

The Clinical Experiences of B-type Natriuretic Peptide Blood Concentrations for Diagnosis in Congestive Heart Failure

– The Single Hospital Experience Based on the Large Clinical Database –

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ABSTRACT

Background : B-type natriuretic peptide (BNP) has been used as a standard diagnostic tool to define heart failure. The aim of this study was to evaluate the clinical experiences of BNP levels based on a large clinical database. **Methods** : From Oct. 2002 to July 2003, 3830 patients were analyzed. The patients were divided into the 3 groups: control, systolic (SHF) and diastolic heart failure (DHF) patient groups, via an echocardiography and the Framingham clinical criteria. The BNP was measured with a Triage[®] kit. Both the clinical and echocardiography profiles were analyzed. **Results** : The mean age of the patients was 62.8 years, with 49.0% males. The control group included 661, the SHF group 475 and the DHF group 287 patients. In the control group, the mean BNP level was 31.5 ± 24.0 pg/mL, with the BNP level in the women higher than in the men (28.0 ± 23.8 vs. 34.9 ± 23.7 pg/mL, $p=0.041$). The SHF patients group had significantly higher BNP levels than the other groups ($p=0.008$). In the patients with SHF, the BNP levels, according to the NYHA grade, showed significant differences (I: 169.3 ± 138.7 , II: 391.1 ± 231.4 , III: 780.1 ± 698.3 and IV: 1078.9 ± 946.2 pg/mL, $p=0.009$). In the patients with diastolic dysfunction ($n=787$) according to the diastolic dysfunction, the BNP levels, showed significant differences (relaxation abnormality: 108.2 ± 78.2 , pseudo-normal: 419.0 ± 109.8 and restrictive physiology: 510.4 ± 231.6 pg/mL, $p=0.009$). The accuracy in the BNP level when separating the SHF from the control patients was 0.98 (AUC=0.98), with 92.5% sensitivity and 86.1% specificity at a cut-off of 108 pg/mL. **Conclusions** : The levels of blood BNP were present in various ranges according to the clinical situation and extent of heart failure. (Korean Circulation J 2004;34(7):684-692)

KEY WORDS : Natriuretic peptide ; Congestive heart failure ; Diagnosis.

Introduction

The pathophysiology of heart failure is its association with the activation of neuro-endocrines and the release of cytokines. In addition, several clinical syndromes have been reported that include not only the symptoms in the

heart, but also pathology in other organs as well.¹⁾ As the present population ages and the number of cardiovascular patients increases, the overall incidence of heart failure is increasing rapidly. Similarly, the incidence of heart failure in Korea is anticipated to rise substantially.²⁾ The application of the classical criteria from the Framingham study to diagnosis of heart failure shows low sensitivity and specificity and thus, the physician arriving at the correct diagnosis requires numerous differential diagnosis.³⁾⁴⁾ Although echocardiography was the most useful tool and the gold standard for the diagnosis of heart failure, it is expensive. Furthermore, it may be ineffective in some cases such as for patients with ch-

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ronic pulmonary diseases who require the differential diagnosis from respiratory failure, and obese patients.⁵⁾ In addition, for those patients visiting a hospital for acute respiratory difficulties and so they require immediate diagnosis and treatment, echocardiography may have poor accessibility and a high cost for repeated test. The plasma B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) concentration has been reported to be a marker of ventricular dysfunction as it is primarily produced and released by the ventricles in response to hemodynamic stimuli such as the increased volume of the ventricles, pressure load, etc. This peptide's level has been recently proven to be useful by numerous clinical studies of the differential diagnosis of dyspnea.^{6,7)} However, reports on a large number of patients in Korea are rare.^{8,9)} Here, we examined the clinical experiences of the BNP measurement in heart failure patients on a large number of patients that visited a single hospital.

Methods

Study population

We analyzed 3830 consecutive patients who were admitted in the Wonju Christian Hospital, Wonju College of Medicine, Yonsei University from October 2002 to July 2003 from whom BNP and echocardiogram were obtained. For all the patients, their height, weight, electrocardiogram, chest X-ray and plasma creatinine level were measured at the first visit. Echocardiograms were performed using routine echocardiographic parameters via Hewlett Packard 5500, and the M-mode and trans-mitral Doppler were analyzed. 187 patients in the study group underwent coronary angiography and an evaluation of the ventricular end-diastolic pressure at the same time at 2.7 ± 2.3 days after admission.

