Clin. Cardiol. 29, 155–160 (2006)

Amount of Left Ventricular Hypertrophy Determines the Plasma N-Terminal Pro-Brain Natriuretic Peptide Level in Patients with Hypertrophic Cardiomyopathy and Normal Left Ventricular Ejection Fraction

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Summary

Background: N-terminal pro-brain natriuretic peptide (NT-proBNP) is increased in patients with hypertrophic cardiomyopathy (HCM); however, the determinants of NT-proBNP level have not been clarified in HCM.

Hypothesis: This study was performed to determine the relationship between NT-proBNP levels and various echocardiographic variables of patients with HCM and normal left ventricular ejection fraction (LVEF).

Methods: We assessed plasma NT-proBNP levels and echocardiographic variables of 36 patients (19 men, 58 ± 14 years) with HCM and an LVEF of ≥ 55%. Echocardiographic variables measured were LV wall thickness, end-diastolic LV internal dimension (LVIDd) and volume (LVEDV), LV mass, and LV mass index (LV mass/body surface area, LVMI). Left ventricular outflow tract pressure gradient, transmitral E and A velocities, deceleration time (DT) of the transmitral E wave, and septal annular E' velocity were measured by Doppler technique. The relationship between echocardiographic variables and plasma NT-proBNP level was analyzed.

Results: The plasma NT-proBNP level was 775.2 ± 994.2 pg/ml (range 33.1–4729.0 pg/ml). It showed positive correlations with LV end-diastolic septal thickness ($r = 0.39$, $p = 0.010$) and LVMI ($r = 0.27$, $p = 0.050$), while it revealed negative correlations with LVIDd ($r = -0.44$, $p = 0.004$), LVEDV ($r = -0.44$, $p = 0.004$) and DT ($r = -0.31$, $p = 0.034$). The NT-proBNP level was higher in the patients with than in those without LV diastolic dysfunction ($p = 0.033$) and was independently related to LVIDd ($p = 0.001$), LVMI ($p = 0.006$) and DT ($p = 0.031$) by multivariate analysis.

Conclusion: In patients with HCM and normal LVEF, the amount of LV hypertrophy and LV diastolic dysfunction may exert a significant role in determining plasma NT-proBNP level.

Key words: hypertrophic cardiomyopathy, natriuretic peptide, hypertrophy, diastolic dysfunction

Introduction

Brain natriuretic peptide (BNP) is a biologically active peptide synthesized and released predominantly from the cardiac ventricles in response to increased myocardial stretch and wall tension.[1–3] It is synthesized by cardiac myocytes and formed as a prohormone that is made of 108 amino acids. After secretion, it is divided into the physiologically inactive N-terminal pro-brain natriuretic peptide (NT-proBNP) and the physiologically active BNP.[3] Although NT-proBNP has an unknown biological function,[3] it is more stable than BNP, and its interpersonal variation is lower than BNP.[3–5] The plasma BNP level is known to be increased in hypertrophic cardiomyopathy (HCM);[2, 6–8] however, few studies have reported on plasma NT-proBNP levels in patients with HCM.[9, 10] The present study was performed to determine the relationship of plasma

This study was partially supported by a grant from the Samsung Medical Center and the Sungkyunkwan University School of Medicine.

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Received: October 13, 2005
Accepted with revision: January 5, 2006

NT-proBNP level and various echocardiographic variables in patients with HCM and normal left ventricular (LV) ejection fraction (EF) and to find the most reliable echocardiographic determinants of plasma NT-proBNP level.

Methods

Subjects

The study included 36 patients (19 men, mean age 58 ± 14 years) with HCM and normal LVEF. The diagnosis of HCM was made by M-mode and two-dimensional echocardiographic evidence of hypertrophied, nondilated left ventricles with no identifiable causes of secondary hypertrophy.[11, 12] Normal LVEF was defined as ≥ 55%. All patients were in sinus rhythm and none had any disease, such as conduction disturbances, significant valvular heart disease, ischemic heart disease, or renal disease, that could have influenced plasma NT-proBNP levels. The institutional review board of Samsung Medical Center approved this study, and informed consent was obtained from all participants.

