B-Type Natriuretic Peptide Predicts Clinical Presentations and Ventricular Overloading in Patients with Heart Failure

Boyoung Joung[1], Byung-eun Park[1], Dong Soo Kim, Bum Kee Hong, Dong-Yeon Kim, Yun-Hyeong Cho, Sang Hak Lee, Young Won Yoon, Hyun-Seung Kim, Jeong-Ho Kim[2], and Hyuck Moon Kwon

[1]Cardiology Division, Department of Internal Medicine, [2]Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea.

Brain natriuretic peptide (BNP), a neurohormone secreted from the ventricular myocardium in response to hemodynamic load/wall stress, in congestive heart failure (CHF). This study was performed to evaluate the correlation between BNP level and clinical presentations and hemodynamic parameters obtained by echo-Doppler (echo-Doppler) analysis, and its relation with disease severity and ventricular load/wall stress. CHF patients (n=246) were subgrouped by clinical presentations and echo-Doppler findings into 4 groups: diastolic HF only, chronic HF, acute HF, and chronic HF with acute exacerbation. A BNP level of 81.2 pg/ml showed a sensitivity/specificity of 53.3%/98.4% for detecting CHF (AUC, 0.882; $p < 0.0001$), and was found to be closely related with the NYHA classification ($p < 0.0001$). Log BNP was related with LVEF (r^2=0.3015, $p < 0.0001$) and the Meridional wall stress index (r^2=0.4052, $p < 0.0001$). The difference between the BNP levels of the subgroups and BNP control was significant ($p < 0.0001$), exept between the HF group and the controls; control (n=114, 20.9 ± 31.4 pg/ml), only diastolic HF (n=84, 89.8 ± 117.6 pg/ml), chronic HF (n=60, 208.2 ±210.2 pg/ml), acute HF (n=28, 477.9 ± 498.4 pg/ml), chronic HF with acute exacerbation (n= 74, 754.1 ±419.2 pg/ml). The BNP level was significantly higher in the only diastolic HF group than in the asymptomatic control group with diastolic dysfunction (89.8 ± 12.8 vs. 22.8 ± 5.1 pg/ml, $p < 0.0001$). BNP may be a good indicator for the differential diagnosis of a broad spectrum of heart failures. And, elevated BNP might help to diagnose diastolic HF in patients with diastolic dysfunction.

INTRODUCTION

Congestive heart failure (CHF) is a serious disease with a high prevalence and mortality rate,[1-3] and needs standardized methods for early diagnosis and proper management.[4] Currently, most physicians rely on clinical and echocardiographic severity for the diagnosis and treatment of CHF, in which the role of echo-Doppler is very important. But, since this tool has some limitations, a more accessible, less expensive and accurate diagnostic approach is required. In addition, CHF is manifested by a variety of clinical symptoms, and is classified by disease causes, underlying disease, duration, and the degree to which daily activities are affected.

Recently, many reports have been issued about BNP, a neurohormone secreted from the ventricular myocardium in response to wall stress, which is significantly elevated in symptomatic patients with systolic and diastolic dysfunction,[5-7] and which has a very high sensitivity and specificity.[5,8-10] However, few reports have been issued on changes in plasmic BNP according to the clinical presentation of CHF and ventricular hemodynamic loading. Moreover, the value of BNP in detecting early HF is not well known. The present study was performed to evaluate the usefulness of serum BNP in evaluating the clinical presentation of CHF and in detecting early CHF. Also, we examined the correlation between BNP level and

hemodynamic parameters obtained by echo-Doppler analysis, and its usefulness in predicting ventricular load/wall stress.

MATERIALS AND METHODS

Study population

A sample of 246 patients with a previous history and evidence of HF was studied. The patients had all been referred for echo-Doppler study to evaluate left ventricular (LV) function and hemodynamic parameters at the YongDong Severance Hospital between January 2002 and September 2002 was studied. Patients referred for valve disease assessment, the determination of vegetation presence, or to rule out a cardiac cause of stroke were excluded, as were patients with diseases that could increase extracellular fluid, like pulmonary thromboembolism, acute and chronic renal failure, end stage renal disease, sepsis, liver cirrhosis, chronic obstructive lung disease, Cushing's syndrome, hyperthyroidism, primary aldosteronism, and adult respiratory distress syndrome. One hundred and fourteen patients, without evidence of HF, during the same period were enrolled as a control group. The same exclusion criteria were used in the control group.

All patients were questioned as to whether they had any history of CHF. In addition, medical records were examined for objective findings of CHF, including abnormalities on physical examination, hospitalization for CHF, or regular visits to a cardiology clinic. Patients without a history of CHF were additionally characterized by the lack of any prior study of LV function. Clinical CHF was determined to be present by cardiologists, who were blinded to the echocardiogram results, on the basis of standard Framingham criteria, admission and treatment for CHF, and emergency department visits for CHF. In all patients, the pulse-pressure product was calculated by multiplying the mean blood pressure by the pulse rate.

Patients groups

The 246 patients were classified into 4 groups

according to systolic and diastolic function and symptoms. Group 1 (diastolic HF only group, n=84) contained those with only diastolic HF, which is a clinical syndrome characterized by the symptoms and signs of HF, an ejection fraction (EF) of more than 50%, and abnormal diastolic function.[11,12] Group 2 (chronic HF, n=60) contained those diagnosed with HF more than 3 months previously without evidence of acute exacerbation. Group 3 (acute HF, n=28) contained those who developed symptoms of HF less than 3 months previously and had no history of HF, and group 4 (chronic HF with acute exacerbation, n=74) contained those who had evidence of acute exacerbation of HF with a history of HF.

The New York Heart Association (NYHA) classification[13] for HF was used to evaluate the level of symptoms, as follows; Class I-No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation. Class II-Slight limitation of physical activity: Such patients are comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or angina. Class III-Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary activity will lead to symptoms. Class IV-Inability to carry on any physical activity without discomfort: Symptoms of HF are present even at rest, and any physical activity, increases discomfort.

