Determination of the B-type Natriuretic Peptide Level as a Criterion for Abnormalities in Japanese Individuals in Routine Clinical Practice: The J-ABS Multi-center Study (Japan Abnormal BNP Standard)

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Abstract

Objective The present study was undertaken to establish a useful range for the B-type natriuretic peptide (BNP) level, with the ultimate goal of determining a cut-off BNP level that will make it possible to identify patients with clinically important organic heart disorders among patients encountered in clinical practice.

Methods A total of 11,967 outpatients were evaluated for this study, and, after applying the exclusion criteria, 361 patients were finally recruited for the analysis. Compared to the factors of gender and body mass index, aging was considered to be an indispensable factor in this analysis. The 'median' plasma BNP level was found to increase slowly with age, but remained lower than 30 pg/mL, even in patients aged 60 years or older. In contrast, the overall '95th percentile' of the plasma BNP level in the patients younger than 60 years was 41 pg/mL, which increased to 139.8 pg/mL in the patients aged 60 years or older.

Conclusion These findings suggest that the lower range of the BNP level allowing for identification of patients with clinically important organic heart disorders increases with age; however, it might be appropriate to adopt a level of approximately 40 pg/mL, even in elderly patients, in order to avoid any possible age-related effects of diastolic dysfunction or other factors.

Key words: aging, plasma B-type natriuretic peptide level, multi-center study, organic heart disorders

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Introduction

B-type or brain natriuretic peptide (BNP) is a cardiac hormone (1) that has been utilized to detect early heart failure, estimate the severity of heart failure and predict the prognoses of cardiac patients (2-12). Measuring the plasma BNP level has been shown to be useful for determining the differential diagnosis in patients presenting with respiratory symp-

toms or other problems (13, 14) and identifying asymptomatic patients with heart disease among individuals undergoing regular health checkups (15).

When the BNP level is used in clinical practice, its reference level (the criterion level) is 18.4 pg/mL, as we have previously reported (16). The lower the plasma level of BNP, the better the prognosis (10); thus, a level of 18.4 pg/mL or lower is theoretically preferable in all patients. However, some clinical physicians in hospitals have expressed

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opinions that 18.4 pg/mL may be too strict for diagnosing heart failure and significant organic heart disorders. Therefore, it has been suggested that a slightly higher cut-off level of plasma BNP would be preferable and more realistic for regular use in the clinical setting. Indeed, a considerable number of patients encountered in clinical practice, not only in cardiology clinics, but also in other departments, have demonstrated plasma BNP levels over 18.4 pg/mL without the presence of any organic heart disorders. It is therefore considered necessary to establish a new reference BNP level applicable for clinical use in hospitals.

The ultimate goal of this study was to determine a cut-off plasma BNP level that makes it possible to identify patients with clinically important organic heart disorders among the patients normally encountered in clinical practice. In other words, to identify a cut-off value that is the minimal level of plasma BNP that can exclude a diagnosis of clinically-relevant heart problems.

Materials and Methods

Study population

A total of 11,967 patients were recruited for this study among the individuals who visited the outpatient cardiology clinics of five facilities (Fujita Health University Hospital, Jikei University Hospital, Jikei University Kashiwa Hospital, Kumamoto Kinoh Hospital and Kyoto University Hospital) that participated in the J-ABS multicenter study (Japan Abnormal BNP Standard) between 2004 and 2008. This study was approved by the Ethics Committee of The Jikei University School of Medicine [20-238 (5528)] (and each committee of the other participating facilities, respectively).

Exclusion and inclusion criteria

The exclusion criteria included patients with structural heart disease without signs or symptoms of heart failure [stage B of the American College of Cardiology Foundation (ACC)/American Heart Association (AHA) heart failure classification guidelines for the evaluation and management of chronic heart failure in adults], more advanced stage C and D conditions meeting the ACC/AHA guidelines (13), ischemic heart disease (including patients with acute myocardial infarction, unstable angina pectoris or acute coronary syndrome and those undergoing coronary angiography or percutaneous coronary intervention), valvular heart disease (including patients with heart failure caused by moderate valvular disease and those scheduled to undergo surgery for valvular repair) or cardiomyopathy (dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy and secondary cardiomyopathies). Patients who met any of these criteria were excluded from the analysis.