Measurement of N-Terminal Pro-Brain Natriuretic Peptide Levels

Peripheral venous blood samples were carefully taken from the antecubital vein and then transferred into standard sampling tubes containing heparin. N-terminal proBNP was measured by employing the electrochemiluminescence principle (Elecsys® 2010/Molecular analytics E710, Roche Diagnostics, Indianapolis, Ind., USA) using sandwich immunoassay with two polyclonal antibodies in stable hemodynamic condition.

Echocardiography

Echocardiographic studies were performed at the time of NT-proBNP determination. Median interval between echocardiographic examination and blood sampling for plasma NT-proBNP was 15.6 h. The images were stored on super VHS videotape, and an independent researcher blinded to the plasma NT-proBNP levels analyzed echocardiographic variables thereafter.

Interventricular septal thickness (IVST) at end diastole, LV posterior wall thickness (PWT) at end diastole, and LV internal dimension at end diastole and end systole (LVIDd and LVIDs, respectively) were measured by two-dimensional echocardiographically guided M-mode examination. Left ventricular end-diastolic volume (LVEDV) was obtained by Teichholz modification,[13, 14] and LV mass was calculated using the regression equation described by Devereux and Reichek.[1, 13, 15] Left atrial (LA) volume was measured by the length-diameter prolate ellipsoid method at end systole.[16] Individual indices for LV mass and LA volume were obtained by division of LV mass and LA volume by body surface area (BSA), respectively. On Doppler echocardiographic examination, LV outflow tract (LVOT) obstruction was defined as peak blood velocity at LVOT > 2 m/s. Peak LVOT pressure gradient was measured using the modified Bernoulli equation. Transmitral E/A ratio (E/A), transmitral E velocity/septal annular E' velocity (E/E'), and deceleration time (DT) were also measured. Diastolic function was evaluated by comprehensive interpretation criteria of the Mayo diastolic function reporting system.[17]

Statistical analysis

Data were expressed as mean ± standard deviation (SD). All statistical calculations were performed using the Statistical Package for Social Sciences for Windows 11.5 (SPSS Inc., Chicago, Ill., USA). The NT-proBNP values were transformed into a natural logarithm (ln) to overcome the problem of the non-normal distribution of plasma NT-proBNP levels. Student's *t*-test was used to compare differences of continuous variables between the two groups. Simple linear regression analysis was performed to determine the correlation between ln NT-proBNP level and echocardiographic continuous variables. Stepwise multivariate regression analysis was performed to establish independent echocardiographic variables that determine plasma NT-proBNP levels. A p value of < 0.05 was considered significant.

Results

Patient Characteristics

All subjects were in New York Heart Association (NYHA) functional class I or II. The principal baseline echocardiographic characteristics are listed in Table I. Seven patients had apical HCM, 28 patients had asymmetrical septal hypertrophy, and 1 patient had midventricular hypertrophy. The septal to LV posterior wall thickness ratio in patients with asymmetric septal hypertrophy was 1.72 ± 0.76. Only 4 patients had significant LVOT pressure gradient at rest; 10 patients showed significant LVOT pressure gradients upon performing a Valsalva maneuver and 7 had LVOT pressure gradients > 30 mmHg; 29 patients (81%) had diastolic dysfunction.

Plasma Concentration of N-Terminal Pro-Brain Natriuretic Peptide

The mean NT-proBNP level was 775.2 ± 994.2 pg/ml (range 33.1–4729.0 pg/ml) overall. In subgroup analysis, plasma levels of NT-proBNP were 554.8 ± 511.8 pg/ml for hypertrophic obstructive cardiomyopathy (HOCM, n = 10) and 859.9 ± 1061.6 pg/ml for hypertrophic nonobstructive cardiomyopathy (HNCM, n = 26). Plasma NT-proBNP seemed to be higher in women than in men (1066.6 ± 1199.9 pg/ml, 514.4 ± 549.3 pg/ml, respectively, p = 0.050); it showed no correlation with age.

