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ORIGINAL ARTICLE

What factors are associated with high plasma B-type natriuretic peptide levels in a general Japanese population?

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There are few community-based epidemiologic studies that have dealt with risk factors for heart failure in non-Western populations. It has been reported that the measurement of plasma B-type natriuretic peptide (BNP) is useful for detecting patients with asymptomatic heart failure. To clarify the determinants of high plasma BNP level, the association of BNP with cardiovascular risk factors in community dwelling residents was examined. The plasma BNP levels were measured in 686 residents aged 35–69 years who received annual health check-up. The relationship of BNP to blood pressure, blood haemoglobin, serum cholesterol (total and high-density lipoprotein cholesterol), plasma glucose, electrocardiographic (ECG) findings, urinary salt excretion, and lifestyle factors (smoking and alcohol consumption) were cross-sectionally analysed. The plasma BNP geometric mean was 13.7 pg/ml. Both linear and logistic regression analyses indicated that the plasma BNP levels were positively associated with age, urinary salt excretion, higher blood pressure, high R-wave voltage in the 12-lead ECG (Minnesota Code 3-1 or 3-3), and female gender. Plasma BNP levels were inversely associated with blood haemoglobin levels. Gender-specific analysis showed similar results. However, plasma BNP did not correlate with other cardiovascular risk factors such as serum lipids.
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Introduction

Approximately 15% of deaths in Japan are due to heart diseases, of which about one-third are due to heart failure.[1] In 2001, mortality due to heart failure was 36.9 per 100 000 person-years, which is approximately two-thirds of that due to coronary heart disease (56.4 per 100 000 person-years).[1] The risk factors for coronary heart disease have been well described in several epidemiologic studies in Japan.[2–6] However, there are few available epidemiologic studies that deal with the risk factors for heart failure, even though it is a major problem in the Japanese population.[7,8] Accordingly, it is very important to clarify the risk factors for heart failure in Japan.

Congestive heart failure is usually regarded as the end-stage of the progressive deterioration of left ventricular function, which cannot be compensated for by cardiovascular homeostatic mechanisms.[9,10] Although heart failure is usually progressive, it can remain asymptomatic for many years. Thus, it would be of benefit to identify latent patients who have asymptomatic left ventricular dysfunction. However, in the general population, it is difficult and expensive in the primary care setting to screen the general population using Doppler echocardiography or exercise tolerance tests to diagnose left ventricular dysfunction.

B-type natriuretic peptide (BNP) is synthesized and released from the myocardium in response to an increase in ventricular filling pressure.[11] Recently, it was reported that the measurement of plasma BNP has a high sensitivity and a high specificity for detecting patients with asymptomatic heart failure or left ventricular dysfunction.[12–15] However, there are only a few studies that have examined the factors that are associated with high plasma BNP levels in the non-Western population.[16,17]

The purpose of this study is to clarify the risk factors for high plasma BNP levels, which is an important marker of asymptomatic heart failure, in a Japanese general population.

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Population and methods

Study population

The participants were 957 residents aged 35–69 years, who received regular annual health check-ups for the residents except for employees under the Health and Medical Service Law for the Aged, in SA town, Shiga Prefecture, a rural community in Western Japan. Well-trained nurses interviewed each participant to obtain a medical history and lifestyle information such as smoking and alcohol consumption. Of the 827 participants who gave informed consent, 13 participants did not have the complete data needed for the analysis. Of a total of 814 eligible participants, 128 were excluded for the following reasons: past or present history of coronary heart disease ($n=18$), diabetes mellitus ($n=48$), atrial fibrillation ($n=2$), and having symptoms suspected of heart failure, such as some clinical conditions that preclude physical exercise ($n=60$). No participants had a past or present history of renal disease. Thus, 686 residents aged 35–69 years participated in the study (209 men and 477 women; mean age $\pm$ s.d., 56.1 ± 9.7 years).

All the procedures of this study were reviewed and approved by the Institutional Review Board of Shiga University of Medical Science (No.14-10, 2002).