Definition of heart failure and patient grouping

Clinical symptoms of heart failure were defined by the Framingham clinical criteria.¹⁰⁾ Systolic heart failure was defined as clinical symptom stated by Framingham, with the following echocardiographic findings: an ejec-

tion fraction $<50\%$ and an end-diastolic dimension of left ventricle >5.5 cm.¹¹⁾ Diastolic heart failure was defined using clinical symptoms presented by Framingham's criteria with diastolic dysfunction on the echocardiograph. Diastolic dysfunction was defined by applying the conventional echocardiography standard.¹¹⁾ Relaxation abnormality was defined as less than 1 or DT >240 msec. In patients over 55 years, relaxation abnormality was defined as an E/A ratio less than 0.8 and a DT more than 240 msec.⁹⁾ Isolated diastolic dysfunction was defined as patients with diastolic dysfunction on echocardiography, but their symptoms did not concur to the Framingham clinical criteria. Systolic heart failure was classified by the severity determined by the New York Heart Association (NYHA) classification. Acute heart failure was defined as those patients with symptom deterioration within the last one month. Patients diagnosed with heart failure and currently taking medicine, and without deterioration of the symptoms within the last one month were defined as stable chronic heart failure. The control group were patients without a history of heart failure, without any evidence of coronary artery disease (history of atherosclerosis, positive exercise test, or significant coronary artery stenosis on coronary angiography), and they had normal findings on echocardiography. The control subjects were 4 volunteers (mean age 23 years), 28 individuals who underwent a routine check-up without specific symptoms or medical history (mean age 44 years), 311 patients presenting non-cardiac chest pain with structurally normal hearts, and 318 patients presenting mild dyspnea with structurally normal hearts. The patients with typical clinical symptoms, but they had not received echocardiography were excluded in this study. Patients that were without NYHA classification in their medical records were excluded from the analysis (n=110). Patients with nephrotic syndrome in their medical history or if this was found on physical examination were also excluded.

Measurement of plasma BNP level

The plasma BNP concentration was measured by

drawing 3–5 mL blood in a tube containing EDTA, and then it was quantified by immunofluorescence using BNP kit (Triage[®], Biosite, San Diego, USA). For the measurement, the minimum value was 5 pg/mL and the maximum value was 5000 pg/mL.

Data analysis and statistics

All data were presented as means \pm standard deviation and analyzed using SPSS version 10.0. Continuous variables among the controls, the systolic heart failure group, and the diastolic heart failure group were analyzed by one-way ANOVA. Discontinuous variables were analyzed by Pearson's Chi-square test. Continuous variables between the two groups were compared by t-test and discontinuous variables were compared by Chi-square test. To assess the accuracy of the BNP value for the diagnosis of heart failure, the sensitivity and the specificity were obtained by comparing the BNP values of systolic heart failure patients and the control subjects. The accuracy of the test was assessed by the area under the receiver operating characteristic curve (AUROC). The cut-off value was determined by the highest sensitivity and 1-specificity by using a 2×2 table obtained by applying ROC curve. The correlation of plasma BNP values, echocardiography factors, and the enddiastolic left ventricle pressures were evaluated by linear regression analysis. p values less than 0.05 were considered statistically significant.

Results

The clinical characteristics of the study population and echocardiographic findings

For 3830 patients who underwent the BNP test, the males were 49.0% (n=1877), and their mean age was 62.8 ± 13.8 years. The reasons for BNP testing were the evaluation of dyspnea or the differential diagnosis of heart failure (n=2378, 62.1%), follow-up of heart failure (n=774, 20.2%), coronary artery disease (n=582, 15.2%), and the volunteers and to assess the heart's condition prior to surgery and others causes were 12.7% (n=486).

