, including DM and hypertension. Impaired glucose tolerance preceding mild DM, characterized as both postprandial hyperglycemia and insulin resistance, is heavily involved in the pathophysiology of HF.[12,13] Intriguingly, insulin resistance has been suggested to be involved in LV concentric remodelling,[14,15] which induces LV diastolic dysfunction and is a poor prognostic factor.[16,17] Plasma BNP levels are positively correlated with

Figure 1 Study population. The analyzed study population consisted of 675 participants without history of cardiovascular disease or treatment for diabetes mellitus. They all had BNP level and HOMA-IR measured, and had an LVEF ≥50 and BNP < 35. BNP, B-type natriuretic peptide; EF, ejection fraction; HOMA-IR, homeostatic model assessment of insulin resistance; LV, left ventricle.



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LV remodelling in patients with hypertension, DM, or HF.[18–20] However, the relationship between NP levels and LV morphological abnormalities in subclinical populations without DM or HF has not been fully elucidated.

Therefore, we investigated the association between plasma BNP level, HOMA-IR, and LV remodelling in a large subclinical population independent of HF with plasma BNP within the normal physiological range.

Methods

Study design

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committees of the National Cerebral and Cardiovascular Center and Arita-cho (M28-077-3). Written informed consent was obtained from each participant before their inclusion in the study.

The study population included 1632 participants in the Arita-cho health check program (Saga, Japan) from 2005 to 2008 (the Arita-cho cohort study). Participants who had history of cardiovascular diseases, such as HF, atrial fibrillation, angina, myocardial infarction, cardiovascular surgery, pacemaker implantation, and/or valvular disease at baseline were excluded, as were those who did not undergo measurements of their plasma levels of BNP, fasting blood glucose, and insulin. Moreover, we excluded individuals with DM under treatment, considering the effect of antidiabetic drugs on insulin resistance, and excluded those with BNP $\geq$ 35 and/or LV ejection fraction (LVEF) $<$50% to avoid participants with subclinical HF.[21] Ultimately, we enrolled 657 participants in the Arita-cho cohort study (*Figure 1*).

Laboratory tests

Blood was collected from each participant at least 10 h after the last food intake to measure their plasma levels of fasting glucose, insulin, and BNP. The plasma concentration of BNP was measured with a commercial immunoradiometric assay kit for human BNP (Shionoria; Shionogi, Osaka, Japan). The insulin resistance index was determined by the HOMA-IR method. Insulin resistance was defined as HOMA-IR $\geq$ 1.37 according to the optimal HOMA-IR cutoffs to identify individuals with dysglycaemia in the normal Asian population.[22]

Echocardiographic analysis

Echocardiography was performed by experienced technicians using commercially available ultrasonography systems. Assessments were performed in accordance with the guidelines of the American Society of Echocardiography (ASE).[23,24] LV end-diastolic and end-systolic diameters (LVDd and LVDs, respectively), interventricular septal thickness (IVST), LV posterior wall thickness (PWT), and peak E wave and septal e′ velocities were measured. Relative wall thickness (RWT) and LV mass (LVM) were calculated according to the ASE guidelines, and LVM index (LVMI) was calculated by correcting for the body surface area: RWT [mm] = (IVST + PWT)/LVDd, LVM[g] = 0.8{1.04 [(LVDd + IVST + PWT)^3 − (LVDs)^3]} + 0.6. RWT was considered increased if $>$0.42, and LVMI was considered increased if LVMI was $>$115/95 in men/women, which was the definition of cardiac hypertrophy.[25] Such analyses generated four categories: normal, concentric remodelling, eccentric hypertrophy, and concentric hypertrophy. In patients with normal geometry, either RWT or LVMI was not increased. Concentric remodelling was defined as normal LVMI but increased RWT; eccentric hypertrophy was defined as increased LVMI with normal RWT; and concentric LV hypertrophy was defined as both increased LVMI and RWT. Diastolic function abnormality was evaluated using the E/e′ ratio, which was stratified as either normal ($<$9.0) or increased ($\geq$9.0), based on the algorithm given by the Heart Failure Association of the European Society of Cardiology.[26]

Statistical analysis

Values were expressed as mean ± standard deviation if the variable was normally distributed, or median (interquartile range) if not. Groups were compared using Student's *t* test, the Wilcoxon test, or the Kruskal–Wallis test for continuous values, and the χ^2 test for categorical data, as appropriate. The Shapiro–Wilk test was used to assess whether the data were normally distributed. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Multiple logistic regression analysis investigated the factors associated with insulin resistance, LV geometry, and diastolic abnormality. Adjusted ORs (aORs) and their 95% confidence intervals (CIs) were calculated. As potential confounders, factors that were biologically essential and considered to be associated with dependent variables from previous studies were included in the multivariable analyses. There were no instances of missing data in the variables included in multivariate analysis. We modelled plasma BNP levels as tertiles, both as categorical and continuous variables, and constructed two types of multivariate models to confirm the robustness of the results. Multicollinearity among the variables in the model was assessed by calculation of the variance inflation factor and correlation coefficient. All the statistical analyses were performed with SPSS version 26 (SPSS Inc., Chicago, IL, USA) software.