Two-Dimensional Echocardiographic Variables

The plasma ln NT-proBNP level showed negative correlation with LVIDd ($r = -0.44$, $p = 0.004$), LVIDs ($r = -0.34$, $p =$

TABLE I Baseline echocardiographic characteristics of patients with hypertrophic cardiomyopathy

Variables	Mean ± SD	Range
Age	58 ± 14	22–81
NT-proBNP (pg/ml)	775.2 ± 944.2	33.1–4729.0
LV ejection fraction (%)	67.3 ± 6.7	56.0–81.9
LV fractional shortening (%)	42.6 ± 6.2	33.3–57.5
LV internal diameter at end diastole (mm)	45.4 ± 5.8	31.0–56.0
LV internal diameter at end systole (mm)	26.0 ± 4.4	17.0–34.0
IVSTd (mm) [a]	15.1 ± 4.7	7.0–29.0
PWTd (mm)	10.2 ± 2.3	5.0–16.0
IVSTd/PWTd	1.6 ± 0.7	0.9–4.0
LA diameter (mm)	42.8 ± 5.9	31.0–58.0
LV end-diastolic volume (ml)	96.4 ± 28.0	37.9–153.7
LV mass (g)	218.7 ± 60.0	106.9–378.4
LVMI (g/m^2)	128.9 ± 34.7	75.2–219.9
LA volume (ml)	55.0 ± 18.9	19.2–94.9
LAVI (ml/m^2)	32.6 ± 11.6	12.4–62.5
Transmitral inflow		
E/A	0.93 ± 0.46	0.41–2.48
E/E'	11.9 ± 5.1	5.6–30.0
Deceleration time (ms)	255 ± 76	135–418
LVOT peak PG (mmHg)		
At rest	18.4 ± 11.9	5.0–42.0
At Valsalva maneuver	47.3 ± 24.9	17.1–83.6

[a] Of our 36 patients, 7 who had normal interventricular septal wall thickness were patients with apical HCM.
Abbreviations: SD = standard deviation, NT-proBNP = N-terminal pro-brain natriuretic peptide, LV = left ventricular, LA = left atrial, LVMI = LV mass index, LAVI = LA volume index, IVSTd = interventricular septal thickness at end-diastole, PWTd = LV posterior wall thickness at end-diastole, LVOT peak PG = LV outflow tract peak pressure gradient.

TABLE II Correlation of echocardiographic variables with plasma NT pro-BNP level

Echocardiographic variables	r Value	p Value
LV ejection fraction (%)	0.02	0.457
LV fractional shortening (%)	0.02	0.469
LVIDd (mm)	−0.44	0.004 [a]
LVIDs (mm)	−0.34	0.021 [a]
IVSTd (mm)	0.39	0.010 [a]
PWTd (mm)	0.06	0.368
IVSTd/PWTd	0.30	0.081
LA diameter (mm)	−0.02	0.451
LV end-diastolic volume (ml)	−0.44	0.004 [a]
LV mass (g)	0.08	0.316
LVMI (g/m^2)	0.27	0.050 [a]
LA volume (ml)	−0.02	0.454
LAVI (ml/m^2)	0.11	0.261
Transmitral inflow		
E/A	0.10	0.285
E/E'	0.01	0.477
Deceleration time (ms)	−0.31	0.034 [a]
LVOT peak PG		
At rest	−0.50	0.140
At Valsalva maneuver	−0.47	0.169

[a] p Value < 0.05.
Abbreviations as in Table I.

0.021), and LVEDV (r = −0.44, p = 0.004) (Table II) and positive correlation with IVST (r = 0.39, p = 0.010) and LVMI (r = 0.27, p = 0.050) (Table II, Fig. 1B). Left ventricular and LV fractional shortening showed no significant correlation with ln NT-proBNP level (Table II). There was no difference in ln NT pro-BNP level as far as the location of LV muscular hypertrophy is concerned.

Doppler Variables

The DT of mitral inflow showed significant negative correlation with ln NT-proBNP level (r = −0.31, p = 0.034) (Table II). The other Doppler variables as well as the severity of intraventricular dynamic flow obstruction showed no significant correlation with ln NT pro-BNP level (Table II).

Left Ventricular Diastolic Function

Plasma ln NT-proBNP concentration in patients with LV diastolic dysfunction (6.28 ± 1.05 pg/ml) was significantly higher than that in patients with normal diastolic function (5.32 ± 0.91 pg/ml) (p = 0.033).

Multivariable Analysis

On multivariable analysis, ln NT-proBNP level was independently related to LVIDd (p = 0.001), LVMI (p = 0.006), and DT (p = 0.031) with overall r^2 = 0.43 (Table III, Fig. 1).

