ORIGINAL ARTICLE

Cut-off values of B-type natriuretic peptide for the diagnosis of congestive heart failure in patients with dyspnoea visiting emergency departments: a study on Korean patients visiting emergency departments

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Emerg Med J 2007;24:343–347. doi: 10.1136/emj.2006.041368

Objectives: To determine the optimal cut-off values of B-type natriuretic peptide (BNP) for the diagnosis of congestive heart failure (CHF) in 1040 Korean patients with dyspnoea visiting emergency departments.

Methods: BNP values were measured for 662 patients without CHF to examine whether significant relationships existed between the BNP values and age, gender or underlying disease. In 378 patients with CHF, a similar analysis was performed in addition to the examination of the relationship between the mean BNP values and CHF severity.

Results: The optimal threshold for the detection of heart failure was a BNP concentration of 296.5 pg/mL, regardless of age, sex and underlying disease among the Korean study population. In the non-CHF patients, women showed significantly higher mean BNP values than did men. Further, in these patients, the mean BNP values of men with underlying disease (hypertension, angina pectoris, chronic renal failure, chronic obstructive pulmonary disease) and those with at least two underlying diseases, one of which was hypertension, was higher than those without underlying disease, whereas no difference was observed between women with and without underlying disease. Based on the New York Heart Association classification, echocardiography findings and mortality rate of the CHF patients, the BNP value was found to be related to both the severity of heart failure and its prognosis.

Conclusions: The BNP concentration used for the diagnosis of CHF in Korean people is considerably higher than the normal cut-off value of 100 pg/mL. In the non-CHF patients, the BNP values of women were influenced less by underlying disease. This suggests that the factors that influence BNP values in women are different from those in men.

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Accepted 6 March 2007

The cardiac neurohormone, B-type natriuretic peptide (BNP), which is secreted in response to the ventricular volume increase and pressure load, is known to be useful for the diagnosis of congestive heart failure (CHF).¹ BNP is a valuable tool in the emergency department because it enables a quick diagnosis to be made of those patients who visit emergency departments because of dyspnoea; it can determine, without having the patient examined by radiography and echocardiography, whether the cause of the condition was CHF.² Many studies are being conducted on the cut-off values of BNP; however, these values vary depending on the conditions.³ Currently, the studies indicate that BNP values can be used only for screening CHF cases among healthy populations.^{4–5} However, it would be clinically helpful to use the same process for determining whether dyspnoea in patients visiting emergency centres is a result of CHF. This study attempted to determine the optimal cut-off value of BNP for the diagnosis of CHF in Korean patients visiting emergency departments with dyspnoea as their chief complaint, and examined the differences in the BNP values with respect to age, gender and underlying disease. It aimed to evaluate the relationship between the BNP values and the severity of CHF.

MATERIALS AND METHODS

Materials

This study was conducted on 1040 patients (582 men, 458 women; mean age 63 years) (table 1), whose BNP values were measured following their arrival at emergency departments because of dyspnoea from 1 October 2004 to 31 October 2005.

Other parameters (respiratory rate, oxygen saturation) were not included as a screening test was conducted to find out whether the condition of the patients with dyspnoea was caused by CHF. Patients who had suffered from trauma, who had undergone cardiopulmonary resuscitation or who had been transferred to other hospitals were excluded from the study. The study was carried out in accordance with the principles of the Declaration of Helsinki, and approved by the local ethics committee.

Methods

Venous blood samples (5 mL) obtained from patients with dyspnoea visiting the hospital were dispensed into tubes treated with EDTA prior to analysis (Triage BNP test; Biosite, San Diego, California, USA).

CHF was diagnosed at the beginning of the visit based on Framingham's criteria, followed by a transthoracic echocardiography (Philips Sonos 5500, Andover, Massachusetts, USA) conducted within 24 h by two independent echocardiologists who were blinded to the BNP assay. The final diagnosis of CHF was defined by transthoracic echocardiography. The findings from the transthoracic echocardiography that led to the diagnosis of CHF were as follows:

Abbreviations: BNP, B-type natriuretic peptide; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ROC, receiver operating characteristic

Table 1 Characteristics of patients (n = 1040)

Characteristics	Non-CHF (n)	CHF (n)
Sex		
Male	365	217
Female	297	161
Age		
<45 years	73	44
45–64 years	235	132
65–74 years	200	98
≥75 years	154	104
Underlying disease		
No underlying disease	91	45
Diabetes	50	30
Hypertension	118	65
Angina	45	25
COPD	35	21
CRF	11	4
HTN + diabetes	66	31
HTN + COPD	30	21
HTN + CRF	25	19
HTN + diabetes + COPD	23	18
HTN + diabetes + angina	24	19
Others	144	60
Total	662	378

CHF, congestive heart failure; HTN, hypertension; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure.