Table 1 Patient characteristics classified by tertiles of BNP

	All cohort $N = 675$	1st tertile of BNP $N = 226$	2nd tertile of BNP $N = 224$	3rd tertile of BNP $N = 225$	P value
Age, years	62 (51–69)	55 (45–63)	63 (51–69)	67 (60–71)	<0.001
Male, *n* (%)	227 (34)	100 (44)	65 (29)	62 (28)	<0.001
Body mass index, kg/m^2	22.4 (20.6–24.2)	22.7 (20.7–24.8)	22.4 (20.7–23.9)	22.3 (20.3–24.2)	0.277
Obesity—body mass index ≥25 kg/m^2 (%)	130 (19)	53 (24)	38 (17)	39 (17)	0.146
Waist circumference, cm	82.0 (75.8–88.5)	82.5 (77.4–89.0)	81.5 (75.0–88.0)	82.0 (75.9–88.9)	0.279
Smoker (%)					<0.001
Current	93 (14)	52 (23)	24 (11)	17 (8)	
Past	96 (14)	38 (17)	32 (14)	26 (12)	
None	486 (72)	136 (60)	168 (75)	182 (81)	
Alcohol intake (%)					0.136
Every day	136 (20)	53 (24)	43 (19)	40 (18)	
Sometimes	196 (29)	72 (32)	67 (30)	57 (25)	
Never	343 (51)	101 (45)	114 (51)	128 (57)	
Systolic blood pressure, mm Hg	127 (114–141)	124 (112–124)	127 (114–140)	131 (116–144)	0.002
Diastolic blood pressure, mm Hg	79 (71–86)	78 (70–85)	79 (70–87)	79 (72–87)	0.423
Pulse rate, beats/min	65 (59–72)	66 (59–73)	66 (60–72)	63 (58–71)	0.088
Medical history					
Hypertension, n (%)	141 (21)	31 (14)	56 (25)	54 (24)	0.005
Dyslipidemia, n (%)	65 (10)	19 (8)	25 (11)	21 (9)	0.602
Laboratory data					
Fasting blood glucose, mg/dL	89 (82–95)	91 (83–97)	89 (83–95)	90 (84–97)	0.180
Hemoglobin A1c, %	5.6 (5.2–5.8)	5.5 (5.2–5.8)	5.6 (5.4–5.8)	5.6 (5.4–5.8)	0.316
Total cholesterol, mg/dL	202 (182–225)	201 (180–224)	200 (179–228)	204 (185–225)	0.453
Triglycerides, mg/dL	90 (64–122)	91 (65–122)	88 (63–119)	91 (67–124)	0.601
HDL-cholesterol, mg/dL	58 (50–69)	57 (50–68)	59 (50–71)	61 (50–69)	0.300
LDL-cholesterol, mg/dL	124 (104–144)	120 (101–142)	124 (101–143)	126 (109–146)	0.178
Fasting insulin, μU/mL	4.6 (3.0–6.5)	5.1 (3.3–7.0)	4.5 (3.1–6.0)	4.1 (3.0–6.0)	0.015
HOMA-IR	1.15 (0.69–1.64)	1.33 (0.76–1.74)	1.05 (0.72–1.59)	0.95 (0.66–1.58)	0.005
Insulin resistance–HOMA-IR ≥ 1.37 (%)	251 (37)	103 (46)	73 (33)	75 (33)	0.006
Estimated GFR, mL/min	82.7 (72.3–94.9)	84.7 (74.1–97.9)	85.5 (73.1–95.5)	77.0 (66.4–91.2)	0.001
Hemoglobin, g/dL	13.6 (12.7–14.5)	14.0 (13.0–15.3)	13.4 (12.5–14.2)	13.3 (12.7–14.2)	<0.001
Brain natriuretic peptide, pg/mL	14.4 (7.9–22.5)	6.1 (4.5–8.0)	14.4 (12.0–17.0)	26.1 (22.5–30.7)	<0.001

Numeric values are expressed as mean ± standard deviation or median (interquartile range).
GFR, glomerular filtration rate; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein.

