Bradyarrhythmia Can Increase the Plasma Level of N-Terminal Pro-Brain Natriuretic Peptide

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ABSTRACT

Background and Objectives: Myocardial wall stretch is the main trigger for pro-brain natriuretic peptide (pro-BNP) secretion. The reduced heart rate associated with bradyarrhythmia increases stroke volume, resulting in increased wall tension. Therefore, we propose that bradyarrhythmia could increase plasma N-terminal pro-BNP (NT-pro-BNP) levels.

Subjects and Methods: We enrolled 125 patients who received a temporary pacemaker because they had sinus node dysfunction (SND) or atrioventricular blocks (AVBs). Patients with renal dysfunction, hyperkalemia, reduced left ventricular systolic function (left ventricular ejection fraction [LVEF], <40%), and atrial fibrillation were excluded. Heart failure (HF) was defined as an NT-pro-BNP level of >300 pg/mL. We evaluated history of hypertension, diabetes mellitus, and ischemic heart disease, plasma NT-pro-BNP levels, body mass index (BMI), LVEF, left atrial diameter (LAD), and escape rhythm rate.

Results: The log plasma NT-pro-BNP level of the patients with AVBs was significantly increased compared to that of the patients with SND (3.17 ± 0.55 vs. 2.93 ± 0.64 pg/mL, respectively; $p=0.03$). The incidence of HF was 72.5% (106 patients; 44 male patients). Further, the incidence of HF was significantly higher among patients with AVBs than among patients with SND. The type of bradyarrhythmia was found to be the only predictor of HF after adjusting for age, history of hypertension, LAD, and LVEF. The LVEF, LAD, and ventricular rate were similar between the 2 groups.

Conclusion: As in the case of patients with tachyarrhythmia, bradyarrhythmia may increase plasma NT-pro-BNP levels, leading to HF. Therefore, the possibility of HF should be considered in patients with bradyarrhythmia.

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Introduction

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) have been used as markers for diagnosis or risk stratification in patients with heart failure (HF), stable coronary artery disease, and acute coronary syndrome.¹ BNP secretion is mainly triggered by myocardial wall stretch.² Tachycardia-induced cardiomyopathy is a well-known cause of arrhythmia-induced elevation in natriuretic peptide levels.³⁻⁵ Therefore, we decided to investigate whether bradyarrhythmia causes an increase in plasma NT-pro-BNP levels.

Subjects and Methods

We retrospectively enrolled 125 patients who received a temporary pacemaker because they were found to have sinus node dysfunction (SND) or atrioventricular blocks (AVBs) at the emergency department of Daegu Catholic University Medical Center from March 2006 to February 2012. The SND cases included symptomatic marked sinus bradycardia (<40 bpm) or long sinus pause (>3.0 s). AVB cases included high degree AVBs or complete AVBs. Patients with renal dysfunction, hyperkalemia, reduced left ventricular systolic function (left ventricular ejection fraction [LVEF] <40%), and atrial fibrillation were excluded. Heart failure (HF) was defined as a NT-pro-BNP level of >300 pg/mL, as described in the 2012 European Society of Cardiology (ESC) Guidelines.⁶ We evaluated history of hypertension, diabetes mellitus, ischemic heart disease, plasma NT-pro-BNP levels, body mass index (BMI), LVEF, left atrial diameter (LAD), and ventricular rate. Blood samples were drawn from patients within 1 hour after arrival at the emergency department, and specimens were placed in 5-mL ethylenediaminetetraacetic acid tubes and immediately centrifuged. Plasma NT-pro-BNP levels were measured by using an automated system (Elecsys 2010™, Roche Diagnostics, Indianapolis, IN, USA). The current study was conducted in accordance with the Declaration of Helsinki, and the Institutional Review Board of Daegu Catholic University Medical Center approved the study protocol.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 19.0 (SPSS Inc., Armonk, NY, USA) statistical software package was used for all calculations. Data are presented as mean $\pm$ standard deviation for continuous variables and as percentages for categorical data. The included patients were divided into 2 groups (HF versus no HF) according to the measured plasma NT-pro-BNP levels. The unpaired Student t-test was used to analyze differences between each group. The categorical data were analyzed by using the chi-square test. The predictors of HF were analyzed by multivariate logistic regression. A *p* value of <0.05 was regarded as statistically significant.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the patients with SND (n=53) and AVBs (n=72). Age and BMI did not differ between the 2 groups. In addition, the levels of electrolytes such as sodium and potassium, thyroid function, and transthoracic echocardiographic parameters such as LVEF, LAD, and mitral inflow pattern determined by using Doppler were similar between SND and AVB patients. The ventricular rate was found to be slower in patients with AVBs than in those with SND, although the difference was not significant. However, NT-pro-BNP levels were significantly higher in patients with AVBs than in those with SND (Figure 1).