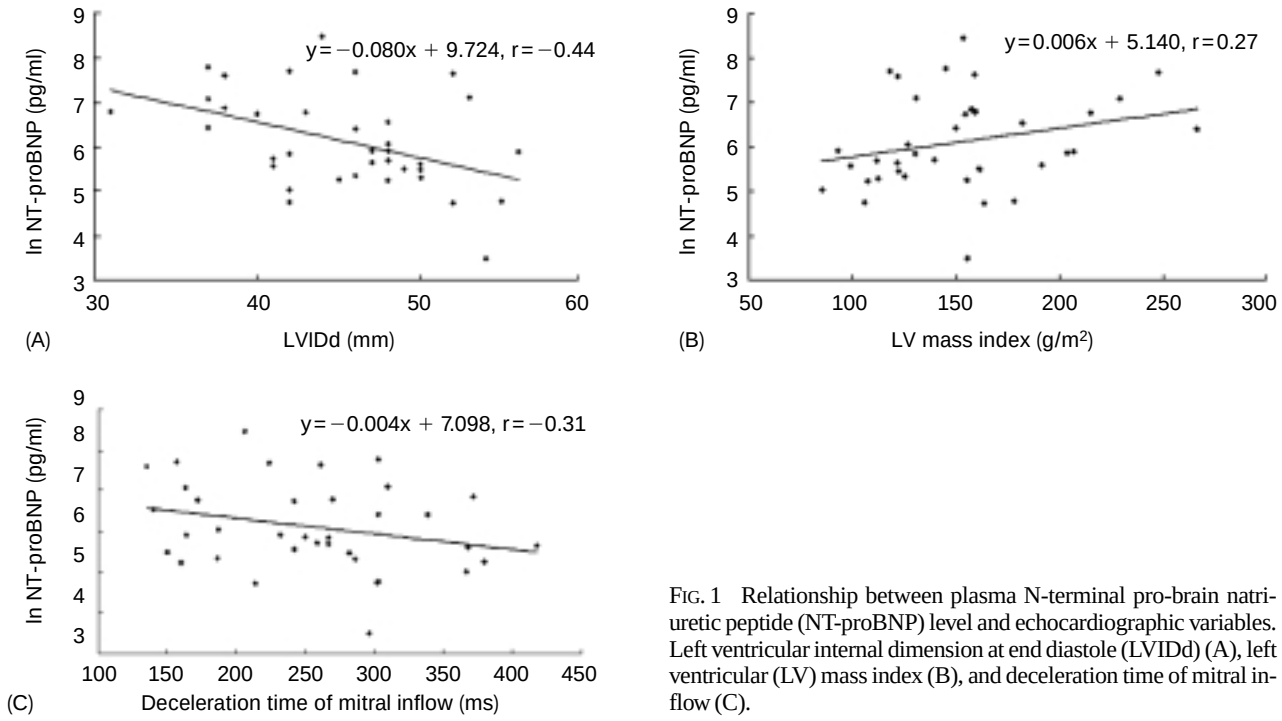

FIG. 1 Relationship between plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) level and echocardiographic variables. Left ventricular internal dimension at end diastole (LVIDd) (A), left ventricular (LV) mass index (B), and deceleration time of mitral inflow (C).

Discussion

Many reports have revealed increased plasma BNP levels in patients with HCM.[2, 7, 10, 13] As pressure-stretch release coupling mechanisms have been suggested as the principal stimulus of natriuretic peptide secretion,[9] LVOT obstruction, LV diastolic dysfunction, and degree of LV hypertrophy have been considered to be involved in the elevation of plasma BNP levels in patients with HCM.[2, 9, 10] The main regulatory mechanism for BNP and NT-proBNP is similar, although the biological effects of plasma NT-proBNP are unknown.[3] Furthermore, NT-proBNP level is known to be more reliable, less expensive for diagnosing cardiac disease, and may provide more reliable guidelines for the physician's decisions during follow-up treatment.[3, 6] Therefore, plasma NT-proBNP level was measured for evaluating the disease status of patients with HCM in the current study.