Results

Plasma B-type natriuretic peptide level and insulin resistance are inversely related

Among 1632 participants in the Arita-cho health check program between 2005 and 2008, those with normal physiological range of plasma BNP (BNP < 35 pg/mL) and without reduced LV systolic function (LVEF <50%), heart disease, or diabetic treatment were extracted. The cut-off value for plasma BNP was set at <35 pg/mL to exclude potential HF and was based on guidelines provided by the European Society of Cardiology, which recommends a plasma BNP value of <35 pg/mL in non-acute settings.[21] The remaining participants who underwent both echocardiographic examinations and measurements of plasma BNP, fasting blood glucose, and plasma insulin levels were ultimately analyzed in the current study (n = 675). To confirm the relationship between plasma BNP levels and insulin resistance in this cohort, the participants were stratified into groups of tertiles based on their plasma BNP level: Tertile 1 (BNP < 9.7 pg/mL), Tertile 2 (9.7 ≤ BNP < 19.1 pg/mL), and Tertile 3 (BNP ≥ 19.1 pg/mL). *Table 1* lists the testing groups' clinical characteristics and laboratory examination data. Among the three groups, there were no significant differences in clinical characteristics, including body mass index (BMI), prevalence of obesity (BMI ≥ 25 kg/m^2), waist circumference, alcohol intake, or prevalence of dyslipidemia. The participants in the lowest BNP tertile (Tertile 1) were younger, had greater prevalence of men and smokers, and had less prevalence of hypertension compared with that in the other tertiles. Regarding the data from the laboratory examination, there were no significant differences among the three tertiles in lipid profile or in levels of fasting blood glucose and hemoglobin A1c. However, the participants in Tertile 1 had significantly higher HOMA-IR, fasting insulin levels, and prevalence of insulin resistance (HOMA-IR ≥ 1.37), suggesting that lower plasma BNP was associated with higher insulin resistance.

For an-in-depth analysis of the correlation between plasma BNP tertiles and insulin resistance (HOMA-IR ≥ 1.37), the BNP level was associated with insulin resistance in a logistic regression model, as shown in *Table 2*. The results from Model 1 (adjusted for age and sex) showed that each 1-SD increment of BNP was associated with reduced odds of insulin resistance (aOR 0.680; 95% CI 0.567–0.816; P < 0.001), which remained significant even in Model 2 (additionally adjusted for BMI, waist circumference, regular smoking, regular alcohol intake, systolic blood pressure, estimated glomerular filtration rate, plasma levels of triglycerides, and HDL-cholesterol) (aOR 0.740; 95% CI 0.601–0.912; P = 0.005). Thus, these results showed that the odds of higher insulin resistance decreased significantly across BNP level tertiles, suggesting that a lower plasma BNP level is associated with increased risk of insulin resistance, even in individuals without HF (plasma BNP < 35 pg/mL).

Low basal B-type natriuretic peptide level, as well as insulin resistance, is independently associated with left ventricular concentric remodelling

Because both plasma BNP levels and insulin resistance are well-known to be associated with LV geometric and functional changes in patients with either HF or DM, we next

Table 2 Logistic regression analysis examining BNP in tertiles in relation to insulin resistance having HOMA-IR ≥ 1.37

	High insulin resistance (HOMA-IR ≥ 1.37) vs. low insulin resistance (HOMA-IR < 1.37)		
	aOR	(95% CI)	P value
Model 1			
Model with tertile group as categorical variables			
Group 1 (lowest values)		Reference	
Group 2	0.459	0.305–0.690	<0.001
Group 3 (highest values)	0.419	0.274–0.640	<0.001
P for trend	0.648	0.523–0.802	<0.001
1 SD change of BNP included as continuous variables	0.680	0.567–0.816	<0.001
Model 2			
Model with tertile group as categorical variables			
Group 1 (lowest values)		Reference	
Group 2	0.506	0.318–0.804	0.004
Group 3 (highest values)	0.470	0.290–0.761	0.002
P for trend	0.688	0.540–0.876	0.002
1 SD change of BNP included as continuous variables	0.740	0.601–0.912	0.005

Number of participants was 675. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, body mass index, waist circumference, regular smoking, regular alcohol intake, systolic blood pressure, estimated glomerular filtration rate, plasma levels of triglycerides, and HDL-cholesterol. BNP levels within tertiles are as follows [median (25–75% inter-tertile range)]: Tertile 1, 6.1 (4.5–8.0) pg/mL; Tertile 2, 14.4 (12.0–17.0) pg/mL; Tertile 3, 26.1 (22.5–30.7) pg/mL.
aOR, adjusted odds ratio; CI, confidence interval.
For abbreviations, refer to *Table 1*.

compared the parameters of the echocardiographic examination among the three tertiles based on the plasma BNP level in this cohort, as shown in *Table 3*. Participants in the highest BNP tertile (Tertile 3) had higher LV mass index, larger left atrial diameter, lower E/A ratio and e′, and higher E/e′ values, indicating elevated LV end-diastolic pressure (LVEDP), all of which increased or decreased across the individual tertile with a positive or negative association with BNP levels. However, there were no significant differences in RWT among the three tertiles. Therefore, we further investigated the clinical factors associated with LV geometrical changes, including LV concentric remodelling and hypertrophy among participants with normal plasma BNP, using multivariable polytomous logistic regression analysis and used data from participants with normal LV geometry as reference. Further, factors associated with diastolic function abnormality were investigated using multivariable binary logistic regression analysis.