Clinical examination

The body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). The blood pressure was measured twice after 5 min of rest using an automatic sphygmomanometer (COLIN CORPORATION, BP-103i II, Aichi, Japan) placed on the right arm of participants in the sitting position. The mean of the two measurements was used for this analysis. The blood pressure was classified into the following four categories using WHO criteria of 1999:[18] optimal and normal—systolic blood pressure (SBP) under 130 mmHg and diastolic blood pressure (DBP) under 85 mmHg; high normal—SBP 130–139 mmHg and/or DBP 85–89 mmHg; grade 1—SBP 140–159 mmHg and/or DBP 90–99 mmHg; and grades 2 and 3—SBP 160 mmHg or greater and/or DBP 100 mmHg or greater.

Blood samples were drawn from an antecubital vein of nonfasting participants, and then analysed in one laboratory (KINKIYOKEN, Shiga). Plasma samples for the BNP measurements were transferred immediately to tubes with 1.0 mg/ml of EDTA-2Na and 500 kallikrein inhibitory units (KIU)/ml of aprotinin. Plasma was obtained by centrifugation at 3000 rpm for 10 min at 4°C and stored at −80°C until analysis. Plasma BNP concentration was measured with specific immunoradiometric assays for human BNP (ShionoRIA BNP kit, Shionogi & Co., Ltd, Osaka, Japan).[12–14,16,19,20] For BNP, the intra- and inter-assay coefficients of variation for this assay were 1.3 and 3.2%, respectively. Plasma BNP level of 18 pg/ml or greater were considered indicative of potential left ventricular dysfunction. This was based on a previous study conducted in the UK that showed this BNP cutoff value had a sensitivity of 77% and a specificity of 87% in 1252 participants aged 25–74 years for diagnosing left ventricular systolic dysfunction (left ventricular ejection fraction 30% or less).[15]

Total cholesterol and high-density lipoprotein (HDL) cholesterol in serum were measured enzymatically. Lipid measurement at the reporting laboratory has been standardized at the Osaka Medical Center for Health Science and Promotion, by a member of the Cholesterol Reference Method Laboratory Network (CRMLN).[21,22] Plasma glucose was measured by the hexokinase method. Blood haemoglobin was determined by the latex coagulation method.

Electrocardiography (ECG) was performed by standard 12-lead ECG after the patient had rested sufficiently. Findings of high R-wave voltage, ST-T depression, and an inverse- or flat-T-wave in the ECG were defined according to the Minnesota Code (MC).[23] High R-wave voltage in the 12-lead ECG was defined by the following: an R-wave in V5 or V6 of 2.6 mV or greater (MC 3-1) and/or the height of the R-wave in V1 plus V5 or V6 of 3.5 mV or greater (MC 3-3). Other findings that were documented if present included ST-T depression (MC 4-1 or 4-3), and inverse or flat T-waves (MC 5-1 or 5-3).

Daily salt excretion was estimated by Tanaka's formulas,[24] which estimate populational daily urinary salt excretion from the sodium and creatinine levels in casual urine samples. Using a self-reported questionnaire administered by well-trained nurses, the participants were asked about daily alcohol intake and smoking habits.

Statistical analyses

The possible determinants of BNP were divided into quartiles or categories. Geometric means of BNP were used for the analysis of each determinant because the distribution of BNP was positively skewed. To compare these with the crude geometric means of BNP in each quartile or category, analysis of variance was used. Comparisons with age- and gender-adjusted geometric means of BNP were performed using analysis of covariance. Gender-specific analysis was also performed.

Linear regression analysis was used to clarify the contribution of each independent variable to BNP. Multiple logistic regression analysis was used to assess the contribution of each independent variable to a high plasma BNP level (18 pg/ml or greater). The significance of the interaction of sex with risk factors related to BNP was tested using an inter-

action term in multivariate models in the gender-combined analysis.

The Statistical Package for the Social Sciences (SPSS Japan Inc., version 11.0J, Tokyo, Japan) was used for the analyses. All probability values were two-tailed and all confidence intervals were estimated at the 95% level.

Results

Table 1 shows the means and the prevalence of risk factors. The mean plasma BNP was 13.7 pg/ml in the entire population, 10.7 pg/ml in men and 15.3 pg/ml in women.