Measurement of BNP levels

Blood was sampled for BNP analysis within 6 hours of admission in the study group and echo-Doppler study was performed within at least 6 hours of blood sampling. Sampling for BNP and echo-Doppler study was also done within 6 hours in the control group. All blood samples were collected by venipuncture into EDTA tubes. The blood samples were kept at room temperature and analyzed within 4 hours of the draw time. Before analysis, each tube was inverted several times to ensure homogeneity. The whole blood was then analyzed in triplicate by Immunofluorescence BNP assay (Biosite Diagnostics, San Diego, CA, USA), which can measure BNP from 5 pg/mL to 1300 pg/mL. BNP levels lower than 5 pg/mL were considered

to be 2.5 pg/mL in the statistics. The intra-assay and inter-assay coefficients of variation for BNP determinations were 7.9% and 10.8%, respectively.

Echocardiography-Doppler study

M-mode and 2D images and spectral and color flow Doppler recordings were obtained using commercially available instruments operating at 2.0 to 3.5 MHz. Two-dimensional imaging examinations were performed in the standard fashion in the parasternal long- and short-axis views and apical 4- and 2-chamber views. Pulsed Doppler spectral recordings were obtained in the apical 4-chamber view from a 4 × 4-mm sample volume positioned at the tips of the mitral leaflets and in the right upper paraseptal pulmonary vein, and were adjusted to yield velocity signals of maximum amplitude. All data were hard copied to a 1/2-in VHS videotape for subsequent playback, analysis, and measurement.

Two-dimensional echocardiograms were subjected to careful visual analysis to detect regional contractile abnormalities. LV systolic and diastolic volumes and ejection fraction were derived from biplane apical (2- and 4-chamber) views by using a modified Simpson's rule algorithm. Left atrial and LV dimensions were measured from M-mode images according to standard criteria. The transmitral pulsed Doppler velocity recordings from 3 consecutive cardiac cycles were used to derive measurements as follows: E and A velocities were the peak values reached in early diastole and after atrial contraction, respectively, and deceleration time (DT) was defined as the interval from the E-wave peak to the point when the velocity reached baseline. In those cases in which velocity did not return to baseline, the deceleration signal was extrapolated. In addition, pulmonary venous systolic and diastolic flow velocities were obtained as the maximal values reached during the respective phases of the cardiac cycle, and the pulmonary venous "A" reversal was the maximal velocity of retrograde flow into the vein after the P wave of the ECG. Finally, the LV isovolumetric relaxation time (IVRT) was obtained in the apical 5-chamber view with a continuous-wave cursor or, if possible, a pulsed Doppler sample volume positioned to straddle the LV outflow tract and the mitral orifice to obtain signals of aortic valve closure, the termination of ejection and mitral valve opening, or the onset of transmitral flow. IVRT was taken as the time in milliseconds from the end of ejection to the onset of LV filling. All echocardiograms were interpreted by two experienced cardiologists who were blinded to the BNP levels.

Echo-doppler classifications

Ventricular function
Normal ventricular function was defined by normal LV end-diastolic (3.4 to 5.4 cm) and end-systolic (2.5 to 3.6 cm) dimensions, no major wall motion abnormalities, an ejection fraction (50%, and no evidence of impaired or restrictive abnormalities, as described below. Systolic dysfunction was defined by an ejection fraction of < 50% or any wall motion abnormality.

Left ventricle filling pattern
Left ventricle filling pattern was classified follows.

Normal left ventricle filling pattern
A normal left ventricle filling pattern was defined as having an E/A ratio of 1 to 2 and a DT of 160 to 240 ms in patients showing normal systolic function without a history or symptoms of heart failure.

Impaired relaxation
Impaired relaxation was defined as an E/A ratio of <1 or a DT of >240 ms in patients <55 years of age and an E/A ratio of <0.8 and a DT of >240 ms in patients 55 years of age. IVRT measurement, which was available in approximately one half of the patients, was >90 ms in 60% of patients with abnormal E/A changes and/or a DT of >240 ms.

Pseudonormal
Pseudonormal was defined as an E/A ratio of 1 to 1.5 and a DT of >240 ms. Confirmation included a PVd/PVs of >1.5 or an IVRT of <90 ms or by reversal of the E/A ratio (to <1.0) by valsalva when possible.

Restrictive

Restrictive filling patterns were defined as a DT of <160 ms with 1 of the following: a left atrial size of >5 cm, an E/A of >1.5, an IVRT of <70 ms, a PVd/PVs of >1.5, or pulmonary "A" reversal duration exceeding forward mitral A-wave duration. Eighty-five percent of patients had 2 abnormalities, and 51% had 3 abnormalities.

Chamber abnormalities

Left ventricular enlargement was defined as a left ventricular size of more than 5.4 cm. LV hypertrophy was defined as a mean LV wall thickness of the septum and posterior wall of more than 1.2 cm. Patients with hypertrophic cardiomyopathy were excluded.

Meridional Wall Stress Index

The Meridional Wall Stress Index (MWSI) was defined as being p (systolic LV pressure, dyne/cm^2) multiplied by r (LV systolic diameter, mm) divided by 2 h (1+h/2 r) (h being the posterior wall thickness (mm)).

Statistical analysis

Group comparisons of BNP values were made by using t tests for independent samples and ANOVA with post hoc Tukey tests when indicated. In all cases, these were computed with raw BNP values, and repeated with log-transformed BNP values because the BNP distribution was positively skewed. Both versions yielded the same conclusions. Results are expressed as means ± SEM of the raw values. The sensitivity, specificity, and accuracy were computed for BNP using of a selection of possible cutoff points. The sensitivity and specificity of the BNP upper limit (81.2 pg/ml) were compared with the echocardiographic probability of LV dysfunction by using the receiver-operating characteristic (ROC) curves in Analyse-it^{TM} software (version 1.62, Analyse- it^{TM} software, Leeds, UK). Results are expressed in terms of the area under the curve (AUC) and the 95% CI of this area. The software used for the statistical calculations was SAS version 8.01 (SAS institute, Cary, NC, USA).