- Systolic dysfunction: left ventricular ejection fraction (LVEF) <50% or the inner diameter of the left ventricle at diastole >5.2 cm or global hypokinesia detected.
- Diastolic dysfunction: the E-wave/A-wave (E/A) ratio was <1 and the deceleration time >240 ms or the E/A ratio was >1.5 and the deceleration time <150 ms.

The patients were grouped into CHF and non-CHF groups, and the cut-off values of the BNP of 1040 patients were examined. The BNP cut-off values of those patients without underlying disease regardless of CHF were also measured in order to exclude the possibility of the influence of these diseases on the values.

To examine the influence of gender and age on the values, the non-CHF patients without underlying disease were grouped according to gender and age, and their BNP values were compared.

To determine the influence of underlying disease on the values, the non-CHF patients were grouped into groups with and without underlying disease. The former group was further subdivided into groups of diabetes, hypertension, angina pectoris, chronic obstructive pulmonary disease (COPD) and chronic renal failure (CRF), and the mean BNP value of each subgroup was compared with that of the group without underlying disease. In addition, comparisons were also made between the group without underlying disease and the subgroups with at least two underlying diseases. A patient was defined to have an underlying disease if they were being treated due to a history of diabetes, hypertension, angina pectoris, COPD or CRF, or were diagnosed to have one or more of the above diseases at the time of discharge.

To evaluate the relationship between the BNP values and the severity of dyspnoea, LVEF and prognosis in the CHF patients, the New York Heart Association (NYHA) classification, LVEF and mortality rate of the CHF patients were examined.

Statistical analysis

The SPSS 11.0 program was used for statistical analysis, and the optimal cut-off value of each patient group was determined using the receiver operating characteristic (ROC) curve.⁶ The data of the groups were compared using Student's *t* test and

Figure 1 Receiver operating characteristic (ROC) curve of the ability of plasma B-type natriuretic peptide concentration to predict precursors of heart failure. The area under the ROC curve was 0.961. The optimal threshold for the detection of heart failure was 296.5 pg/mL, with 90.5% sensitivity and 91.4% specificity.

one way analysis of variance. Statistical values were expressed as mean (SE). A *p* value of <0.05 was considered to be statistically significant.

RESULTS

Cut-off values of BNP

Of the 1040 patients, 378 had CHF and 662 had no CHF; the mean BNP values were 1338.1 (69.5) pg/mL and 131.0 (15.8) pg/mL, respectively (*t*-test, *p*<0.05) (table 1). As both sensitivity and specificity of the BNP analysis were important, the BNP cut-off value was determined so that the values of these two parameters were >90%. The cut-off value was estimated to be 296.5 pg/mL with 90.5% sensitivity, 91.4% specificity, 94.4% negative predictive value and 85.7% positive predictive value (χ^2 *p*<0.05) (fig 1, table 2). In the 136 patients without underlying disease, 45 had CHF and 91 had no CHF, and the cut-off value was 271.5 pg/mL; this value was similar to the estimated value.

Table 2 Range of cut-off values for the BNP

BNP (pg/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
12.5	100	27.8	43.6	100	44.9
100	98.7	67.1	76.0	98.9	78.6
191	96.1	83.5	63.5	97.4	88.1
296.5	90.5	91.4	85.7	94.4	91.3
400	84.7	96.2	92.8	91.7	92.0
496	70.1	97.3	69.2	85.1	87.4
601	60.6	97.7	97.9	80.3	84.2
983.5	39.9	98.8	95.0	74.2	77.4

BNP, B-type natriuretic peptide; PPV, positive predictive value; NPV, negative predictive value.

Table 3 Plasma mean BNP concentration according to age and sex in the 91 non-CHF patients among 136 patients without underlying disease

Age (years)	Male			Female		
	n	Mean (SD)	p Value	n	Mean (SD)	p Value
33–44	9	67.3 (22.1)	NS†	6	93.8 (33.3)	NS†
45–64	22	53.8 (17.1)		12	104.4 (21.4)	
65–74	12	61.9 (6.0)		11	97.2 (29.4)	
75+	11	72.2 (20.1)		8	113.4 (29.3)	
Total	54	61.6 (8.8)		37	103.1 (13.5)	0.007*

BNP, B-type natriuretic peptide; CHF, congestive heart failure.

p<0.05.

*t-Test (comparison with male and female); †analysis of variance (comparison with age group); ‡NS, not significant.

Influence of gender and age on BNP values in non-CHF patients

Of the non-CHF patients, 91 (37 women and 54 men) had no underlying disease; the mean BNP values of these patients were 103.1 (13.5) pg/mL and 61.6 (8.8) pg/mL, respectively (p<0.05). However, age did not influence the BNP values (table 3).