As shown in *Table 4*, the results from Model 1 (adjusted for age and sex) showed that each 1-SD increment of BNP levels was associated with reduced odds of LV concentric remodelling to normal geometry (aOR 0.715; 95% CI 0.551–0.927; $P = 0.011$), which also remained significant in Model 2 (additionally adjusted for BMI, waist circumference, regular smoking, regular alcohol intake, systolic blood pressure, plasma levels of triglycerides, log BNP, and log HOMA-IR) (aOR 0.714; 95% CI 0.544–0.938; $P = 0.015$). In Model 1, the participants in the middle tertile (aOR 0.505; 95% CI 0.281–0.906; $P = 0.022$) and the highest tertile of BNP levels (aOR 0.501; 95% CI 0.277–0.904; $P = 0.022$) were similar in low risk of LV concentric remodelling. This association remained significant in model 2 (the middle tertile: aOR 0.495, 95% CI 0.270–0.907, $P = 0.023$; and the highest tertile: aOR 0.510, 95% CI 0.275–0.945, $P = 0.032$). However, increment in BNP was not associated with LV hypertrophy or LV diastolic function abnormalities after the adjustment for other variables. High insulin resistance (HOMA-IR $\geq$ 1.37) was also independently and positively associated with LV concentric remodelling (Model 1: aOR 2.136, 95% CI 1.349–3.384, $P = 0.01$; Model 2: aOR 1.694, 95% CI 1.004–2.857, $P = 0.048$) but not with LV hypertrophy and LV diastolic function abnormalities. Both age $\geq$65 years and systolic blood pressure $\geq$130 mm Hg were independently associated with all types of LV geometric changes in model 2: LV concentric remodelling (aOR 4.097, 95% CI 2.368–7.090, $P < 0.001$; and aOR 1.720, 95% CI 1.050–2.817, $P = 0.031$, respectively); LV hypertrophy (aOR 1.771, 95% CI 1.121–2.800, $P = 0.014$; and aOR 1.853, 95% CI 1.189–2.889, $P = 0.006$, respectively); and LV diastolic function abnormalities (aOR 1.922, 95% CI 1.303–2.835, $P = 0.001$; and aOR 1.855, 95% CI 1.276–2.695, $P = 0.001$, respectively). These findings suggested that the lower the plasma BNP levels, the greater the prevalence of concentric LV remodelling, and that high insulin resistance was positively associated with concentric LV remodelling even in the participants within normal physiological range of BNP levels $<$35 pg/mL.

Table 3 Echocardiographic parameters classified by tertiles of BNP

	All cohort $N = 675$	1st tertile of BNP $N = 226$	2nd tertile of BNP $N = 224$	3rd tertile of BNP $N = 225$	P value
Interventricular septal thickness, mm	8.6 (7.1–9.7)	8.7 (7.3–9.7)	8.1 (7.0–9.0)	8.8 (7.8–10.0)	0.099
Posterior wall thickness, mm	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–9.0)	0.204
LV end-diastolic dimension, mm	46 (43–49)	46 (43–50)	46 (43–48)	46 (42–49)	0.142
LV end-systolic dimension, mm	28 (25–30)	28 ± 4	27 ± 4	27 ± 4	0.012
LV ejection fraction, %	65 (59–70)	63 (58–70)	64 (58–70)	66 (60–72)	0.023
Relative wall thickness, mm	0.37 (0.33–0.42)	0.37 (0.33–0.42)	0.37 (0.33–0.42)	0.38 (0.34–0.43)	0.247
LV concentricity–RWT $>$ 0.42 mm (%)	170 (25)	56 (25)	50 (22)	64 (28)	0.323
LV mass, g	131 (106–159)	133 (108–164)	122 (104–153)	133 (109–163)	0.068
LV mass index, g/m^2	85 (71–100)	83 (71–98)	83 (70–98)	91 (73–105)	0.006
LV hypertrophy–LVMI $>$ 115/95 m/f (%)	145 (21)	33 (15)	43 (19)	69 (31)	$<$0.001
LV geometry					0.003
Normal geometry	423 (63)	153 (68)	149 (67)	121 (54)	
LV concentric remodelling	107 (16)	40 (18)	32 (14)	35 (16)	
LV concentric hypertrophy	63 (9)	16 (7)	18 (8)	29 (13)	
LV eccentric hypertrophy	82 (12)	17 (8)	25 (11)	40 (18)	
LA diameter, mm	36 (32–39)	35 (31–39)	35 (32–38)	37 (33–40)	0.034
E wave velocity, m/s	63 (52–74)	63 (52–74)	65 (53–76)	63 (52–74)	0.355
A wave velocity, m/s	68 (55–82)	63 (50–79)	71 (58–85)	70 (58–84)	$<$0.001
E/A ratio	0.89 (0.73–1.17)	1.00 (0.76–1.29)	0.88 (0.73–1.13)	0.83 (0.70–1.07)	$<$0.001
Deceleration time, ms	208 (183–244)	208 (172–239)	207 (183–237)	213 (187–250)	0.154
e′, cm/s	6.6 (5.3–8.8)	7.3 (5.8–9.1)	6.7 (5.3–8.9)	6.1 (5.0–7.8)	$<$0.001
E/e′	9.3 (7.4–11.4)	8.6 (6.9–10.6)	9.1 (7.6–11.7)	9.9 (8.2–12.1)	$<$0.001
LV diastolic function abnormality–E/e′ ratio $\geq$9.0 (%)	347 (51)	98 (43)	113 (50)	136 (60)	0.002

Numeric values are expressed as mean ± standard deviation or median (interquartile range).
LA, left atrium; LV, left ventricle; LVMI, left ventricular mass index; RWT, relative wall thickness.