There was no relationship between BNP level and each quartile for BMI, DBP, total cholesterol, HDL cholesterol, plasma glucose, and current smoking. Table 2 shows the geometric means of BNP according to the quartiles or categories (blood pressure category, high R-wave voltage, and current alcohol consumption) for each risk factor that was statistically significant in the analysis of variance or covariance. SBP, Grade 2 or severe hypertension category (SBP $\geqslant$ 160 mmHg and/or DBP $\geqslant$ 100 mmHg), high R-wave voltage in the ECG, and daily salt excretion were positively associated with BNP, and their values were higher in the higher BNP quartiles. There was a statistically significant relationship between the BNP levels and haemoglobin quartiles, with higher BNP levels in patients with haemoglobin values in the lower quartiles.

Since the interaction term between sex and risk factors related to BNP was not statistically significant in the multivariate regression analyses,

Table 1 Levels and prevalence of risk characteristics for males, females, combined among 686 subjects aged 35–69 years old in SA-Town, Shiga, Japan, 2002

Variables	*Males* (n = *209*)	*Females* (n = *477*)	*Combined* (n = *686*)
	mean$\pm$*s.d.*	*mean*$\pm$*s.d.*	*mean*$\pm$*s.d.*
Age (years)	57.1$\pm$9.1	55.6$\pm$9.9	56.1$\pm$9.7
Body mass index (kg/m)	23.8$\pm$2.9	23.0$\pm$3.0	23.3$\pm$3.0
Systolic blood pressure (mmHg)	130.1$\pm$18.0	124.0$\pm$18.3	125.8$\pm$18.4
Diastolic blood pressure (mmHg)	82.4$\pm$11.1	75.5$\pm$11.1	77.6$\pm$11.5
Total cholesterol (mmol/l)	5.29$\pm$0.79	5.59$\pm$0.91	5.50$\pm$0.89
High density lipoprotein (HDL) cholesterol (mmol/l)	1.39$\pm$0.38	1.63$\pm$0.39	1.56$\pm$0.40
Plasma glucose (mmol/l)	5.31$\pm$0.77	5.07$\pm$0.50	5.15$\pm$0.60
Haemoglobin (g/dl)	14.7$\pm$1.0	12.9$\pm$1.1	13.5$\pm$1.4
Salt excretion (g/day, estimated)	12.6$\pm$3.4	12.1$\pm$3.3	12.3$\pm$3.3
B type natriuretic peptide (BNP) (pg/ml, geometric mean)	10.7	15.3	13.7
	Prevalence (%)	*Prevalence (%)*	*Prevalence (%)*
ECG findings			
High R-wave voltage[a]	13.4	5.9	8.0
ST-depression[b]	0.0	1.9	1.3
Inverse or flat T-wave[c]	1.4	2.1	1.9
Blood pressure category[d]			
Optimal+normal	47.4	62.5	57.9
High–normal	16.3	14.5	15.0
Grade 1	27.8	17.6	20.7
Grade 2+3	8.6	5.5	6.4
Subject using antihypertensive agents	14.4	14.7	14.6
Smoking habit			
Nonsmoker	24.4	91.8	71.3
Ex smoker	23.4	1.9	8.5
Current smoker	52.2	6.3	20.3
Alcohol consumption			
Nondrinker	22.5	76.7	60.2
Ex drinker	1.0	0.4	0.6
Current drinker	76.6	22.9	39.2
Menopause	—	69.0	—
High plasma BNP (18 pg/ml or greater)	24.4	43.2	37.5

[a]High R-wave voltage:high R criteria:V5 or V6 > 2.6 mV, and/or V1 and V5 or V6 > 3.5 mV.
[b]ST-depression: the criteria for ST depression was the Minnesota Code 4-1 or 4-3.
[c]Inverse- or flat-T-wave: the criteria for inverse- or flat-T was the Minnesota Code 5-1 or 5-3.
[d]Blood pressure category: Optimal+normal: SBP < 130 mmHg and DBP < 85 mmHg, high–normal: SBP 130–139 mmHg and/or DBP 85–89 mmHg, grade 1:SBP 140–159 mmHg and/or DBP 90–99 mmHg, grade 2+3: SBP $\geqslant$ 160 mmHg and/or DBP $\geqslant$ 100 mmHg.