Influence of underlying disease on BNP values in non-CHF patients

The mean BNP value of 78.5 (7.8) pg/mL (men: 61.6 (8.8) pg/mL, women: 103.1 (13.5) pg/mL) was compared with the values of each underlying disease group. As the BNP values differed between men and women in the group without underlying disease, the male and female groups were divided into groups with and without underlying disease, and their mean BNP values compared.

In the group of non-CHF patients, those with only one of the following underlying disease (diabetes, hypertension, angina pectoris and COPD) did not show differences in the average BNP values when compared with the group without underlying disease. However, 11 CRF patients showed a significantly high BNP value of 534.2 (448.1) pg/mL (p<0.05). With regard to gender, higher BNP values were observed for men with hypertension, angina pectoris and CRF. In women, the BNP values were hardly influenced by underlying disease, and patients with hypertension showed relatively low BNP values (table 4).

In the group of non-CHF patients, those with certain combinations of underlying disease (hypertension and diabetes;

hypertension and COPD; hypertension and CRF; hypertension, diabetes and angina pectoris; and hypertension, diabetes and COPD) showed significantly higher mean BNP values than those without underlying disease. It is noteworthy that all these combinations include hypertension, and the BNP values of men were significantly higher (p<0.05) than those of women (table 4).

Relationship between BNP values and LVEF and NYHA classification in CHF patients

In the CHF patients, examination of the relationship between the BNP values and NYHA classification and echocardiography findings showed that the severity of dyspnoea according to the NYHA classification was proportional to the BNP values. In addition, the lower the LVEF measured by echocardiography, the higher the BNP value (table 5). With regard to prognosis, the mean BNP value of nine patients who died was 3621.2 (667.9) pg/mL, which was higher than that (1282.7 (66.9) pg/mL) of the surviving group (p<0.05).

DISCUSSION

The optimal cut-off value of BNP was 296.5 pg/mL for all patients visiting emergency departments with dyspnoea as their chief symptom. This value was higher than the cut-off value of BNP in CHF from a previous study—that is, 100 pg/mL with 90% sensitivity, 76% specificity, 89% negative predictive value and 79% positive predictive value.⁷ It was considered that difference in this research result and the cut-off value of BNP from the previous study resulted from the differences between healthy people and dyspnoea patients or from racial differences.⁸ It has also been suggested that Koreans, who tend to be less obese

Table 4 Plasma mean BNP concentration in the non-CHF patients according to underlying disease and gender

Mean BNP concentration (pg/mL)								
Underlying disease	Male			Female			All patients	
	n	Mean (SD)	p Value	n	Mean (SD)	p Value	Mean (SD)	p Value
None	54	61.6 (8.8)		37	103.1 (13.5)		78.5 (7.8)	
DM	26	54.9 (14.7)	0.588	24	119.2 (24.7)	0.576	80.6 (13.9)	0.705
HTN	61	99.9 (17.2)	0.014*	57	77.2 (13.0)	0.040*	88.9 (10.9)	0.600
Angina	25	116.4 (22.5)	0.042*	20	119.7 (34.4)	0.759	117.6 (18.8)	0.154
COPD	18	70.2 (35.1)	0.437	17	107.3 (40.0)	0.252	84.2 (26.2)	0.985
CRF	8	792.6 (702.7)	<0.001*	3	82.0 (72.0)	0.846	534.2 (448.1)	<0.001*
HTN + DM	32	298.3 (156.7)	0.005*	34	127.2 (26.0)	0.162	210.2 (127.3)	0.011*
HTN + COPD	16	183.7 (64.1)	<0.001*	14	80.7 (20.7)	0.535	123.5 (38.7)	0.029*
HTN + CRF	14	561.7 (445.8)	<0.001*	11	85.2 (33.9)	0.571	347.3 (246.4)	<0.001*
HTN + DM + COPD	13	924.7 (816.4)	<0.001*	10	175.5 (65.7)	0.026*	521.4 (375.5)	<0.001*
HTN + DM + angina	14	269.7 (124.3)	<0.001*	10	152.6 (91.6)	0.034*	38.9 (94.1)	<0.001*

BNP, B-type natriuretic peptide; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure.

All data are mean (SE).

*p<0.05, t-Test (comparison with no underlying disease).

Table 5 Relationship between the NYHA classification, left ventricular ejection fraction (echocardiography) findings and BNP concentration in the CHF (+) patients

	Patients (n)	BNP (pg/mL), mean (SE)	p Value*
NYHA†			
II	78	662.70 (89.90)	0.002
III	140	1188.65 (162.11)	
IV	160	1899.65 (162.11)	
LVEF			
40%–50%	75	655.36 (75.42)	0.000
20%–40%	238	1399.67 (98.59)	
<20%	65	3044.11 (233.28)	

BNP, B-type natriuretic peptide; NYHA, New York Heart Association classification; LVEF, left ventricular ejection fraction.