661 cases were control subjects, 475 cases were systolic heart failure, and 787 cases were diastolic dysfunction including 500 cases with isolated diastolic dysfunction, and 287 cases were diastolic heart failure. 687 cases were ischemic heart disease patients, 305 cases were patients with acute or chronic pulmonary diseases, 148 cases were patients with atrial fibrillation and other ventricular arrhythmia without heart failure symptoms, 168 cases were patients who complained of dyspnea without having echocardiography performed on them, and 166 cases were abnormal echocardiography without any previous history of heart disease on the medical records, anasarca patients without heart failure, multiple trauma and primary valvular heart disease. 269 cases were cardiac arrest or cardiopulmonary resuscitation (Figure 1). We compared the characteristic echocardiography and biochemical markers in the control group, the systolic heart failure group, and the diastolic heart failure group. From the medical history, the incidence of hypertension in the control group, systolic heart failure group and diastolic heart failure group was 33.1%, 42.3%, and 43.8%, respectively. The incidence was significantly higher in the heart failure group (p=0.040). The incidence of diabetes

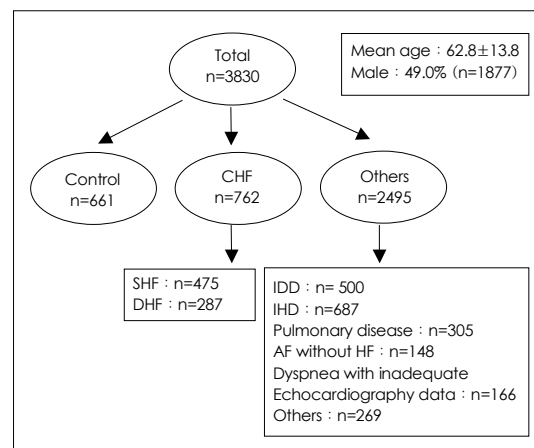


Figure 1. The flow diagram of the patients. CHF: congestive heart failure, SHF, DHF: systolic and diastolic heart failure, IDD: isolated diastolic dysfunction, IHD: ischemic heart disease, Pulmonary disease: COPD, pneumonia, etc., Others: general edema, post-operation, multiple trauma, cardiac resuscitation, chronic renal failure, etc.

was 15%, 19%, and 21% and smoking was 37%, 31%, and 37%, respectively, and the difference was not significant ($p>0.05$). The incidence of ischemic heart disease in systolic heart failure cases was 32.4%, and in the diastolic heart failure patients it was 14.8%, and this was significantly higher than in the systolic heart failure patients. From the medical history, myocardial infarction was 16.8% and 2.5%, respectively ($p=0.021$). Patients with significant mitral or aortic valve regurgitation were 29.8% in the systolic heart failure group and 10.3% in the diastolic heart failure group ($p=0.035$). The plasma creatinine level and body mass index were not significantly different in these three groups ($p>0.05$). In regard to echocardiography findings, the left ventricular ejection fraction was 33.1% in the systolic heart failure patients, which was significantly lower than the diastolic heart failure patients' rate (59.1%) and the control rate (61.2%) ($p=0.021$). Similarly, the left ventricular end-diastolic dimension was significantly increased in the systolic heart failure patients ($p=0.019$). The left ventricular mass value in systolic heart failure patients was 134.3 g, which was significantly higher than the control value 86.3 g and the diastolic heart failure group 109.3 g ($p=0.044$). The left ventricular end-diastolic pressure in systolic heart failure group was significantly higher than

the diastolic heart failure group or the control group ($p=0.0091$), and in the diastolic heart failure group, it was significantly higher than the control group ($p=0.042$, Table 1).

The BNP concentration in study groups

The BNP value in the controls ($n=661$) was 31.5 ± 24.0 pg/mL (Figure 2A); in males it was 28.0 ± 23.8 pg/mL, and in females it was 34.9 ± 23.7 pg/mL. The BNP level in females was significantly high ($p=0.041$, Figure 2B). In control subjects, the BNP level increased as their age increased: the level for under 30 years old was 10.8 ± 8.2 , 40 years old was 23.3 ± 12.6 , 50s was 27.4 ± 19.9 , 60s was 26.4 ± 19.3 , and over 70s was 46.8 ± 28.5 pg/mL ($p=0.042$, Figure 3). In the systolic heart failure group ($n=475$) and diastolic heart failure group ($n=287$) the values were 564.1 ± 418.2 and 193.2 ± 108.1 pg/mL, respectively. It was significantly higher in the systolic heart failure group than the other groups ($p=0.008$, Figure 4). Within systolic heart failure group, its value in acute heart failure patients ($n=128$) was significantly higher than in chronic heart failure patients (859.8 ± 1032.7 vs. 342.3 ± 482.9 pg/mL, $p=0.008$). The values were significantly different according to the severity of heart failure; according to the