In more detail, we excluded patients based on the following criteria in this study: (1) patients with an ejection fraction (EF) <55%, a left ventricular end-diastolic dimension (LVDd) ≥60 mm, a left atrial dimension (LAD) ≥40 mm and

a left ventricular mass index (LVMI) >125 g/m² in men and 110 g/m² in women on echocardiography, (2) patients with a current and overt history of atrial fibrillation (including patients with a history of catheter ablation, implantable cardioverter-defibrillators or cardiac resynchronization therapy and patients with pacemakers or syncope), (3) patients with a compromised renal function (estimated glomerular filtration rate: eGFR <60 mL/min/1.73m²), (4) patients with evident inflammatory disease (e.g. pericarditis, myocarditis, infective endocarditis, pneumonia, urinary tract infections or sepsis) and (5) patients with moderate or severe anemia.

Patients with risk factors for heart disease (diabetes mellitus, hypertension, dyslipidemia, obesity and other conditions) and patients receiving treatment for these risk factors (stage A of the ACC/AHA heart failure guidelines) were included in the analysis unless they met any of the exclusion criteria listed above. Based on the patient's height and weight on admission, the body mass index (BMI) was calculated as the weight (kg) divided by the square (m²) of the height.

Measurement of plasma BNP

The plasma BNP level was measured by a contract laboratory using an MI02 Shionogi BNP instrument (Shionogi & Co., Ltd., Osaka, Japan) or within each facility using the E Test TOSOH II (Tosoh Corporation, Tokyo, Japan). Good correlations were found between the measurements obtained with the Shionogi BNP (the gold standard for BNP measurement) and those obtained using the other method at the individual facilities, with correlation equations and coefficients of $y = 1.01x - 4.223$ ($r = 0.981$) and $y = 0.97x + 3.83$ ($r = 0.996$), respectively, with the Shionogi BNP denoted. The intra-day reproducibility (determined using the coefficient of variation: CV) was 1.6-3.6 and 2.0-2.7, respectively, while the inter-day reproducibility (CV) was 1.3-4.5 and 1.4-3.2, respectively (17, 18). Each blood sample was collected into an EDTA-2Na-treated blood sampling tube that was centrifuged at a low temperature to separate the plasma for the assay.

Doppler echocardiogram and renal function

In this study, Doppler echocardiograms were obtained for all patients at each facility, and the EF was measured in the M-mode (Teichholz formula) and/or using quantitative 2D (biplane modified Simpson's rule) methods for each subject. The correlation among the methods was excellent. Calculation of the LV mass on echocardiogram uniformly employed the equation for estimation reported by Devereux et al. (19). The body surface area (BSA) used for the LVMI calculation was derived from the actual height and body weight of each patient. The LVMI and BSA were calculated using the following Devereux equation and Du Bois equation (20), respectively:

$$\begin{aligned} \text{LVMI} &= \{ \{ 1.04 \times [(\text{LVDd} + \text{PW} + \text{IVS})^3 - \text{LVDd}^3] \} - 13.6 \} \\ &\quad \times \text{BSA}^{-1} \text{ (g/m}^2\text{);} \\ \text{BSA} &= \text{height}^{0.725} \times \text{body weight}^{0.425} \times 0.007184 \text{ (m}^2\text{).} \end{aligned}$$