Differences in patient characteristics according to the incidence of HF

Table 2 shows the differences in patient characteristics according to the incidence of HF. A total of 166 patients (84.8%) were diagnosed with HF. The incidence of HF was significantly higher in patients with AVBs than in those with SND (66/72; 91.7% versus 40/53; 75.5%, respectively; *p*<0.05). The HF patients were significantly older and had lower BMI values than those without HF. Serum sodium levels were significantly lower in patients with HF as compared to those without HF. Transthoracic

Table 1. Baseline characteristics of the patients with SND and AVB

	SND	AVB	P
Patients No.	53	72	
Age (years)	70.8±12.3	72.1±11.5	0.524
BMI (kg/m ²)	23.5±3.7	23.5±4.4	0.951
Ventricular rate (beats/minute)	43.3±11.2	39.4±11.1	0.064
hs-CRP (mg/dL)	10.7±12.8	16.8±34.9	0.181
Log NT-pro-BNP* (pg/mL)	2.93±0.64	3.17±0.55	0.030
NT-pro-BNP (pg/mL)	2011.4±2756.3	3482.5±5737.6	0.060
Sodium (mg/dL)	139.0±4.2	139.9±3.7	0.193
Potassium (mg/dL)	4.47±0.41	4.34±0.60	0.172
TSH (μU/mL)	3.39±7.86	4.20±12.5	0.695
Free T4 (ng/dL)	1.18±0.31	1.28±0.29	0.083
LVEF (%)	59.8±9.5	59.8±10.5	0.993
LA diameter (mm)	41.5±7.1	42.2±8.5	0.624
Mitral inflow E/E'	16.2±9.5	14.4±8.8	0.308

AVB, atrioventricular block; BMI, body mass index; bpm, beats per minute; hs-CRP, high-sensitive C-reactive protein; LA, left atrium; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-brain natriuretic protein; SND, sinus node dysfunction; TSH, thyroid stimulating hormone.

*Log NT-pro-BNP indicates the logarithmic data of NT-pro-BNP levels.

Figure 1. The level of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) between atrioventricular block (AVB) and sinus node dysfunction (SND).

echocardiographic parameters were similar between the patients with and without HF. Multivariate analysis revealed that the presence of AVBs was the only independent predictor of HF after adjusting for age, history of hypertension, LVEF, and LAD (Table 3).

Discussion

The present study demonstrated that bradyarrhythmia can cause an increase in plasma NT-pro-BNP levels. Furthermore, NT-pro-BNP levels were higher in patients with AVBs as compared to those with SND.

Kovats *et al*⁷ reported that in elderly women with beta-blocker therapy-induced sinus arrest with a 40 bpm junctional escape rhythm and elevated NT-pro-BNP serum levels, the stroke volume increased at the lower heart rate in order to keep up the cardiac output. Increased stroke volume results in increased wall

Table 2. Differences in patient characteristics according to the incidence of heart failure