Table 2 Plasma BNP levels and quintiles for proportional variables among 686 males and females aged 35–69 years old in SA-Town, Shiga, Japan, 2002

Variables	*Number of subjects*	*Crude geometric mean (pg/ml)*	P*	*Age- and gender-adjusted geometric mean (pg/ml)*	P**
Systolic blood pressure (mmHg)					
Quartile 1 −111.3	171	12.7	0.004	13.6	0.041
Quartile 2 111.4−123.4	170	13.0		13.3	
Quartile 3 123.5−138.9	169	12.9		12.5	
Quartile 4 139.0−	176	16.5		15.5	
Blood pressure category[a]					
Optimal+normal	397	12.7	0.001	13.2	0.047
High–normal	103	14.1		13.2	
Grade 1	142	15.0		14.6	
Grade 2+3	44	19.5		17.8	
Haemoglobin (g/dl)					
Quartile 1 −12.5	159	17.5	0.000	17.0	0.000
Quartile 2 12.6−13.3	168	15.6		15.2	
Quartile 3 13.4−14.2	175	13.6		13.2	
Quartile 4 14.3−	184	10.0		10.8	
High R-wave voltage in the ECG[b]					
−	631	13.3	0.000	13.3	0.000
+	55	20.3		19.7	
Salt excretion (g/day, estimated)					
Quartile 1 −9.9	166	11.0	0.000	11.7	0.000
Quartile 2 10.0−11.8	171	12.3		12.3	
Quartile 3 11.9−13.9	171	15.7		15.1	
Quartile 4 14.0−	178	16.5		16.2	
Alcohol consumption					
Non-/ex drinker	417	14.4	0.037	13.1	0.053
Current drinker	269	12.7		14.8	

[a]Blood pressure category: Optimal+normal: SBP < 130 mmHg and DBP < 85 mmHg, high–normal: SBP 130–139 mmHg and/or DBP 85–89 mmHg, grade 1: SBP 140–159 mmHg and/or DBP 90–99 mmHg, grade 2+3: SBP ⩾ 160 mmHg and/or DBP ⩾ 100 mmHg.
[b]High R-wave voltage+high R criteria: V5 or V6 > 2.6 mV, and/or V1 and V5 or V6 > 3.5 mV.
*P: analysis of variance, **P: analysis of covariance.

the following analyses were carried out to combined men and women with adjustment for gender.

Table 3 shows the partial regression coefficients from the linear regression analysis. In this model, age, daily salt excretion, high R-wave voltage, female gender, and SBP were positively associated with plasma BNP levels. Blood haemoglobin was negatively associated with BNP levels. The multiple correlation coefficient (R) of this model was 0.49 and the degrees of freedom (df)-adjusted coefficient of determination (R^2) was 0.23 ($F = 30.0$, $P < 0.001$). Alcohol consumption was positively associated with BNP levels, although it did not reach statistical significance ($P = 0.051$). BMI showed no association with BNP levels.

Table 4 shows the odds ratios of each risk factor with a high plasma BNP level (18 pg/ml or greater) determined using multiple logistic regression analysis. Age, daily salt excretion, high R-wave voltage, female gender, and grade 2 or greater hypertension were positively associated with high plasma BNP levels, and blood haemoglobin concentration was negatively associated. The significant relationship between BNP and salt excretion was also observed even after we excluded participants with high R-wave voltage or participants taking antihypertensive agents, although the relationship between BNP and SBP or hypertension disappeared when these patients were excluded.

Gender-specific analysis showed that plasma BNP levels were significantly correlated with age, urinary salt excretion, and low haemoglobin for each gender. We also observed positive relations of plasma BNP levels with SBP and high R-wave voltage for each gender, which indicated similar magnitude of regression coefficients or odds ratio, although the relation with SBP for women and high R-wave voltage for men did not reach statistical significance.