Table 1. Clinical Characteristics of the Study Population

Factors	Male		Female		Total		
	n	mean $\pm$ SD	n	mean $\pm$ SD	n	mean $\pm$ SD	min, max
BNP (pg/mL)	197	20.02 $\pm$ 26.53	164	26.22 $\pm$ 34.56	361	22.84 $\pm$ 30.55	(2.0, 268.2)
Age (years old)	197	48.2 $\pm$ 18.3	164	52.8 $\pm$ 17.9	361	50.3 $\pm$ 18.3	(12, 90)
Height (cm)	196	168.78 $\pm$ 6.91	162	155.42 $\pm$ 5.76	358	162.73 $\pm$ 9.24	(140.0, 183.0)
Weight (kg)	196	65.85 $\pm$ 11.15	162	53.95 $\pm$ 10.49	358	60.47 $\pm$ 12.36	(29.7, 105.0)
BMI (kg/m ²)	196	23.06 $\pm$ 3.27	162	22.36 $\pm$ 4.30	358	22.74 $\pm$ 3.78	(13.7, 41.4)
BSA (m ²)	196	1.750 $\pm$ 0.160	162	1.512 $\pm$ 0.133	358	1.642 $\pm$ 0.190	(1.10, 2.14)
Systolic blood pressure (mm Hg)	187	126.7 $\pm$ 16.6	159	124.3 $\pm$ 19.7	346	125.6 $\pm$ 18.1	(82, 198)
Diastolic blood pressure (mm Hg)	187	75.4 $\pm$ 10.5	159	73.6 $\pm$ 13.4	346	74.5 $\pm$ 12.0	(37, 120)
Heart rate (/min)	182	71.7 $\pm$ 13.2	159	74.3 $\pm$ 12.7	341	73.0 $\pm$ 13.0	(37, 127)
eGFR (mL/min/1.73 m ²)	197	89.32 $\pm$ 22.92	164	90.48 $\pm$ 22.37	361	89.85 $\pm$ 22.65	(60.2, 259.1)
Serum creatinine (mg/dL)	197	0.78 $\pm$ 0.13	164	0.57 $\pm$ 0.09	361	0.69 $\pm$ 0.15	(0.4, 1.1)
EF (%)	197	66.68 $\pm$ 6.34	164	67.24 $\pm$ 6.80	361	66.93 $\pm$ 6.55	(55.0, 90.0)
LAD (mm)	197	32.35 $\pm$ 4.96	164	31.49 $\pm$ 4.57	361	31.96 $\pm$ 4.80	(9.2, 40.0)
LVDd (mm)	197	45.96 $\pm$ 3.74	164	42.80 $\pm$ 4.14	361	44.52 $\pm$ 4.22	(27.3, 54.8)
LVMI (g/m ²)	196	93.94 $\pm$ 16.22	162	84.60 $\pm$ 14.84	358	89.72 $\pm$ 16.27	(36.5, 124.1)

BNP: B-type natriuretic peptide, BMI: body mass index, BSA: body surface area, eGFR: estimate glomerular filtration rate, EF: ejection fraction, LAD: left atrial dimension, LVDd: left ventricular end-diastolic dimension, LVMI: left ventricular mass index

Table 2. Percentile BNP Values for Gender Difference

	Male (n = 197)	Female (n = 164)	p
	Median (25 th , 75 th , 95 th percentiles)	Median (25 th , 75 th , 95 th percentiles)	Wilcoxon rank sum test
BNP (pg/mL)	10.4 (4.9, 24.0, 71.9)	16.4 (9.0, 29.7, 84.8)	0.0003

BNP: B-type natriuretic peptide

To evaluate the renal function, the following equation for estimation announced in May 2008 by the Japanese Society of Nephrology was employed instead of the conventionally used Modification of Diet in Renal Disease (MDRD) Study equation and the Cockcroft-Gault equation for conversion (21). Patients with an eGFR <60 mL/min/1.73m² were excluded from the analysis:

$$\text{eGFR} = 194 \times \text{age}^{-0.287} \times \text{Scr}^{-1.094} \quad (\times 0.739, \text{ for women}) \quad (\text{mL/min/1.73m}^2)$$

Statistical analysis

Continuous variables are expressed as the mean $\pm$ standard deviation (SD) or percentile values (from the 25th percentile to the 95th percentile). The correlations from the analysis of the plasma BNP levels (logarithmically converted data) and other various measurements were expressed as the correlation coefficients (r). Comparisons of two groups were made using the Wilcoxon rank-sum test where necessary. All tests were two-tailed, and p <0.05 was considered to be statistically significant.