Table 4 Multivariate adjusted relations between BNP/insulin resistance/age/blood pressure and indexes of LV remodelling, LV hypertrophy, and LV diastolic function abnormality

	LV concentric remodelling vs. normal geometry			LV hypertrophy vs. normal geometry			LV diastolic function abnormality (E/e′ ratio ≥9.0)		
Variables	aOR	(95% CI)	*P* value	aOR	(95% CI)	*P* value	aOR	(95% CI)	*P* value
Model 1									
BNP									
Model with tertile group as categorical variables									
Group 1 (lowest values)		Reference			Reference			Reference	
Group 2	0.505	0.281–0.906	0.022	0.812	0.469–1.404	0.456	0.898	0.587–1.374	0.619
Group 3 (highest values)	0.501	0.277–0.904	0.022	1.292	0.760–2.196	0.344	1.016	0.655–1.577	0.942
P for trend	0.711	0.528–0.959	0.025	1.173	0.900–1.529	0.238	1.010	0.811–1.258	0.927
1 SD change of BNP included as continuous variables	0.715	0.551–0.927	0.011	1.108	0.872–1.409	0.400	1.021	0.848–1.231	0.825
Insulin resistance									
Low insulin resistance (HOMA-IR < 1.37)		Reference			Reference			Reference	
High insulin resistance (HOMA-IR ≥ 1.37)	2.136	1.349–3.384	0.001	1.101	0.729–1.663	0.646	1.372	0.968–1.945	0.076
Age									
<65 years		Reference			Reference			Reference	
≥65 years	4.663	2.951–7.368	<0.001	2.702	1.829–3.992	<0.001	3.167	2.271–4.417	<0.001
Blood pressure									
Systolic blood pressure <130 mm Hg		Reference			Reference			Reference	
Systolic blood pressure ≥130 mm Hg	1.989	1.239–3.192	0.004	2.144	1.406–3.268	<0.001	2.114	1.476–3.027	<0.001
Model 2									
BNP									
Model with tertile group as categorical variables									
Group 1 (lowest values)		Reference			Reference			Reference	
Group 2	0.495	0.270–0.907	0.023	0.774	0.433–1.381	0.385	0.926	0.596–1.440	0.734
Group 3 (highest values)	0.510	0.275–0.945	0.032	1.318	0.746–2.327	0.342	1.089	0.687–1.725	0.717
P for trend	0.721	0.528–0.984	0.039	1.198	0.902–1.590	0.212	1.047	0.832–1.317	0.697
1 SD change of BNP included as continuous variables	0.714	0.544–0.938	0.015	1.127	0.872–1.456	0.361	1.054	0.866–1.283	0.600
Insulin resistance									
Low insulin resistance (HOMA-IR < 1.37)		Reference			Reference			Reference	
High insulin resistance (HOMA-IR ≥ 1.37)	1.694	1.004–2.857	0.048	0.675	0.416–1.096	0.112	1.053	0.708–1.567	0.797
Age									
<65 years		Reference			Reference			Reference	
≥65 years	4.097	2.368–7.090	<0.001	1.771	1.121–2.800	0.014	1.922	1.303–2.835	0.001
Blood pressure									
Systolic blood pressure <130 mm Hg		Reference			Reference			Reference	
Systolic blood pressure ≥130 mm Hg	1.720	1.050–2.817	0.031	1.853	1.189–2.889	0.006	1.855	1.276–2.695	0.001

Model 1 was adjusted for age (except for variable of age) and sex. Model 2 was adjusted for age (except for variable of age), sex, body mass index, waist circumference, regular smoking, regular alcohol intake, systolic blood pressure (except for variable of blood pressure), plasma levels of triglycerides, log BNP (except for variable of BNP), and log HOMA-IR (except for variable of insulin resistance). BNP levels within tertiles were as follows [median (25–75% inter-tertile range)]: Tertile 1, 6.1 (4.5–8.0) pg/mL); Tertile 2, 14.4 (12.0–17.0) pg/mL; Tertile 3, 26.1 (22.5–30.7) pg/mL.
For abbreviations, refer to *Tables 1* and *2*.