Table 1. Basic Characteristics, Echocardiographic Parameters and BNP Level Comparison between the Control Group and the Heart Failure Group

	Control (n=114)	Heart failure (n=246)	p Value
Age (years)	52.2 ± 15.3	65.7 ± 12.6	< 0.0001
Sex (female/male)	45/69	104/142	0.6155
SBP (mmHg)	150.2 ± 129.4	133.2 ± 19.6	0.1659
DBP (mmHg)	88.4 ± 68.4	79.1 ± 10.9	0.1537
PPP (per min)	7,436.9 ± 2,682.2	7,214.7 ± 1,364.7	0.4047
LVEDD (mm)	48.8 ± 4.2	58.5 ± 5.8	0.0123
LVESD (mm)	32.4 ± 4.3	38.0 ± 9.9	< 0.0001
LA (mm)	38.4 ± 4.7	42.4 ± 7.4	< 0.0001
LVEF (%)	65.2 ± 7.6	53.7 ± 16.5	< 0.0001
MWSI (dyne/cm^2)	180,945 ± 192,538	193,528 ± 93,955	< 0.0001
BNP (pg/ml)	20.9 ± 31.4	362.7 ± 417.4	< 0.0001
Log BNP	2.5 ± 1.1	4.9 ± 1.7	< 0.0001

PPP, Pulse pressure product; LVEDD, LV end-diastolic dimension; LVESD, LV end-systolic dimension; LA, Left atrium; LV, Left ventricle; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

RESULTS

Patient demographics, echocardiographic parameters, and BNP level

The basic characteristics, echocardiographic parameters, and BNP levels are shown in Table 1. The percentage of male patients was 58.6%. Patients were divided into 2 groups based on whether they had HF or not. The age of the HF group was significantly higher than that of the control (52.2 ± 15.3 vs. 65.7 ± 12.6 years, $p <$ 0.0001). The left ventricular end-diastolic dimension (LVEDD), the left ventricular end-systolic dimension (LVESD), and the left atrium were significantly larger in the HF group than in the control group (LVEDD: 48.8 ± 4.2 vs. 58.5 ± 5.8 mm, $p=0.0123$, LVESD: 32.4 ± 4.3 vs. 38.0 ± 9.9 mm, $p < 0.0001$, LA: 38.4 ± 4.7 vs. 42.4 ± 7.4 mm, $p < 0.0001$). The control group had a significantly better left ventricular ejection fraction than the HF group (65.2 ± 7.6 vs. 53.7 ± 16.5%, $p < 0.0001$). MWSI was significantly higher in the HF group than in the controls (180,945 ± 192,538 vs. 193,528 ± 93,955 dyne/cm^2, $p < 0.0001$). BNP and log BNP were significantly higher in the HF group than in the controls (BNP: 20.9 ± 31.4 vs. 362.7 ± 417.4 pg/ml, $p < 0.0001$, log BNP: 2.5 ± 1.1 vs. 4.9 ± 1.7, $p < 0.0001$).

The diagnostic significance of BNP in HF, and the relationship between systolic function and wall stress

The ability of BNP to detect HF was assessed by using ROC analysis (Fig. 1). The AUC for the ROC curve when BNP was used to detect HF was 0.88 (95% CI, 0.86 to 0.92, $p < 0.0001$). A BNP value of 81.2 pg/mL had a sensitivity of 53.3% and a specificity of 98.4% for detecting HF.

Fig. 2 represents the BNP levels in the control and HF groups, by the NYHA classification. The difference between the groups was significant ($p <$ 0.001) except between NYHA 1 and the control. BNP was 20.9 ± 31.4 pg/ml in control (n=114), 72.9 ± 82.6 pg/ml in NYHA 1 (n=72), 214.5 ± 235.2 pg/ml in NYHA 2 (n=85), 419.4 ± 237.7 pg/ml in NYHA 3 (n= 50), and 1147.6 ± 265.9 pg/ml in NYHA 4 (n=39).
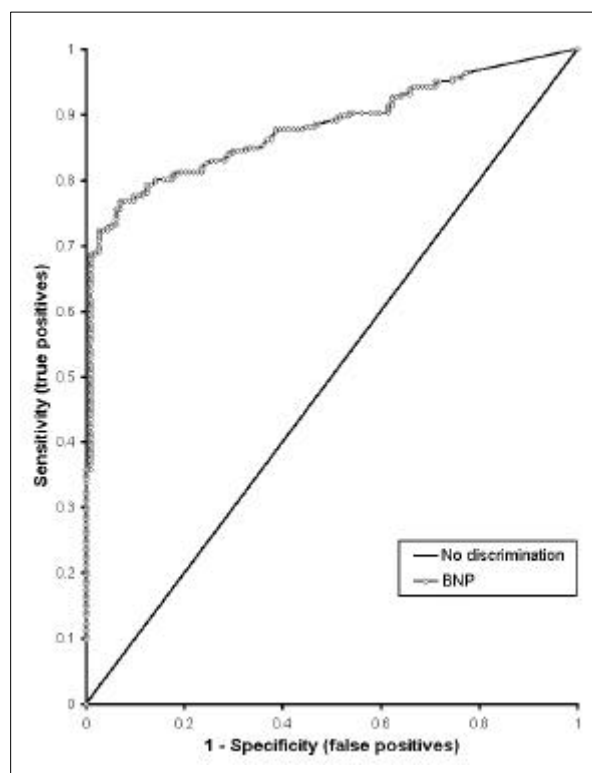

Fig. 1. ROC curve comparing the sensitivity and specificity of BNP and heart failure with symptoms. A BNP level of 81.2 pg/ml showed a sensitivity of 53.3% and a specificity of 98.4%. Area under curve (AUC) was significant (0.882, $p < 0.001$).

Log BNP showed a significant correlation with LVEF ($r^2=0.3015$, $p < 0.0001$, Fig. 3) and with MWSI ($r^2=0.4052$, $p < 0.0001$, Fig. 4).