Results

Characteristics of the final study population

Among the 11,967 recruited patients, the final number of patients was reduced to only 361 (3%) after applying the exclusion criteria. Among the finally adopted study population, 197 patients were men and 164 patients were women,

and their mean age was 50.3 $\pm$ 18.3 (mean $\pm$ SD) years ranging from 12 to 90 years. All other clinical characteristics are shown in Table 1.

Plasma BNP levels and gender differences

The plasma BNP levels (median values) were significantly higher in the women than in the men, as shown in Table 2.

Plasma BNP levels and BMI

Fig. 1 shows the relationship between the plasma BNP levels and BMI. The logarithmically-converted plasma BNP levels decreased as the BMI increased, and the BNP level was found to be significantly correlated with BMI (n =358, r =-0.239, p <0.0001).

Plasma BNP levels and age

Fig. 2 shows the relationship between the plasma BNP levels and age. The logarithmically-converted plasma BNP levels increased with age and were found to be significantly correlated with age (n =361, r =0.5168, p <0.0001). As shown in Table 3, the 95th percentile of the plasma BNP level gradually increased with age; however, it increased at a value of three to four times in the patients aged 60 years or older compared to that observed in the other age groups. For patients younger than 60 years of age, the overall 95th percentile of the plasma BNP level was 41 pg/mL (Tables 3, 4).

Figure 1. Relationship between the plasma BNP level and BMI. BNP: B-type natriuretic peptide, BMI: body mass index. Solid line: the curve yielded from exponential conversion of the regression line for logarithmically-converted data ($n=358$, $r=-0.239$, $p<0.0001$).

Figure 2. Relationship between the plasma BNP level and age. BNP: B-type natriuretic peptide. Solid line: the curve yielded from exponential conversion of the regression line for logarithmically-converted data. Broken line: the curve yielded from exponential conversion of the 95% prediction interval for logarithmically-converted data ($n=361$, $r=0.5168$, $p<0.0001$).

Discussion

In the present study, we attempted to determine a reference level for the plasma BNP level that would be useful for identifying patients with clinically important organic heart disorders among patients encountered in routine clinical practice. This cut-off value would be considered the minimum plasma BNP value used to identify patients with stage B or higher ACC/AHA heart failure (13).

Relationship between the plasma BNP levels and gender

The present study demonstrated a significant effect of gender on the plasma BNP level (Tables 1-3), consistent with the findings of a previous report (22). We found the plasma BNP levels (the mean or percentile of the values) to be slightly higher in women than in men (Tables 1, 2). In each age group, the median plasma BNP level was slightly higher in the women than in the men, and the absolute difference in this parameter between the women and men was approximately 6 pg/mL. One reason why gender influences the BNP level may involve hormonal regulation of estrogen (22), as Redfield et al. reported that hormone replacement therapy (HRT) increased the plasma BNP levels in each of their age-matched female patient groups.

Relationship between the plasma BNP levels and BMI

BMI was also identified to be a significant factor determining the plasma BNP level in the present study (Fig. 1). Consistent with the previous finding that the plasma BNP levels tend to be lower in obese individuals (23), the present study revealed a negative correlation between the plasma BNP level and obesity (Fig. 1). This finding suggests that increases in obesity can suppress the plasma BNP levels. However, the BMI-related change observed in the present study population was relatively small. If heart failure becomes advanced, then the influence of obesity on the plasma

BNP level may become stronger (24).