*One way analysis of variance $p < 0.05$; †the NYHA I classification was excluded as there were no patients in this category.

than their western counterparts, have slightly higher BNP values.^{9, 10}

For the group of non-CHF patients, the BNP values of women were significantly ($p < 0.05$) higher than those of men. This suggests that oestrogen influences the BNP values but it is believed that there may be other factors.¹¹ For the non-CHF patients, age did not appear to influence the BNP values. It is suggested that BNP values increase following the dilated insufficiency of cardiac muscles with increasing age, which often cannot be diagnosed.¹² However, we consider that the BNP values do not fluctuate with increasing age, because our study suggests that their values differ depending on the health of the individual patients.

In the group of non-CHF patients, diabetes, hypertension or angina pectoris alone hardly influenced BNP values, concurring with previous results.¹⁴ However, in men, the mean value of the hypertension group was substantially higher than that of the group without underlying disease. This is considered to result from an increase in the left-ventricle mass index caused by high blood pressure.^{13, 14} In contrast, women did not show an increase in the mean BNP values (the values even declined), thus this result warrants further research. The existence of angina pectoris in the male groups increased the mean BNP value to 116.4 pg/mL, which is considerably higher than that of the group without underlying disease. This could have resulted from the increase in arterial stiffness, as suggested by reports on the increase in BNP values following an increase in the pulse wave velocity.¹⁵ However, the female groups did not show an increase in BNP values, suggesting that their arterial stiffness did not increase substantially, which could be due to the influence of female hormones or to lower exposure to smoking and hyperlipidaemia than for Korean men. Although the number of patients with CRF only was small within the non-CHF group, the mean BNP value was high; this suggests that CRF is associated with raised BNP levels even in the non-CHF group.¹⁶ With regard to gender, differences in BNP values were found for men but not for women. However, it was difficult to evaluate the statistical significance of the differences in the BNP values in the case of women with CRF because of the small number of subjects (only three). We examined the BNP values of patients with two or more underlying disease. The mean BNP value of those having hypertension as one of the diseases was significantly ($p < 0.05$) higher than that of the group without underlying disease. However, differences in the BNP values were observed in men rather than women. Although the mechanism remains unclear, it may be that the increase in the left ventricle mass index due to hypertension generates synergic effects when accompanied by other disease.

The results of the analysis of the severity of CHF in our patients were consistent with those of the previous reports.^{17, 18} The mortality rate of the CHF patients showed significant differences in the mean BNP values.^{19, 20}

The present study had the following limitations. First, when evaluating the influence of underlying disease on the BNP values, the criteria for diagnosing the underlying disease were unclear and the severity of the disease was not measured. Although the administration of drugs to treat these diseases should have been examined in order to rule out their influence on BNP values, it was difficult to measure the blood concentration of these drugs; this must be overcome in future studies. Second, the causes of dyspnoea in those patients without CHF and underlying disease (diabetes, hypertension, CRF, COPD, angina pectoris) were allergy, psychogenic (hyperventilation, neurosis, etc), infection (upper respiratory infection, pneumonia, pleural effusion, sepsis) and unknown origin. However, we did not take these causes into account in this study because it was considered that they were unlikely to influence BNP value, therefore further study including such conditions is necessary. Third, the comparisons between CHF patient groups with the same severity should have been made to examine the influence of underlying disease, which was not possible due to the relatively small number of patients. However, it was worthwhile to examine the cut-off values of BNP in patients arriving at emergency departments; this study may contribute to clinical practice because it led to the identification of the factors that influence BNP values.

CONCLUSIONS

The cut-off value of BNP in Korean patients for the diagnosis of heart failure in the present study was 296.5 pg/mL, with the value for patients without underlying disease being 271.5 pg/mL; both values were significantly higher than the widely accepted value of 100 pg/mL. Within the non-CHF group, BNP values were higher in women than in men. No differences in BNP values were observed between age groups. For male non-CHF patients, mean BNP values of those with underlying disease such as hypertension, angina pectoris or CRF was higher than those without underlying disease. In contrast, for female non-CHF patients, there were no differences in the mean BNP values between those with and without underlying disease. Therefore, it is suggested that the factors that influence the BNP values in women are different from those in men. The BNP values of the patients suffering from dyspnoea were related to the severity of CHF and LVEF.

ACKNOWLEDGEMENTS

We thank Professor Chang-hee Lee of the Graduate School of Translation and Interpretation at Ewha Women's University, Seoul, Korea, for carefully reading the manuscript and correcting its English.

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Competing interests: None declared

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