BNP levels and the severity of HF

Fig. 5 represents the BNP levels in the control and in the 4 HF groups subdivided by systolic and diastolic function and symptoms. The difference between the groups was significant except between group 1 (diastolic HF only) and the control. BNP]was 20.9 ± 31.4 pg/ml in the controls (n=114), 89.8 ± 117.6 pg/ml in the diastolic HF only group (group1, n= 84), 208.2 ± 210.2 pg/ml in chronic HF (group 2, n=60), 477.9 ± 498.4 pg/ml in acute HF (group 3, n=28), 754.1 ± 419.2 pg/ml in chronic HF with acute exacerbation (group 4, n=74). The p value was less than 0.0001.
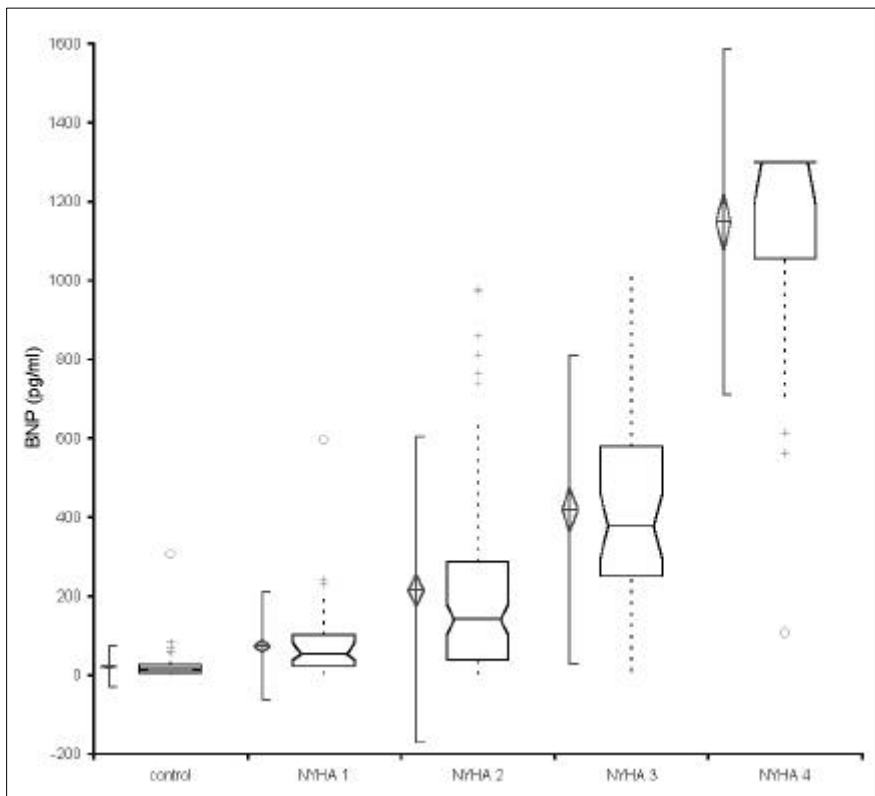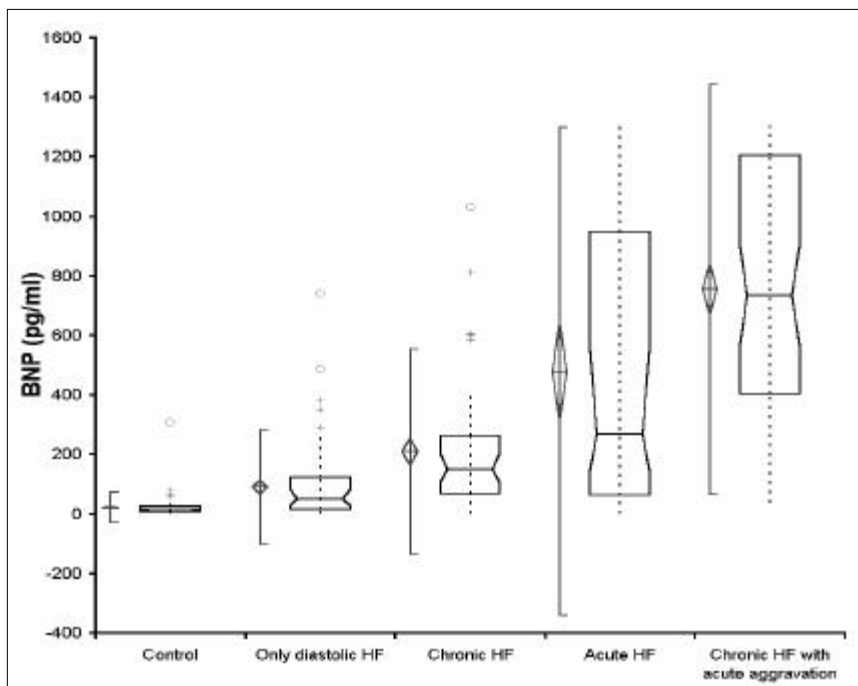
Fig. 2. Means ± SEM of BNP values for control group vs. heart failure groups subdivied by NYHA classification. Differences between the groups were significant, except between NYHA 1 and the control. BNP was 20.9 ± 31.4 pg/ml in control (n=114), 72.9 ± 82.6 pg/ml in NYHA 1 (n=72), 214.5 ± 235.2 pg/ml in NYHA 2 (n=85), 419.4 ± 237.7 pg/ml in NYHA 3 (n=50), and 1147.6 ± 265.9 pg/ml in NYHA 4 (n=39). The p value was less than 0.0001.
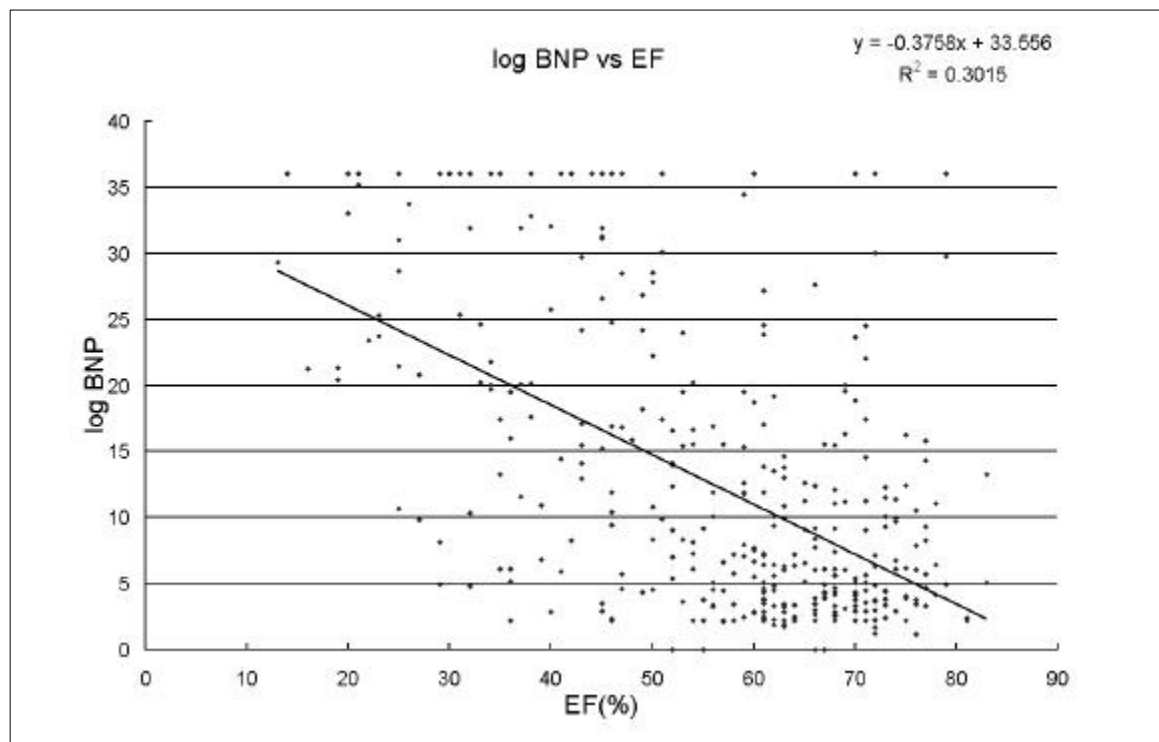
Fig. 3. Correlation between left ventricular ejection fraction and Log BNP. Log BNP was found to be significantly correlated with the left ventricular ejection fraction (r^2=0.3015, $p<0.0001$).
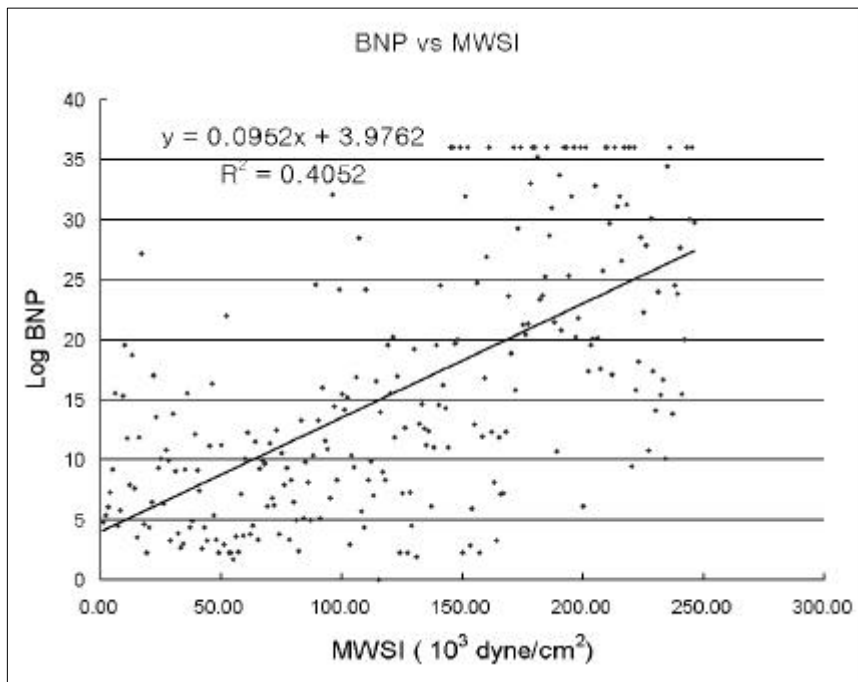
Fig. 4. Correlation between meridional wall stress index (MWSI) and Log BNP. Log BNP was found to be significantly correlated with the meridional wall stress index (r^2=0.4052, $p < 0.0001$).