Table 1. Clinical and echocardiographic characteristics of study patients

Clinical characteristics	Control (n=661)	Systolic HF (n=475)	Diastolic HF (n=287)
Age	60.8 \pm 10.2	63.2 \pm 7.1	59.8 \pm 9.3
Sex (male)	49.2%	52.1%	49.3%
BMI	1.68 \pm 0.28	1.70 \pm 0.33	1.71 \pm 0.34
Hypertension*	33.1%	42.3%	43.8%
Diabetes	15.3%	19.2%	21.2%
Smoking	37.1%	31.3%	37.8%
Serum Cr (mg/dL)	0.9 \pm 0.2	1.2 \pm 0.2	1.0 \pm 0.3
LVEF (%) *	61.21 \pm 8.7	33.1 \pm 10.4	59.1 \pm 9.3
E/A ratio*	1.23 \pm 0.2	1.79 \pm 1.12	0.69 \pm 0.2
LVEDD (mm) *	4.73 \pm 0.49	5.97 \pm 0.9	4.91 \pm 0.58
LVMI (g/m ²) *	86.3 \pm 14.2	134.3 \pm 41.2	109.3 \pm 21.8
LVEDP (mmHg) *	10.9 \pm 2.2	18.7 \pm 1.8	13.9 \pm 1.7

HF: heart failure, BMI: body mass index, Cr: creatinine, LVEF: left ventricular ejection fraction, E/A ratio: peak velocity during phasic phase of diastolic filling of left ventricle/late peak of velocity following atrial contraction ratio, LVMI: left ventricular mass index, LVEDD: left ventricular end diastolic dimension, LVEDP: left ventricular end diastolic pressure.

*: $p<0.05$

The BNP Level in Congestive Heart Failure

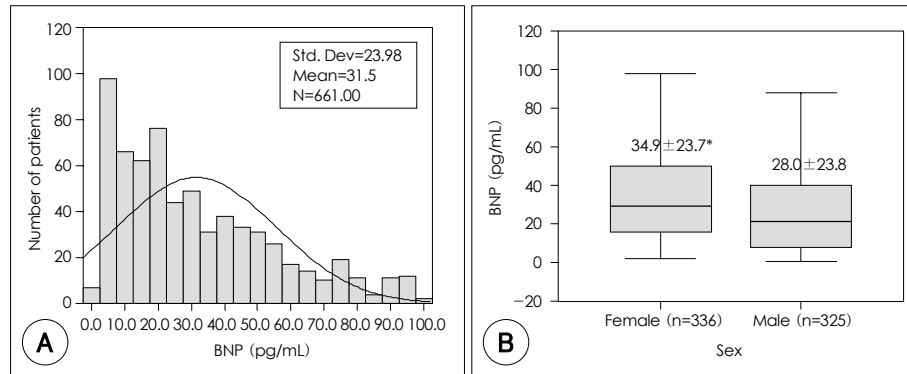


Figure 2. A: the distribution of BNP levels in control patients. B: comparison of BNP levels according to the sex in control patients. Data: mean \pm SD, $p=0.041$ between the groups, BNP: B-type natriuretic peptide. *: $p<0.05$.

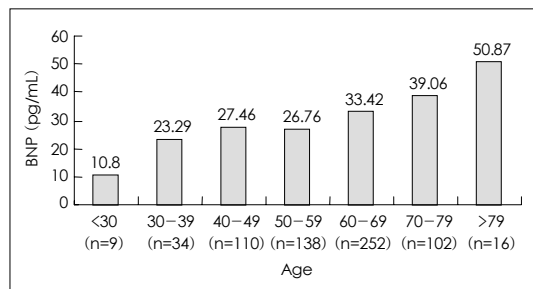


Figure 3. Comparison of BNP levels according to the aging in control patients. BNP: B-type natriuretic peptide. Data: mean \pm SD, $p=0.041$ between the groups.