Effect of Gender and Age

The higher NT-proBNP levels in female patients may be explained by the study that reported NT-proBNP to be higher in female than in male adults;[18] it could be associated with sex hormonal variation.[18] In contrast to previous reports, there was no association of NT-proBNP level with age in the current study.[10, 18] This may be because the effect of age on NT-proBNP level is not strong enough to have a significant effect on patients with HCM and normal LVEF.

TABLE III Univariate and multivariable regression analysis for NT pro-BNP with regard to echocardiographic variables in 36 patients with hypertrophic cardiomyopathy

		Multivariate		
Variables	Univariate P	Coefficients(β) ± SEM	t	p Value
LVIDd	0.004	−0.528 (0.025)	−3.837	0.001
DT	0.034	−0.301 (0.002)	−2.261	0.031
LVMI	0.050	0.407 (0.004)	2.959	0.006
IVSTd	0.010			NS

Overall $R^2 = 0.43$.

Abbreviations: LVIDd = left ventricular internal dimension at end diastole, DT = deceleration time, SEM = standard error of the mean. Other abbreviations as in Table I.

Effect of Structural Change

In the current study, LVIDd, LVIDs, and LVEDV showed negative correlation with ln NT-proBNP level on univariate analysis, and this relationship was constant for the LVIDd on multivariate analysis. The latter relationship contrasts with that seen in dilated cardiomyopathy, for which researchers have proposed that an increase in intraventricular cavity size is a key factor regulating the secretion of BNP and atrial natriuretic peptide (ANP).[1] This may be explained by the fact that a reduced cavity size is the only consequence of increased LV wall thickness, and that LV end-diastolic dimension is inversely related to the amount of LV hypertrophy.[19] Thus, both small LV end-diastolic dimension and increased LV mass index could be important stimuli for elevating plasma NT-proBNP level. The same relationship between plasma BNP level and LV mass index was reported in patients with LV hypertrophy due to aortic valvular stenosis.[20]

Effect of Hemodynamic Change

The influence of LVOT pressure gradient on the natriuretic peptides in patients with HCM has been reported previously;[7] however, we found no association between plasma concentrations of NT-proBNP levels and LVOT obstruction in this study. The reason could be the relatively small number of patients with significant LVOT obstruction, but also that their pressure gradients may not have been high enough to increase the plasma level of NT-proBNP (resting phase: 18.4 ± 11.9 mmHg [range 5.0–42.0] and latent phase: 47.3 ± 24.9 mmHg [range 17.1–83.6]). Although NT-proBNP levels are influenced by altered hemodynamics associated with poor ventricular systolic function,[1, 9] LVEF was not related to plasma NT-proBNP levels in this study, possibly due to the fact that LVEF was normal in all our subjects.

Effect of Diastolic Function

Abnormalities in LV relaxation, filling, and compliance are common in patients with HCM.[11, 21, 22] Left ventricular diastolic dysfunction as suggested by impaired LV relaxation may cause an increase in LV diastolic stress and so stimulate the synthesis and secretion of plasma BNP.[9, 23] In the current study, plasma NT-proBNP levels were significantly higher in patients with diastolic dysfunction, which is consistent with the results of previous studies on plasma BNP.[13, 22, 23] In particular, the negative correlation of DT with ln NT-proBNP levels may imply that plasma NT-proBNP levels increase with the aggravation of LV diastolic dysfunction in HCM, because the shortening of DT suggests a worsening of LV diastolic function.[17]

Limitations of the Study

There are several limitations to be noted in this study in addition to its retrospective nature and the relatively small number of subjects. Plasma samples were mostly obtained from patients who were taking various drugs (angiotensin-converting enzyme [ACE] inhibitors, beta blockers, or calcium-channel blockers). Because ACE inhibitors[24] and beta blockers[25, 26] have been reported to change plasma natriuretic peptide concentrations in previous studies, they may have affected the results of the current study. However, we believe that altered plasma natriuretic peptide concentration in patients taking drugs for cardiovascular diseases are more reflective of the altered cardiac functional status even with the patients' hearts under the influence of medications.[26]

Conclusions

We demonstrated that plasma concentration of NT-proBNP increased with the progression of LV hypertrophy and the worsening of LV diastolic dysfunction in patients with HCM and normal LVEF. These findings may be helpful for analyzing the mechanisms causing the structural changes that affect the hemodynamics in the mild form or early stages of HCM.

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