**Fig. 5.** Mean ± SEM of BNP values for the control group vs. the heart failure group subdivided by systolic and diastolic function and symptoms. Differences between the groups were significant, except between group 1 (diastolic HF only) and the controls. BNP was 20.9 ± 31.4 pg/ml in the control (n=114), 89.8 ± 117.6 pg/ml in diastolic HF only (group1, n=84), 208.2 ± 210.2 pg/ml in the chronic HF (group 2, n=60), 477.9 ± 498.4 pg/ml in the acute HF (group 3, n=28), 754.1 ± 419.2 pg/ml in the chronic HF with acute exacerbation (group 4, n=74). The P value was less than 0.0001.

Comparison between the control group with relaxation abnormality and the diastolic HF only group

BNP levels were significantly higher in symptomatic patients with diastolic HF only (group 1, n=84) than in the asymptomatic control group with relaxation abnormality (n=61). BNP level was 89.8 ± 117.6 pg/ml in group 1, and 22.8 ± 5.1 pg/ml in the asymptomatic control group with relaxation abnormality. The *p* value was less than 0.0001 (Fig. 6).
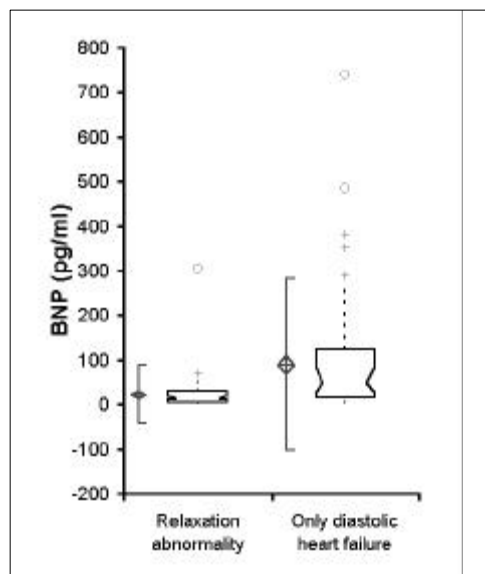
Fig. 6. BNP levels expressed in the asymptomatic control group with relaxation abnormality (n=61) and in the symptomatic patients with diastolic heart failure only (group 1, n=84). Values are means ± SEM. The mean BNP level was 89.8 ± 12.8 pg/ml in group 1, and 22.8 ± 5.1 pg/ml in the control group with relaxation abnormality. The p value was less than 0.0001.