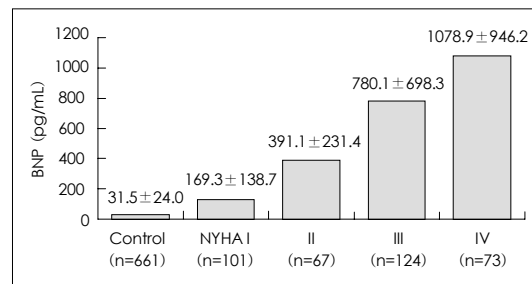


Figure 5. BNP levels according to the NYHA class in patients with systolic heart failure ($n=365$). Some patients ($n=110$) was missed the record for NYHA class. BNP: B-type natriuretic peptide, NYHA: New York Heart Association. Data: mean \pm SD, $p=0.009$ among the groups.

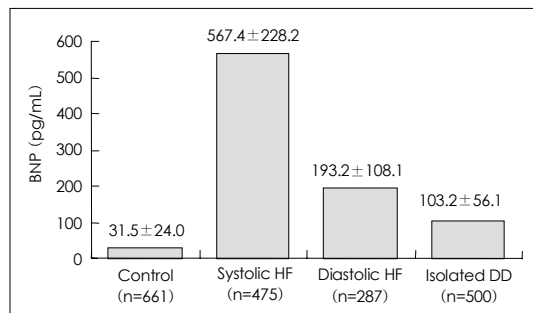


Figure 4. Comparison of BNP levels in congestive heart failure. Data: mean \pm SD, HF: heart failure, DD: diastolic dysfunction, BNP: B-type natriuretic peptide. $p=0.008$ among the groups.

NYHA class, the values were: NYHA class I was 169.3 ± 138.7 , class II was 391.1 ± 231.4 , class III was 780.1 ± 698.3 , and class IV was 1078.9 ± 946.2 pg/mL ($p=0.009$, Figure 5). In isolated diastolic dysfunction patients, the mean BNP value was 103.2 ± 56.1 pg/mL:

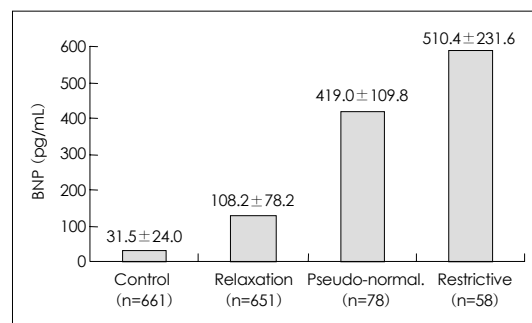


Figure 6. BNP levels according to the transmitral doppler parameters in patients ($n=787$) with diastolic dysfunction by echocardiography. BNP: B-type natriuretic peptide. Data: mean \pm SD, $p=0.009$ among the groups.

it was lower than in diastolic heart failure patients and systolic heart failure patients. In all patients with abnormal diastolic dysfunction on echocardiography ($n=787$),