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Additional analysis to support our results

As the European Society of Cardiology guidelines have defined 100 pg/mL as the upper limit of normal BNP in acute settings,[21] we performed an identical analysis in participants with BNP < 100 pg/mL (*N* = 836, Supporting information *Figure* S1) and found that, similar to results with BNP < 35 pg/mL, low BNP was independently associated with insulin resistance and LV concentric remodelling (*Figure* S1; *Tables 2* and *4*). Even though the association between BNP and insulin resistance disappeared when BNP was <100 pg/mL, it remained significant when we analysed the same as tertiles of categorical variables in the population with BNP < 35 pg/mL alone (*Table 2*). Furthermore, because antihypertensive drugs or lipid-lowering-drugs may affect cardiac remodelling or glucose metabolism, the therapeutic effects of these drugs should be excluded; however, as detailed information on therapies was unavailable, only data from participants without hypertension or dyslipidemia in their medical history who were not prescribed antihypertensive drugs or lipid-lowering-drugs was used (*N* = 500, *Figure* S2). We demonstrate that, even in a population without the medical history of hypertension or dyslipidemia, low BNP was independently associated with insulin resistance and LV concentric remodelling (*Table* S2).

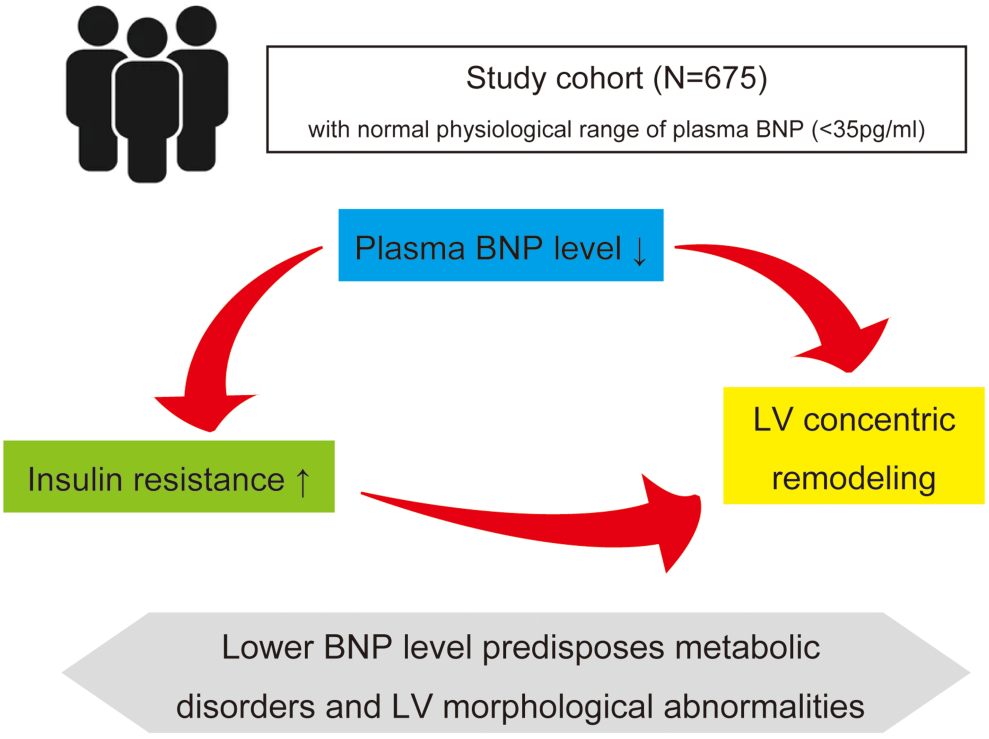
Discussion

Natriuretic peptides have been established as a biomarker of HF and have been attracting attention as a mediator not only for the cardiac remodelling process but also for metabolic regulation.[1] In the current study, we explored the associations of plasma BNP levels, insulin resistance, and LV geometric (or morphological) changes in a subclinical cohort free from cardiovascular diseases with normal ranges of BNP plasma levels. Our findings in the current study were as follows: Plasma BNP levels were inversely associated with insulin resistance; high insulin resistance was associated with LV concentric remodelling; and the plasma BNP level was also inversely associated with LV concentric remodelling, independent of insulin resistance (*Figure 2*). We should emphasize that this is the first report of an inverse association between basal plasma BNP levels and LV concentric remodelling in populations with normal plasma BNP levels.