Relationship between the plasma BNP levels and age

Compared to gender and BMI, age was identified to be a more important factor in this analysis. When analyzing the 'median' plasma BNP level, this parameter was found to increase slowly with age [6.4 pg/mL at ages of 29 years or younger (the ≤ 29 years group); 8.4 pg/mL at ages between 30 and 39 years (the 30-39 years group); 10.6 pg/mL at ages between 40 and 49 years (the 40-49 years group); 11.1 pg/mL at ages between 50 and 59 years (the 50-59 years group); 25.0 pg/mL at ages of 60 years or older (the ≥ 60 years group)] (data not shown in Results) and remained lower than 30 pg/mL, even in the patients aged 60 years or older (Fig. 2). Significant differences in the BNP levels among the four age groups under the age of 60 years were found: between the ≤ 29 years group and the 30-39 years group, and between the ≤ 29 years group and the 50-59 years group (using the Wilcoxon rank-sum test, data not shown). These results indicate that the BNP levels in the ≤ 29 years group were lower than those in the other age groups, although there were no significant differences in the BNP levels in the remaining age groups (30-39, 40-49 and 50-59). On the other hand, the '95th percentile' of the plasma BNP level rose more markedly with age; however, it did not uniformly increase in the four age groups under 60 years of age (Table 3), reaching 139.8 pg/mL in the patients aged 60 years or older (Fig. 2, Table 3). These findings indicate that the plasma BNP level does not uniformly exhibit age-related elevations in all individuals, although the overall percentage of individuals with elevated plasma BNP levels does increase with age. While it is known that the physiological function gradually decreases with age, it remains unclear whether the decrease should be considered an illness or an inevitable natural change.

Therefore, in the present study, we excluded some of the

Table 3. 95th Percentile BNP Values for Each Age Group

95 th percentile BNP (pg/mL), (n)	Age: <29	Age: 30-39	Age: 40-49	Age: 50-59	Age: 60-69	Age: 70-
ALL	29.6, (62)	46.2, (48)	33.3, (47)	50.9, (76)	41.0, (123)	139.8, (128)
Male	21.3, (39)	64.4, (31)	31.9, (26)	53.0, (39)	42.7, (65)	84.4, (62)
Female	37.9, (23)	46.2, (17)	33.3, (21)	44.0, (37)	39.4, (58)	147.2, (66)

BNP: B-type natriuretic peptide

Table 4. 95th Percentile BNP Values for Each Age Group

	Age: <59	Age: 60-
Number	233	128
95 th percentile BNP (pg/mL)	41.0	139.8

BNP: B-type natriuretic peptide

data for the elderly group from the analysis because we wanted to exclude patients with diastolic dysfunction caused by aging as much as possible. Reductions in the diastolic function in the Japanese population tend to become evident at ages over 60 years (25, 26); therefore, we calculated the 95th percentile plasma BNP level for individuals younger than 60 years of age and found it to be 41 pg/mL. Indeed, elderly persons with a well maintained diastolic function who demonstrate low plasma BNP levels generally show good prognoses (27, 28). It thus appears appropriate to adopt a level of approximately 40 pg/mL as a useful reference level for patients younger than 60 years of age.

The cut-off levels of plasma BNP in other studies

A plasma BNP level of approximately 40 pg/mL is equivalent to the cut-off levels reported in other studies of individuals undergoing thorough health checkups (15, 29). These studies attempted to determine the plasma BNP level that is useful for identifying patients with heart disease by means of receiver operating characteristic (ROC) analyses and obtained cut-off levels of 40 or 50 pg/mL. The cut-off level obtained in the present study is identical to these reported levels, despite the fact that our study used a different study population. Therefore, a value of approximately 40 pg/mL is considered to be highly significant.

In other countries, plasma BNP level measurements have been reported to be useful in the differential diagnosis of patients presenting with heart disease when the cut-off level was set at 80-100 pg/mL (30, 31). Because the plasma BNP levels obtained using the measurement system generally used in the United States are approximately 1.6-fold the levels obtained using the Japanese system (32), the reported non-Japanese cut-off levels are also considered to be equivalent to a cut-off level of approximately 50-62.5 pg/mL in Japan. This provides further evidence that a cut-off level of approximately 40 pg/mL is useful.