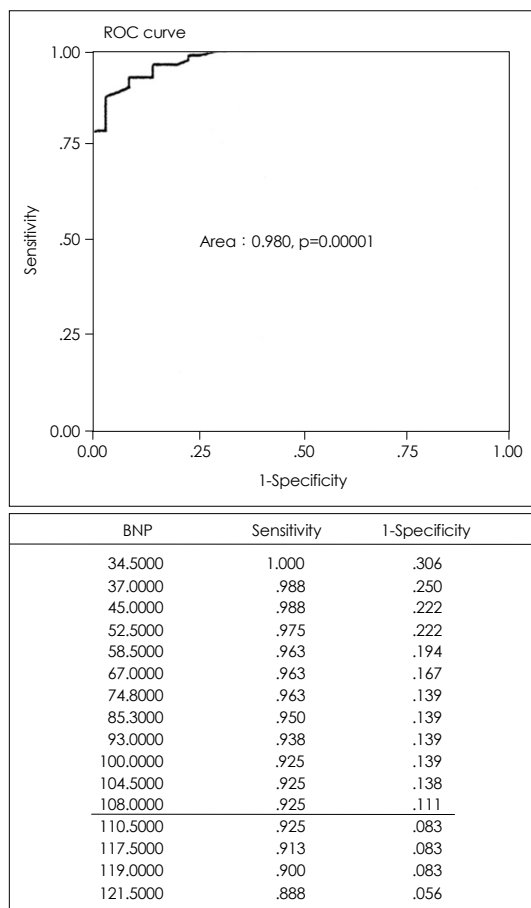


Figure 7. Receiver operating characteristic (ROC) curve of BNP in diagnosis of systolic heart failure. Diagonal segments are produced by ties. BNP: B-type natriuretic peptide.

the significant difference was noted according to the severity of diastolic dysfunction as detected by transmitral Doppler: in patients with relaxation abnormality it was 108.2 ± 78.2 , pseudo-normalization was 419.0 ± 109.8 , and restrictive physiology was 510.4 ± 231.6 pg/mL ($p=0.009$, Figure 6).

The accuracy of the BNP test in the diagnosis of heart failure and their correlation

The accuracy of the BNP test at 108 pg/mL was 98% on the ROC curve, which was the most accurate. The sensitivity and specificity was 92.5% and 88.9%, respectively (Figure 7). The plasma BNP concentration was not significantly correlated to the left ventricular end-diastolic pressure as tested by linear regression analysis ($r=0.193$, $p=0.078$, Figure 8A), and it was significantly and inversely correlated to the left ventricular ejection fraction ($r=-0.491$, $p=0.012$, Figure 8B).

Discussion

BNP, a hormone predominantly derived from the ventricular myocardium in compensation for increased pressure or the activation of neuro-endocrinal system, has been recently used as an indicative marker for the left ventricular failure.¹²⁾¹³⁾ It has been reported that the BNP level in females is higher than males and its concentration has increase with an individual's age in some studies.¹⁴⁾ Our data are in agreement with the findings.

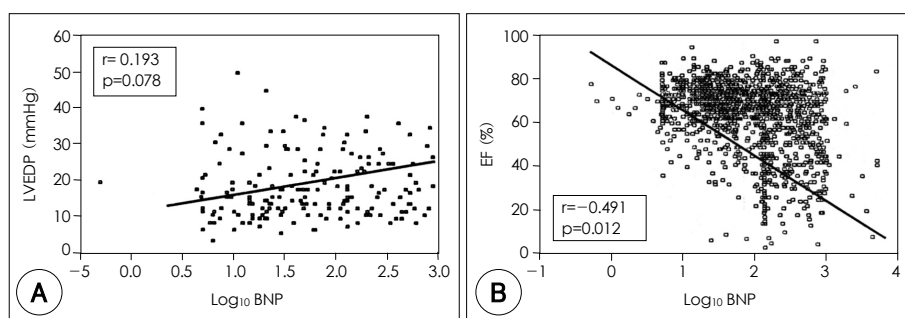


Figure 8. A: correlation between BNP level and EF (ejection fraction) in systolic heart failure patients. B: correlation between BNP level and LVEDP (left ventricular end-diastolic pressure) in systolic heart failure patients ($n=187$). BNP: B-type natriuretic peptide.

Particularly, the mean value in patients over 70 years old was 46.8 ± 8.5 pg/mL, which was higher than in young patients. This may be due to the deterioration of heart function in older aged person. Hence, we believe that this finding must be taken into consideration in the analysis of BNP for old patients. However, although our control patients were shown to be free of cardio-vascular diseases on the tests, they complained symptoms for chest pain or dyspnea and thus, the interpretation of the data using such patients as controls may be a limiting factor. Recently, the result of BNP test can be accurately and rapidly obtained. The test facilitates the correct care of patients, and particularly to make clinical decisions for diseases requiring immediate diagnosis and treatment.¹⁵⁾¹⁶⁾ In fact, the test is useful for clinicians in the differential diagnosis for the causes of dyspnea for patients visiting the hospital or emergency room. In addition, the BNP measurement has been reported to be a non-invasive, simple, and accurate test for older patients, obese patients, patients with chronic pulmonary diseases, and even for those patients having difficulty being tested by echocardiogram. Thus, its clinical usefulness for the differential diagnosis of heart failure is important.¹⁶⁻¹⁸⁾ Recent clinical studies by Dao, et al.¹⁷⁾ have reported that when a BNP value of 100 pg/mL was applied as the cut-off value, the test was a good tool for the diagnosis of heart failure with an accuracy of 83.4 %. Furthermore, they reported that the efficacy of the diagnosis could be improved by combining the results of clinical examinations and the BNP values together. In our hospital, we performed the prospective study on patients who visited the emergency room complaining of dyspnea. For a diagnosis based on doctor's decision by basic tests and clinical examination, the sensitivity was 85% and the specificity was 51%. On the other hand, when the patient was diagnosed based on the BNP value, the sensitivity was 96% and the specificity was 82%. Our data demonstrated that the differential diagnosis based on the BNP value is more accurate.¹⁹⁾ Recently, Tang, et al.²⁰⁾ have reported that in stable chronic systolic heart failure patients, 21.3% of patients showed