Further analysis adjusting for administration of antihypertensive agents, smoking, serum lipids, and plasma glucose did not substantially affect the results shown in Tables 3 (data not shown in the table).

Table 3 Determinants of plasma BNP levels: linear regression analysis, 686 males and females aged 35–69 years old in SA-Town, Shiga, Japan, 2002

Variables	*Partial regression coefficients*	*s.e.*[a]	t	P
Age (10 years)	0.210	0.029	7.296	0.000
Haemoglobin (1 s.d., 1.36 g/dl)	−0.196	0.034	−5.681	0.000
Salt excretion (1 s.d., 3.4 g/day)	0.133	0.027	4.892	0.000
High R-wave voltage in the ECG (0 = no, 1 = yes)[b]	0.325	0.098	3.326	0.001
Gender (0 = male, 1 = female)	0.251	0.080	3.140	0.000
Systolic blood pressure (1 s.d., 18.4 mmHg)	0.070	0.029	2.454	0.014
Alcohol consumption (0 = non- or ex drinker, 1 = current drinker)	0.123	0.062	1.987	0.051
Body mass index (1 s.d., 3.0 kg/m^2)	−0.021	0.028	−0.759	0.448

[a]Standard error.
[b]High R-wave voltage was defined by height of R-wave in the ECG ;V5 or V6 is 2.6 mV or greater, and/or height of R-wave for V1 plus V5 or V6 is 3.5 mV or greater.

Table 4 Multivariate odds ratio and 95% confidence intervals for having high plasma BNP (⩾18.0 pg/ml), 686 males and females aged 35–69 years old in SA-Town, Shiga, Japan, 2002

Variables	*Odds ratio*	*95% confidence interval*		
Age (years)	1.05	1.03	—	1.07
Haemoglobin (g/dl)	0.69	0.58	—	0.81
Salt excretion (g/day)	1.09	1.03	—	1.15
High R-wave voltage in the ECG (0 = no, 1 = yes)[a]	2.05	1.10	—	3.81
Gender (0 = male, 1 = female)	2.01	1.18	—	3.41
Blood pressure category[b]				
Optimal+normal	1.00		—	
High–normal	0.92	0.56	—	1.51
Grade 1	1.28	0.82	—	2.01
Grade 2+3	2.09	1.04	—	4.22
Alcohol consumption (0 = non- or ex drinker, 1 = current drinker)	1.45	0.97	—	2.17
Body mass index (kg/m^2)	0.99	0.93	—	1.06

[a]High R-wave voltage was defined by height of R-wave in the ECG; V5 or V6 is 2.6 mV or greater, and/or height of R-wave for V1 plus V5 or V6 is 3.5 mV or greater.
[b]Blood pressure category: Optimal+normal: SBP < 130 mmHg and DBP < 85 mmHg, high–normal: SBP 130–139 mmHg and/or DBP 85–89 mmHg, grade 1: SBP 140–159 mmHg and/or DBP 90–99 mmHg, grade 2+3: SBP ⩾ 160 mmHg and/or DBP ⩾ 100 mmHg.

Discussion

The present study suggests that higher blood pressure, urinary salt excretion (a surrogate measure of dietary salt intake), high R-wave voltage in the ECG, and low blood haemoglobin as well as age and female gender are important determinants of plasma BNP levels in a general Japanese population.

Previous studies have reported a positive relationship between heart failure and hypertension.[19,25] The present study has also shown a positive relationship between grade 2 or greater hypertension and high levels of plasma BNP. Similar to previous reports dealing with Western populations, hypertension of moderate or greater degree may be one of the risk factors for asymptomatic heart failure or left ventricular dysfunction in the Japanese population. Hypertension, which is derived mainly from increased systemic vascular resistance and/or expanded intravascular volume, causes a sustained increase in left ventricular afterload that decreases cardiac output or ejection fraction, ultimately resulting in congestive heart failure.[19]