Significance of BNP values of 18.4 pg/mL and 40 pg/mL

The cut-off level obtained in this study is not inconsistent with the existing cut-off level (not more than 18.4 pg/mL or 20 pg/mL). The cut-off level 'not more than 18.4 pg/mL' was derived from healthy individuals, and hence, only pertains to healthy individuals. Moreover, this cut-off value could be considered the borderline between a no-risk population and subjects with stage A ACC/AHA heart failure (13). In contrast, the cut-off level '40 pg/mL' obtained in the present study indicates that the levels above this value are very likely to be associated with cardiac abnormalities or heart failure on existing tests and examinations. In other words, this cut-off level is thought to be the minimal plasma BNP level necessary to detect clinical heart abnormalities as well as the approximate border between stage A and stage B of the ACC/AHA heart failure classification (13). We therefore propose that this cut-off level be considered a 'standard for plasma BNP abnormality' for clinical utilization and verification. Fortunately, this standard is applicable not only in routine clinical practice, but also in cardiac screening performed during health checkups, thorough health checkups, critical care and other clinical situations, as described in the previous reports discussed above.

Limitations

First, BNP is not the only marker of organic heart disorders, and it is sometimes impossible to rule out heart diseases if patients demonstrate levels of less than 40 pg/mL. For example, there may be patients whose plasma BNP levels are less than 40 pg/mL but who nevertheless have ischemic heart diseases, including acute coronary syndrome, apical hypertrophic cardiomyopathy, pericarditis, infective endocarditis, sarcoidosis, amyloidosis, cardiac tamponade, etc. In addition, caution should be exercised in patients with unwitnessed symptomless arrhythmias (e.g. paroxysmal atrial fibrillation), since the plasma BNP levels are known to fluctuate widely in such individuals. Other examinations should therefore be used in combination with the BNP level, as appropriate.

Second, among the exclusion criteria used in this study, the LVMI may need to be considered. Cardiac hypertrophy arises as an early compensatory phenomenon in the presence of either poor blood pressure control or a compromised renal function and is a strong risk factor for the occurrence of cardiovascular events (33). When designing exclusion crite-

ria related to cardiac hypertrophy, we noted that few reports have been published on LVMI in the Japanese population (25, 26). We therefore determined the cut-off LVMI levels reported in approximately 50 papers dealing with LVMI in Japanese subjects published over the past decade and found the cut-off levels based on the European Society of Cardiology Guidelines (2003), i.e., men $>125 \text{ g/m}^2$ and women $>110 \text{ g/m}^2$, to have been the most frequently applied (34). However, the influence of cardiac hypertrophy may still not be sufficiently excluded even when using an LVMI cut-off level and other exclusion criteria.

Finally, this research study targeted outpatients who visited the cardiovascular unit at each hospital. Almost all of the patients had some form of cardiac disease, and only 3% (361/11,967) of the total outpatients who visited the clinic had no-event cardiovascular disorders. Therefore, it was impossible to draw a ROC curve from the present data. Moreover, in this study, the level of 40 pg/mL was not investigated with regard to its significance for determining subsequent prognosis. A prognostic study should be performed in another series of patients. In addition, the age-related reference levels of plasma BNP for use in detecting heart abnormalities, including diastolic dysfunction, might also need to be determined in another series of studies.

Conclusion

We herein attempted to determine a reference level for the plasma BNP level that would be useful for identifying patients with clinically important structural heart disease among patients encountered in routine clinical practice. The lower range of BNP allowing for identification of patients with clinically important organic heart disorders increases with age; however, it might be appropriate to adopt a level of approximately 40 pg/mL, even in elderly patients, in order to avoid possible age-related effects of diastolic dysfunction or other factors. It is advisable to explore the underlying diseases in patients whose plasma BNP levels exceed this standard.

The authors state that they have no Conflict of Interest (COI).

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