The reverse association between natriuretic peptides and insulin resistance

Some clinical studies have investigated the association between NP levels and insulin resistance.[1] According to one of

Figure 2 Relationship between plasma BNP level, insulin resistance, and LV concentric remodelling. The plasma BNP level was inversely associated with insulin resistance and LV concentric remodelling, and high insulin resistance was also associated with LV concentric remodelling. BNP, B-type natriuretic peptide; LV, left ventricle.



these studies, NH_2-terminal pro-BNP was inversely associated with fasting glucose, insulin levels, and diabetes risk in a community-based population without diabetes or cardiovascular disease.[10] A similar inverse association between plasma BNP levels and HOMA-IR was observed in patients with HF, suggesting that an elevated plasma BNP level counteracts the progression of diabetes by improving insulin resistance, even in the metabolically harmful condition of HF.[8] Our current study extended the concept of an inverse association between NPs and the risk of insulin resistance in individuals with plasma BNP levels in the normal range (<35 ng/mL), suggesting that lower plasma BNP levels are associated with a significantly higher prevalence of insulin resistance, even in the populations with normal plasma BNP. These results from clinical studies are supported by animal studies showing the favorable effects of NPs against insulin resistance.[7] Interestingly, lower BNP levels were independently associated with insulin resistance, and even though obesity is a known cause of lower BNP,[1] there were no significant differences in BMI, waist circumference, or prevalence of obesity among the BNP tertiles. Therefore, it is possible that lower level of plasma BNP worsens insulin resistance through mechanisms unrelated to obesity in this cohort.

Also, when we analysed the association between BNP and insulin resistance and compared that between BNP < 35 pg/mL and 35–100 pg/mL, the association disappeared. This blunted the association between BNP and insulin resistance may have been caused by additional synthesis of BNP due to unknown hypertrophic stimuli related to latent HF in the population with BNP 35–100 pg/mL. Thus, we suggest that our analysis using only the population with BNP < 35 pg/mL has clinical implications.

A role of natriuretic peptides for left ventricular remodelling

Cardiomyocytes secrete NPs into the systemic circulation in response to myocardial mechanical loading[2]; thus, the elevation of plasma NP is essential to cardiac hypertrophy or failure.[1] Previous studies have shown that plasma BNP levels are well correlated with LVMI, that is, LV hypertrophy and LV diastolic function.[27,28] LV hypertrophy is an established independent risk factor for cardiovascular morbidity and mortality.[29] However, LV concentric remodelling, defined as increased RWT and normal LVMI, is also associated with poorer prognoses compared with the normal LV geometry.[16,17] In addition, LV concentric remodelling could be a prerequisite for LV hypertrophy and diminished LV diastolic function,[30] and LV concentric remodelling is one of the major age-related LV remodelling patterns, which could confer adverse cardiovascular outcomes, particularly when present earlier in life.[31]

In contrast to previous studies showing a positive association between plasma BNP levels and LV morphological abnormalities,[18] we demonstrate, for the first time, that a lower BNP level was associated with a higher prevalence of LV concentric remodelling even after multiple adjustment for clinical factors, including age, sex, blood pressure, and insulin resistance, by analysing only participants within the normal BNP range. This discrepancy may be due to differences in study populations; specifically, while we analyzed data from consenting participants of a health check program who did not have a history of cardiac disease and had normal plasma BNP levels, previous studies included participants with higher BNP levels. Further, although basal BNP synthesis in the ventricles is typically low in healthy participants, factors such as mechanical overload, neurohumoral factors, or cytokines can trigger greater synthesis, which can overcome the anti-hypertrophic effect of NPs—effectively, it is possible that this study population experienced fewer hypertrophic stimuli and/or triggers of 'additional' NP synthesis. Therefore, while it is possible that previous studies have evaluated the relationship between such 'additional' synthesis of BNP and left ventricular remodelling, we investigated the relationship between 'basal' BNP and left ventricular remodelling, which has yielded contradictory results. Our findings also suggest that the plasma 'basal' BNP levels could be directly involved in LV concentric remodelling even in the absence of cardiovascular disease. Experimental studies demonstrating that mice lacking NPRA have marked cardiac hypertrophy independent of blood pressure[32] and that NPs suppress cancer cell proliferation in vitro by inhibiting DNA synthesis, partly through cGMP,[33] support our findings. On the other hand, unlike previous studies, plasma BNP level was not significantly associated with either LV hypertrophy or LV diastolic dysfunction after adjusting for other variables such as age and blood pressure. The positive correlation between BNP levels and LV mass index or E/e′ in our cohort may be largely influenced by age and blood pressure. A likely explanation could be that hypertrophic stimuli are negligible in our cohort with normal BNP levels and without cardiovascular diseases. Therefore, the LV morphology might become sensitive to the 'basal' level of NPs in these individuals, and the lower BNP level could predispose them to LV concentric remodelling. Given previous studies included individuals with elevated plasma BNP, the hypertrophic stimuli could have overwhelmed the protective effect of NPs, leading to LV hypertrophic remodelling and LV diastolic dysfunction, although 'additional' NP synthesis and secretion were induced by the hypertrophic stimuli in these patients.