DISCUSSION

CHF is an important clinical problem, particularly in the elderly. HF is one of the main causes of hospitalization in industrialized countries. It is estimated that 4.6 million persons in the United States are currently being treated for heart failure, and 550,000 new cases are diagnosed each year.[1,2] Approximately 45,000 deaths/year are caused primarily by HF and heart failure is listed as a contributing cause in 260,000 deaths.[3] Thus the early diagnosis and proper treatment of CHF are very important.[4] However, the reliability of a clinical diagnosis of HF is poor, especially in primary care. Although clinical assessment, when combined with chest x-ray and electrocardiography, allows a preliminary diagnosis of HF, echocardiography and Doppler (echo-Doppler) analysis provide an objective assessment of cardiac structure and function. Echo-Doppler analysis is the single most useful non-invasive test for the assessment of left ventricular function, severity of disease, and prognosis.[14] But, echo-Doppler analysis has limits in the diagnosis of

mild HF and early diastolic HF with normal systolic function. The technique is often based on visual assessment, which is difficult in uncooperative patients with a poor echocardiographic window, and depends on the observer's experience.[14] Moreover, the logistic and health/economic aspects of large-scale screenings with echo-Doppler are debatable. The limitations of this technique suggest the need for another objective measurement for early diagnosis and severity assessment, with high sensitivity and specificity.[15,16]

In CHF, many neurohormonal factors increase or decrease in an effort to adapt to the pathophysiologic state and drugs administered. Studies using drugs to inhibit the function of some natriuretic peptide receptors or to prevent the degradation of natriuretic peptides (NPs) have confirmed the importance of these peptides.[17] The NP family are secreted to maintain the homeostasis of the cardiovascular system. Atrial natriuretic peptide (ANP) was first described in 1981 by de Bold, et al.[18] who found a natriuretic and vasodilating substance in the atria of rats, the structure of ANP was defined later in 1984.[19] In 1991, brain natriuretic peptide (B-type natriuretic peptide; BNP) first isolated from the porcine brain.[20] However, it was subsequently found that BNP is better sourced from heart ventricles rather than brain. Among these NPs, BNP proportionally increases according to the severity of CHF.[18,21] BNP consists of a 32 amino acid peptide ring,[8,12] left ventricular stretch or wall tension are the primary regulators of BNP release.[18,21,22] BNP increases the excretion of urine by the kidney and has a vasodilatory effect. BNP also inhibits renin angiotensin aldosterone system (RAAS) and sympathetic nervous system (SNS), and decrease the blood pressure and extracellular volume. Therefore, BNP is more closely related with the prognosis of HF than ANP, endothelin, or norepinephrine,[23-26] and is independent of clinical and hemodynamic prognostic factors.[27] Regulation of BNP synthesis and excretion occurs mainly at the gene expression level. The secretion and mRNA turnover of BNP are faster than that of ANP. Therefore, it is easier to measure in acute stage HF.[17]

Echo-Doppler analysis is necessary to differentiate patients with diastolic dysfunction and nor-

mal systolic function.[5,28,29] However, pitfalls in the echo-Doppler assessment of diastolic dysfunction exist, as the transmitral velocity pattern can be altered by changes in heart rate, preload, afterload, contractility, valvular regurgitation, and position of the sample volume. Accordingly, a simple, rapid blood test that reflects diastolic dysfunction in settings with normal systolic function would be of significant clinical benefit. Plasmic BNP levels are known to be elevated in patients with symptomatic LV dysfunction, and to be correlated with NYHA classification and prognosis with high sensitivity and specificity.[8-10,28,29]

The present study was performed to characterize any correlation between BNP and clinical and hemodynamic parameters, for the determination of disease severity and myocardial wall stress. High BNP levels showed good sensitivity and specificity in HF. The BNP level increased proportionally with clinical status, as determined by the NYHA classification, and hemodynamic parameters obtained by echocardiography (LVEF and MWSI). This result indicates that the secretion of BNP from the ventricular myocardium occurs as a compensatory mechanism, according to increased wall stress cause by systolic and diastolic dysfunction in HF. Moreover, acute HF, in which wall stress increases abruptly, showed a higher BNP level than chronic HF. The significant correlation between BNP level and wall stress shows that a continuous compensatory mechanism is involved in the increase of wall stress in HF.[5,7,17,21] The BNP level was found to be higher in chronic HF with acute exacerbation than in acute HF. This may have been caused by a desensitization of NP receptors by continuous stimulation in chronic HF. Harrison, et al.[30] reported that BNP is related to mortality and prognosis in HF. Because the chronic HF with acute exacerbation group had the highest BNP level, their prognoses are expected to be poorer than those of the other patients. Rudolf, et al.[31] also emphasized the significance of BNP as a predictor of sudden death in CHF patients. The high incidence of sudden death in CHF is mainly caused by ventricular tachycardia, pulmonary thromboembolism, cerebral infarction, aneurysmal rupture, myocardial infarction, hyperkalemia, and bradyarrhythmia.[32,33] Preventive ICD (an implantable DC cardiovertor) is suggested in this situa-

tion and BNP may be useful in the screening of high risk patients. Chronic HF with acute exacerbation is expected to have a higher mortality rate, which would include sudden death and complications.