	No HF*	HF	P
Patient No. (%)	19 (15.2%)	106 (84.8%)	
Age (years)	66.3±12.5	72.5±11.5	0.035
Male (%)	8 (42.1 %)	44 (41.5 %)	0.577
BMI (kg/m ²)	25.8±3.3	23.0±4.1	0.009
Hypertension (%)	8 (42.1 %)	53 (50.0 %)	0.351
Diabetes (%)	4 (21.1 %)	23 (21.7 %)	0.609
Ischemic heart disease (%)	2 (10.5 %)	8 (7.5 %)	0.469
Ventricular rate (beats/minutes)	38.9±16.8	41.4±10.1	0.555
SND/AVB	13/6	40/66	0.013
hs-CRP (mg/dL)	4.05±2.70	16.00±29.79	<0.001
Log NT-pro-BNP† (pg/mL)	2.17±0.29	3.23±0.49	<0.001
NT-pro-BNP (pg/mL)	176.5±92.3	3339.5±5011.5	<0.001
Sodium (mg/dL)	141.0±2.4	139.3±4.1	0.014
Potassium (mg/dL)	4.22±0.36	4.43±0.55	0.123
TSH (μU/mL)	2.80±2.13	4.07±11.74	0.641
Free T4 (ng/dL)	1.15±0.25	1.25±0.31	0.188
LVEF (%)	61.8±6.7	59.5±10.6	0.356
LA diameter (mm)	42.2±9.1	41.9±7.7	0.883
Mitral inflow E/E'	13.3±10.2	15.6±8.9	0.318

AVB, atrioventricular block; BMI, body mass index; bpm, beats per minute; HF, heart failure; hs-CRP, high-sensitive C-reactive protein; LA, left atrium; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-brain natriuretic protein; SND, sinus node dysfunction; TSH, thyroid stimulating hormone.

*HF was defined as a patient who complained dyspnea and increased NP-pro-BNP levels (>300 pg/mL).

†Log NT-pro-BNP indicates the logarithmic data of NT-pro-BNP levels.

tension, which in turn triggers natriuretic peptide secretion.⁸ Further, Meiracker *et al.*⁹ demonstrated that in hypertensive patients, decreased heart rate due to beta-blocker therapy increased plasma atrial natriuretic peptide and BNP concentrations.

Pan *et al.*¹⁰ reported that patients with SND, AVB, and atrial fibrillation had increased plasma NT-pro-BNP levels as compared to the controls, and NT-pro-BNP levels were lower in patients with SND than in patients with AVB; this finding is consistent with our result. They also demonstrated that the severity of

atrioventricular asynchrony was an independent determinant of NT-pro-BNP levels. Atrioventricular asynchrony leads to stretching of the atrial wall and increased ventricular end-diastolic pressure, resulting in increased secretion of NT-pro-BNP from the atrium and ventricle.¹¹⁻¹² Koch *et al.*¹³ reported that patients with dual-chamber pacing had significantly lower BNP values as compared to those with single-chamber ventricular pacing due to the loss of atrioventricular synchrony.

Taken together, bradyarrhythmia due to beta-blocker therapy, AVBs, or SND can lead to elevated plasma NT-pro-BNP levels by

Table 3. Multivariate logistic analysis to determine the predictor of heart failure

	Odds ratio	95% CI	P
Age	1.046	0.997, 1.097	0.066
Hypertension	1.602	0.509, 5.041	1.602
LVEF	0.963	0.910, 1.019	0.194
LA diameter	0.968	0.904, 1.036	0.349
Type of bradyarrhythmia (AVB)	3.915	1.274, 12.029	0.017

AVB, atrioventricular block; CI, confidence interval; LA, left atrium; LVEF, left ventricular ejection fraction.

Figure 2. The mechanisms for increased plasma BNP level by bradycardia.
ANP, atrial natriuretic peptide; AV, atrioventricular; BNP, brain natriuretic peptide.

increasing cardiac wall stretch through an increase in stroke volume or loss of atrioventricular synchrony (Figure 2).

Conclusion

As in the case of patients with tachyarrhythmia, bradyarrhythmia, especially that caused by AVBs, may cause an increase in plasma NT-pro-BNP levels, leading to HF. Therefore,

the possibility of HF should be considered in patients with bradyarrhythmia.

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