Association between natriuretic peptides, insulin resistance, and left ventricular concentric remodelling

The previous study showed a significant association between insulin resistance as evaluated by HOMA-IR and reduced LV

diastolic function in patients with metabolic disorders without HF.[34] Recently, concentric LV remodelling was reported to be mediated, in part, by increased insulin levels and insulin resistance,[35] suggesting direct growth promoting the effect of an insulin-dependent signaling pathway on cardiomyocytes. This idea is supported by animal studies in which insulin-dependent cardiac growth is mediated by the Akt signaling pathway.[36] The current study also demonstrated a significant association between insulin resistance and LV concentric remodelling, even after multiple adjustment for age, sex, blood pressure, and BNP level. These findings suggested that both lower BNP levels and higher insulin resistance contribute to the development of LV concentric remodelling in populations with a normal BNP level. However, insulin resistance was associated with neither LV hypertrophy nor LV diastolic dysfunction. It is important to follow up this cohort on echocardiographic data, and BNP level in the future to investigate whether lower basal BNP is involved in the development of cardiac hypertrophy and diastolic dysfunction.

Natriuretic peptides as a therapeutic target

Recently, it has become evident that there is a subpopulation of patients with HF and unexpectedly low BNP levels,[37] implying that the physiological and clinical consequences of relative or absolute NPs deficiency need to be defined in both HF patients and healthy populations. Considering that lowering NP levels by deleting the enhancer element of either *Nppa* or *Nppb* genes induced spontaneous cardiac hypertrophy in a mouse model,[5] our findings suggested that lower basal BNP can cause LV concentric remodelling even in individuals without either HF or diabetes. It is widely recognized that cardiac concentric remodelling contributes to LV diastolic dysfunction.[38] Insulin resistance due to lower plasma BNP levels could also contribute to the development of diastolic dysfunction because insulin resistance is considered one of the causes of its development.[11] In a study of acute HF, preserved ejection fraction (EF) and lower baseline ANP levels were reported to be independent predictors of a greater diuretic effect of exogenous ANP, and it has been suggested that patients with HF and preserved EF might have NP deficiency and hence represent a promising therapeutic target for modulating circulating NP levels.[39] Additionally, LCZ696 (sacubitril valsartan sodium hydrate), which enhances the action of NPs by inhibiting neprilysin, increases insulin sensitivity index among patients with obesity and hypertension.[40] Therefore, neprilysin inhibition might be efficacious in individuals with lower basal BNP levels for preventing the development of LV concentric remodelling beyond the effects of antihypertensive therapy.

Study limitations

The present study has several limitations. First, the associations revealed in the study do not indicate causation or causality because of its cross-sectional nature. Future longitudinal studies, including assessment of repetitive echocardiographic measurement during follow up, are needed to uncover whether development of cardiovascular disease and improvements after correcting NP deficiency are related. Second, despite accounting for background characteristics when adjusting for potential confounders in multivariate analyses, residual bias cannot be ruled out. Notably, because this was an epidemiological study that used data from a health check program, we were unable to evaluate other biomarkers related to LV fibrosis and hypertrophy or detailed functional analysis of echocardiography, such as global longitudinal strain, and atrial strain and function. Third, we excluded participants for whom data on echocardiogram, plasma BNP, glucose, or insulin levels, were not available, and this may have led to selection bias. Fourth, the percentage of men was relatively low in the present cohort; thus, there could be a gender bias. Fifth, this cohort study consisted of rural residents; therefore, these outcomes could differ from those among urban residents. Finally, given it was a subclinical population, the number of clinical events were limited, so it was not possible to sufficiently analyze prognosis following the present conclusion.

Conclusions

In the cohort before the onset of HF, a lower basal BNP level was significantly associated with insulin resistance and LV concentric remodelling, suggesting that NP deficiency could cause metabolic disorders and LV morphological abnormalities.

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Conflict of interest

None declared.

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Supporting information

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

Table S1. Logistic regression analysis examining BNP in relation to insulin resistance having HOMA-IR $\geq$ 1.37, indexes of LV remodelling, LV hypertrophy, and LV diastolic function abnormality in the population with BNP less than 100 pg/ml.

Table S2. Logistic regression analysis examining BNP in relation to insulin resistance having HOMA-IR $\geq$ 1.37, indexes of LV remodelling, LV hypertrophy, and LV diastolic function abnormality in the population with BNP less than 35 pg/ml without hypertension and dyslipidemia in their medical history.

Figure S1. Study population of the first additional analysis to support our results.

The additional analyzed study population consisted of 836 participants without history of cardiovascular disease or treatment for diabetes mellitus. They all had BNP level and HOMA-IR measured, and had an LVEF $\geq$50 and BNP $<$ 100. BNP, B-type natriuretic peptide; HOMA-IR, homeostatic model assessment of insulin resistance; LV, left ventricle; EF, ejection fraction.

Figure S2. Study population of the second additional analysis to support our results.

The additional analyzed study population consisted of 500 participants without history of cardiovascular disease or treatment for diabetes mellitus. They all had BNP level and HOMA-IR measured, had an LVEF $\geq$50 and BNP $<$ 35 and were without hypertension or dyslipidemia in their medical history.

BNP, B-type natriuretic peptide; HOMA-IR, homeostatic model assessment of insulin resistance; LV, left ventricle; EF, ejection fraction.

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