Plasmic BNP levels may also reflect diastolic dysfunction.[34,35] Diastolic dysfunctions can be observed in the normal aging process, but diastolic HF is different. Recently diastolic HF was regarded as CHF due to the increased resistance to diastolic filling of part or all of the heart.[36] Depending on the cohort studied and the exact definition, the prevalence of diastolic HF increases with age and is higher in women than men. Hypertension and left ventricular hypertrophy (LVH) are common causes of diastolic HF. Compared with classic systolic HF, the prognosis is unclear, but long-term mortality may be similar, especially in older patients.[37,38] The pathophysiology of diastolic HF involves impaired relaxation, increased passive stiffness, endocardial and pericardial disease, microvascular flow impairment, and upregulated RAS. Impaired diastolic filling is the first manifestation of active ischemia, and evidence in from animals and humans confirms that demand ischemia results in an upward shift of the left ventricular diastolic pressure-volume relationship.[39] In addition to the active relaxation process, the left ventricle also has passive compliance and becomes stiffer with age. This typical change can elevate serum BNP levels. In this study, the BNP level was significantly higher in the only diastolic HF group than in the asymptomatic control group with diastolic dysfunction. However, our BNP cut-off value of 81.2 pg/ml may be insufficient to differentiate diastolic HF and normal patients, because we compared BNP levels between whole HF patients and control. Our study indicates that elevated BNP might to use to find diastolic HF in patients with diastolic dysfunction. Lubien, et al.[28] found that BNP seems to have utility in isolated diastolic HF, by distinguishing diastolic HF from chronic obstructive lung disease and by identifying pseudonormal and restrictive echocardiographic filling patterns with a sensitivity and specificity of about 85%, by using an upper limit of 62 pg/mL. Angeja, et al. suggested that the simplest definition of diastolic HF might be an elevated BNP with normal systo-

lic function.[36] Recently, Senthil, et al.[40] found that BNP is elevated in proportion to the severity of diastolic abnormality and is correlated significantly with the traditional and the newer echo indices of diastolic dysfunction. Considering that diastolic function is impaired earlier than systolic function, BNP might be useful to find early changes in heart failure.

Increased maximal O_2 consumption (VO_2) during exercise helped to achieve clinical stability and decreased hospital admission times.[41] It was reported that maximal VO_2 is useful in the prognosis of heart failure.[42] Stefan, et al.[43] tried to measure functional impairments in HF objectively and studied the BNP levels and O_2 consumption in CHF patients. They reported that a BNP level of 532 pg/ml is a good indicator of a maximal VO_2 of less than 10 ml/min/kg, and that a BNP level of 316 pg/ml as a good indicator of a maximal VO_2 of less than 14 ml/min/kg. This finding shows that the BNP level can reflect functional activity in HF. We also found that BNP levels are closely related to HF, in terms of the NYHA classification and their clinical symptoms. BNP levels were especially useful for the early diagnosis of acute deterioration in chronic HF, and may reflect the effect of treatment or the prognosis. In addition, BNP levels were significantly higher in symptomatic patients with only diastolic HF than in the asymptomatic control group with diastolic dysfunction. High BNP levels in diastolic HF may indicate the development of more severe HF and the need for early treatment.[5,31,32]

This study has limitations. Because we compared BNP levels between whole HF and control, our BNP cut-off value might have insufficient power to differentiate diastolic HF and normal patients. We did not evaluate BNP levels with respect to to invasive hemodynamic parameters, like LVEDP (left ventricular end diastolic pressure) and the newer Doppler parameters of diastolic HF. Therefor, we are unable to present a more detail mechanism of BNP changes. Moreover, BNP levels are reported to be decreased after treatment with beta blockade,[44] ACE inhibitors,[45-47] and to be increased after treatment with digitalis.[48] However, change in BNP levels after medication were not evaluated in the present study.

In conclusion, BNP levels were found to be related to the severity of HF and to left ventricular wall stress, and could be useful for discriminating diastolic HF patients from normal patients with diastolic dysfunction. However, more sophisticated studies are needed to determine the exact BNP cut-off levels to identify diastolic HF in diastolic dysfunction. BNP might have an extra advantage as a surrogate end point for the evaluation of various HF treatments. Thus, monitoring BNP levels in future treatment protocols for chronic diastolic heart failure and acute exacerbation may provide a valuable information regarding drug efficacy and patient outcome.

REFERENCES

1. 2000 Heart and Stroke Statistical Update. Dallas, TX: American Heart Association; 1999.
2. Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventing strategies and compressive disease management. Am Heart J 1997;133:703-12.
3. Centers for Disease Control and Prevention. National Vital Statistics Report, vol 47. Hyattsville, MD: National Center for Health Statistics; 1999.
4. Levin ER, Gardener DG, Samson WK. Mechanism of disease; Natriuretic peptides. N Engl J Med 1998;339: 321-8.
5. Talwar S, Downie PF, Ng LL, Squire IB. Towards a blood test for heart failure: the potential use of circulating natriuretic peptides. Br J Clin Pharmacol 2000; 50:15-20.
6. Alan M. B-type natriuretic peptide levels: diagnostic and prognostic in congestive heart failure: what's next? Circulation 2002;105:2328-31.
7. Richards AM, Nicholls MG, Yandle TG, Ikram H, Espiner EA, Turner JG, et al. Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction. Heart 1999;81:114-20.
8. Cowie M, Struthers AD, Wood DA. The value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997; 350:1349-53.
9. McDonanagh T, Robb SD, Murdoch DR. A formal assessment of how good natriuretic peptide concentrations are in screening for LV systolic dysfunction in the community. Biochemical detection of LV systolic dysfunction. Lancet 1998;351:9-13.
10. Struthers AD. The diagnosis of heart failure. Heart 2000;84:334-8.
11. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. Eur Heart J 1998;19:

990-1003.

12. Zile MR, Brutsaert DL. New Concepts in Diastolic Dysfunction and Diastolic Heart Failure: Part I. Diagnosis, Prognosis, and Measurements of Diastolic Function. Circulation 2002;105:1387-93.