In general, urinary salt excretion is nearly equal to the dietary salt intake. High salt intake is an important factor that can expand intravascular volume, and it is a major causal risk factor for hypertension.[26–29] A recent study suggested that high salt intake *per se*, independent of hypertension, can have a harmful effect on the general population owing to the high risk of total mortality and mortality due to coronary heart disease and stroke.[30,31] A previous study reported that chronic high dietary salt intake increases the plasma concentration of BNP, even in the absence of hypertension.[32] It has also been reported that high dietary salt intake is related to the incidence of congestive heart failure in overweight men and women in the United States.[20] Furthermore, it has been emphasized that high salt intake is a risk factor for left ventricular hypertrophy.[33–35] High salt intake may be directly correlated to plasma BNP concen-

tration due to an increase in the circulating blood volume, which may indirectly lead to an increase in myocardial mass due to hypertension. The relationship between BNP and daily salt excretion was present after exclusion of subjects taking antihypertensive agents or those who had high R-wave voltage.

BNP, as a cardioprotective factor, has a diuretic effect that promotes the excretion of water and sodium by the kidneys.[36,37] As a result of the high sodium excretion promoted by BNP, the amount of urinary salt excretion may overestimate the actual dietary salt intake in participants with high plasma BNP levels. However, participants with high urinary salt excretion are continually exposed to high salt intake, which results in a situation that high BNP secretion is needed in order to protect their circulatory system. Consequently, we believe that a high salt intake may be a causal risk factor for heart failure or left ventricular dysfunction.

Left ventricular hypertrophy, which is usually accompanied by hypertension, is an example of target organ damage caused by an increase in circulating blood volume and/or vascular resistance occurring over many years. In the Framingham study, cardiac mass was assessed using echocardiography.[12] In the present study, we used the presence of high R-wave voltage in the 12-lead ECG as an index of left ventricular hypertrophy. An ECG is a more convenient and inexpensive method than an echocardiogram, and it is suitable for mass screening in the community. Moreover, people aged 40 years or greater in Japan are able to have an annual ECG under the Health and Medical Service Law for the Aged or the Industrial Safety and Health Law. In a previous study, significantly higher BNP levels were noted in patients with heart disease or hypertension who had abnormal electrocardiographic findings, such as high R-wave voltage.[38] Our finding seems to be consistent with this previous study, although our participants were healthy community dwelling residents.

Hypertension, high salt excretion, and high R-wave voltage in the ECG, which are associated with high BNP levels, are also the classical risk factors for stroke reported in previous Japanese cohort studies.[39–42] However, serum total cholesterol, which is a risk factor for ischaemic heart disease and not for stroke in Japan,[2–5] was not associated with plasma BNP levels. Since mortality due to ischaemic heart disease in Japan is lower than that in Western populations,[1,6,43] it may be reasonable to assume that the risk factors for latent heart failure are similar to those for stroke in the Japanese population.

Another interesting finding in the present study was the negative correlation between blood haemoglobin and BNP. It has been reported that anaemia is an independent prognostic factor for mortality in congestive heart failure patients living in the community.[44] Our result suggests that a low blood haemoglobin concentration, even within the clinically normal range, is associated with high plasma BNP. A reduced haemoglobin concentration might be a maker for advanced heart failure that may occur as a result of haemodilution due to volume overload and renal insufficiency.[44] Other factors in heart failure that are associated with anaemia include iron deficiency, chronic inflammation, and impaired erythropoietin production.[45]

Several limitations of this study should be acknowledged. First, we dealt with high R-wave voltage in the ECG as a marker for left ventricle hypertrophy, which may not always reflect true cardiac mass. Although body mass may affect R-wave amplitude, we statistically adjusted for the effect of body mass index. Unfortunately, due to the low prevalence of other abnormal findings in the ECG such as ST-T depression (1.3%) and inverse or flat T-waves (1.9%), we were not able to use these findings in our analysis. Second, our study used a cross-sectional design, which does not prove causal relations between plasma BNP levels and the above-mentioned risk factors.

In conclusion, we clarified the relationship between the elevated plasma BNP and hypertension, urinary salt excretion, high R-wave voltage in the ECG, age, and low haemoglobin concentration in a Japanese general population. We found some possible determinants for the elevation of plasma BNP in the Japanese general population. These factors — age, urinary salt excretion, hypertension — are similar to the classical risk factors for stroke in Japan.

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