the BNP value within the normal range and the mean value was 147 pg/mL. In our study, in chronic systolic heart failure patients, the average was 342.3 pg/mL, and it varied widely from 19 pg/mL to 968 pg/mL. In acute systolic heart failure patients, it was 859.8 pg/mL; it was significantly high and it was higher than the value obtained by Tang, et al.²⁰⁾ The difference may be due to the difference of the definition of patients as well as the difference in the causality of disease.

Most clinical studies applying the BNP value have been performed on systolic heart failure patients. This may be because the diagnosis of the study group is relatively easy, the definition of the diagnosis is easy, and clinical study can be performed readily. Maisel, et al.²¹⁾ have reported that in diastolic heart failure or non-systolic heart failure, the BNP value is higher than in normal individuals and significantly lower than in systolic heart failure patients. Similarly, in our study, the BNP value in diastolic heart failure patients was higher than in isolated diastolic dysfunction patients. Such results suggest that the evaluation of the BNP value may be helpful for the diagnosis of patients who visit the hospital for the dyspnea on exertion without any clear and distinct heart failure symptoms. In addition, as the BNP value varies according to the severity of diastolic dysfunction, it may be of help for the follow-up of diastolic heart failure.²¹⁾ In addition, in diastolic heart failure and diastolic dysfunction, the BNP test result facilitates the application of echocardiography and other heart imaging studies more efficiently. Furthermore, echocardiography and other test modalities are anticipated to provide parameters for the application of the BNP test and appropriate treatment.²²⁾

In our study, the correlation of the left ventricular end-diastolic pressure and the BNP concentration was not significant. This is in contrast to other reports showing the correlation of the left ventricular end-diastolic pressure and the BNP concentration, and the BNP level reflecting the left ventricular end-diastolic pressure.⁸⁾²³⁾²⁴⁾ A recent study reported that for in-patients, even after their left ventricular end-diastolic pressure was decre-

ased to the normal level within a few days of admission, the BNP value continued to decrease.¹³⁾ This may have occurred because although the BNP level is affected by the left ventricular end-diastolic pressure, the BNP release continued after the stabilization of the left ventricular end-diastolic pressure as the continuous compensation by the activation of neuro-endocrine system. The BNP value may reflect the heart failure condition more accurately than the follow-up of the actual heart failure condition by hemodynamic parameters. Based on these, we speculate that the BNP level may have limits in the evaluation of the left ventricular end diastolic pressure at the first hospital visit because in our study, the BNP was measured at the time of the first visit and the left ventricular end-diastolic pressure was performed several days later after the treatment of dyspnea with diuretics drugs, among other treatments. In addition, as we mentioned above, in heart failure patients after treatment, although the left ventricular diastolic pressure is decreased, BNP may continue to show as an abnormal value.

We strongly believe that our present study is meaningful as we obtained the basic clinical data on the BNP test from a large study population. However, as our study was a cross-section study and the study population was not homogenous, further prospective study will be required. In addition, although the accuracy of the test was high, in some patients, their clinical results did not correlate to the BNP value. In the interpretation of the BNP test, therefore, clinical results and echocardiography must also be taken into consideration. Further studies will be required on patients showing a discrepancy of clinical features and symptoms and the BNP value.

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