13. Rector TS, Cohn JN. Prognosis in congestive heart failure. Annu Rev Med 1994:45;341-50.

14. Davies MK, Gibbs CR, Lib YM. ABC of heart failure; investigation. BMJ 2000;320:297-300.

15. Maisel AS, Koon J, Krishnaswamy P, Kazenegra R, Clopton P, Gardetto N, et al. Utility of B-natriuretic peptide as a rapid, point-of care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. Am Heart J 2001;141: 367-74.

16. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol 2001;37:379-85.

17. Mair J, Hammerer-Lercher A, Puschendorf B. The impact of cardiac natriuretic peptide determination on the diagnosis and management of heart failure. Clin Chem Lab Med 2001;39:571-88.

18. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extracts in rats. Life Sci 1981;28:89-94.

19. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441-6.

20. Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. Nature 1988;322: 78-81.

21. Cowie MR. BNP: soon to become a routine measure in the care of patients with heart failure? Heart 2000;83: 617-8.

22. Cheung BM, Kumana CR. Natriuretic peptides-relevance in cardiovascular disease. JAMA 1998;280:1983-4.

23. Omland T, Aarsland T, Aakvaag A. Prognostic value of plasma atrial natriuretic factor, norepinephrine and epinephrine in acute myocardial infarction. Am J Cardiol 1993;72:255-9.

24. Davidson NC, Naas AA, Hanson JK. Comparison of atrial natriuretic peptide, B-type natriuretic peptide, and N-terminal proatrial natriuretic peptide as indicators of left ventricular systolic dysfunction. Am J Cardiol 1996;77:828-31.

25. Richards AM, Doughty R, Nicholls MG, Macmahon S, Ihram H, Sharpe N, et al. Neurohumoral prediction of benefit from carvedilol in ischemic left ventricular dysfunction. Circulation 1999;99:786-92.

26. Francis GS, Benedict C, Johnstone DE. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. Circulation 1990;82:1724-9.

27. Tsutamoto T, Wada A, Maeda K. Plasma brain natriuretic peptide level as a biochemical marker of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction: comparison with plasma angiotensin II and endothelin-1. Eur Heart J 1999;20:1799-807.

28. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R. Utility of B-natriuretic peptide in detecting diastolic dysfunction. Comparison with Doppler velocity recordings. Ciculation 2002;105:595-601.

29. Bettencourt P, Ferreira A, Dias P, Castro A, Martins L, Cerqueira-Gomes M. Evaluation of brain natriuretic peptide in the diagnosis of heart failure. Cardiology 2000;93:19-25.

30. Harrison A, Morrison LK, Krishnaswamy P. B-type natriuretic peptide (BNP) predicts future cardiac events in patients presenting to the emergency department with dyspnea. Ann Emerg Med 2002;39:131-8.

31. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, et al. B-type natriuretic peptide predicts sudden cardiac death in patients with chronic heart failure. Circulation 2002;105:2392-7.

32. Stevenson WG, Stevenson LW, Middlekauff HR. Sudden death prevention in patients with advanced ventricular dysfunction. Circulation 1993;88:2953-61.

33. Pratt CM, Greenway PA, Schoenfeld ML. Exploration of the precision of classifying sudden cardiac death : implication for the interpretation of the clinical trials. Circulation 1996;93:519-24.

34. Yamamoto K, Burnett JC Jr, Jougasaki M, Nishimura RA, Bailey KR, Saito Y, et al. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hypertension 1996;28:988-94.

35. Yu CM, Sanderson JE, Shum IOL, Chan S, Yeung LY, Hung YT, et al. Diastolic dysfunction and natriuretic peptides in systolic heart failure. Eur Heart J 1996;17: 1694-702.

36. Angeja BG, Grossman W. Evaluation and management of diastolic heart failure. Circulation 2003;107:659-63.

37. Senni M, Redfield MM. Heart failure with preserved systolic function: a different natural history? J Am Coll Cardiol 2001;38:1277-82.

38. Gottdiener JS, McClelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med 2002;137:631-9.

39. Aroesty JM, McKay RG, Heller GV, Royal HD, Als AV, Grossman W. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. Circulation 1985;71:889-900.

40. Thambidorai SK, Troughton RW, Parakh K, Tang WH, Francis GS, Klein AL. Utility of B-type natriuretic peptide in primary diatolic dysfunction: A quantitative comparison with Doppler echocardiographic indices. ACC 2003 abstract.

41. Stevenson LW, Steimle AE, Fonarow G. Improvement in exercise capacity of candidates awaiting heart transplantation. J Am Coll Cardiol 1995;25:163-70.

42. Pardaens K, van Cleemput J, Vanhaecke J, Fagard RH. Peak oxygen uptake better predicts outcome than submaximal respiratory data in heart transplant candidates. Circulation 2000;101:1152-7.

43. Stefan K, Jürgen G, Dagmar K, Tina S, Peter H, Uwe J. Brain natriuretic peptide levels predict functional capacity in patients with chronic heart failure. J Am Coll Cardiol 2002;40:718-22.

44. Kawai K, Hata K, Takaoka H, Kawai H, Yokoyama M. Plasma brain natriuretic peptide as a novel therapeutic indicator in idiopathic dilated cardiomyopathy during beta-blocker therapy: a potential of hormone-guided treatment. Am Heart J 2001;141:925-32.

45. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325: 293-302.

46. Troughton RW, Frampton CM, Yandle TG. Treatment of heart failure guided by plasma amino terminal brain natriuretic peptide (N-BNP) concentrations. Lancet 1994;355:1126-30.

47. Murdoch DR, McDonaugh TA, Byrne J. Titration of vasodilator therapy in chronic heart failure according to plasma brain natriuretic peptide concentration: randomized comparison of hemodynamic and neuroendocrine effects of tailored versus empirical therapy. Am Heart J 1998;138:1126-32.

48. Tsutamoto T, Wada A, Maeda K. Digitalis increases brain natriuretic peptide in patients with severe congestive heart failure. Am Heart J 1997;134:910-6.